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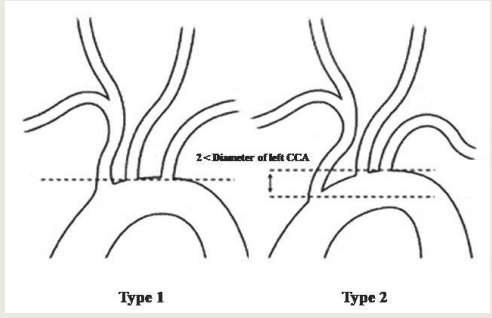

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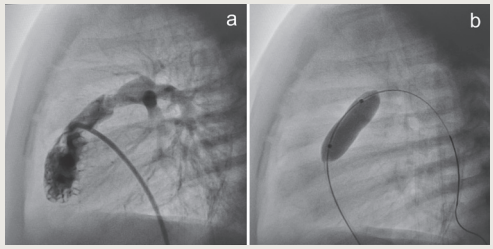

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Volume: 1 • Issue: 2 • August 2021

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Volume: 1 • Issue: 2 • August 2021

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CSMJ

Volume: 1 • Issue: 2 • August 2021

Editorial Board

CSMJ

Volume: 1 • Issue: 2 • August 2021

Editorial Board

CSMJ

Volume: 1 • Issue: 2 • August 2021

Editorial Board

CSMJ

Volume: 1 • Issue: 2 • August 2021

Editorial Board

CSMJ

Volume: 1 • Issue: 2 • August 2021

Editorial Board

CSMJ

Volume: 1 • Issue: 2 • August 2021

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Cam and Sakura Medical Journal (CSMJ) is an international, scientific, open access periodical published journal. It has independent, unbiased, and double-blinded peer-review principles. The journal is the official publication of the Basaksehir Cam & Sakura City Hospital. It is published three times per year (April-August-December). A special supplement including interesting, novel and attractive theme has also been published every year. The publication language of the journal is English.

Cam & Sakura Medical Journal publishes original experimental or clinical research, review articles, case reports, technical reports, diagnostic puzzle, clinical images, video article, novel insight, and letters to the editor in the field of general medicine. Review articles will be only prepared by expert academicians upon invitation. The journal's target audience includes academics and expert physicians working in all fields of general medicine.

The editorial policies are based on the "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (ICMJE Recommendations)" by the International Committee of Medical Journal Editors (2013, archived at http://www.icmje.org/) rules.

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Volume: 1 • Issue: 2 • August 2021

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The editorial and publication processes of the journal are established in accordance with the international guidelines. The most important criteria of the manuscripts for publication include originality, scientific quality, and citation potential. The authors should guarantee that the manuscripts have not been previously published and/or are under consideration for publication elsewhere. The scientific and ethical liability of the manuscripts belongs to the authors and the copyright of the manuscripts belongs to CSMJ. Authors are responsible for the contents of the manuscript and accuracy of the references. All manuscripts submitted for publication must be accompanied by the Copyright Agreement and Authorship Acknowledgement Form. The manuscript should be submitted when this form has been signed by all the authors. By the submission of this form, it is understood that neither the manuscript nor the data it contains have been submitted elsewhere or previously published and authors declare the statement of scientific contributions and responsibilities of all authors.

Manuscripts submitted to the CSMJ will be evaluated by a double-blind peer-review process. Each submission will be reviewed by the chief editor, deputy and associate editors and at least two external, independent peer expert reviewers. The editorial board will invite an external and independent editor to manage the evaluation processes of manuscripts submitted by editors or by the editorial board members of the journal. The reviewers will be requested to complete review process within 6-8 weeks. Authors will be informed within a period of 8 weeks about the process. Upon review, those manuscripts, which are accepted, shall be published in the journal and issued on the http://www.csmedj.org.

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General Guidelines

Manuscripts can only be submitted electronically through the Manuscript Manager website (csmedj.manuscriptmanager.net) after creating an account. This system allows online submission and review.

Format: Manuscripts should be prepared using Microsoft Word, size A4 with 2.5 cm margins on all sides, 12 pt Arial font and 1.5 line spacing.

Abbreviations: Abbreviations should be defined at first mention and used consistently thereafter. Internationally accepted abbreviations should be used; refer to scientific writing guides as necessary.

Cover letter: The cover letter should include statements about manuscript type, single-journal submission affirmation, conflict of interest statement, sources of outside funding, equipment (if applicable), approval of language for articles in English and approval of statistical analysis for original research articles.

The Editorial Policies and General Guidelines for manuscript preparation specified below are based on "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (ICMJE Recommendations)" by the International Committee of Medical Journal Editors (2016, archived at http://www.icmje.org/).

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/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).

Manuscripts are accepted only online and can be submitted electronically through web site (http://csmedj.org) after creating an account. This system allows online submission and review. The ORCID (Open Researcher and Contributor ID) number of the correspondence author should be provided while sending the manuscript. A free registration can be done at http://orcid.org. The manuscripts gathered with this system are archived according to ICMJE-www.icmje.org, Index Medicus (Medline/PubMed) and Ulakbim-Turkish Medicine Index Rules. Rejected manuscripts, except artworks are not returned.

All pages of the manuscript should be numbered at the top right-hand corner, except for the title page. Papers should include the necessary number of tables and figures in order to provide better understanding. The rules for the title page, references, figures and tables are valid for all types of articles published in this journal. Manuscripts submitted to the journal will first go through a technical evaluation process where the editorial office staff will ensure that the manuscript has been prepared and submitted in accordance with the journal's guidelines. Submissions that do not conform to the journal's guidelines will be returned to the submitting author with technical correction requests.

Ethical Guidelines

An approval of research protocols by the Ethics Committee in accordance with international agreements (World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects," amended in October 2013, www.wma.net) is required for experimental, clinical, and drug studies. Information about patient consent, the name and approval number of the ethics committee should be stated in the manuscript. Submission which do not have ethical approval will be rejected after editorial review due to the lack of approval.

For experimental studies performed on animals, an approval research protocols by the Ethics Committee in accordance with international

CSMJ

Volume: 1 • Issue: 2 • August 2021

agreements is required. Also, a statement including measures for prevention of pain and suffering should be declared in the manuscript. For manuscripts concerning experimental research on humans, a statement should be included that written informed consent of patients and volunteers was obtained following a detailed explanation of the procedures that they may undergo. The authors have responsibility to protect the patients' anonymity carefully. For photographs that may reveal the identity of the patients, signed releases of the patient or their legal representative should be obtained and the publication approval must be provided in the manuscript.

Authors must provide disclosure/acknowledgment of financial or material support, if any was received, for the submitted study. If the article includes any direct or indirect commercial links or if any institution provided material support to the study, authors must state in the cover letter that they have no relationship with the commercial product, drug, pharmaceutical company. concerned; or specify the type of relationship. Authors must provide conflict of interest statement and provide authorship contributions.

The scientific board guiding the selection of the papers to be published in the Journal consists of elected experts of the Journal and if necessary, selected from national and international authorities. The Editor-in-Chief, Associate Editors, biostatistics expert and language editors may make minor corrections to accepted manuscripts that do not change the main text of the paper.

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Cam & Sakura Medical Journal is sensitive about plagiarism. All submissions are screened by a similarity detection software (iThenticate by CrossCheck) at any point during the peer-review and/or production process. Authors are strongly recommended to avoid any form plagiarism and ethical misconduct for prevention of acceptance and/or publication processes. Results indicating plagiarism may result in manuscripts being returned for revision or rejected. In case of any suspicion or claim regarding scientific shortcomings or ethical infringement, the journal reserves the right to submit the manuscript to the supporting institutions or other authorities for investigation. CSMJ accepts the responsibility of initiating action but does not undertake any responsibility for an actual investigation or any power of decision.

Statistics

Every submission that contains statistical analyses or data-processing steps must explain the statistical methods in a detailed manner either in the Methods or the relevant figure legend. Any special statistical code or software needed for scientists to reuse or reanalyse datasets should be discussed. We encourage authors to make openly available any code or scripts that would help readers reproduce any data-processing steps. Authors are also encouraged to summarize their datasets with descriptive statistics which should include the n value for each dataset; a clearly labelled measure of centre (such as the mean or the median); and a clearly labelled measure of variability (such as standard deviation or range). Ranges are more appropriate than standard deviations or standard errors for small datasets. Graphs should include clearly labelled error bars. Authors must state whether a number that follows the ± sign is a standard error (s.e.m.) or a standard deviation (s.d.). Authors must clearly explain the independence of any replicate measurements, and 'technical replicates' – repeated measurements on the same sample – should be clearly identified. When hypothesis-based tests must be used, authors should state the name of the statistical test; the n value for each statistical analysis; the comparisons of interest; a justification for the use of that test (including, for example, a discussion of the normality of the data when the test is appropriate only for normal data); the alpha level for all tests, whether the tests were one-tailed or two-tailed; and the actual p-value for each test (not merely 'significant' or '$p < 0.05$'). It should be clear what statistical test was used to generate every p-value. Use of the word 'significant' should always be accompanied by a p-value; otherwise, use 'substantial', 'considerable', etc. Multiple test correction must be used when appropriate and described in detail in the manuscript.

All manuscripts elected for full peer review will be assessed by a statistical editor and their comments must be addressed in full.

Preparation of the Manuscript

a. Title Page

The title page should include the full title of the manuscript; information about the author(s) including names, affliations, highest academic degree and ORCID numbers; contact information (adress, phone, mail) of the corresponding author. If the content of the paper has been presented before, and if the summary has been published, the time and place of the conference should be denoted on this page. If any grants or other financial support has been given by any institutions or firms for the study, information must be provided by the authors.

For regular article submissions, "**What's known on this subject?**" and the "**What this study adds?**" summaries.

This page should include the title of the manuscript, short title, name(s) of the authors and author information. The following descriptions should be stated in the given order:

1. Title of the manuscript (English), as concise and explanatory as possible, including no abbreviations, up to 135 characters
2. Short title (English), up to 60 characters
3. Name(s) and surname(s) of the author(s) (without abbreviations and academic titles) and affiliations
4. Name, address, e-mail, phone and fax number of the corresponding author
5. The place and date of scientific meeting in which the manuscript was presented and its abstract published in the abstract book, if applicable.
6. The ORCID (Open Researcher and Contributor ID) number of the all authors should be provided while sending the manuscript. A free registration can be done at http://orcid.org.

b. Abstract

The abstract should summarize the manuscript and should not exceed 300 words. The abstract of the original articles consist of the subheadings including "Objective, Methods, Results, and Conclusion". Separate abstract sections are not used in the submission of the review articles, case reports, technical reports, diagnostic puzzle, clinical images, and novel articles. The

CSMJ

Volume: 1 • Issue: 2 • August 2021

Instructions to Authors

use of abbreviations should be avoided. Any abbreviations used must be taken into consideration independently of the abbreviations used in the text.

c. Keywords

A list of minimum 4, but no more than 6 key words must follow the abstract. Key words in English should be consistent with "Medical Subject Headings (MESH)" (www.nlm.nih.gov/mesh/MBrowser.html).

d. Original Article

The instructions in general guidelines should be followed. The main headings of the text should include "Introduction, Material and Methods, Results, Discussion, Study Limitations and Conclusion". The introduction should include the rationale and the background of the study. Results of the study should not be discussed in this part. "Materials and methods" section should be presented in sufficient details to permit the repetition of the work. The statistical methods used should be clearly indicated. Results should also be given in detail to allow the reproduction of the study. The Discussion section should provide a correct and thorough interpretation of the results with the relevant literature. The results should not be repeated in the Discussion Part. The references should be directly related to the findings of the authors. Study Limitation should be detailed in the section. Conclusion section should provide highlighted and interpreted with the study's new and important findings.

The excessive use of abbreviations is to be avoided. All abbreviations should be defined when first used by placing them in brackets after the full term. Abbreviations made in the abstract and in the text are taken into consideration separately. Abbreviations of the full terms stated in the abstract must be re-abbreviated after the same full term in the text.

Original Articles should be no longer than 3500 words and include no more than 6 tables and 7 or total of 15 figures and 40 references. The abstract word limit must be 250.

Introduction

The article should begin with a brief introduction stating why the study was undertaken within the context of previous reports.

Materials and Methods

These should be described and referenced in sufficient detail for other investigators to repeat the work. Ethical consent should be included as stated above.

The name of the ethical committee, approval number should be stated. At the same time, the Ethics Committee Approval Form should be uploaded with the article.

Results

The Results section should briefly present the experimental data in text, tables, and/or figures. Do not compare your observations with that of others in the results section.

Discussion

The Discussion should focus on the interpretation and significance of the findings with concise objective comments that describe their relation to other work in that area and contain study limitations.

Study Limitations

Limitations of the study should be detailed. In addition, an evaluation of the implications of the obtained findings/results for future research should be outlined.

Conclusion

The conclusion of the study should be highlighted.

e. References

The reference list should be typed on a separate page at the end of the manuscript. Both in-text citations and the references must be prepared according to the Vancouver style. Accuracy of reference data is the author's responsibility. While citing publications, preference should be given to the latest, most up-to-date references. The DOI number should be provided for citation of ahead-of-print publication, Journal titles should be abbreviated in accordance with the journal abbreviations in Index Medicus/MEDLINE/PubMed. All authors should be listed in the presence of six or fewer authors. If there are seven or more authors, the first three authors should be listed followed by "et al." References should be cited in text, tables, and figures should be cited as open source (1,2,3,4) in parenthesis numbers in parentheses. References should be numbered consecutively according to the order in which they first appear in the text. The reference styles for different types of publications are presented as follows:

i) Standard Journal Article

Salminen P, Paajanen H, Rautio T, et al. Antibiotic therapy vs appendectomy for treatment of uncomplicated acute appendicitis: the APPAC randomized clinical trial. JAMA 2015;313:2340-2348.

ii) Book

Getzen TE. Health economics: fundamentals of funds. New York: John Wiley & Sons; 1997.

iii) Chapter of a Book

Volpe JJ: Intracranial hemorrhage; in Volpe JJ (ed): Neurology of the Newborn, ed 5. Philadelphia, Saunders, 2008, pp 481-588.

Porter RJ, Meldrum BS. Antiepileptic drugs. In: Katzung BG, editor. Basic and clinical pharmacology. 6th ed. Norwalk, CN: Appleton and Lange; 1995. p. 361-380.

If more than one editor: editors.

iv) Conference Papers: Bengtsson S, Solheim BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Reinhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sep 6-10;Geneva, Switzerland: North-Holland; 1992. p. 1561-1565.

CSMJ

Volume: 1 • Issue: 2 • August 2021

v) Journal on the Internet: Morse SS. Factors in the emergence of infectious disease. Emerg Infect Dis [serial online] 1995 1(1):[24 screens]. Available from:s URL:http://www/cdc/gov/ncidoc/EID/eid.htm. Accessed December 25, 1999.

vi) Thesis: Kaplan SI. Post-hospital home health care: the elderly access and utilization (thesis). St. Louis (MO): Washington Univ; 1995.

f. Tables, Graphics, Figures, Pictures, Video:

All tables, graphics or figures should be numbered consecutively according to their place in the text and a brief descriptive caption should be given. Abbreviations used should be explained further in the figure's legend. The text of tables especially should be easily understandable and should not repeat the data of the main text. Illustrations already published are acceptable if supplied by permission of the authors for publication. Figures should be done professionally and no grey colors should be used. Authors are responsible for obtaining permission to publish any figures or illustrations that are protected by copyright, including figures published elsewhere and pictures taken by professional photographers. The journal cannot publish images downloaded from the Internet without appropriate permission.

Figures or illustrations should be uploaded seperately.

