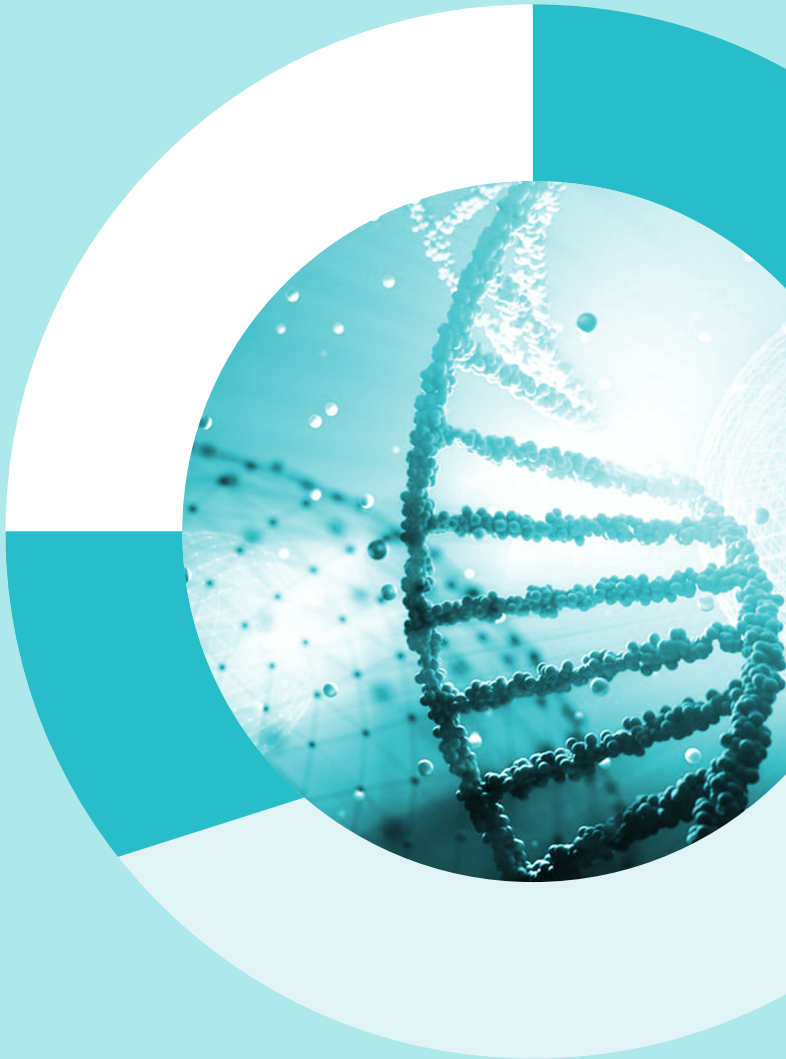
ISSN:2149-7893 E-ISSN: 2536-507X

CYPRUS JOURNAL OF MEDICAL SCIENCES

Indexed in the Web of Science

Volume: 8 Issue: 5 October 2023

ORIGINAL ARTICLES



Official Journal of Cyprus Turkish Medical Association

galenos yayınevi

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Indexed in Web of Science
Volume: 8 | Issue: 5 | October 2023

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Publication Date: Ekim 2023/October 2023
E-ISSN: 2536-507X
ISSN: 2149-7893
International scientific journal published bi-annually.

CYPRUS
JOURNAL OF MEDICAL SCIENCES
Indexed in Web of Science
Volume: 8 | Issue: 5 | October 2023

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AIMS AND SCOPE

Cyprus Journal of Medical Sciences (Cyprus J Med Sci), the official organ of Cyprus Turkish Medical Association.

This journal is an international, open access, scientific, peer-reviewed journal in accordance with independent, unbiased, and double-blinded peer-review principles. As of 2022, the journal has become a bimonthly publication, publishing in February, April, June, and August, October and December. The journal's publication language is English. (E-ISSN:2536-507X)

The aim of the journal is to publish original research papers of the highest scientific and clinical value in all medical fields. Cyprus Journal of Medical Sciences also publishes reviews, rare case report and letters to the editors.

The target audience of the journal includes healthcare professionals physicians, and researchers who are interested or working in in all fields of medicine.

The editorial and publication process of the Cyprus Journal of Medical Sciences are shaped in accordance with the guidelines of the International Committee of Medical Journal Editors (ICMJE), World Association of Medical Editors (WAME), Council of Science Editors (CSE), Committee on Publication Ethics (COPE), European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal is in conformity with the Principles of Transparency and Best Practice in Scholarly Publishing.

Cyprus Journal of Medical Sciences is indexed in Web of Science-Emerging Sources Citation Index, TUBITAK ULAKBIM TR Index, EBSCO, J-GATE and Gale.

All manuscripts must be submitted via the online submission system, which is available at www.cyprusjmedsci.com. The journal guidelines, technical information, and the required forms are available on the journal's web page.

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The journal aims to publish original research papers of the highest scientific and clinical value in all medical fields. Cyprus Journal of Medical Sciences also publishes reviews, rare case reports and letters to the editors.

The target audience of the journal includes healthcare professionals, physicians, and researchers who are interested or working in all fields of medicine.

To read the Article Processing Charge (APC) Policy, please click here.

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

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Manuscripts submitted to Cyprus Journal of Medical Sciences will go through a double-blind peer-review process. Each submission will be reviewed by at least two external, independent peer reviewers who are experts in their fields in order to ensure an unbiased evaluation process. 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 Editor in Chief is the final authority in the decision-making process for all submissions.

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For photographs that may reveal the identity of the patients, signed consent of the patient or their legal representative should be enclosed, and the publication approval must be provided in the "Materials and Methods" section. However, the identities of the patients should be concealed in the photographs.