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Reviews

Reviews will be prepared by authors who have extensive knowledge on a particular field and whose scientific background has been translated into a high volume of publications with a high citation potential are welcomed. These authors and subjects will be invited by the journal. All reviews within the scope of the journal will be taken into consideration by the editors; also the editors may solicit a review related to the scope of the journal from any specialist and experienced authority in the field.

The entire text should not exceed 25 pages (A4, formatted as specified above).

Reviews should be no longer than 5000 words and include no more than 6 tables and 10 or total of 20 figures and 80 references. The abstract word limit must be 250.

Case Reports

Case reports should present important and rare clinical experiences. It must provide novel, and/or rare clinical data, or new insights to the literature. Case reports should consist of an unstructured abstract (maximum 150 words) that summarizes the case. They should consist of the following parts: introduction, case report, discussion. Informed consent or signed releases from the patient the patient or legal representative should be obtained and stated in the manuscript.

Reviews should be no longer than 1000 words and include no more than 200 tables and 10 or total of 20 figures and 15 references. The abstract word limit must be 150.

Clinical Images

The journal publishes original, interesting, and high quality clinical images having a brief explanation (maximum 500 words excluding references but including figure legends) and of educational significance. It can be signed by no more than 5 authors and can have no more than 5 references and 1 figure or table. Any information that might identify the patient or hospital, including the date, should be removed from the image. An abstract is not required with this type of manuscripts. The main text of clinical images should be structured with the following subheadings: Case, and References.

Video Article

Video articles should include a brief introduction on case, surgery technique or a content of the video material. The main text should not exceed 500 words. References are welcomed and should not be more than 5. Along the main document, video material and 3 images should be uploaded during submission. Video format must be mp4 and its size should not exceed 100 MB and be upto 10 minutes. Author should select 3 images, as highlights of the video, and provide them with appropriate explanations. Video and images must be cited within main text.

Technical reports

Technical reports are formal reports designed to convey technical information in a clear and easily accessible format. A technical report should describe the process, progress, or results of technical or scientific research or the state of a technical or scientific research problem. It might also include recommendations and conclusions of the research. Technical reports must include the following sections: abstract, introduction, technical report, discussion, conclusions, references. Technical reports should contain less than 20 references.

Diagnostic puzzle

Diagnostic puzzles report unusual cases that make an educational point. Since the aim of these articles is to stimulate the reader to think about the case, the title should be ambiguous and not give away the final diagnosis immediately. Diagnostic puzzles should include an introduction and answer part. The introduction part should include a brief clinical introduction to a case (maximum 250 words) followed by an image and a question designed to stimulate the reader to think about what the image shows. The legend should not indicate the diagnosis but should simply describe the nature of the image. Then, the answer part should appear later (maximum 250 words) outlines a brief description of the key diagnostic features of the image, the outcome, and a teaching point.

Diagnostic puzzles will not include more than 5 references. The quality of the image must be at least 300dpi and in TIFF, JPEG, GIF or EPS format. Videos are also welcome and should be in .mov, .avi, or .mpeg format.

CSMJ

Volume: 1 • Issue: 2 • August 2021

Instructions to Authors

Novel insight

This section will offer an opportunity for articles instead of the traditional category of Case Reports. Submissions to this section should contribute significant new insights into syndromological problems, molecular approach and real novelties on recognized or entirely new genetic syndromes or a new technique. The novel aspect(s) can be in the phenotype and/or genotype, the presentation, and the investigation. Submissions can be based around a single case or serial cases. Manuscripts for this section will go through the usual peer reviewing process. The manuscripts should contain abstract (maximum 150 words), a brief introduction, case report(s) and discussion.

Letters to the Editor

This section welcomes for manuscripts that discuss important parts, overlooked aspects, or lacking parts of a previously published article in this journal. In addition, articles on subjects within the scope of the journal that might have an attraction including educative cases, may also be submitted in the form of a "Letter to the Editor." The manuscripts for this section should be written in an unstructered text including references. The editor may request responses to the letters. There are no separate sections in the text.

Letter to the editors should be no longer than 500 words.

Revision Process

During the submission of the revised version of a manuscript, the authors should submit a detailed "Response to the reviewers and editors" that states point by point how each issue raised by the reviewers and/or editors has been replied and where it can be found (each reviewer's comment, followed by the author's reply and line numbers where the changes have been made) as well as an annotated copy of the main document. Revised manuscripts should be submitted within 30 days from the date of the decision letter. If the revised version of the manuscript is not submitted within the allocated time, the revision option may be cancelled.

Accepted manuscripts are copy-edited for grammar, punctuation, and format. Once the publication process of a manuscript is completed, it is published online on the journal's webpage as an ahead-of-print publication before it is included in its scheduled issue.

LIMITATION TABLE

Type of Manuscript	Word Limit	Abstract Word Limit	Reference Limit	Table Limit	Figure Limit
Original Article	3500	250 (Structured)	40	6	7 or total of 15 images
Review	5000	250	60	6	10 or total of 20 images
Case Report	1000	150	20	200	10 or total of 20 images
Letter to the Editor	500	No Abstract		No tables	No media
Video Article	500		5		
Diagnostic Puzzle	250 (as a brief clinical introduction		5		
Clinical Images	500 (as a brief explanation)		5	1	1
Technical Reports			20		

CSMJ

Volume: 1 • Issue: 2 • August 2021

Contents

CSMJ

Volume: 1 • Issue: 2 • August 2021

Editorial

Dear Colleagues,

It is our great pleasure to meet you in the second issue of Cam & Sakura Medical Journal (CSMJ). Although it is difficult to perform clinical studies during the pandemics all over the world, we thank all the authors of the articles published in this issue for their valuable support.

In this issue of CSMJ, you can read the review about the pathophysiological basis of feeding intolerance in critically ill children. The cardiac catheterization has been increasingly performed in neonates with congenital heart diseases and you can find a single center experience about this topic. You can also read a study that investigated the association between preoperative prolonged coagulation tests and bleeding risk in children. Another study in this issue compared the colposcopic biopsy results of patients with positive high risk of non-human papilloma virus 16/18 subtypes regardless of cytology results. The relationship between the aortic art structure and the success of endovascular reperfusion therapy in acute ischemic stroke was investigated in another study. In addition, filtration face mask induced anaphylaxis in a heath care staff during pandemics was presented as an interesting case report. We think that all these articles from different fields of general medicine will take attention of the readers.

I want to state that our primary objective is to include CSMJ in well establihed indexes and Pubmed in near future. For this, your contributions including reviews, articles and case reports are very important. Therefore, we wellcome all articles for the following issues.

Hoping to meet you on the third issue.

On behalf of Deputy Editors, Associate Editors and Editorial Secretary

Merih Çetinkaya

Editor in Chief

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CSMJ

Understanding of Pathophysiological Basis of Feeding Intolerance in Critically ill Children

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ABSTRACT

Children with critical illnesses are at increased risk for intestinal injury, gastrointestinal dysfunction, and feeding intolerance, which are associated with delayed recovery and increased morbidity and mortality during their course in the pediatric intensive care unit (PICU). Optimizing energy and protein delivery significantly reduces the incidence of infectious complications and multiorgan failure in critical illness. Enteral nutrition (EN) is the preferred mode of nutrient intake in patients with critical illnesses. Despite the growing awareness of the benefits of EN in patients with critical illnesses, subsequent maintenance of EN delivery in PICUs remains suboptimal. In children with critical illnesses, little data are reported on the factors that influenced EN. Feeding intolerance in children with critical illnesses may be due to alterations in gastrointestinal motility secondary to underlying disease or medication administration. This study aimed to summarize recent insights into the role of hyperglycemia, EN caloric density, and gastrointestinal feedback mechanism, and routine intensive care management, such as sedation, analgesia, and catecholamine on feeding intolerance in children with critical illnesses.

Keywords: Feeding intolerance, gastric emptying, opioid, catecholamine, children

Introduction

Children with a critical illness are at increased risk for intestinal injury, gastrointestinal dysfunction, and feeding intolerance, which are associated with delayed recovery and increased morbidity and mortality during their course in the pediatric intensive care unit (PICU). Moreover, malnutrition is a frequent finding in children with a critical illness (1,2). The prevalence of severe malnutrition in PICU admission of children with a critical illness is reported to be over 30%, as it was 30 years ago (1,2). Optimizing energy and protein delivery significantly reduces the incidence of infectious complications and multiorgan failure in critical illness (3,4,5). Therefore, the provision of optimal nutritional therapy is a fundamental goal of critical care.

Enteral nutrition (EN) is the preferred mode of nutrient intake in patients with critical illness with a functional gastrointestinal system because studies have shown multiple beneficial effects of EN compared with parenteral nutrition (PN). EN allows the use of the nutrients better than PN, and maintains gastrointestinal integrity, and

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improves gastrointestinal barrier dysfunction by its trophic effect, stimulates the immune system, and reduces intestinal bacterial translocation (3,4,5). The Society of Critical Care Medicine and the American Society for Parenteral and Enteral Nutrition promoted early EN of patients in the PICU (6).

Despite the growing awareness of the benefits of EN in patients with critical illness, subsequent maintenance of EN delivery in PICUs remains suboptimal (2). On average, nearly 50% of children with critical illness in most reports fail to reach nutrition goals, with 37-70% of prescribed energy delivery before discharge from the PICU (7,8). EN is frequently impeded or interrupted in the PICU for a variety of reasons, failing to achieve nutrition goals (2,7). An important factor contributing to inadequate provision of EN is feeding intolerance, which occurs frequently due to delayed gastric emptying and gut dysmotility in critical illness. The reported prevalence of feeding intolerance in a recent systematic review ranged from 0.0% to 57.1% with a median prevalence of 20.0% (Interquartile range 7.4-33.0) (9). This wide range is due to the confusion in feeding intolerance definition, which often results in unnecessary feeding interruptions in children with a critical illness (9,10).

Generally, feeding intolerance means the presence of high gastric residual volume, vomiting, diarrhea, and abdominal distention (9,10). However, compared to adults, signs of feeding intolerance in children are difficult to quantify and can be easily confused with gastrointestinal symptoms associated with a patient's medications or underlying illness.

In children with critical illness, little data is reported on the factors that influenced EN. Feeding intolerance in children with critical illness may be due to alterations in gastrointestinal motility secondary to the underlying disease or medication administration. This study aimed to summarize recent insights into the role of hyperglycemia, the caloric density of EN, and gastrointestinal feedback mechanism, and routine intensive care management, such as sedation, analgesia, and catecholamine, on the feeding intolerance in children with a critical illness.

Pathophysiological Basis of Feeding Intolerance

Control of Gastric Emptying

The main function of the stomach is to act as a reservoir of ingested food and perform a mechanical and chemical breakdown of the contents to a fluid chyme that is delivered to the duodenum at a controlled rate. The regulation of gastric emptying is a complex process, which allows optimal intestinal digestion and absorption of foodstuffs. The rate of gastric emptying is determined by the integrated activity of the proximal stomach, antrum, pylorus, and proximal small intestine (11).

The proximal fundus of the stomach functions as a reservoir, and the muscles are adapted to maintain a continuous contractile tone, whereas the antro pyloro duodenal region exhibits phasic and peristaltic contractile activity and functions both as a pump and a grinding mill. The pyloric sphincter tone regulates the outflow to the small intestine. The interaction of nutrients with the small intestine plays a major role in gastric emptying regulation; small-intestinal nutrients slow gastric emptying, which is associated with proximal stomach relaxation, antral contraction suppression, and pyloric motility stimulation (12). Moreover, other factors, including the systemic hormonal environment, enteric nerve activity, central nervous system drive, and ingested meal properties, appear to regulate gastric emptying. Consequently, changes in any of these factors will affect the rate of gastric emptying (13).

Delayed Gastric Emptying in Critical Illness

In patients with critical illness, a marked reduction in antral motility and poor coordination of antroduodenal contractions has been reported during fasting. In addition, proximal and distal gastric motor responses to small-intestinal nutrient stimulation are abnormal in critical illnesses. Moreover, proximal gastric relaxation and the recovery of proximal gastric volumes to pre-stimulation levels are delayed and fundic wave activity and antral motility are reduced (14,15). Failure of the relaxed proximal stomach to return to baseline volume after nutrient stimulation in these patients provides a reservoir for gastric residue retention in the fundus.

Factors Contributing to Gastric Emptying Delay in Children with Critical Illness

The pathophysiology of delayed gastric emptying in children with critical illness is multifactorial. Delayed gastric emptying was reported to be due to impaired gastroduodenal motility related to patients' clinical severity, premorbid conditions, and pharmacological and surgical treatments. Only a few studies specifically focus on delayed gastric emptying in children with critical illnesses. Thus, this study reviewed the outstanding animal and observational adult studies that clarify the factors that contribute to a gastric emptying delay in children with critical illnesses.

Food Composition Effects

In healthy subjects, a relaxed proximal stomach, reduced antro-duodenal motility, and increased isolated pyloric

pressure waves were found in response to small-intestinal feedback (12). Lin et al. (16) demonstrated that the proximal, as well as the distal small intestine, are capable of participating in negative feedback control.

Gastric emptying appears to be regulated by factors, such as the systemic hormonal environment, enteric nerve activities, central nervous system drive, and ingested meal properties. The relative importance of these factors has not been exactly established; however, some evidence presented that the rate of emptying of both solids and liquids depends on their chemical compositions. Several studies have identified different meal properties, which influence the rate of gastric emptying. Low pH and temperature, as well as high osmolality, viscosity, fiber content, and caloric density, delay gastric emptying (17,18). However, Calbet and MacLean (19) reported that the rate of gastric emptying is mainly a function of the caloric density of the ingested meal and that a linear relationship exists between these variables when solutions of similar volumes and osmolalities are administered at the same temperature and pH in healthy humans. For example, an increasing caloric density of 6-fold resulted in a 3-fold decreased rate of gastric emptying (19). Moreover, the rates of gastric emptying for isocaloric amounts of fat, protein, and carbohydrates were reported to be similar, suggesting that the delaying effect of caloric density on gastric emptying seems to be independent of the nature of the solutes (20,21). In addition, the energy properties of the meal are detected by duodenal receptors, which regulate the rate of gastric emptying (17).

Caloric content plays a crucial role in gastric emptying; however, differences in solution osmolality may also change the rate of gastric emptying. A hyperosmolar solution is thought to slow gastric emptying by triggering duodenal osmoreceptor feedback on the stomach (22,23), which may be especially important in patients who receive post-pyloric feeding. Nevertheless, the influence of osmolality on the rate of gastric emptying may be of physiological relevance only at high tonicity levels (1,200 mosmol/kg H_2O) (23).

Enterogastric Feedback Hormones Effects

Cholecystokinin (CCK) and peptide YY (PYY) are important enterogastric feedback hormones, which regulate gastric emptying. In response to the presence of fat and protein in the small intestine, CCK and PYY are released in a dose-dependent fashion from the enteroendocrine cells, which are predominantly located in the proximal small intestine for CCK and the distal small intestine for PYY (24,25). The initial release of PYY after food intake is likely to be mediated by CCK (26). Endogenous CCK has been demonstrated as an important regulator of gastric emptying of both the solid and liquid meal phases and thus a major determinant of gastric emptying of a physiological meal in humans (27). An exogenous administration of CCK and PYY is associated with proximal stomach relaxation, antral motor activity inhibition, isolated pyloric contraction stimulation, and gastric emptying slowing (27,28).

Proximal and distal gastric motor responses to small-intestinal nutrient stimulation are demonstrated to be abnormal in critical illness. In addition, proximal gastric relaxation and proximal gastric volumes recovery to pre-stimulation levels are delayed and fundic wave activity and antral motility are reduced (14). Failure of the relaxed proximal stomach to return to baseline volume after nutrient stimulation in these patients provides a reservoir for gastric residue retention in the fundus. Nguyen et al. (29,30) demonstrated in their studies that both fasting and nutrient-stimulated plasma CCK and PYY concentrations are increased in patients with critical illnesses, particularly in those with feeding intolerance, suggesting a contribution of this hormone in delayed gastric emptying. Moreover, a close relationship has been reported between nutrient-stimulated plasma PYY and CCK concentrations in these patients (29). As gastric emptying was inversely related to postprandial plasma CCK and PYY concentrations in patients with critical illnesses, these studies suggested that hypersensitivity to a small-intestinal nutrient leads to motility changes, which result in reduced gastric emptying, is found in critical illness (29,30).

Blood Glucose Concentration Effects

Changes in blood glucose concentration are among the most frequently encountered components of disturbed homeostasis in children with critical illnesses. Hyperglycemia is a risk factor for poor outcomes in patients with critical illness, and tight glycemic control improves clinical outcomes, including survival (31). Mechanical ventilation, vasopressor/inotropic infusion, continuous renal replacement therapy, and high illness severity scores were known to be associated with hyperglycemia in these patients (32). No definite criteria for hyperglycemia diagnosis among patients without diabetes mellitus, thus the authors used more than two cut-off values to present the hyperglycemic status of children with critical illness in their studies. Through the use of cut-off values of blood glucose level >110 mg/dL, 120 or 126 mg/dL, 150 mg/dL, and 200 mg/dL, the reported incidence of hyperglycemia in children with critical illness ranged from 85% to 95%, 70-86%, 61-72%, and 16.7-35.2%, respectively (33,34,35).

Acute changes in the blood glucose concentration were well recognized to have a major reversible effect on gastrointestinal motility and rate of gastric emptying in both healthy participants and those with diabetes. Acute hyperglycemia that is induced by intravenous glucose infusion was shown to slow the emptying of nutrient-containing liquid and solid meals in patients with and those without diabetes (36), whereas hypoglycemia has the opposite effect and increases the gastric emptying rate for both liquid and solid meals in healthy volunteers and patients with insulin-dependent diabetes mellitus (37). In healthy volunteers and patients with type 1 diabetes, hyperglycemia stimulates phasic pressure waves that are localized to the pylorus, reduces the frequency and propagation of antral pressure waves under fasting and postprandial conditions, and increases proximal gastric compliance, which reflects a gastric tone reduction (38,39). Furthermore, marked hyperglycemia (blood glucose 210-270 mg/dL) showed to decrease in the motility index and propagation of duodenal and jejunal waves and slow small-intestinal transit in healthy volunteers (38,40).

Recent observations indicate that not only pathological but also physiological changes in the blood glucose concentration within the normal postprandial range (140-180 mg/dL) act synergistically with stimuli that arise from the small intestine to slow gastric emptying of solid and liquid meals. For example, at a blood glucose concentration of 180 mg/dL (10 mmol/L), the phasic and tonic pyloric responses to duodenal distension are greater than during euglycemia (41). Antral motility index was noted to be significantly reduced when intravenous glucose infusions raised serum glucose levels to approximately 120 mg/dL (6.6 mmol/L) in fasting humans (42). Moreover, the stimulation of pyloric tone by exogenous CCK was demonstrated to be greater and gastric emptying is slower at a blood glucose level of 144 mg/dL (8 mmol/L) compared with 72 mg/dL (4 mmol/L) in both healthy participants and patients with diabetes (43,44). Furthermore, the evidence presented that hyperglycemia attenuates the prokinetic effect of intravenous erythromycin on gastric emptying in both healthy participants and patients with diabetes (45).

Contrarily, patients with type 1 diabetes without complications had markedly accelerated gastric emptying during hypoglycemia compared with euglycemia, as in healthy participants (37). The finding that cholinergic muscarinic blockade with atropine inhibited the hypoglycemia-induced acceleration of gastric emptying indicates that vagal stimulation plays an important role in this mechanism (46,47).

Sedation and Analgesic Effects

Many sedative and analgesic agents that are commonly administered in the PICU are known to have negative effects on the digestive system with gastric emptying inhibition and small-bowel transit prolongation (48,49,50).

Propulsive gut motility inhibition is especially marked after an opioid-based technique. The inhibitory effect of opioids on gastrointestinal motility has been extensively studied, but the mechanism and understanding are complex. Opioid receptors are known to be present in the gastrointestinal tract. Gut motility inhibition is mainly mediated via opioid receptors because recently developed opioid antagonists reverse opioid-induced gastrointestinal motility inhibition (51,52). Another effect of opioid analgesics is the inhibition of the release of acetylcholine from the mesenteric plexus, thereby increasing colonic muscle tone and reducing propulsive activity in the gastrointestinal tract (53,54). Moreover, the pylorus has been clearly shown to have rich enkephalinergic innervation, and opioids may therefore increase pyloric tone (55).

Morphine, even at a low dose, markedly inhibits gastric emptying due to enhanced proximal gastric relaxation, increased pyloric tone, and increased retrograde duodenal contractions in healthy humans (48,49,50). Remifentanil, an ultra-short-acting opioid, increases pyloric tone and thereby delays gastric emptying (56). Using a guinea-pig small-bowel model, Fruhwald et al. (57) demonstrated that sufentanil, an ultra-short-acting opioid and μ-receptor agonist, had a very strong inhibitory effect on small-bowel motility at moderate concentrations. The most striking finding of this study was that the antiperistaltic effect of epinephrine on intestinal motility is intensified by the combination of sufentanil, especially if the opioid is given at moderate and higher concentrations. Contrary to epinephrine, dobutamine seems to be less capable of depressing peristalsis even when combined with higher sufentanil concentrations (57). Therefore, the physician in the ICU should be alert to possible negative interactions during the long-term combination of opioids and catecholamines, such as epinephrine, norepinephrine, dopamine, and vasopressin combinations, in patients with critical illnesses.

In a laboratory setting, propofol exhibits an inhibitory effect on spontaneous contractile activity and concentration-dependent depression of acetylcholine-induced contraction on human gastric and colonic smooth muscles at clinically relevant concentrations (58). Clinical studies involving human volunteers who are lightly sedated with propofol demonstrated a significantly increased orocecal transit time

(59,60). Contrarily, propofol at low doses (up to 5 mg/kg/h over 1-3 h) has been reported to not affect gastric emptying in healthy humans or in patients who have undergone minor surgery (60,61). In addition, Nguyen et al. (62) recently demonstrated that 56% of patients with critical illness who are sedated with propofol in their study at a mean rate of ~2 mg/kg/h had delayed gastric emptying. However, the incidence of delayed gastric emptying in patients who received propofol was significantly lower than in patients who are sedated with morphine and midazolam. Moreover, whether the delayed gastric emptying is an effect of propofol or critical illness remains unclear (62). An animal study reported that midazolam slows gastric emptying in mice (63). The inhibitory effects of morphine and midazolam on gastric motility are also observed in patients with critical illnesses (64,65).

Ketamine is a unique drug because it is a powerful analgesic in addition to its dissociative anesthetic property. Ketamine was previously demonstrated to suppress endotoxin-induced production of proinflammatory cytokines, such as tumor necrosis factor-alpha and interleukin-6 production in the intestine (66,67). Recently, Suliburk and Mercer (68) demonstrated that ketamine attenuates lipopolysaccharides that induced increases in gastric volume and gastric pH in rats.

Clonidine and dexmedetomidine are potent and selective α2-adrenoceptor agonists with sedative and analgesic properties, which are used for perioperative and intensive care sedation. Moreover, clonidine and dexmedetomidine have been reported to facilitate some signs and symptoms of opioid and benzodiazepine withdrawal. Therefore, they are preferred as a non-opioid alternative for managing opiate withdrawal syndrome, not only in adults but also in infants and children with a critical illness (69,70,71). The physiological role of α2-adrenoceptors in the regulation of gastrointestinal function has been documented (72,73). Activation of α2-adrenoceptors has been reported to mediate several responses in the gastrointestinal tract (72,73). Clonidine and dexmedetomidine were shown to inhibit gastric acid secretion, gastric emptying, and gastrointestinal transit in animal and human studies (73,74,75). Recently, Iirola et al. (76) demonstrated that dexmedetomidine markedly inhibited gastric emptying and orocecal transit compared with placebo and morphine in healthy volunteers.

In conclusion, patients who are sedated with opioids and midazolam are more likely to have slow gastric emptying, and proximal meal retention and may be at higher risk of feeding intolerance, gastroesophageal reflux, and aspiration pneumonia than those receiving propofol or ketamine. Ketamine may be preferred as the analgesic drug of choice, combined with propofol rather than a high-dose barbiturate, midazolam, or opioids in patients with critical illness, especially with sepsis or septic shock.

Catecholamine Effects

In the 1970s, catecholamines, which are frequently used in patients with critical illness because of their cardiovascular effects, were described to significantly alter the rate of gastric emptying (77). The role of alfa- and beta-adrenoceptors and dopamine receptors in the regulation of gastrointestinal motility were well documented (78,79,80). Catecholamines can affect gastric and intestinal motility through direct activation of smooth muscle adrenoceptors, which may belong to the alfa-1, alfa-2, beta-1, beta-2, and beta-3-class (74,81,82). In general, both alfa- and beta-adrenoceptor agonists inhibit gastric or intestinal motility in experimental animals by a direct effect on the smooth muscle or by neural inhibition (83). However, the inhibitory effect of catecholamines on gastric emptying and intestinal motility are dominantly due to the activation of alfa-2 and dopamine-2 receptors. The alpha receptors are found not only in the smooth muscle, such as beta-adrenoceptors, but also on the nerves that modify the release of neurotransmitters, such as acetylcholine, which is an excitatory neurotransmitter in the intestine, and its release increases smooth muscle contraction. The inhibition of acetylcholine release is mediated by alpha-adrenoceptors. Moreover, the activation of DA-2 neural receptors appears to depress digestive motility via an inhibition of acetylcholine that is a release from cholinergic motor neurons that innervate gastrointestinal smooth muscle (84).

Dopamine receptors (DA-2) are known to be present in the human enteric nervous system (85). In mechanically ventilated patients with critical illness, Dive et al. (86) demonstrated that continuous intravenous administration of dopamine at a low dose (4 µg/kg per min) decreased the number of contractions in the gastric antrum and induced phase III motor activity in the duodenum both during fasting and during continuous nasogastric feeding. Similar results were observed by Levein et al. (87) in healthy male participants. They reported that a continuous infusion of dopamine at 5 micrograms kg^{-1} min^{-1} slows gastric emptying and prolongs orocecal transit time (87). In addition to its depressing effect on the antrum, Hartley et al. (88) have shown that dopamine that is infused at a rate of 2 µg/kg per min is normally used to promote renal function and produced a profound relaxation of the corpus fundus of the stomach in healthy volunteers. The authors concluded that giving dopamine at that dose to patients who are receiving nasogastric feeding may put them at risk of vomiting, regurgitation, and gastric content aspiration.

Recently, an experimental study of pharmacologic effects of catecholamines on intestinal motility demonstrated that catecholamines markedly differ in their inhibitory and stimulatory actions on the peristaltic motility of guinea-pig ileum (79). Dobutamine and dopexamine are ~500 times less potent in inhibiting peristalsis than epinephrine, which shows the most inhibitory potency among the catecholamines (79). The authors concluded that the low inhibitory potency of dobutamine (beta 1-adrenoceptor agonist) and dopexamine (beta 2-adrenoceptor agonist and dopamine receptor agonist) are consistent with the finding that alpha-adrenoceptor agonists are more active in inhibiting acetylcholine release from the enteric neurons and suppressing peristalsis than beta-adrenoceptor agonists (79,81). The α2-adrenoceptor agonists clonidine and dexmedetomidine are used as additive analgesic drugs that inhibit gastric, small bowel, and colonic motility in animal and human studies (74,75,78).

Fruhwald et al. (79) ranked inhibitory potency of catecholamines on the peristaltic motility of guinea-pig ileum *in vitro* as follows: Epinephrine > norepinephrine > dopamine > dobutamine ~ dopexamine (Table 1 summarizes the effects of different catecholamines on different receptors). The use of dobutamine and dopexamine may be preferred in patients with critical illness because of their low potency in suppressing intestinal propulsion, but this recommendation is only based on their effects on intestinal motility and does not take their effects on gut perfusion into account (79). Inadequate splanchnic perfusion in the critically ill is known to compromise the gut barrier that leads to bacterial translocation, which may ultimately lead to multiple organ dysfunction. The evidence demonstrates that dopexamine, dobutamine, and dopamine increase splanchnic perfusion, thereby protecting the gut from further injury.

The effect of vasopressin on the GI tract is only rudimentary examined. Using a dog model, Xu et al. (89) showed that that vasopressin significantly delayed gastric emptying and induced gastric and intestinal dysrhythmia. Compared with the gastric slow wave, the inhibitory effect of vasopressin on the intestinal slow wave was relatively mild. Similar results were reported by Langhans et al. (90) in rats, which demonstrated that intraperitoneally injected vasopressin inhibits gastric emptying and reduces food intake in rats. This effect was mediated by an alpha-adrenergic mechanism (91).

Caras et al. (92) studied the effects of vasopressin on gastric myoelectrical activity in healthy women. They demonstrated that intravenous vasopressin influences gastric motility and result in gastric arrhythmia, predominantly bradyarrhythmias, and caused significant nausea and abdominal cramping compared with baseline and controls in dose-dependent fashions (92).

In conclusion, several studies support that the use of dobutamine and dopexamine in critical illness may be more protective on the gastrointestinal system than other catecholamines, including preservation of gut mucosal integrity and lower risk of delayed gastric emptying.

CONCLUSION

Causes for feeding intolerance remain unclear and are probably multifactorial during critical illness. A better understanding of its pathophysiology in children with critical illness may allow an optimized strategy to avoid motility disorders. Therapeutic options, however, are still limited. Current recommendations mostly focused on optimizing all factors that contribute to delayed gastric emptying, early initiation of EN, and individual use of prokinetic agents. Insufficient studies preclude the routine use of newer therapeutic approaches, such as μ-opioid and CCK receptor agonists in children with critical illness and the further investigation appears warranted based on their risk/benefit ratios.

Table 1. Effects of different catecholamines on different receptors

	Receptor				
Catecholamine	α	β1	β2	DA1	DA2
Dopamine (μg/kg/min)					
0-3	0/+	+	+	++	++
3-10	+	++	+	++	++
>10	++	++	+	++	++
Dopexamine	0	+	+++	++	+
Dobutamine	+	+++	++	0	0
Epinephrine	+++	++	+++	0	0
Norepinephrine	+++	++	+	0	0

DA: Dopamine

Ethics

Peer-review: Internally peer-reviewed.

Authorship Contributions

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Evaluation of the Outcomes of Cardiac Catheterization in Newborns

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What is known on this subject?

Pediatric cardiac catheterization in newborns is highly risky. Procedures must be performed with caution.

What this study adds?

Cardiac catheterization and angiography procedures can be safely and effectively performed in experienced centers for neonatal cases. The presence of experienced staff and the support of the surgical team during the procedures are crucial in overcoming the complications that may occur during and/or after the procedure.

ABSTRACT

Objective: Cardiac catheterization and angiography can be performed for diagnostic or interventional purposes in patients with congenital heart diseases. This study aimed to evaluate the outcomes of cardiac catheterization in neonates as a newly established unit.