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In the event of alleged or suspected research misconduct, e.g., plagiarism, citation manipulation, and data falsification/fabrication, the Editorial Board will follow and act following COPE guidelines.

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Each person listed as an author should fulfill the authorship criteria recommended by http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html). The ICMJE recommends that authorship is based on the following four criteria:

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

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

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

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

In addition to being accountable for the parts of the work he/she has done, an author should be able to identify which co-authors are responsible for specific other parts of the work. Also, authors should have confidence in the integrity of the contributions of their co-authors.

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

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

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The manuscripts should be prepared in accordance with ICMJE-Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (updated in December 2019). Authors are required to prepare manuscripts in accordance with the CONSORT guidelines for randomized research studies, STROBE guidelines for observational original research studies, STARD guidelines for studies on diagnostic accuracy, PRISMA guidelines for systematic reviews and meta-analysis, ARRIVE guidelines for experimental animal studies, and TREND guidelines for non-randomized public behavior.

Manuscripts can only be submitted through the journal's online manuscript submission and evaluation system, available at www.cyprusjmedsci.com. Manuscripts submitted via any other medium and submissions by anyone other than one of the authors will not be evaluated.

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.

Authors are required to submit the following:

- Copyright Agreement and Acknowledgement of Authorship Form, and
- ICMJE Potential Conflict of Interest Disclosure Form (should be filled in by all contributing authors) during the initial submission. These forms are available for download at www.icmje.org.

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Title page: A separate title page should be submitted with all submissions and this page should include:

The full title of the manuscript as well as a short title (running head) of no more than 50 characters,

- Name(s), affiliations, highest academic degree(s), and ORCID IDs of the author(s),
- Grant information and detailed information on the other sources of support,
- Name, address, telephone (including the mobile phone number), and e-mail address of the corresponding author,
- Acknowledgment of the individuals who contributed to the preparation of the manuscript but who do not fulfill the authorship criteria.

Abstract: An abstract should be submitted with all submissions except for Letters to the Editor. The abstract of Original Articles should be structured with subheadings (Background/Aims, Material and Methods, Results and Conclusion). Please check Table 1 below for word count specifications.

Keywords: Each submission must be accompanied by a minimum of three to a maximum of five keywords for subject indexing at the end of the abstract. The keywords should be listed in full without abbreviations. The keywords should be selected from the National Library of Medicine, Medical Subject Headings database. (https://www.nlm.nih.gov/mesh/MBrowser.html).

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Main Points: All submissions except letters to the editor should be accompanied by 3 to 5 "main points", which should emphasize the most noteworthy results of the study and underline the principle message that is addressed to the reader. This section should be structured as itemized to give a general overview of the article. Since "Main Points" target the experts and specialists of the field, each item should be written as plain and straightforward as possible.

Manuscript Types

Original Articles: This is the most important type of article since it provides new information based on original research. Acceptance of original papers will be based upon the originality and importance of the investigation. The main text of original articles should be structured with Introduction, Material and Methods, Results, and Discussion subheadings. An original article can be signed by maximum 6 authors unless it is a multi-center study or that it required extensive labour. Please check Table 1 for the limitations for Original Articles.

Clinical Trials

Cyprus Journal of Medical Sciences adopts the ICMJE's clinical trial registration policy, which requires that clinical trials must be registered in a publicly accessible registry that is a primary register of the WHO International Trials Registry Platform (ICTRP) or in ClinicalTrials.gov.

Instructions for the clinical trials are listed below.

Clinical trial registry is only required for the prospective research projects that study the relationship between a health-related intervention and an outcome by assigning people.

- To have their manuscript evaluated in the journal, author should register their research to a public registry at or before the time of first patient enrollment.
- Based on most up to date ICMJE recommendations, Cyprus Journal of Medical Sciences accepts public registries that include minimum acceptable 24-item trial registration dataset.
- Authors are required to state a data sharing plan for the clinical trial registration. Please see details under "Data Sharing" section.
- For further details, please check ICMJE Clinical Trial Policy at

http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html

Data Sharing

As of 1 January 2019, a data sharing statement is required for the registration of clinical trials. Authors are required to provide a data sharing statement for the articles that reports the results of a clinical trial. The data sharing statement should indicate the items below according to the ICMJE data sharing policy:

Whether individual deidentified participant data will be shared

- What data in particular will be shared
- Whether additional, related documents will be available
- When the data will be available and for how long
- By what access criteria will be shared

Authors are recommended to check the ICMJE data sharing examples at

http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html

While submitting a clinical trial to Cyprus Journal of Medical Sciences;

- Authors are required to make registration to a publicly accessible registry according to ICMJE recommendations and the instructions above.
- The name of the registry and the registration number should be provided in the Title Page during the initial submission.
- Data sharing statement should also be stated in the Title Page even the authors do not plan to share it.

Statistical analysis to support conclusions is usually necessary. Statistical analyses must be conducted in accordance with international statistical reporting standards (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983: 7; 1489-93). Information on statistical analyses should be

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provided with a separate subheading under the Materials and Methods section and the statistical software that was used during the process must be specified.

Units should be prepared in accordance with the International System of Units (SI).

Editorial Comments: Invited brief editorial comments on selected articles are published in The Cyprus Journal of Medical Sciences. Editorials should not be longer than 1000 words excluding references. Editorial comments aim to provide a brief critical commentary by reviewers with expertise or with high reputation in the topic of the research article published in the journal. Authors are selected and invited by the journal to provide such comments. Abstract, Keywords, and Tables, Figures, Images, and other media are not included.