Material and Methods: Records of neonates (under 28 days), who underwent cardiac catheterization and angiography procedures in our clinic between October 2020 and July 2021, were retrospectively reviewed. The demographic data of patients, echocardiographic diagnosis, cardiac catheterization, and angiography indications, and their outcomes were evaluated.

Results: A total of 76 cardiac catheterization and angiography sessions were performed in 66 neonates (34 males and 32 females), and this number constituted 22% of all angiography procedures performed in our hospital during childhood. Patients' median age and weight were 9 days (range, 1-28) and 3.1 kg (range, 1.7-4.3), respectively. Of the sessions, 88% (67/76) were performed for interventional purposes and 12% (9/76) for diagnostic. In 67 interventional angiography sessions, 74 interventional procedures were performed. The most common interventional procedures were patent ductus arteriosus stenting (n=47/74, 64%); balloon atrial septostomy (n=16/74, 22%); and pulmonary balloon valvuloplasty (n=5/74, 7%). Among the diagnostic procedures, 5 were for post-operative patient evaluation, wherein 3 patients were on extracorporeal membrane oxygenation (ECMO) support. The median procedure and fluoroscopy time were 37 min (range, 9-137) and 468 s (range, 66-2490), respectively. No complications were observed in 64/76 procedures (84%). Hence, complications were observed in 12/76 (16%) procedures, whereas major complications were observed in 8 and minor in 4 procedures. Two patients needed ECMO support in the catheterization

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ABSTRACT

laboratory during the procedure. No case died within the first 24 h. One of the two patients, under ECMO, was successfully discharged.

Conclusion: With the advancement in technological amenities, cardiac catheterization procedures, especially interventional procedures, could be performed with low mortality and high success rates in newborns. Diagnostic catheterizations should be performed for highlighting the underlying problems after cardiac surgery, where other diagnostic tools are insufficient.

Keywords: Neonate, cardiac catheterization, angiography, pediatric cardiology

Introduction

Heart diseases may be seen as congenital or acquired causes. Congenital heart diseases (CHDs) are one of the most leading causes of mortality and morbidity in childhood, especially among newborns. CHDs are heterogeneous diseases constituted by various subgroups with an incidence of 1% in all live births. On-time, accurate diagnosis, and appropriate treatment approaches are crucial to increase the survival rates of patients with CHD (1,2). A case-specific approach should be applied in neonates with CHD due to the variation in hemodynamics and clinical findings, depending on the patient's age and nature of the disease.

Physical examination, teleradiography, electrocardiography (ECG), and echocardiography are frequently used in evaluating and diagnosing cardiac diseases in children as initial tests. The specificity and sensitivity of these methods vary. In cases where these tests are insufficient, computed tomography (CT), magnetic resonance angiography (MRA), and cardiac catheterization and angiography can be performed (3).

Cardiac catheterization and angiography procedures in neonates require more attention, caution, and experience due to their characteristics and risk of high complications rates during the procedure. Catheterization procedures can be performed for interventional purposes, such as electrophysiological study and ablation, balloon atrial septostomy, balloon valvuloplasty (aortic or pulmonary), and stent implantation in the ductus arteriosus, and/or diagnostic purposes, such as revelation before/after surgery and evaluation of anatomical shunt presence and size in different interventional and/or complex heart diseases. Recently, echocardiography and other imaging methods have replaced catheter angiography for diagnostic purposes. Cardiac catheterization has been performed only for interventional procedures in most patients, especially for neonates (4,5).

This study aimed to evaluate neonatal cases who underwent cardiac catheterization and angiography in a newly established unit.

Material and Methods

This study was conducted in the pediatric cardiology department of our newly established hospital. Neonates who underwent diagnostic or interventional cardiac catheterization between October 1, 2020, and July 1, 2021, were retrospectively analyzed. Electrophysiological studies and ablation procedures were excluded. Institutional review board approval was obtained from the University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital Ethical Committee (2021-09-221).

The detailed history and physical examinations of patients were performed during the hospital stay, as well as ECG, echocardiography, and chest X-ray. Cardiac catheterization decisions were evaluated in the pediatric cardiology and cardiac surgery council. The parents of neonates were informed about the procedure and its complications. A proper written and informed consent was taken from all parents of neonates. Complete blood count, basic biochemistry analysis, and bleeding parameters of patients are evaluated. If required, CT or MRA was performed before the procedure to increase the prediction of the catheterization procedure and reduce the amount of contrast agent and the duration of fluoroscopy.

All procedures are performed in the pediatric cardiac catheterization laboratory, using the Philips Biplane Azurion 7 B12/12 (Philips Medical Systems International B.V., Best, Netherlands) device. All procedures were conducted under general anesthesia (Laryngeal mask or intubation). The femoral vein and/or artery (depending on the procedure type) were used for vascular access. In addition, axillary or carotid artery access was used when necessary. Since the beginning of 2021, all arterial or venous punctures were performed with ultrasound guidance.

The study was planned following the Helsinki Declaration and approved by the local ethical committee. A study form, that includes age, gender, body weight, physical examination findings, and transthoracic echocardiography and angiography findings of each case, was created.

Life-threatening complications were considered as major, and those not life-threatening as minor complications. Death, permanent rhythm problems, bleeding that requires blood transfusion, respiratory arrest, cardiac perforation, stent embolization, and postprocedural extracorporeal membrane oxygenation (ECMO) requirement were major complications. In addition, temporary circulatory and rhythm disturbances, bleeding that does not require a blood transfusion, seizure, balloon rupture, etc., were minor complications. The deaths that occurred within the first 24 h after cardiac catheterization and angiocardiography were considered procedure-related deaths.

Statistical Analysis

In the study, the distribution of variables was classified in the computer, and descriptive results were obtained using Statistical Package for the Social Sciences version 15 (Statistical Package for the Social Sciences for Windows). Descriptive statistics were evaluated as median (range) and percent-percentile.

Results

During the study period, 76 cardiac catheterizations were performed on 66 patients (34 males and 32 females), wherein, 88% (67/76) were performed for interventional purposes, whereas 12% (9/76) for diagnostic. In 67 interventional angiography sessions, 74 interventional procedures were performed. The general characteristic of patients, demographic data, and cardiac catheterization outcomes were summarized in Table 1.

The most common diagnoses were pulmonary atresia in 22/66 (33%) and hypoplastic left heart syndrome (HLHS) in 16/66 (24%). These diagnoses were followed by complete transposition of the great arteries, interrupted aortic arch, and critical pulmonary stenosis. Additionally, five patients had atrial isomerism and two had dextrocardia. Detailed information about the diagnoses of patients is listed in Table 2.

Four patients had a definitive genetic anomaly that was diagnosed before the procedure, whereas 11 had suspected genetic anomalies.

Sixty-seven (88%) of 76 procedures were interventional and 9 were diagnostic sessions. Patent ductus arteriosus (PDA) stenting was the most common interventional procedure. Forty PDA stenting procedures were performed as a sole procedure and seven were performed in the same session with a different interventional procedure. The second most frequently performed interventional procedure was balloon atrial septostomy. A total of 16 balloon atrial septostomy procedures were performed (10 as a sole procedure and 6 were simultaneously performed with PDA stenting). The interventional procedures are listed in Table 3. In addition, figures related to the procedures given for hybrid PDA stenting for duct-dependent systemic flow are presented in Figure 1, pulmonary balloon valvuloplasty in Figure 2, and PDA stenting for duct-dependent pulmonary flow in Figure 3.

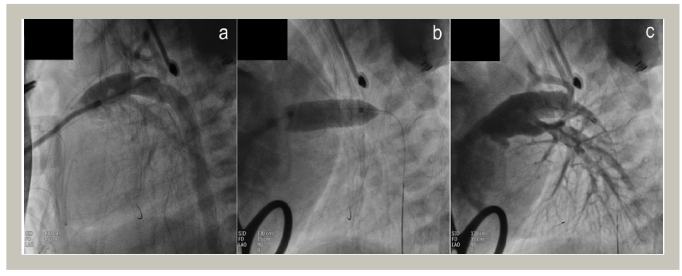

Figure 1. Seven-day-old newborn's cardiac catheterization diagnosed with hypoplastic left heart syndrome (subgroup aortic atresia and mitral hypoplasia). Hybrid patent ductus arteriosus procedure. a) Lateral angiogram showing narrowed ductus, b) stent implantation into the ductus, c) lateral angiogram after stent implantation showing the proper position of the stent and adequate retrograde aortic flow

Table 1. Demographic characteristics of patients and cardiac catheterization information

	Median	Range
Age (days)	9	1-28
Weight (kg)	3.1	1.7-4.3
Height (cm)	49	41-52
Procedure time (minutes)	37.5	9-137
Scopy time (seconds)	468	66-2490
Radiation dose (air kerma, mGy)	59	2.4-450
Radiation dose (DAP, cmGy/cm^2)	3.153	0.3-22.731
Contrast agent (cc)	25	0-40

DAP: Dose area product

Nine of the procedures were diagnostic, wherein five were post-operative patients. Three of the procedures aimed to determine the cause of ECMO requirement after the surgery. These patients were transferred to the catheterization laboratory under ECMO support. The remaining two post-operative patients underwent catheterization to reveal the hemodynamic/anatomical problems following cardiac surgery. In two patients, PDA stenting was terminated as the patients' PDA anatomies were not suitable. Details of the diagnostic procedure data are given in Table 4.

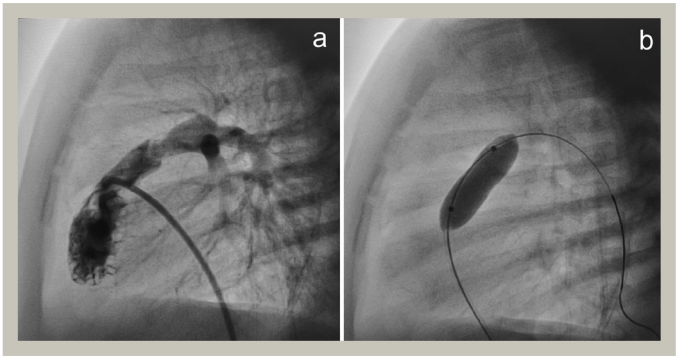

Figure 2. Eleven-day-old newborn's cardiac catheterization diagnosed with valvular pulmonary stenosis. a) Lateral right ventricular angiogram showing pulmonary stenosis, b) lateral angiogram during balloon pulmonary valvuloplasty

Table 2. Diagnoses of patients who underwent cardiac catheterization

	N	%
Pulmonary atresia	22	33.3
PA-VSD	17	-
Tricuspid atresia with PA	3	-
PA-IVS	2	-
HLHS	16	24.2
TGA	7	10.6
IAA	5	7.6
Critical pulmonary stenosis	3	4.5
Tetralogy of Fallot	3	4.5
Pulmonary stenosis	2	3.0
Tetralogy of Fallot with absent pulmonary valve	2	3.0
Coarctation of the aorta	1	1.5
Valvular aortic stenosis	1	1.5
Borderline left ventricle	1	1.5
Scimitar syndrome	1	1.5
Shone complex - aortic stenosis	1	1.5
Taussig bing anomaly	1	1.5
Total	66	100

PA-VSD: Ventricular septal defect pulmonary atresia, PA-IVS: Pulmonary atresia with intact ventricular septum, HLHS: Hypoplastic left heart syndrome, TGA: Transposition of the great arteries, IAA: Interrupted aortic arch

Two patients needed ECMO support during the procedure. In a patient diagnosed with pulmonary atresia with ventricular septal defect, the PDA stent was distally milked and the guidewire position was lost. The stent occluded the PDA, and the oxygen saturation dropped to 20%. ECMO support was urgently initiated in the catheterization laboratory. Then, the patient underwent central shunt surgery. This patient was weaned from ECMO and discharged without any sequela. The other patient had HLHS. He was taken to the catheterization laboratory for a hybrid stage-1 HLHS palliation operation. PDA stenting after balloon atrial septostomy was planned.

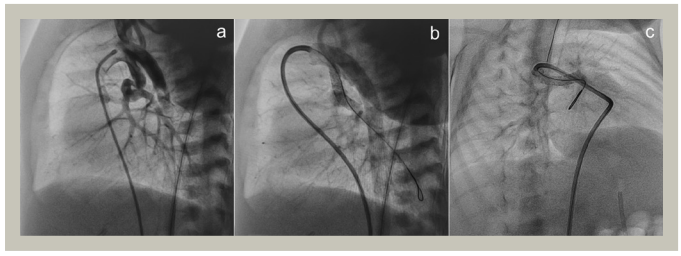

Figure 3. Five-day-old newborn's cardiac catheterization diagnosed with pulmonary atresia with a ventricular septal defect. Ductus arteriosus stenting via an antegrade approach through the femoral vein. a) Lateral angiogram showing vertical ductus. b) Lateral angiogram after two coronary stent implantation into the duct. c) 30LAO-30 kranial angiogram showing proper stent position

Table 3. Procedure types

Procedure	N	%
PDA stenting	40	52.6
Balloon atrial septostomy	10	13.2
Diagnostic cardiac catheterization	9	11.8
Balloon atrial septoplasty and PDA stenting	6	7.9
Balloon pulmonary valvuloplasty	4	5.3
Balloon aortic valvuloplasty	1	1.3
Arcus aorta stenting	1	1.3
Balloon angioplasty of aortic coarctation	1	1.3
Stent implantation of aortic coarctation	1	1.3
Pulmonary balloon valvuloplasty + PDA stenting	1	1.3
RVOT stenting	1	1.3
Sequestration artery embolization	1	1.3
Total	76	100

RVOT: Right ventricular outflow tract, PDA: Patent ductus arteriosus

Atrial and ventricular fibrillation was observed following balloon atrial septostomy. Meanwhile, extrapulmonary cardiopulmonary resuscitation was initiated. PDA stenting was performed under ECMO support. Unfortunately, this patient died during intensive care unit follow-up.

A total of 12/76 (16%) complications occurred, where in 8/76 (16%) were major complications as summarized in Table 5.

No deaths occurred either during or within the 24 h following the procedures. The detailed information about the patients who underwent catheterization under ECMO support was presented in Table 5.

Discussion

This study evaluated the results of cardiac catheterization of neonates in a newly established center. Most procedures were performed for interventional purposes with an acceptable complication rate. This is one of the limited numbers of studies conducted in our country.

Both diagnostic and interventional procedures can be performed safely in neonates with various structural heart diseases. The interventional procedures are less invasive than surgery for neonates and had several advantages, such as decreased hospital stay and provision of palliation, and even definitive treatment in some cases. However, these procedures have some disadvantages, such as vascular complications, and unknown long-term follow-up results (5).