Review Articles: Reviews 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 may even be invited by the journal. Reviews should describe, discuss, and evaluate the current level of knowledge of a topic in clinical practice and should guide future studies. The subheadings of the review articles should be planned by the authors. However, each review article should include an "Introduction" and a "Conclusion" section. Please check Table 1 for the limitations for Review Articles.

Case Reports: There is limited space for case reports in the journal and reports on rare cases or conditions that constitute challenges in diagnosis and treatment, those offering new therapies or revealing knowledge not included in the literature, and interesting and educative case reports are accepted for publication. The text should include Introduction, Case Presentation, and Discussion with an unstructured abstract. Please check Table 1 for the limitations for Case Reports.

Letters to the Editor: This type of manuscript discusses important parts, overlooked aspects, or lacking parts of a previously published article. Articles on subjects within the scope of the journal that might attract the readers' attention, particularly educative cases, may also be submitted in the form of a "Letter to the Editor." Readers can also present their comments on the published manuscripts in the form of a "Letter to the Editor." Abstract, Keywords, and Tables, Figures, Images, and other media should not be included. The text should be unstructured. The manuscript that is being commented on must be properly cited within this manuscript.

Table 1. Limitations for each manuscript type

Type of manuscript	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
Original Article	4000	250 (Structured)	35	6	5 or total of 10 images
Review Article	5000	250	50	6	10 or total of 15 images
Case Report	1200	200	15	No tables	4 or total of 8 images
Letter to the Editor	400	No abstract	5	No tables	No media

Tables

Tables should be included in the main document, presented after the reference list, and they should be numbered consecutively in the order they are referred to within the main text. A descriptive title must be placed above the tables. Abbreviations used in the tables should be defined below the tables by footnotes (even if they are defined within the main text). Tables should be created using the "insert table" command of the word processing software and they should be arranged clearly to provide easy reading. Data presented in the tables should not be a repetition of the data presented within the main text but should be supporting the main text.

Figures and Figure Legends

Figures, graphics, and photographs should be submitted as separate files (in TIFF or JPEG format) through the submission system. The files should not be embedded in a Word document or the main document. When there are figure subunits, the subunits should not be merged to form a single image. Each subunit should be submitted separately through the submission system. Images should not be labeled (a, b, c, etc.) to indicate figure subunits. Thick and thin arrows, arrowheads, stars, asterisks, and similar marks can be used on the images to support figure legends. Like the rest of the submission, the figures too should be blind. Any information within the images that may indicate an individual or institution should be blinded. The minimum resolution of each submitted figure should be 300 DPI. To prevent delays in the evaluation process, all submitted figures should be clear in resolution and large in size (minimum dimensions: 100 × 100 mm). Figure legends should be listed at the end of the main document.

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All acronyms and abbreviations used in the manuscript should be defined at first use, both in the abstract and in the main text. The abbreviation should be provided in parentheses following the definition.

When a drug, product, hardware, or software program is mentioned within the main text, product information, including the name of the product, the producer of the product, and city and the country of the company (including the state if in USA), should be provided in parentheses in the following format: "Discovery St PET/CT scanner (General Electric, Milwaukee, WI, USA)"

All references, tables, and figures should be referred to within the main text, and they should be numbered consecutively in the order they are referred to within the main text.

Limitations, drawbacks, and the shortcomings of original articles should be mentioned in the Discussion section before the conclusion paragraph.

References

Both in-text citations and the references must be prepared according to the Vancouver style.

While citing publications, preference should be given to the latest, most up-to-date publications. Authors are responsible for the accuracy of references If an ahead-of-print publication is cited, the DOI number should be provided. Journal titles should be abbreviated in accordance with the journal abbreviations in Index Medicus/MEDLINE/PubMed. When there are six or fewer authors, all authors should be listed. If there are seven or more authors, the first six authors should be listed followed by "et al." In the main text of the manuscript, references should be cited using Arabic numbers in parentheses. The reference styles for different types of publications are presented in the following examples.

Journal Article: Yazıcı A. The efficacy of endoscopic ventilation tube insertion in pediatric populations. Cyprus J Med Sci. 2019; 4(2): 73-6.

Book Section: Suh KN, Keystone JS. Malaria and babesiosis. Gorbach SL, Barlett JG, Blacklow NR, editors. Infectious Diseases. Philadelphia: Lippincott Williams; 2004.p.2290-308.

Books with a Single Author: Sweetman SC. Martindale the complete drug reference. 34th ed. London: Pharmaceutical Press; 2005.

Editor(s) as Author: Huizing EH, de Groot JAM, editors. Functional reconstructive nasal surgery. Stuttgart-New York: Thieme; 2003.

Conference Proceedings: Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92.

Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp.1561-5.

Scientific or Technical Report: Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

Thesis: Yılmaz B. Ankara Üniversitesindeki öğrencilerin beslenme durumları, fiziksel aktiviteleri ve beden kitle indeksleri kan lipidleri arasındaki ilişkiler. H.Ü. Sağlık Bilimleri Enstitüsü, Doktora Tezi. 2007.

Manuscripts Accepted for Publication, Not Published Yet: Slots J. The microflora of black stain on human primary teeth. Scand J Dent Res. 1974.

Epub Ahead of Print Articles: Cai L, Yeh BM, Westphalen AC, Roberts JP, Wang ZJ. Adult living donor liver imaging. Diagn Interv Radiol. 2016 Feb 24. doi: 10.5152/dir.2016.15323. [Epub ahead of print].

Manuscripts Published in Electronic Format: Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) 1995 Jan-Mar (cited 1996 June 5): 1(1): (24 screens). Available from: URL: http:/ www.cdc.gov/ncidodIElD/cid.htm.