Recently, with the advancement in non-invasive imaging methods, such as CT and MR imaging, the rate of interventional procedures tends to exceed the diagnostic ones. Soylu (6) reported an interventional procedure rate of 30% in their series consisting of 2,265 cardiac catheterizations. Shim et al. (7) stated interventional procedure rate is more

Table 4. Characteristics of patients who underwent diagnostic cardiac catheterization

No	Post-op	Cardiac catheterization indication	Diagnosis
1	Yes	Post-op prolonged intubation	TGA patient after Jaten operation
2	Yes	For coronary artery assessment	After central shunt palliation for PA-IVS, low cardiac output
3	Yes	Investigate the cause of ECMO	Tetralogy of Fallot with absent pulmonary valve
4	Yes	Investigate the cause of ECMO	TGA patient after Jaten operation
5	Yes	Investigate the cause of ECMO	Aortic stenosis after aortic valve repair
6	No	PDA stenting	Ventricular septal defect pulmonary atresia
7	No	PDA stenting	Left isomerism, mitral atresia, aortic outlet right ventricle, pulmonary artery atresia
8	No	MAPCA and PA assessment	Ventricular septal defect pulmonary atresia
9	No	MAPCA and PA assessment	Right atrial isomerism, cAVSD, pulmonary atresia, TAPVC

ECMO: Extracorporeal membrane oxygenation, MAPCA: Major aortopulmonary collateral artery, PA: Pulmonary artery, TGA: Transposition of the great arteries, PA-IVS: Pulmonary atresia with intact ventricular septum, TAPVC: Total anomalous pulmonary venous connection, cAVSD: Complete atrioventricular septal defect

Table 5. Complications, treatments, and clinical outcomes

Major	N	Treatment	Outcome
Stent embolization 7 migration	6	The stent was snared and the procedure was continued. During the procedure, 2 stents were implanted into PDA (n=1)	Discharged
		Stent was secured with a second stent (n=4)	Discharged (n=3) Dead (n=1)
Arrhythmia	2	ECMO support was initiated (n=1)	Discharged after central shunt (n=1)
		ECMO support was initiated (n=1)	Dead (n=1)
Minor			
Arrhythmia	3	Resolved after catheter manipulation	
Bleeding	1	Blood transfusion	

CPR: Cardiopulmonary resuscitation, ECMO: Extracorporeal membrane oxygenator, HLHS: Hypoplastic left heart syndrome, PDA: Patent ductus arteriosus

than half in their series. In our study, the interventional procedure was performed in most cases (88%). In addition, the PDA stenting attempt was given up in two cases because of unsuitable anatomy.

Different studies reported many types of procedures, such as balloon atrial septostomy, balloon angioplasty for aortic coarctation, balloon pulmonary and aortic valvuloplasty, PDA stent implantation, radiofrequency pulmonary valve perforation, and right ventricular outflow tract (RVOT) stenting, as therapeutic procedures in neonates (4,5,6,7,8).

Tekerek (9) reported that balloon atrial septostomy was the most common interventional procedure that was performed on newborns, with a frequency of 35%. Similarly, balloon atrial septostomy was the most common procedure followed by balloon valvuloplasty in Shim et al.'s (7) study. In our study, the most common interventional procedure was PDA stenting. This difference is because the majority of our neonatal cases were diagnosed with pulmonary atresia or HLHS that require PDA stenting. PDA stenting was preferred in patients with duct-dependent pulmonary or systemic circulation. In addition, our center is a referral center for complex heart diseases.

PDA patency is provided with medical methods, such as prostaglandin E1, in the early postnatal period and palliation can be achieved with PDA and RVOT stenting until the definitive surgery is performed (10,11). Akintuerk et al. (11) reported high success rates with the hybrid approach (bilateral pulmonary artery banding and PDA stenting ± balloon atrial septostomy) in HLHS patients. Gibbs et al. (10) stated that most patients with PDA stent had pulmonary atresia with an intact ventricular septum. In the PDA stenting group, pulmonary atresia and HLHS cases were the majority of our patients, consistent with the literature.

Cardiac catheterization complications range from minor problems that do not end up with any sequelae to major problems that lead to emergency cardiac surgery, permanent sequelae, and/or death. The risk of complications may be related to the patient's age, weight, clinical condition at the time of intervention, the type of underlying disease, the purpose of catheter angiography procedure as diagnostic or interventional, and the skill and experience of the performing cardiologist and cardiac team (12). The literature reported that the complication rate after cardiac catheterization is 2-40% in pediatric patients (13). Booth et al. (14) reported that the complication rate was 24% in their series of 160 patients for balloon procedures with the most common complication as vascular problems and 70% of all complications occurred in the neonatal patient group. Uysal (15) reported the complication rate as 5.8% and Tavli et al. (16) as 3.4% in their study. Tekerek (9) encountered a complication rate of 29% in 61 procedures, including 36 minor (17%) and 25 major (12%) complications in the neonatal group in their study consisting of 201 patients who underwent interventional procedures. Our study had a total of 12/76 (16%) complications during the procedures. The major complications were 8/76 (10%), whereas the minors were 4/76 (6%). No deaths occurred in the first 24 h after the procedure.

Study Limitations

The main limitation of this study include the single-center study with a limited number of patients, as well as insufficient experience of the healthcare team who perform the procedures (nurse, technicians, junior cardiologists, etc.) and its impact on the procedure time and success rates.

Conclusion

In conclusion, cardiac catheterization and angiography procedures can be safely and effectively performed in experienced centers for neonatal cases. The presence of experienced staff and support of the surgical team during the procedures are crucial to overcoming the complications that may occur during and/or after the procedure.

Ethics

Ethics Committee Approval: Institutional review board approval was obtained from the University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital Ethical Committee (2021-09-221).

Informed Consent: A proper written and informed consent was taken from all parents of neonates.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: İ.C.T., H.D.Ö., S.S., A.G., K.Y., E.Ö., Concept: İ.C.T., E.Ö., Design: İ.C.T., E.Ö., Data Collection or Processing: H.D.Ö., S.S., A.G., K.Y., Analysis or Interpretation: İ.C.T., A.G., E.Ö., Literature Search: H.D.Ö., S.S., Writing: İ.C.T., E.Ö.

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ORIGINAL ARTICLE
59
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Bleeding Risk in Children with Preoperative Prolonged Coagulation Tests

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What is known on this subject?

Repeated tests and controls are performed in mildly prolonged coagulation tests, and very essential surgical interventions are delayed.

What this study adds?

Repeated tests and checks are unnecessary in mildly prolonged coagulation tests.

ABSTRACT

Objective: Prolonged coagulation test is a common finding before surgery. This study determined the prolonged prothrombin time (PT) and/or activated partial thromboplastin time (aPTT) during the surgical preparation of pediatric patients.

Material and Methods: As a cross-sectional study, 74 children aged 0.25-17 years, who had prolonged preoperative coagulation tests, were included in the Eskişehir State Hospital Pediatric Hematology and Oncology Clinic between September 3, 2013, and September 16, 2014.

Results: The mean age of the children was 5.6±3.4 years, wherein 60 (81%) cases were male. Adenoid-tonsillar operations were planned in 46%, circumcision in 43%, abdominal operations in 5%, and other operations in 6%. A history of bleeding was found in 7 (10%) of the families and 3 (4%) of the cases. Previous surgery or injury was found in 24 (32%) of the children and did not develop more bleeding than expected. The coagulation tests revealed 22 (30%) patients with prolonged PT (value range: 14-35.1 s), 47 (63%) with prolonged aPTT (value range: 37.1-129.6 s), and 5 (7%) with both prolonged PT and aPTT. A necessary operation was performed in 47 patients who did not have a history of bleeding diathesis in the patient or family, with a normal mixed test and factor levels, and PT of <20 s and aPTT of <63.3 s. No bleeding complications were observed during or after the operation in any of these cases.

Conclusion: Our results revealed that in case of prolonged PT or aPTT values before surgery, no risk of bleeding is encountered during the surgery if a history of bleeding diathesis is not present in the patient or family and factor levels are normal.

Keywords: Child, blood coagulation tests, bleeding diathesis, perioperative period

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Introduction

The cost and the effectiveness of coagulation tests that are performed before surgical intervention is a long-debated issue (1,2,3,4). Contrarily, existing habits and efforts are done to prevent possible complications, and problems arise from the delay of the planned surgery together with unnecessary time and financial loss.

Prothrombin time (PT) and activated partial thromboplastin time (aPTT) are used as hemostasis screening tests and are requested in preoperative "routine" analyzes (4,5). The clinical significance of prolonged PT and/or aPTT values that have been reported, especially in patients without anticoagulant therapy and significant liver pathology, is very limited and without bleeding symptoms before and after (6,7).

A limited number of articles have been published in our country on preoperative coagulation tests and evaluations that should be performed in case of prolonged results, and most of them are compiled (8,9,10,11,12,13). This study compiled the cross-sectional data of cases that are referred to Eskişehir State Hospital Pediatric Hematology and Oncology Outpatient Clinic because PT and/or aPTT measurements were longer than normal and discussed these results.

Material and Methods

In this cross-sectional study, 74 pediatric patients aged 0.25-17 years, who were found with prolonged preoperative PT and/or aPTT tests, were admitted to the Eskişehir State Hospital Pediatric Hematology and Oncology Outpatient Clinic between September 3, 2013, and September 16, 2014. PT was 13.5 s and aPTT was 37 s were given as the upper limits of the coagulation laboratory of the hospital where our study was conducted, thus these values were taken as basis in the study. All results included in the study were obtained from the same coagulation laboratory. For interventional procedures, PT and aPTT that is >1.5 times the upper normal limit (PT of >19 s and aPTT of >55 s) was determined as significant elevation and further investigations were planned (14). Age, gender, place of origin of cases, complaint upon arrival, easy bruising, delayed bleeding, nosebleeds, bleeding in other parts of the body, excessive menstrual bleeding during menstruation (the number of pads used in the first 2 days, the need to put a diaper when the bleeding increases, and total duration of menstruation), accompanying symptoms, and drug use was asked. PT and aPTT tests were performed with Greiner Vacuette® 9NC sodium citrate of 3.2%, IL-ACL TOP 500 CTS (USA) device on the samples taken into 3 mL coagulation tubes. Cases with prolonged results that persisted in at least two measurements, those with a family history of bleeding diathesis, and those with prolonged results of >50% of the upper limit in the tests were subjected to, further coagulation factors and mixture tests. The mixture test is an easy and inexpensive test that guides the involvement of factor deficiency or the presence of inhibitors with prolonged coagulation test results. Coagulation tests are based on the principle of re-running the coagulation test by mixing a sample that is within normal limits with a long sample in half. If factor deficiency is the cause, coagulation tests are normal as a result of the mixture but do not return to normal in the presence of an inhibitor. In cases where tests were significantly longer but advanced coagulation studies were normal, the operation approval was given after the informed consent of the patient's parents. Ethical approval was obtained from the Chief Physician of Eskişehir State Hospital on 22.11.2013.

Statistical Analysis

The variables were checked for homogeneity of variance using the Levene statistic. Data were presented as number, ratio, and mean ± standard deviation (SD). Chi-square was used to compare the ratios, and a dependent sample t-test was used to compare the means. Differences were considered to be statistically significant at a p value of <0.05. The Statistical Package for the Social Sciences version 16 for Windows (SPSS® Inc, Chicago, IL) was used for the statistical analysis program.

Results

A total of 60 (81%) male patients, with a mean age of 5.6±3.4 years, were planned for adenoid-tonsillar operation in 46%, circumcision in 43%, abdominal in 5%, and other operations 6%. Even when circumcision operations were removed, prolonged coagulation tests were found to be significantly higher in boys than in girls (p<0.001). Epistaxis was the only bleeding diathesis in the anamnesis that accounts for 3%. The anamnesis for bleeding diathesis in first or second-degree relatives was 7%, but none were diagnosed with bleeding disorders. Surgical intervention was previously undergone by 32% of patients and had no bleeding complications.

In cases with prolonged coagulation tests, 22 (30%) had prolonged PT (range; 14-35.1 s), 47 (63%) had prolonged aPTT (range; of 37.1-129.6 s), 5 (7%) had both prolonged PT and aPTT. Tests were repeated in the same week in all of these cases. The comparison of the mean values of both parameters and international normalized ratio (INR) values before and after surgery revealed no significant difference (p>0.05, Table 1), and both were prolonged after the repetition. PT or aPTT was significantly longer in 5 of all cases. One patient had a

Table 1. The first and second measurement results of patients who were approved for the operation*

	PT (second)		INR		aPTT (second)	
	First	Repeat	First	Repeat	First	Repeat
Mean (± SD)	13.5±3.7	12.9±2.6	1.17±0.34	1.11±0.18	40.1±7.9	41.1±7.0
Shortest	10.6	10	0.92	0.86	20.9	26.1
Longest	35.1	20.2	3.03	1.74	62.3	62

**No significant difference was found between the means of the two measurements for PT, INR, and aPTT (p>0.258). PT: Prothrombin time, INR: International normalized ratio, aPTT: Activated partial thromboplastin time, SD: Standard deviation*

history of suspicious bleeding diathesis (more than 1.5 times the normal value), although aPTT was 40 s, and 3 cases had a family history of bleeding diathesis with epistaxis (1 prolonged PT, 2 prolonged aPTT) examinations were made.

Mixture test in prolonged APTT, factor VIII, vWF, vWF R: C, and factor IX; factor VII levels were studied in patients with a prolonged PT, and factor X levels in those with prolonged PT. Factor VIII level was 44% in one case and factor VII level was 40% in one case. The levels of other cases were found to be within normal limits. Normal values were found in patients who underwent the mixture test, and no case had a significant length in aPTT value after 2 h of incubation.

A total of 65 cases had prolonged coagulation tests with normal factor level, suspected bleeding diathesis in their family, previous surgery but had no bleeding and had normal mixed tests and normal factor level with PT of ≤20.2 s or aPTT of <63.3 s (normal for PT and aPTT was 1.7 times the upper limit) were approved for operation. Of these, 47 cases underwent the necessary surgical intervention, and none had bleeding complications during or after the operation.

Tests were repeated after an average of 80 days in 20 cases with significantly elevated coagulation tests and/or bleeding diathesis, and after an average of 150 days in 10, without significant difference in the mean PT and aPTT values compared to the baseline levels (p>0.121).

Discussion

Prolonged coagulation tests are a common finding in centers where pre-surgical screening is performed. In this case, the planned operation is postponed and the analyzes are repeated, as well as consultations from relevant branches, and new and advanced examinations are started. Surgery for a condition, such as adenoid vegetation, may cause treatment delays and additional complications in the patient, whereas an operation, such as circumcision, that is performed without medical necessity may cause an anxious process for the family. Contrarily, the obtained prolonged coagulation test may be the only finding of bleeding diathesis that was not diagnosed until that time, since tests, such as complete blood count, is uncommon.

The basic hemostatic system is known in detail and quickly analyzed, but the main issue is the result interpretation and follow-up in these cases (15). The benefit of routine basic coagulation tests in surgical procedures or other medical conditions is controversial (6,16). These tests, which have limited sensitivity and specificity, were reported to have high false positivity, low accurate prediction and prediction levels, and high false negativity (4,15). However, prolonged coagulation test results in patients with a history of bleeding before surgery were emphasized to guide the diagnosis of bleeding diathesis (16,17,18). Preoperative coagulation studies in children have been investigated in adenoidectomy and/or tonsillectomy operations, as they are the most frequently performed operations worldwide (4,18,19,20,21).

Various values are accepted as limits in the literature; however, PT of >13 s and aPTT of >36 s are generally accepted as prolonged (6). Our study considered the normal limits of our laboratory, which are PT of 13.5 s, aPTT of 37 s as the upper normal limit. In case of significant increased PT and aPTT values, the tests were repeated, and further coagulation studies were performed with values that are 1.5 times and above the upper normal limit, but no abnormal results were found. Patients and their close relatives without bleeding in cases of previous surgical intervention, circumcision, and injury, and the absence of a diagnosed bleeding disease were supportive factors in the decision to approve the operation. Our study is different from other studies as it consisted of cases that were operated on despite the prolonged coagulation test results (7,17,21,22,23). A study reported that PT and/or aPTT were prolonged and surgical intervention was performed only with pro-coagulants and/or antifibrinolytics in mild factor deficiencies, and none required specific treatment due to bleeding complications (24). Since no specific factor deficiency was detected in our study, procoagulant or antifibrinolytic treatments were planned to be given in case of bleeding.

Cases with more than five nosebleeds annually are considered recurrent nosebleeds (25). In addition, if PT and

aPTT values are determined to be prolonged, studying the FVII, FVIII, FIX, vWF: Ag, and vWF-ristocetin cofactor activity as second-line tests is recommended. Our study found no coagulation factor deficiency in any patients with epistaxis.