REVISIONS

When submitting a revised version of a paper, the author must submit a detailed "Response to the reviewers" that states point by point how each issue raised by the reviewers has been covered 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 must be submitted within 30 days from the date of the decision letter. If the revised version of the

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manuscript is not submitted within the allocated time, the revision option may be canceled. If the submitting author(s) believe that additional time is required, they should request this extension before the initial 30-day period is over.

Accepted manuscripts are copy-edited for grammar, punctuation, and format by professional language editors. 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. A PDF proof of the accepted manuscript is sent to the corresponding author and their publication approval is requested within 2 days of their receipt of the proof.

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ORIGINAL ARTICLES

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EDITORIAL

Dear my colleagues,

"We are the World, we are the children"

Before I start my words, I wish you good health, peace, and successful and beneficial works.

On one side, health workers, farmers, engineers, trainers... are trying to make life healthier, easier, and more comfortable, but on the other side, wars, terrorist attacks, floods, earthquakes, and fires make life unbearable, unlivable, leaving pain behind. Also, unfair income distribution around the world results in poverty, starvation, unhealthy conditions, and invitations to infectious and other diseases.

The World should fight for justice to improve conditions. Rezervs of the world are sufficient for everyone. We don't have to go and live on mars. The world is designed for us in perfect conditions unless we destroy it. Children are our features.

We intensely condemn terrorist attachments, wars, and all kinds of terrorism that destroy democracy and threaten human rights. We wish peace to come in all parts of the world.

Coming to our issue, we are happy to complete the October issue. We hope it will help and be beneficial to our colleagues and will add new information to the literature. We are open and encourage researchers to submit their review and original articles to our journal. We encourage researchers to obey ethical rules and have an iThenticate score around 5-10% using their own words. We accept those lower than 20%, but it will be advantageous for the authors having an iThenticate score around 5-10%. We are trying our best to evaluate and publish manuscripts in a short period of time. Those articles that are accepted for publication will be on the list at the latest in four months.

Before I end my words, we send you our kind regards.

Editor-in-Chief

Sonuç Büyük, MD

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DOI: 10.4274/cjms.2023.2022-57
Cyprus J Med Sci 2023;8(5):324-327

Outcomes of the Transaortic Valve Implantation Procedure in North Cyprus

Alptekin Özkoç[1], Cenk Conkbayır[1,2]

[1]Clinic of Cardiology, Dr. Burhan Nalbantoğlu State Hopsital, Nicosia, North Cyprus
[2]Department of Cardiology, Cyprus Health and Social Sciences University, Morphou, North Cyprus

Abstract

BACKGROUND/AIMS: In Europe, aortic stenosis ranks first when examining patients requiring surgery or percutaneous interventions for the aortic valve. The aging population will bring along aortic stenosis that requires more percutaneous interventions, and transcatheter aortic valve implantation (TAVI) may become a routine procedure in the future. Statistical studies may increase the quality of interventions and reduce complication rates. There are no studies on TAVI in our country. In statistical terms, this study will provide detailed information about the TAVI procedures in North Cyprus and will be a source for future studies.

MATERIALS AND METHODS: In this study, we evaluated 94 patients who underwent TAVI procedures in North Cyprus between 2016 and 2021. Complication, mortality, and morbidity rates from hospitalization to discharge are reported. Echocardiography was performed on all patients with GE Vivid T8 (product year: 2015).

RESULTS: The 7-day mortality rate was found to be 5.31% in 94 patients with TAVI performed in our hospital. Complications related to the peripheral arteries were observed in 20.2% of the patients. The pacemaker implantation rate after TAVI was 9.6%.

CONCLUSION: It would be beneficial for each TAVI center to calculate mortality and morbidity rates regularly and compare them with the world literature. In this way, mortality and morbidity rates can be reduced and better procedural results can be achieved.

Keywords: TAVI, heart valve disease, mortality and morbidty rate of TAVI

INTRODUCTION

Aortic stenosis ranks first when aortic valve patients require surgical or percutaneous intervention in Europe.[1] The one-year mortality rate of symptomatic aortic stenosis increases up to 50% if untreated. The prevalence of the diseases increases parallel to the increase in the length of life.[2] According to the European Society of Cardiology (ESC) guidelines, mean gradient ≥40 mmHg, peak velocity ≥4.0 m/s, valve area ≥1 cm^2 indicate severe aortic stenosis.[3] The ESC guidelines also recommend class I level b treatment (surgical or percutaneous) for symptomatic severe aortic stenosis.[4] Findings of the randomized studies and complications rates may not always show in real life.[1,2-5] Therefore, transcatheter aortic valve implantation (TAVI) centers should conduct retrospective studies to determine complication rates and compare their findings with those of other studies. Such attempts may increase the quality of interventions and reduce complication rates.[6-9]

MATERIALS AND METHODS

In total, 94 patients underwent TAVI procedures between 2016 and 2021 in North Cyprus at a state hospital, and this study included all of these patients. Patients were analyzed with regard to mortality and morbidity rates from the procedure to hospital discharge. Our hospital is the largest heart center in North Cyprus, and most of the TAVI procedures performed all over the country have been performed at this hospital since 2016.

To cite this article: Özkoç A, Conkbayır C. Outcomes of the Transaortic Valve Implantation Procedure in North Cyprus. Cyprus J Med Sci 2023;8(5):324-327

ORCID IDs of the authors: A.Ö. 0000-0001-8704-9875; C.C. 0000-0002-6594-1915.

Address for Correspondence: Alptekin Özkoç
E-mail: alptekinozkoc@hotmail.com
ORCID ID: orcid.org/0000-0001-8704-9875

Received: 25.11.2022
Accepted: 24.09.2023

All TAVI procedures, which were performed from 2016 to 2021 and recorded at the angiography laboratory of the state hospital, were retrospectively analyzed. Medical histories, clinical information, multislice CT scans, electrocardiograms, blood tests, and echocardiography records of 94 patients who underwent the TAVI procedure were analyzed. In addition, puncture sites during interventions, aortic valve type and size, pre- and post-dilatation rates, and methods of closing the puncture site were analyzed. Mortality and morbidity rates during the TAVI procedure and/or until patient discharge were evaluated. Cardiac death, major vascular complications, cerebrovascular events, need for permanent pacemaker implantation, and contrast media nephropathy were examined.

This study was approved by the Dr. Burhan Nalbantoğlu Ethics Committee (approval number: 67/21). Informed consent was obtained from all participants.

Statistical Analysis

All analyses were performed using the Statistical Product and Service Solutions (SPSS) software package (version 25.0, SPSS-IBM, Armonk, NY, USA) at the 95% confidence level and $p<0.05$ significance level. Quantitative variables were reported as the mean and standard deviation; qualitative variables were described as numbers and percentages. Quantitative variables were analyzed using Friedman analysis for dependent groups. Subgroup analysis was performed using Wilcoxon analysis and interpreted using Bonferroni correction. The independent groups were compared using chi-square analysis.

RESULTS

Patients who underwent the TAVI procedure were mostly female (63.8% female, 36.2% male). The mean age was 78.64 years and the mean aortic gradient was 51.6 mmHg. New York Heart Association (NYHA) class III heart failure was observed in 84 patients, whereas advanced heart failure symptoms (NYHA class IV) were evident in 10 patients. 29.8% of the patients had obstructive coronary artery disease and percutaneous coronary intervention, and 8.5% had coronary bypass histories. 8.5% of the patients had pacemakers or implantable cardioverter defibrillators. One patient had severe mitral stenosis, whereas eight patients had severe mitral insufficiency. 15.9% of the patients had left bundle branch block and 4.25% had right bundle branch block.

Of the 94 TAVI procedures, 89 were implanted in the right femoral artery, 4 in the left femoral artery and 1 in the axillary artery. Three of the transfemoral TAVI procedures were closed by surgery and 91 were closed percutaneously (ProGlide). A self-expandable valve was used in 58.52% of the patients, whereas a balloon expandable valve was used in the remaining 41.48%. One TAVI procedure was valve-in-valve implantation. The mean EuroSCORE 2 score was 14.17. We analyzed all 94 TAVI procedures performed at the state hospital between 2016 and 2021. All patients with TAVI had severe symptomatic aortic stenosis. Procedures were performed after consultation with the Cardiology and Cardiovascular Surgery Council. The patients were slightly sedated by the anesthesia team during the procedure. During the procedure, valve implantation was performed in all patients with rapid stimulation by a temporary pacemaker placed in the right ventricle or by an existing pacemaker.

Three patients died during the procedure. Two deaths occurred due to coronary obstruction, whereas one death occurred due to valve dislocation. Consequent pericardial tamponade due to temporary pacemaker lead-induced right ventricle perforation developed in 6 patients, and 1 patient died due to this cause. One patient died because of acute renal failure and metabolic causes.

Peripheral vascular complications were the most frequent complications with a percentage of 20.2%. Of these complications, 68.4% were treated with perkutane transluminal angioplastie or greftstent and 31.6% were treated surgically. Cerebrovascular accident occurred in 1 patient, but there was no sequela during discharge. Nine (9.6%) patients had an advanced heart block after the TAVI procedure. A pacemaker was implanted in these 9 patients. Pacemaker implantation percentages in self-expandable TAVI was 10.9% and in balloon expandable TAVI was 7.7%.

The 7-day mortality rate was found to be 5.31% in 94 patients with TAVI performed in our hospital. Considering the causes of death of these patients, 2 patients died due to coronary obstruction, 1 patient died due to valve dislocation, and 2 patients died due to pericardial tamponade and related metabolic causes.

The peripheral complication rate was 20.2%, and the pacemaker implantation rate after TAVI was 9.6%. Eighty-nine patients were discharged from the hospital in good health, and no problem was encountered in the evaluation at the end of 7 days.

DISCUSSION

Aortic stenosis and TAVI procedures are more common in the contemporary world due to the aging population. TAVI procedures have been performed in North Cyprus since 2016. However, only one study has been conducted on mortality and morbidity rates after TAVI procedures in Cyprus. This study revealed the complication rates in TAVI procedures performed in North Cyprus and compare them with the findings in other TAVI centers.

This study analyzed the mortality and morbidity rates of TAVI procedures performed in North Cyprus between 2016 and 2022.[1] A comparison of our findings with the literature reveals similar mortality and morbidity rates. Inpatient hospital death rates in the meta-analysis ranged from 2.2 to 5.3.[10] This ratio increased in patients with higher EuroSCORE 2 scores.[11,12] On the other hand, the one-year mortality rate in patients who underwent transfemoral TAVI in Cyprus Republic between 2015 and 2020 was 2.6%, which was lower than our findings in North Cyprus.[13,14] This difference may be explained with reference to the EuroSCORE 2 scores. In our study, 85.1% of patients were high-risk patients. Given that morality risk is higher in patients with higher EuroSCORE 2 scores, mortality rates in our study were higher than those in the former study.[15,16]

Vascular complications with a percentage of 20.21% were the most frequent complications, similar to those reported in the literature.[17-19] The primary reasons behind these complications are calcified artery and wrong puncture site.[20-22] Risk factors for vascular complications include calcified vessels, advanced age, chronic kidney failure, and coronary artery disease[23-25].