Karaca et al. (12) reported that 21 of 100 children who underwent preoperative coagulation screening tests (PT, INR, and aPTT) for adenotonsillectomy operation were found to have longer than normal tests, wherein 2 (2%) had coagulation disorder; therefore, regardless of the cost, preoperative coagulation screening tests (PT, INR, and aPTT) were emphasized as necessary examination. However, in this study, the diagnosis of coagulation disorder was made with a value of 44.8% for factor VIII and 52% for vWF. These levels stand as a compelling and unnecessary situation, both for making a diagnosis and for leaving patients and their owners along with the diagnosis of hemorrhagic disease. In addition, with the obtained results, concluding that these tests are necessary before the operation seems impossible.

Bhasin and Parker (4) reported that results were found to be normal in repeated tests in approximately 50% of cases. Samková et al. (24) found a similar rate when the tests were repeated in the hematology laboratory. Since those who were normal in repeated tests in our study were excluded from the study, it is impossible to present the coagulation test results in the second test within the same week. However, patients with significantly prolonged tests and/or findings in bleeding diathesis had no significant changes in the coagulation tests that were performed in the same laboratory after approximately 3 and 5 months, which suggests no significant benefit for tests before 6 months, especially in cases without bleeding symptoms.

Manning et al. (19) determined that preoperative PT and aPTT screening were not associated with surgical bleeding in 994 patients who underwent adenotonsillectomy. A 12-year retrospective study published by Wei et al. (22) found that 90 (1.93%) of 4,662 patients who underwent tonsillectomy had bleeding, of which only 1 case was primary and the remaining 89 had secondary bleeding. Primary bleeding occurs in the first 24 h after tonsillectomy, which usually accompanies coagulation disorder, whereas secondary bleeding was most common on days 5-6 postoperative. The mean bleeding risk after tonsillectomy has been reported to be between 0.1% and 9.3% (22,23). The absence of bleeding observed in any of our cases shows that the risk of bleeding is not different from the others in cases of a certain prolonged level in coagulation tests in patients without bleeding diathesis findings in the anamnesis and examination. A study supporting our finding reported that a higher probability of bleeding after surgery was associated with the standard medical questionnaire, not with abnormal coagulation tests (26).

Conclusion

Prolonged PT and aPTT values before surgery of up to 1.5 times, no diagnosis of bleeding diathesis in the child or family, and result returns to normal with mixed tests, then bleeding will not occur during and after the operation. We concluded that repeated tests and to test renewed before 3 months is not necessary to check for normalization. However, larger studies are needed on this subject.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Chief Physician of Eskişehir State Hospital on 22.11.2013.

Informed Consent: Patient consent was obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: A.A., Design: A.A., Data Collection or Processing: A.A., A.S., Analysis or Interpretation: A.A., Literature Search: A.A., Writing: A.A.

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

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Comparison of Colposcopic Biopsy Results of Non-HPV 16/18 Oncogenic Type Positive Patients

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What is known on this subject?

High-risk human papillomavirus is the most common cause of cervical cancer worldwide.

What this study adds?

If gynecologists follow the algorithms recommended by guidelines, there is a risk of misdiagnosing cervical intraepithelial neoplasia 2+ lesions in 4% of those patients

ABSTRACT

Objective: This study aimed to evaluate and compare the risk in detecting cervical intraepithelial neoplasia (CIN) 2+ or higher lesions by performing immediate colposcopy in patients with positive high-risk non-human papillomavirus (HPV) 16/18 subtypes, regardless of their cytology results.

Material and Methods: A total of 264 patients with HPV-positive subtypes, aged 20-65 years, with any type of cervical cytology results were included in the study. A liquid-based cytologic cervical cancer screening with HPV testing was carried out between November 2020 and May 2021. Cytological specimens were classified according to the Bethesda system (2014), and HPV identification was analyzed with Cobas 4800 system. Colposcopy-guided endocervical curettage and endometrial biopsy were performed.

Results: A total of 123 patients had HPV non-16/18 oncogenic types, wherein 34 (69.3%) had no dysplasia, 9 (18.3%) had CIN 1, and 2 (4.08%) had CIN 2-3.

Conclusion: Colposcopic evaluation may be considered in cases of non-16/18 high-risk HPV subtypes with abnormal cytologic results. Among the patients who had negative cervical cytology and positive non-HPV-16/18, 4.08% were women with CIN 2-3. Following the algorithm according to the guidelines, there will be a risk of 4.08% of misdiagnosing CIN 2+ lesions by gynecologists. Organizing large-scale randomized controlled studies will help in understanding the meaning or importance of this topic.

Keywords: Colposcopy, cytology, genotyping, human papillomavirus subtypes

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Introduction

High-risk human papillomavirus (HR-HPV) is the most common cause of cervical cancer worldwide (1). According to the National Cancer Institute Centers for Disease Control and Prevention, HPV infection is responsible for >90% of cervical cancer cases worldwide. Almost 200,000 women are estimated to be diagnosed with precancerous cervical lesions or abnormal cells, which may lead to cancer. Of those, 11,000 women have lesions that progressed into cervical cancer as a result of chronic HPV infection. Unfortunately, over 4,000 women died because of this disease (2).

Randomized controlled trials have highlighted that HPV screening tests alone compared with cytologic interpretation were thought to facilitate an objective way of providing better protection against high-grade cancer precursors, such as cervical intraepithelial neoplasia (CIN 2+ and CIN 3+) and cervical cancer, than cytology tests, respectively (1,2).

According to the American Society for Colposcopy and Cervical Pathology (ASCCP) 2019 guidelines, co-testing after 1 year has been recommended in the presence of non-HPV 16/18 subtypes with normal cytology for women who are 30-65 years old (3). The difference between the 2012 and 2019 ASCCP guidelines is that in 2019, all positive primary HPV screening tests were recommended, regardless of genotype, to have additional reflex triage testing from the same laboratory specimen. The specificity of HPV testing in CIN 2+ and higher lesions decreased by 2-4% compared with cytology testing, and HPV testing alone would direct patients to overtreatment and over referral (4). Therefore, reflex triage testing is needed (5).

Risk-based management recommendations are the main difference that comes out at the 2019 ASCCP guidelines. The combination of present HPV results in history (including unknown history) for the surveillance, patient treatments, and colposcopy referrals immediately determined the risk for CIN 3+.

A Turkish nationwide study (6) stated that the positive predictive value for the risk of ≥ CIN 2 lesions of some other types of HPV, such as 33, 31, 35, and 45, in addition to HPV 16/18 is approximately 10%. Nevertheless, the current literature contains limited data on the risk of ≥ CIN 2 lesions in cases with non-HPV 16/18 high-risk types regardless of the cytology results.

The recent cervical cancer screening program is mainly based on searching or detecting the chronic HR-HPV subtypes. Direct colposcopic evaluation is recommended when the HPV 16/18 subtypes are detected (7). The prevalence of these HPV 16/18 subtypes may decrease due to HPV vaccination. In addition, the ATHENA study is similar to the study of Keiser and NHANES, without a sharp increase or decrease in the prevalence of HR-HPV (8) because of the underestimation in managing other high-risk non-16/18 HPV subtypes. The contribution of colposcopic evaluation toward the management of non-16/18 HPV high-risk cases is unclear.

This study aimed to evaluate and compare the risk of detecting CIN 2+ or higher lesions by performing colposcopy in patients with a positive high risk of non-16/18 HPV subtypes, regardless of their cytology results.

Material and Methods

This retrospective study was conducted between November 2020 and May 2021 in a tertiary center located in İstanbul at the Obstetrics and Gynecology Department, Oncology Division, after obtaining approval from Çam and Sakura City Hospital Human Research Ethics Committee (approval no: 2021.07.156). A total of 264 patients, aged 20-65 years, who were screened for cervical cancer with liquid-based cytology and HPV testing were included in this study. The study population was grouped according to their HPV 16/18 test results and previous history of abnormal cervical cytology or cancer. After obtaining informed consent from all participants, the colposcopy and biopsy procedures were performed. Patients who rejected the biopsy procedure and inadequate biopsy samples were excluded from the study. A total of 123 patients were retrospectively evaluated (Figure 1).

All cervical cytology samples were implemented using the Bethesda 2014 system (Surepath). HPV type identification was analyzed using Cobas 4800 for 14 types of HR-HPV DNA (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68). Colposcopy was performed on patients who had HR-HPV-DNA types regardless of cytology results. Patients were divided into two categories based on their cytology results as “negative cytology/non-HPV 16/18 positive types” and “positive cytology/non-HPV 16/18 positive types.”

Histological examination with colposcopy was performed in all patients following the procedure of 3-5% acetic acid solution on the cervix and upper vagina. The evaluation of the colposcopy findings is based on the solemnity of acetowhite lesions, an extension of lesion margins, and vascularity within the acetowhite lesion. Subsequently, Lugol’s solution was applied using an injector by direct installation in the same way with acetic acid. A biopsy of at least four parts from the Lugol negative and acetowhite positive areas was conducted. In the absence of abnormal lesions, a random biopsy was performed. All colposcopy-guided biopsies and

large loop electrosurgical excision (LEEP) procedures were performed by specialists in the gynecological oncology division. Endocervical curettage (ECC) was performed during the colposcopy-guided biopsy procedure. LEEP or conization procedures were executed in case of initial biopsy results with substantiated high-grade cervical lesions (CIN 2-3) or carcinoma *in situ*. The International Federation for Cervical Pathology and Colposcopy 2011 nomenclature was used for the transformation zone classification.

Statistical Analysis

All data were statistically analyzed using the SPSS software version 21. Descriptive statistics were used for demographic data. Fisher's Exact test and chi-squared association test were used for categorical data. The Student's t-test was performed for continuous data. A p value of <0.05 was considered statistically significant. Age, obstetric history, contraceptive method, smoking, cytology results, ECC, LEEP/conization, and cervical pathology results were all recorded.

According to the cervical biopsy results, those with low-grade dysplasia were considered CIN 1, and those with high-grade dysplasia were considered CIN 2-3.

Results

A total of 123 patients with non-16/18 HR-HPV subtypes were included and divided into two groups: Negative cytology group and positive cytology group. The mean ages of patients in the negative cytology and positive cytology groups were 40.8 (24-60) years and 40.4 (20-65) years, respectively (p=0.40). No significant difference was found in the demographics (Table 1).

All patients underwent colposcopy, and a colposcopy-guided cervical biopsy was performed in 45 (91.8%) patients (Table 2).

Endocervical canal curettage biopsy was performed in 36 (73.4%) patients of the negative cytology group, wherein all resulted in chronic cervicitis/inflammation (Table 3).

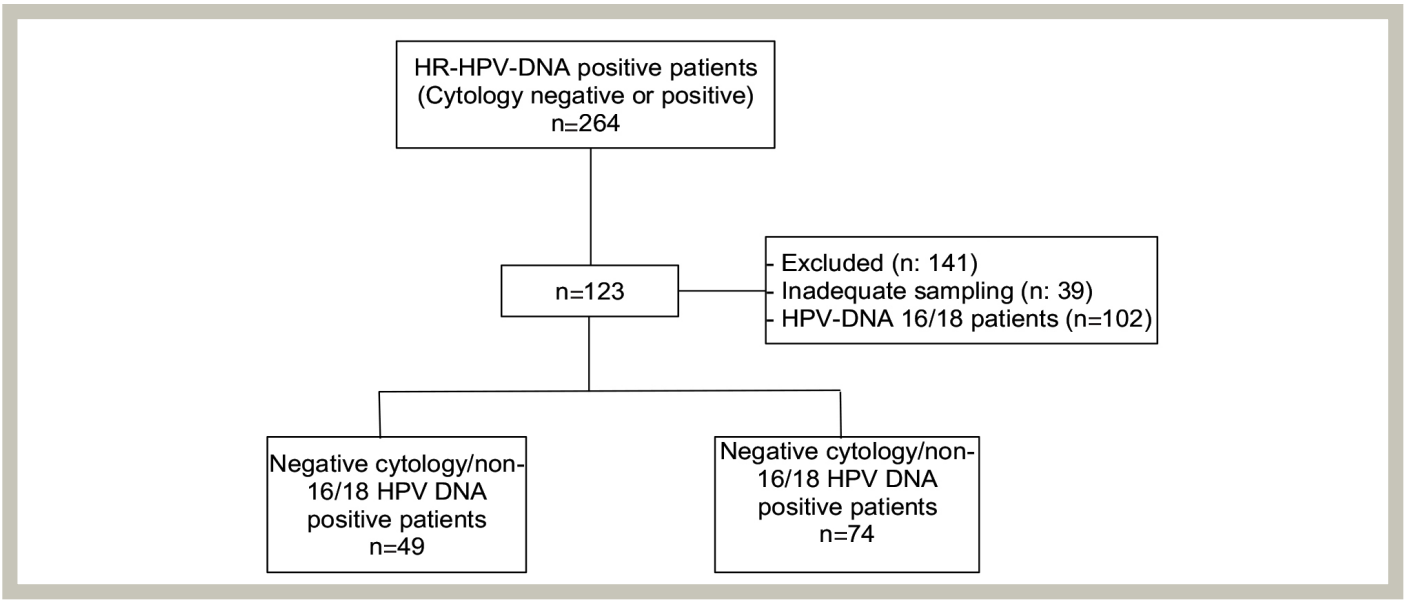

Figure 1. Flow chart of non-HPV-DNA 16/18 positive patient with negative or positive cytology

HR-HPV: High-risk human papillomavirus

Table 1. Comparison of demographics of patients with positive non-16/18 HPV DNA with negative or positive cytology

	Negative cytology (n=49)	Abnormal cytology (n=74)	p value*
Age (mean)	40.8 (24-60)	40.4 (20-65)	0.40
Gravida (mean)	2.38	2.43	0.45
Parite (mean)	1.93	1.9	0.45
Smoker	11(22.4%)	16 (21.6%)	0.82
Contraceptive pill usage	1 (2.05%)	2 (2.70%)	0.06

HPV: Human papillomavirus

Table 2. Comparison of colposcopy-guided cervical biopsy

	Negative cytology (n=45)	Abnormal cytology (n=73)	p value
Chronic cervicitis, inflammation	34 (69.3%)	40 (54.05%)	0.02
Low-grade dysplasia, CIN 1	9 (18.3%)	17 (22.97%)	
High-grade dysplasia (CIN 2-3)	2 (4.08%)	16 (21.6%)	

CIN: Cervical intraepithelial neoplasia

Table 3. Comparison of endocervical canal curettage biopsy results

	Negative cytology (n=36)	Abnormal cytology (n=63)	p value
Chronic cervicitis, inflammation	36 (100%)	60	0.94
Low-grade dysplasia, (CIN 1)	-	2	
High-grade dysplasia (CIN 2-3)	-	1	

CIN: Cervical intraepithelial neoplasia

Discussion

This retrospective cohort study demonstrated that non-16/18 HR-HPV subtypes cause nearly 15% of CIN 2+ lesions. This probability increased to 21.6% with abnormal cytologic results. The subtype analysis of the non-16/18 HR-HPV group in cases, which resulted in CIN 2+ lesions, was not defined.

Gultekin et al. (6) stated that the ratio of CIN 2+ lesions for the non-16/18 HPV subtypes was reported to be nearly 17%, which were nearly 24% of the HPV 16/18 subtypes. They put forward the necessity of reflex cytologic tests for the non-16/18 HPV subtypes to prevent unnecessary colposcopic evaluations. Our results correspond with this research. Our study found that the detection rate of CIN 2+ lesions statistically increased with abnormal cytology.