High-grade heart blocks requiring pacemaker implantation were the second most frequent complications. Pacemaker demand was more frequent in patients of advanced age, coronary artery disease, and diabetes mellitus. In addition, parallel to the literature, pacemaker

demand was lower in patients with balloon expandable valves.[26-28] Perforation due to a temporary pacemaker lead in the right ventricle and consequent pericardial tamponade was another complication observed in this study. A right ventricle lead for more than 24 h increases the perforation risk. In addition, left ventricular stimulation via TAVI stiff wire may reduce ventricular perforation risk caused by temporary pacemaker.[29-31]

Similar to the literature, mortality and morbidity rates of TAVI patients with chronic kidney failure were higher in our study.[32-34] Morbidity and mortality rates in this study were similar to those reported in the literature.[35] We hope that these findings will be used to develop strategies to reduce mortality and morbidity rates in TAVI procedures.

CONCLUSION

It would be beneficial for each TAVI center to calculate the mortality and morbidity rates regularly and compare them with the world literature. In this way, mortality and morbidity rates can be reduced and better procedural results can be obtained. When we look at the statistics in our hospital, it is seen that the complications of peripheral artery injury and pericardial tamponade are high. The risk of pericardial tamponade can be reduced with left ventricular pacing. In addition, we think that angiographic imaging of the puncture site or puncture under ultrasound to reduce peripheral artery injuries will reduce the complication rates.

MAIN POINTS

- This study revealed the complication rates in TAVI procedures performed in North Cyprus and compare them with the findings in other TAVI centers.
- There are no studies on TAVI in North Cyprus. This study may help to reduce the mortality and morbidity rates during and after the TAVI procedure and will be a source for the next studies.
- In this study, 94 TAVI procedures performed in a state hospital in North Cyprus between 2016 and 2021 were examined, and the mortality and morbidity rates from hospitalization to discharge were calculated and the results were reported.
- The 7-day mortality rate was found to be 5.31% in 94 patients with TAVI performed in our hospital.
- The most frequent complications observed in TAVI patients were peripheral vascular complications, and insertion of 5F sheath may be helpful for safety.

ETHICS

Ethics Committee Approval: This study was approved by the Dr. Burhan Nalbantoğlu Ethics Committee (approval number: 67/21).

Informed Consent: Informed consent was obtained from all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.Ö., C.C., Design: A.Ö., C.C., Data Collection and/or Processing: A.Ö., C.C., Analysis and/or Interpretation: A.Ö., C.C., Literature Search: A.Ö., C.C., Writing: A.Ö., C.C.

DISCLOSURES

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

Financial Disclosure: The authors declared that this study had received no financial support.

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CYPRUS
JOURNAL OF MEDICAL SCIENCES

DOI: 10.4274/cjms.2023.2023-47
Cyprus J Med Sci 2023;8(5):328-333

One-Stage Combined Surgical Treatment of Developmental Dysplasia of the Hip in the Children Aged Over 18 Months

Tülin Türközü

Department of Orthopedics and Traumatology, Van Yüzüncü Yıl University Faculty of Medicine, Van, Türkiye

Abstract

BACKGROUND/AIMS: This retrospective study aimed to evaluate the early-term radiological and functional outcomes of one-stage combined surgical treatment in children aged over 18 months with developmental dysplasia of the hip (DDH).

MATERIALS AND METHODS: Thirty-two (32) patients (44 hips) with DDH were included in the study. The Tönnis classification system was used to assess the pre-operative dysplasia grade of the hips. The acetabular index (AI) was measured on AP pelvic radiographs performed preoperatively and at the last control examination. Radiological evaluation was performed according to Severin's criteria, whereas modified McKay's criteria were applied for clinical evaluation. Kalamchi and MacEwen's criteria were preferred for the evaluation of avascular necrosis (AVN).

RESULTS: The mean preoperative AI value of the hips was 44.7±5.0°, whereas that value at the last control AI was 23.5±3.7° ($p<0.001$). According to Tönnis classification, 10 hips were type II, 11 hips were type III, and 23 hips were type IV among 44 hips. According to the modified McKay criteria, excellent clinical results were obtained in 39 (88.7%) hips, good in 4 (9%) hips, and fair in 1 (2.3%) hip. According to Severin's criteria, class 1 radiological results were obtained in 29 (66%) hips, class 2 in 13 (29.5%) hips, and class 3 in 2 (4.5%) hips. The evaluation based on Kalamchi and MacEwen's criteria revealed AVN in 8 (18.2%) hips.

CONCLUSION: Combined surgical procedures involving pelvic and femoral osteotomy with open reduction are effective in the management of DDH in children over 18 months of age. In addition, femoral derotation osteotomy is necessary for stable reduction in children after walking age.

Keywords: Acetabular anteversion, children, derotation osteotomy, femoral anteversion, hip dysplasia, pemberton pericapsuler osteotomy, salter innominate osteotomy, treatment

INTRODUCTION

Developmental dysplasia of the hip (DDH) is a disease that manifests itself with various abnormalities ranging from mild dysplasia to significant dislocation.[1] DDH treatment is determined by the age of the patient, and the best results are obtained if treatment is started at an early age. The main goal of treatment is to achieve concentric reduction of the hip joint at the earliest possible age. Because the development of the hip slows down after 4 years of age, treatment should be started before 4 years of age if possible.[2] As age advances in DDH, treatment interventions become more complex, complication rates increase, and treatment success decreases.

Performing open reduction, pelvic, and femoral osteotomy (varization, derotation, and shortening) operations together is called one-stage combined surgical intervention. These are the most common surgical procedures implemented for realignment of the hip for treating children with high hip dislocation aged over 18 months.