Aydoğmuş and Aydoğmuş (9) reported that the ratio of CIN 2+ lesions in cases of normal cytology results with non-16/18 HPV subtypes was 15.6%. Conversely, in another research, this ratio was reported as 0.01% (10). Our research detected CIN 2+ lesions 4% of patients with negative cytology. Interestingly, Çöl Madendağ et al. (11) reported that the detected CIN 2+ lesions with normal cytology were higher in cases of non-16/18 HPV subtypes, contrary to 16/18 HPV subtypes. Yalcin et al. (12) stated that the colposcopic evaluation of the normal cytologic results of the HPV 16 cases did not increase the detection rate of cervical cancer. Conflicting results are reported in the literature in cases of negative cytology results with positive non-16/18 HPV subtypes. The regional differences and the possible effect on the virulence or the behavior of the non-16/18 HPV subtypes may cause these conflicting results.

The reported cases demonstrated that even with the normal cytology results, non-16/18 HPV subtypes may cause higher dysplastic lesions at the uterine cervix (6,9,10). Colposcopic evaluation seems logical in cases with abnormal cytology results with non-16/18 HR-HPV subtypes. Colposcopic evaluation is considered to be a burden in the healthcare system; however, as a new and modern gynecologic oncology department, our oncology experts can carry out colposcopic examinations. Colposcopic evaluations are easily accessible and applicable. This is the major strength of this research. This research provides information about the management of the non-16/18 HR-HPV-positive cases.

Study Limitations

One of the limitations of this study is the colposcopic evaluation. Reid's colposcopic index was not found in the patients' colposcopy reports. Retrospective design and limited data is also a limitation of this study.

Conclusion

Organizing large-scale randomized controlled studies would be beneficial in understanding the importance of this topic.

Ethics

Ethics Committee Approval: Çam and Sakura City Hospital Human Research Ethics Committee approved (approval no: 2021.07.156).

Informed Consent: Approval received.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ş.E.D., Ö.K., H.T., Concept: H.T., Design: N.A.V., H.T., Data Collection or Processing: N.A.V., G.N.K., H.T., Analysis or Interpretation: N.A.V., G.N.K., O.K., Literature Search: N.A.V., G.N.K., O.K., Writing: N.A.V., G.N.K., O.K., Ş.E.D.

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Is the Anatomical Type of the Arcus Aorta an Effective Factor for the Success of Endovascular Therapy?

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What is known on this subject?

Contrary to popular belief, anatomical differences in aortic arch structure are not rare. Knowing the anatomical features of this region before surgery and interventional procedures is very valuable in terms of being a road map to the operator. Namely, this different anatomic feature can cause technical difficulty and secondary ischemic problems caused by loss of time for the surgical or interventional procedure to be performed. As it is known, endovascular treatment, class I, level of evidence A, is recommended as a life-saving method recommended in appropriate patients with acute ischemic stroke. While modified-thrombolysis-in-cerebral-infarction (mTICI) 2b and above for reperfusion in endovascular treatment is considered as a technical success, it is predicted to be TICI 3 for clinical success. The patient received intravenous recombinant tissue plasminogen activator before the procedure, the time to start the procedure/the duration of the procedure, the location/structure of the clot, the patient's age/co-morbid condition, the material/technique used, the number of procedures, and the operator's experience are also very important for success, which is important. In addition, the anatomical feature of the aortic arch may be another factor affecting this success.

What this study adds?

In this study, we aimed to investigate the effect of aortic arch structure on the endovascular treatment procedure in patients with acute ischemic stroke and to discuss the clinical outcomes.

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ABSTRACT

Objective: This study aimed to investigate the relationship between the aortic arch structure classification and the success of endovascular reperfusion therapy in acute ischemic stroke (AIS).

Material and Methods: Between January 2018 and December 2018, 207 patients, who were brought to the Stroke Center of Gaziantep University, Şahinbey Research and Practice Hospital due to AIS and who underwent endovascular therapy, were analyzed retrospectively. The demographic features of patients, aortic arch classification, and modified-thrombolysis-in-cerebral-infarction (mTICI) scores used for reperfusion in endovascular therapy were evaluated. Findings were statistically analyzed ($p<0.05$).

Results: A total of 207 patients underwent endovascular procedures with the mean age was 64.4±13 years, wherein 69 (33.3%) had type 1 aortic arch, 99 (47.8%) had type 2 aortic arch, and 39 (18.8%) patients had type 3 aortic arch, whereas 47 (22.7%) patients had a bovine arch. TICI 2b and above recanalization were achieved in 188 (90.8%) patients after endovascular therapy. At the end of the third month, good clinical outcomes were observed as modified Rankin scale of 0-2 in 78 (37.7%) patients, whereas 61 (29.5%) patients had mortality. The prognosis was worse in patients with type 3 aortic arch structure ($p=0.016$).

Conclusion: Our study revealed that complex aortic arch structure had no negative effect on the success of endovascular therapy. However, the prognosis was poor at the end of the third month in patients with complex aortic arch structures.

Keywords: Aortic arch, endovascular therapy, mechanical thrombectomy, mRS, mTICI

Introduction

Contrary to popular belief, anatomical differences in the aortic arch structure are not rare. Knowing the anatomical features of this region before surgery and interventional procedures is very valuable in the road map of the operator (1). Different anatomic features can cause technical difficulty and secondary ischemic problems due to the time consumed for the surgical or interventional procedure. Class I endovascular treatment with a level of evidence A is recommended as a life-saving method for appropriate patients with acute ischemic stroke (AIS) (2), whereas modified-thrombolysis-in-cerebral-infarction (mTICI) 2b and above for endovascular reperfusion treatment is considered as a technical success and is predicted to be TICI 3 for clinical success (3,4). Intravenous (IV) recombinant tissue plasminogen activator (r-tPA) administration before the procedure, the starting time or the duration of the procedure, the location/structure of the clot, patient's age and comorbid conditions, the material/technique used, the number of procedures, and the surgeon's experience are also very important for success (5,6). In addition, the anatomical feature of the aortic arch may be another factor that affects this success.

This study aimed to investigate the effect of the aortic arch structure on the endovascular treatment of patients with AIS and discuss its clinical outcomes.

Material and Methods

Between January 2018 and December 2018, 207 patients, who were admitted to the Stroke Center of Gaziantep University, Şahinbey Research and Practice Hospital due to AIS and who were treated with endovascular treatment (single-center digital angio device-Philips Brand Allura Xper FD 20 model), were retrospectively reviewed. In this study, 188 patients had anterior and 19 had posterior system large vessel occlusion. In addition to the demographic and clinical features of patients, the National Institutions of Health Stroke Scale (NIHSS) scores, Alberta Stroke Program Early Computed Tomography Score (ASPECT) scores, occlusion location, IV r-tPA administration before the procedure, intraarterial r-tPA administration during the procedure, symptom puncture/recanalization times (min), total intracranial procedure numbers, reperfusion mTICI scores, biochemistry-hemogram values, aortic arch types, and modified Rankin scale (mRS) scores in the third month, as well as mortality development, were analyzed.

The arch structure of all patients was determined with a 6-F pigtail catheter at the beginning of all procedures that are performed under general anesthesia. The arch was divided into three types according to the aortic anatomy that was based on the distance from the point where the brachiocephalic trunk originated from the aorta to the aortic arch apex. The distance in type 1 aortic arch was less than the left common carotid artery (CCA) diameter, type 2 was less than twice the left CCA diameter, and type 3 was more than twice the left CCA diameter. These arch types, which are important in performing endovascular procedures, are listed from simple to complex as type 1, type 2, and type 3 (Figure 1). The effect of bovine arch structure on the processes was also evaluated (7,8).

Ethics committee approval was obtained from the Gaziantep University Clinical Research Ethics Committee dated 12.25.2019 and 2019/479.

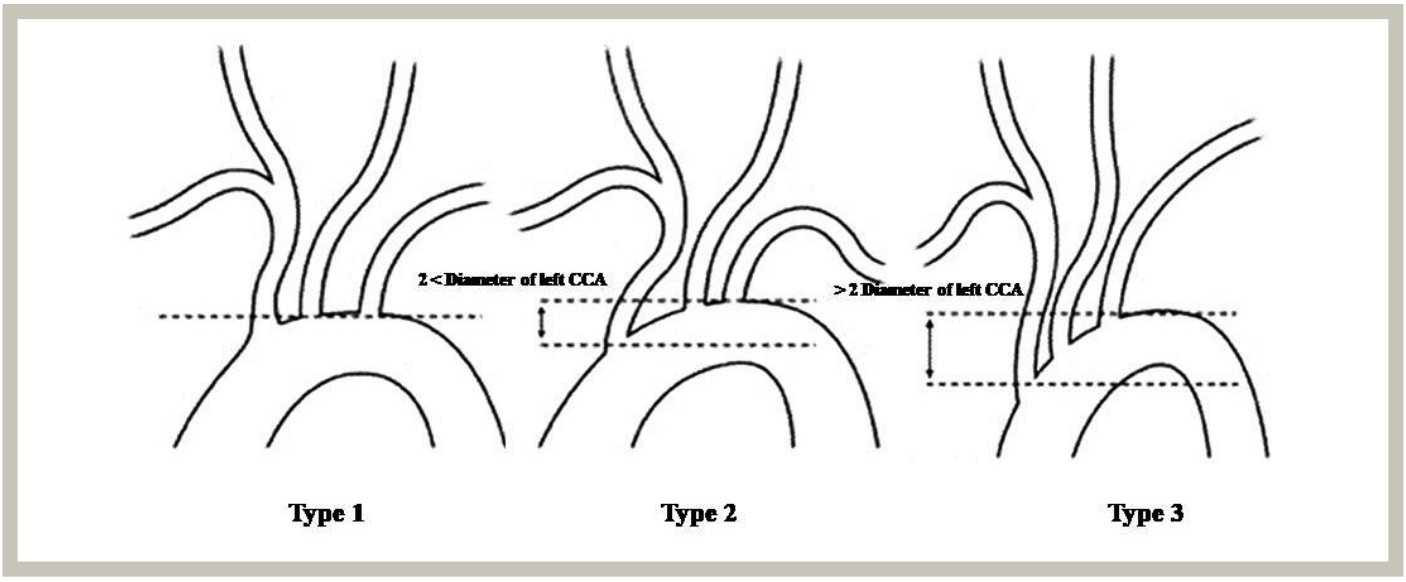

Figure 1. Anatomical types of the arcus aorta

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences version 23 (Statistical Package for Social Sciences) package software program. Continuous variables were expressed in mean ± standard deviation or median with interquartile range (25-75), and categorical variables in proportions. The distribution of quantitative data was analyzed using the Shapiro-Wilk test and all quantitative data was distributed non-parametrically. Non-normally distributed data were compared with non-parametric tests and normally distributed data with parametric tests. Results were analyzed using the Mann-Whitney U test and chi-squared test for non-parametric quantitative variables and categorical variables, respectively.

P values of univariate analyses were adjusted for multiple testing with the false discovery rate method. Regression results were expressed in odds ratios and respective 95% confidence intervals.

Results

A total of 207 patients underwent endovascular procedures with a mean age of 64.4±13 years. The NIHSS score was calculated as median at 15 (12-19) (percentile 25-75) and the ASPECT score at first arrival was calculated as median at 9 (8,9,10). The IV r-tPA was administered to 36 (17.4%) patients before endovascular treatment. Great vessel occlusion was detected in 145 (70%) patients. Type 1 arch was found in 69 (33.3%) patients, whereas 99 (47.8%) had type 2 arch and 39 (18.8%) had type 3 arch. The bovine arch was seen in 47 (22.7%) patients. TICI 2b and above recanalization were achieved in 188 (90.8%) patients after endovascular treatment. At the end of the third month, good clinical outcomes were observed as mRS 0-2 in 78 (37.7%) patients, whereas 61 (29.5%) had mortality. The aortic arch structures of patients were divided into two groups as type 1 and type 2/type 3 and compared to the demographic data, which revealed that the arch structure deteriorated with increasing age (p=0.001). Decreased hemoglobin values were inversely proportional to age attracted attention. No statistically significant difference was found between the other data (Table 1). Demographic data were compared according to types 1 and 3 arch structures of patients, which revealed no statistically significant difference (Table 2). TICI 2b and TICI 3 reperfusion results of types 1 and 3 arch structures were not statistically significant; however, type 3 arch structure decreased the TICI 2b-3 and above recanalization success (p=0.99) (Table 3). The presence of bovine arch type did not make a significant difference for recalculation of TICI 2b-3 and above (p=0.333). However, the recanalization rate in the first 45 min was lower in those with bovine arch type and left anterior system occlusion (p=0.021) (Table 4). Compared with the use of stent retriever of type 1 and types 2 and 3 arch structure, the use of stent retriever decreased in types 2 and 3 rather than type 1. The complex arch structure made the stent usage difficult, which was statistically significant (p=0.017) (Table 5). The use of the arch structure types 2 and 3 rather large (6-F) Distal Access Catheter (DAC) was decreasing. Smaller (5-F) DAC was used in a complex arch structure (p=0.021). The number of patients with good clinical outcomes between 0-2 mRS in the third month decreased in type 3 arch compared to type 1. The complexity of the arch structure has a clinically poor prognosis (p=0.016) (Table 6).

Table 1. Comparison of patients according to type 1 and type 2/type 3 arch structures

Demographic data	Arcus arch type		p value*
	Type 1 Median (25-75)	Type 2 and 3 Median (25-75)	
Age	59 (48-67)	69 (60-76)	0.001
First NIHSS	16 (12-18)	15 (11-19)	0.604
ASPECT score	9 (8-10)	9 (8-10)	0.527
Symptom puncture time (min)	200 (120-260)	200 (120-245)	0.768
Symptom recanalization time (min)	260 (195-310)	263 (195-315)	0.839
Total intracranial procedures	3 (1-4)	2 (1-4)	0.119
Third-month mRS	3 (2-5)	3 (2-6)	0.426
Glucose	138 (113-177)	148 (119-212)	0.161
Leukocyte	10360 (8470-12980)	10280 (8290-12700)	0.866
Platelet	258 (209-310)	264 (212-316)	0.776
Hemoglobin	13.9 (12.2-15.1)	13 (11.8-14.3)	**0.014**
RDW	14.1 (13.4-15)	14.2 (13.4-15.3)	0.470

**Mann-Whitney U test (median, 25-75 percentile), NIHSS: National Institutes of Health Stroke Scale, ASPECT: Alberta Stroke Program Early Computed Tomography, mRS: Modified Rankin scale, RDW: Red blood cell distribution range*

Table 2. Comparison of patients according to types 1 and 3 arch structures

Demographic data	Arcus arch type		p value*
	Type 1 Median (25-75)	Type 3 Median (25-75)	
Age	59 (48-67)	71 (62-77)	**0.001**
First NIHSS	16 (12-18)	16 (14-20)	0.414
ASPECT score	9 (8-10)	9 (8-10)	0.252
Symptom puncture time (min)	200 (120-260)	190 (120-265)	0.851
Symptom recanalization time (min)	260 (195-310)	265 (190-315)	0.823
Total intracranial procedures	3 (1-4)	2 (1-5)	0.702
Third-month mRS	3 (2-5)	3 (3-6)	0.099
Glucose	138 (113-177)	146 (117-200)	0.823
Leukocyte	10360 (8470-12980)	10600 (8930-13110)	0.531
Platelet	258 (209-310)	237 (202-304)	0.593
Hemoglobin	13.9 (12.2-15.1)	13 (11.9-14.3)	0.106
RDW	14.1 (13.4-15)	14 (13.5-15.7)	0.489