Pemberton pericapsular osteotomy (PPO) and Salter innominate osteotomy (SIO) are the most preferred types of pelvic osteotomy

To cite this article: Türközü T. One-Stage Combined Surgical Treatment of Developmental Dysplasia of the Hip in the Children Aged Over 18 Months. Cyprus J Med Sci 2023;8(5):328-333

ORCID IDs of the authors: T.T. 0000-0002-0966-9080.

Address for Correspondence: Tülin Türközü
E-mail: dktrtulin@gmail.com
ORCID ID: orcid.org/0000-0002-0966-9080

Received: 18.04.2023
Accepted: 26.09.2023

for treating DDH of the early childhood age. SIO is a redirectional osteotomy, whereas PPO is a reshaping osteotomy type, and they are preferred depending on the morphology of the acetabulum. In most patients with DDH, acetabular insufficiency is usually anterior, and both osteotomies increase anterior acetabular coverage. However, PPO provides more anterior coverage than SIO.[3,4]

Femoral shortening should be performed in high hip dislocations where reduction cannot be achieved and in conditions where tight reduction occurs to prevent the development of avascular necrosis (AVN).[5] Although DDH is associated with increased femoral anteversion, some studies have shown no difference in femoral anteversion compared with normal hips, whereas other studies have demonstrated an increase in anteversion.[6-8] Therefore, there is still no consensus on whether femoral derotational osteotomy is necessary for the treatment of DDH.

In patients with DDH, the femoral neck-shaft angle is usually normal. Although many authors have emphasized in the past that coxa vara formation due to varus osteotomy contributes to the stable reduction of the hip, coxa vara is a deformity and cannot be accepted as a functional position.[9,10] It leads to limb shortness, lateralization of the femoral shaft, shift of the mechanical axis toward the medial aspect of the knee, and consequent mechanical complications in the knee. Hence, variation osteotomy is usually not preferred.[11,12] This retrospective study evaluated the early-term radiological and functional outcomes of one-stage combined surgical treatment in children aged over 18 months with DDH.

MATERIALS AND METHODS

This study was approved by the Van Yüzüncü Yıl University Non-Invasive Clinical Research Ethics Committee (approval number: 2023/01-12, date: 20.01.2023).

Patients with DDH aged 18 months who were treated by a single surgeon in the orthopedics and traumatology clinic of a tertiary health center between 2018 and 2022 were retrospectively screened. The study included patients who underwent one-stage combined surgical treatment. Patients treated with isolated pelvic or femoral osteotomy, hip dysplasia that developed secondary to neuromuscular disease, and patients who did not come for follow-up examinations were excluded from the study. Demographic data, clinical evaluations, and radiological results of the patients were obtained from medical records. The Tönnis classification system was used to assess the pre-operative dysplasia grade of the hip.[13] Acetabular index (AI) values were measured on AP pelvic radiographs performed preoperatively, postoperatively, and at the last control examination. Radiological evaluation was performed according to Severin's criteria, whereas clinical evaluation was performed according to modified McKay's criteria.[14,15] Kalamchi and MacEwen's criteria were preferred for the evaluation of AVN, which is one of the commonly seen complications.[16]

Surgical Method

The surgery was initiated with adductor tenotomy. The Bikini approach was used for open reduction, capsulorrhaphy, and pelvic osteotomy. A second separate lateral incision was made in the proximal thigh for femoral shortening and/or femoral derotation. To increase the coverage of the femoral head, SIO was applied to the acetabulum with spherical and anterolateral insufficiency, whereas PPO was applied to the shallow and ellipsoid acetabulum.[17]

To obtain maximum joint compliance, the necessity of derotation osteotomy was evaluated in the flexion, abduction, and internal rotation positions in the reducible hips. Femoral shortening osteotomy was performed on irreducible hips or those with tight reduction. To determine the amount of derotation before femoral osteotomy, two pieces of Kirschner wires were sent to the femur from the distal and proximal of the osteotomy line parallel to the operating table. For shortening and/or derotation osteotomy, the femur was transversely osteotomized from the subtrochanteric region.

After femoral osteotomy and shortening for high hip dislocations, the hip joint was reduced using a Kirschner wire in the proximal femur like a joystick, and the proximal fragment was internally rotated until maximum compliance between the acetabulum and femoral head. After the distal fragment was positioned with the patella facing up, the angle between the two Kirschner wires was determined as the amount of derotation. The amount of shortening was determined as the amount of overlap of the distal fragment on the proximal fragment when the hip was in the reduced position after osteotomy and longitudinal traction was applied from the knee level, and the distal fragment was shortened (Figure 1).

After performing derotation and/or shortening, the osteotomy region was fixed with a 4-hole 1/3 semitubular plate. Varization osteotomy was applied in none of the patients. Capsulorrhaphy was performed after the reduction. For preserving the reduction, the patients were implemented spica cast with hips at 30° flexion, 30° abduction, and neutral rotation. All hips underwent CT for postoperative reduction