**Mann-Whitney U test (median, 25-75 percentile), NIHSS: National Institutes of Health Stroke Scale, ASPECT: Alberta Stroke Program Early Computed Tomography, mRS: Modified Rankin scale, RDW: Red blood cell distribution range*

Discussion

Dividing the anatomical differences of the aortic arch into two groups, as congenital and acquired, was possible. The first group had heterogeneous vascular anomalies, such as variations during the aortic arch development, and changes in the position of the arch and its branches that were accompanied by specific anatomical and clinical findings. In this group, six types of branching were found (9). The literature showed this type of aortic anomalies to be particularly associated with chromosomal defects, such as 22q11 deletion (10). Our study did not examine such abnormal branching patterns of the aortic arch. In the second group, anomalies were determined based on the distance from the point where

Table 3. Comparison of types 1 and 3 arch structure with TICI 2b and TICI 3 reperfusion results

Successful recanalization (≥ mTICI 2b)	Arcus arch type		p value*
	Type 1 N (%)	Type 3 N (%)	
No	4 (40)	6 (60)	
Yes	65 (66.3)	33 (33.7)	**0.99**
Total	69 (63.9)	39 (36.1)	

**Chi-square test, mTICI: Modified-thrombolysis-in-cerebral-infarction*

Table 4. Recanalization success in the bovine arch in the first 45 minutes compared to occlusion side

Recanalization in the first 45 minutes	Bovine arch		p value*
	Right occlusion N(%)	Left occlusion N(%)	
Unsuccessful	12(48)	13(52)	**0.021**
Successful	17(81)	4(19)	

**Chi-square test*

Table 5. Comparison of type 1 and types 2 and 3 structure with stent retriever use

Use of stent retriever	Arcus arch type		p value*
	Type 1 N (%)	Type 2 and 3 N (%)	
No	16 (22.5)	55 (77.5)	
Yes	53 (39)	83 (61)	**0.017**
Total	69 (33.3)	138 (66.7)	

**Chi-square test*

Table 6. Comparison of types 1 and 3 arc structure with mRS

mRS (0-2)	Arcus arch type		p value*
	Type 1 N (%)	Type 3 N (%)	
No	39 (55.7)	31 (44.3)	
Yes	30 (78.9)	8 (21.1)	**0.016**
Total	69 (63.9)	39 (36.1)	

**Chi-square test, mRS: Modified Rankin scale*

the brachiocephalic trunk originated from the aortic arch to its peak. In this group, the aortic arch is divided into three types (7).

Wang et al. (11) investigated the characteristics of the aortic arch in an adult population in Chinese society. This study evaluated the arch structure of 2,370 patients using a thoracic computed tomography and revealed that type 1 arch structure was detected in 1,384 (58.4%) patients, type 2 in 752 (31.7%) patients, and type 3 in 234 (9.9%) patients. The mean age of patients with type 1 arch structure was 55.4±12.3 years, type 2 was 60.9±10.7 years, and type 3 was 65.2±9.9 years. Type 2 arch structure was more common in males than females ($p<0.01$) (11). Some changes in the cardiovascular system as in many tissues were seen with aging. Smooth arteries and collagen rate increase, elastic tissue ratio decreases, and arteries stiffen and become curvier. Thus, the left ventricle of the heart, which tries to pump blood into the systemic circulation, puts more burden and may develop heart failure. In addition, the risk and frequency of chronic diseases, such as hypertension and type 2 diabetes, increase with age (12,13). Thus, with increasing age, the arc structure deteriorates. Similarly, our study paralleled the increase in age with the increase in type 2 and type 3 aortic arch structures.

The relatively low hemoglobin level in the elderly group of this study may suggest the presence of chronic additional diseases. In addition, smaller (5-F) DAC is used in this group during the endovascular procedure, which can be explained by the deterioration of age-related distal vascular structure (p=0.021). A study conducted in our country evaluated 270 patients with cerebral angiography and revealed type 1 arch structure in 195 (72.2%) patients, type 2 in 40 (14.8%) patients, and type 3 in 35 (13%) patients (9). Another study in our country by İnanç et al. (8) examined 288 patients with cerebral angiography and revealed 175 (61%) patients with type 1, 99 (34%) with type 2, and 14 (5%) with type 3 arch structure. Unlike these studies, our study had a higher type 2 arch structure than the others due to the slightly low average age of our patients. A few studies investigated the relationship between the anatomical difference of the aortic arch and cerebrovascular disease. Patil et al. (14) argued that a relationship was found between the aortic anatomy and cerebrovascular disease, whereas İnanç et al. (8) revealed that the aortic arch and its branching features did not have a direct effect on the increased risk of cerebrovascular disease.

AIS is a clinical condition that is common among cerebrovascular diseases, caused by sudden inhibition of blood flow to some part of the brain for thromboembolic causes. If left untreated, it can result in serious injury and death. In the light of studies using new generation, thrombectomy and thromboaspiration devices in AIS, patients with proximal artery occlusion showed to provide higher rates of recanalization and reperfusion compared to IV r-tPA treatment (2). Many studies on "How can I achieve better clinical functional outcomes in endovascular treatment?" have been reported in the literature to date. For example, two major meta-analysis studies compared the effectiveness of direct aspiration and use of stent retriever in AIS treatment, which revealed an equally similar efficacy in achieving good clinical results in both studies (5,15). Our study used direct aspiration and stent retriever techniques alone or together. Comparing patients with types 1 and 3 arch structures that result in successful recanalization (≥ mTICI 2b), mTICI 2b reperfusion was observed to be higher in patients with type 1 arc structure compared to type 3, but without statistically significant differences. Bovine arch structure delayed the reperfusion time in patients with left anterior system occlusion. In addition, the use of stent retriever in patients with type 3 arch structure was less than the other types. Slater et al. (16) evaluated the endovascular treatment results in AIS of two important studies. According to the age distribution, TICI 2b-3 reperfusion rates were higher in the elderly group (>70 years) compared to TICI 0-2a reperfusion rates (16). The difference in our study was that patients with type 3 aortic arch structure have a worse prognosis compared to the third month of mRS. Here, patients with type 3 aortic arch structure also had advanced age and additional chronic problems.

Today, the quality and features of angiographic materials increase with the development of technology, which makes it possible to pass the complex arc structure simpler. Intravascular procedures are important for the diagnosis and treatment of the aortic type supra-aortic and cerebral vessels, and with types 1 to 3, vascular catheterization and procedures will be difficult. The surgeon's experience and ability are other important factor. In addition, this allows the selection of the right technique and angiographic material, thereby shortening the time of the imaging and reducing the contrast agent to be used. Studies reported that brachial/radial access routes usage is easier than the femoral artery or direct carotid intervention for stent insertion into the carotid artery with complex aortic arch or interventions for intracranial arteries (8,9,17,18,19).

Study Limitations

Very few studies reported on the aortic arch anatomy in the literature. Our study was performed retrospectively with file records. Therefore, some limitations are possible, such as having experienced and inexperienced surgeons and the use of different materials and techniques, thus, no pre-standardized standardization. However, this retrospective study determined the total relationship between aortic arch classification and endovascular treatment success.

Conclusion

In conclusion, the complex arch structure was thought to have a negative effect on the success of endovascular treatment; however, this was not statistically significant. In addition, patients with the complex aortic arch structure are relatively older and the clinical prognosis after the procedure was found to be worse than younger patients with a simple aortic arch structure, which was statistically significant.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from the Gaziantep University Clinical Research Ethics Committee dated 12.25.2019 and 2019/479.

Informed Consent: Patient consent was obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.Ç., N.Ş., A.E., Y.İ., S.G., Concept: M.Ç., Design: M.Ç., Data Collection or Processing: M.Ç., N.Ş., A.E., Analysis or Interpretation: M.Ç., N.Ş., Literature Search: M.Ç., Writing: M.Ç., N.Ş.

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Filtration Face Mask 3-induced Anaphylaxis in a Healthcare Worker During the COVID-19 Pandemic: A Case Report

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What is known on this subject?

Nothing is known about this subject.

What this study adds?

This case shows the importance of using good quality materials to produce facial masks for the health of health care providers as well as for the people. Using poor-quality materials or unchecked products can cause life-threatening problems for consumers.

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ABSTRACT

This study aimed to focus on using high quality personal protective equipment (PPE). Low quality PPE usage can cause life-threatening problems for health care workers and public health. The coronavirus disease-2019 pandemic has led to a substantial increase in the usage of face mask wordwide. Fabric, surgical, N95, filtration face mask 2 (FFP2), and FFP3 masks are used to avoid the increased risk of transmission. These masks directly contact the skin; therefore, they may cause the inhalation of the filtration fibers on the mask. Thus, the materials and methods used in mask production are an important public health concern. A 37-year-old healthcare worker was admitted to the emergency department with shortness of breath and cough after wearing an FFP3 mask for an hour. The patient presented with following vital signs: Oxygen saturation (SpO_2) of 89%, heart rate of 120 beats/min, blood pressure of 89/60 mmHg, and respiratory rate of 25 breaths/min. Stridor and bilateral wheezing were noted on physical examination. Considering that the patient developed an anaphylactic reaction due to the fiber material on the inner surface of the mask worn by the patient, anaphylaxis treatment was administered. Following the treatment, patient's clinical status had improved and SpO_2 reached up to 98%. The patient had a history of atopy; therefore, antihistamines were prescribed and dietary modifications were recommended. We report the first case of anaphylactic reaction in a healthcare worker, resulting from the fiber part of a face mask. When foreign body aspiration is suspected, the possibility of anaphylactic reaction to the aspirated material should also be considered. Our case emphasizes that before using face masks, the inner surface should be checked and it must be intact. Additionally, people with the history of atopy should be more careful in selecting the materials used in masks; they should carefully examine the product they bought. Being competent and careful in the controls during the production phase has a great importance in protecting the lives of healthcare workers.

Keywords: Anaphylaxis, FFP3 mask, personal protective equipment, dyspnea

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Introduction

Anaphylaxis is a severe multi-systemic reaction that occurs within minutes of exposure to an allergen (1). It is classified into allergic and non-allergic anaphylaxis. Allergic anaphylaxis is mediated by immunologic mechanisms, whereas non-allergic anaphylactic reaction is triggered by other mechanisms. However, the clinical diagnosis and management for both are identical. All systems and organs can get affected during anaphylaxis, especially the cutaneous, respiratory, cardiovascular, and gastrointestinal systems (Table 1) (2,3).

The cause of anaphylaxis varies across the regions and societies; however, the most common causes of anaphylactic reactions include foods, drugs, and insect bites (4).

The acute management of anaphylaxis involves airway stabilization, adequate oxygenation, and decontamination. Epinephrine is the first-line of treatment for anaphylaxis. If hypotension or tachycardia is present, fluid resuscitation with intravenous crystalloids should begin immediately. Steroids and antihistamines are usually recommended as the second-line of treatment. Selective bronchodilators (salbutamol) are used for allergic bronchospasm and magnesium therapy for resistant bronchospasm (4).

Due to the coronavirus disease-2019 (COVID-19) pandemic, the use of face masks has increased worldwide to reduce transmission by droplets (5). Enormous global demand for face masks has led to a dramatic increase in the production over a very short period. This rapid change raises some quality concerns because these masks have a direct contact with skin and indirect contact with airway. Errors that may occur in the production of masks on their inner surface can lead to life-threatening consequences.

This study aimed to focus on using high quality personal protective equipment (PPE). Low quality PPE usage can cause life-threatening problems for health care workers and the public.

Table 1. Clinical manifestations of anaphylaxis (4)

System	Signs and symptoms
Respiratory	Rhinitis, pharynx edema, laryngeal edema, cough, bronchospasm, and dyspnea
Cardiovascular	Dysrhythmia, collapse, and cardiac arrest
Cutaneous	Itching, urticaria, angioedema, and rash
Gastrointestinal	Nausea, vomiting, cramping, and diarrhea
Ocular	Itching, tears, and redness
Genitourinary	Urgency and cramping

Case Report

A 37-year-old female healthcare worker presented to the emergency department (ED) with shortness of breath and cough after wearing an FFP3 mask for an hour. She did not take any medication, ate something strange, or wore something new that could cause anaphylaxis before being admitted to the ED. She had a history of atopy and latex allergy.

Upon arrival, the patient was awake, cooperative, and oriented. Mild respiratory distress was noted. The patient's vital signs were oxygen saturation (SpO_2) of 89%, heart rate (HR) of 120 beats/min, blood pressure of 89/60 mmHg, and respiratory rate of 25 breaths/min. The physical examination revealed a normal review of systems, except for tachypnea, bilateral wheezing, and stridor on inspiration. No rash, angioedema, cyanosis, and foreign body in the oropharynx were seen on initial examination.

The patient's face mask examination revealed a defective inner surface and a piece of fiber that protruded from the midline (Figure 1, 2).

The patient's progressive airway obstruction was treated with 5 L/min of oxygen therapy through a non-rebreather mask. For hypotension and progressive airway obstruction, 0.5 mg of adrenaline was immediately administered intramuscularly through the left vastus lateralis femoris. Resuscitative efforts also involved 80 mg of prednisolone, 45.5 mg of pheniramine, and 3 doses of salbutamol inhaler.

Following these treatments, the patient showed dramatic clinical improvement with no signs of respiratory distress and tachycardia. SpO_2 reached up to 98% and HR became 80 beats/min. After monitoring the patient for 8 hours, she was

Figure 1. Surface of mask

Figure 2. Innerface of mask

discharged with an antihistamine and dietary modifications were recommended.

Discussion

Anaphylaxis can occur from a variety of substances such as foods, medications, and insect bites. Some medical products may pose a risk as an important allergen for healthcare workers. Healthcare workers are at a higher risk for developing latex allergies. Latex allergy is reported to be present in 12% of healthcare workers (6). Another study in 2014 revealed that 4.8% of healthcare workers in Turkey have latex allergy (7).

Face mask-induced contact dermatitis has been reported in the medical literature with increasing numbers during the COVID-19 pandemic. A study conducted in China reported a patient who developed contact dermatitis due to the sponge band on the nose of the FFP2 mask (8).

According to a study conducted among healthcare professionals, 39.5% of patients using PPE were reported to have irritant contact dermatitis, and the most common causes were glasses (51%), N95 masks (30.77%), and face protectors (17%). Nasal dorsum and cheeks have been reported as the most affected anatomical areas (9).

Another study reported an increasing number of contact dermatitis among healthcare workers caused by frequent hand wash, prolonged use of latex gloves, and usage of disinfectant during the COVID-19 pandemic.

In medical literature, anaphylactic reaction due to fiber material of a face mask has not been reported yet (10).

A detailed statement of written patient consent was signed by the patient for case presentation.

We reported the first case of anaphylactic reaction that resulted from the fiber part of a face mask in a healthcare worker. When foreign body aspiration is suspected, the possibility of anaphylactic reaction to the aspirated material should also be considered. Our case emphasizes that before using face masks, the inner surface should be checked and it must be intact. In addition, people with a history of atopy should be more careful in selecting the materials used in masks and should carefully examine the product they bought. Being competent and careful in the controls during the production phase is of great importance in terms of protecting the lives of healthcare workers.

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Ethics

Informed Consent: The patient's consent and sgnature taken with hand writing.

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Authorship Contributions

Surgical and Medical Practices: S.Ö., R.G., B.A., Concept: S.Ö., R.G., B.A., Design: S.Ö., R.G., B.A., Data Collection or Processing: S.Ö., R.G., B.A., Analysis or Interpretation: S.Ö., R.G., B.A., Literature Search: S.Ö., R.G., B.A., Writing: S.Ö., R.G., B.A.

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