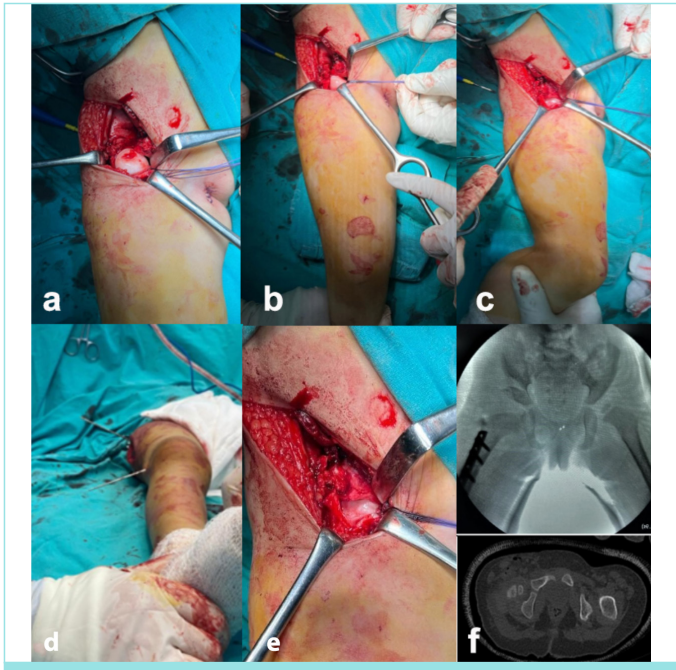

Figure 1. a) View of aspheric femoral head after capsulotomy, b) After pelvic osteotomy, the view of joint incompatibility while the leg is in flexion, abduction, and neutral rotation, c) the joint appears to be maximally compatible when the leg is in flexion, abduction, and internal rotation, d) determination of the degree of derotation between two Kishner wires after femoral osteotomy, e) the appearance of the joint after fixation of the osteotomy area with a semitubular plate after derotation, f) postoperative pelvic X-ray and CT image of the patient.

control. After 6 weeks of follow-up in spica cast, a full-time abduction orthosis was administered for 6 weeks. Rehabilitation was initiated 3 months after surgery to reduce joint stiffness.

Statistical Analysis

SPSS 26.0 software was used for statistical analysis. The mean, standard deviation, median, minimum, maximum, frequency, and percentage values were used in the descriptive statistics of the data. The distribution of the variables was measured using the Kolmogorov-Smirnov test. The Mann-Whitney U test was used in the analysis of quantitative independent data. The chi-square test was used in the analysis of qualitative independent data, and Fisher's exact test was used when the chi-square test conditions were not met. A paired t-test was used to evaluate the difference between the pre-operative AI (AI1) and the final control AI (AI2). P-values <0.05 were considered significant.

RESULTS

The study included 44 hips from 32 patients. Of the patients, 29 (90.6%) were female and 3 (9.4%) were male. Bilateral DDH was present in 12 patients, 21 (47.7%) had right hip involvement, and 23 (52.3%) had left hip involvement in 32 patients. The mean age at surgery of the patients was 31.2±11.1 months, and the mean follow-up duration was 25.6±11.6 months. The demographic data of the patients are presented in Table 1.

The mean AI1 value of the hips was 44.7±5.0° whereas that AI2 value was 23.5±3.7°. The mean postoperative improvement in the AI1-AI2 was 21.2±6.6° and statistically significant (p<0.001) (Table 1).

According to Tönnis classification, 10 hips were type II, 11 hips were type III, and 23 hips were type IV among 44 hips (Table 2). To increase acetabular coverage, 12 (27.3%) hips were reconstructed with SIO and 32 (72.7) hips were reconstructed with PPO. Femoral derotation osteotomy was performed in 44 (100%) hips, whereas 33 (75%) hips were applied femoral shortening. The mean derotation angle was 22.6±3.9° (Table 1). The correlation between Tönnis hip type and degree of derotation was significant (p<0.01). In other words, it was observed that the amount of derotation increased as the Tönnis grade increased.

According to the modified McKay criteria, excellent clinical results were obtained in 39 (88.7%) hips, good in 4 (9%) hips, and fair in 1 (2.7%) hip (Table 3). In the evaluation of the last control radiographies according to Severin's criteria, class 1 radiological results were obtained in 29 (65.9%) hips, class 2 in 13 (29.5%) hips, and class 3 in 2 (4.5%) hips (Table 4).

Evaluation of the last control radiography based on Kalamchi and MacEwen's criteria revealed that no AVN was present in 36 (81.8%) hips, whereas AVN was present in 8 (18.2%) of 44 hips. There was type I AVN in 5 hips and type III AVN in 3 hips. The types and rates of AVN are presented in Table 5 in detail.

Redislocation and subluxation were not observed in any hip. The allergic reaction developed due to the cotton under the cast in the postoperative 2nd week. The cast was removed, hip reduction was preserved in the abduction orthosis, and cast was reapplied after recovery of the skin lesions. In another patient, superficial wound site infection was detected in the surgical site of femoral osteotomy and was treated with antibiotherapy.

Preoperative, early term, and postoperative recent control images of two patients with excellent outcomes and without AVN are presented in Figure 2, 3.

Table 1. Demographic data and radiological evaluation of the hips (n=44)

	Patient data
Age (months)	31.2±11.1
Follow-up time (months)	25.6±11.6
Preoperative acetabular index (degrees)	44.7±5.0
Follow-up acetabular index (degrees)	23.5±3.7
Tönnis radiological classification (n, %)	
- Type I	-
- Type II	10 (22.7)
- Type III	11 (25)
- Type IV	23 (52.3)
The type of pelvic osteotomy (n, %)	
- Salter	12 (27.3)
- Pemberton	32 (72.7)
Femoral deoration osteotomy (n, %)	44 (100)
Femoral shortening (n, %)	33 (75)
Deoration degrees	22.6±3.9

Table 2. DDH types according to Tönnis classification

Grade	Criteria	Number	Percentage (%)
Type I	Femoral capital epiphysis medial to Perkins line and below Hilgenreiners line	-	-
Type II	Epiphysis below the Hilgenreiners line but lateral to Perkins	10	22.7
Type III	Epiphysis lateral to the Perkins line at the level of the acetabular margin	11	25
Type IV	Epiphysis lateral to the Perkins line and above the acetabular rim	23	52.3

DDH: Dysplasia of the hip.

Table 3. Results of clinical assessments according to modified McKay's criteria

Grade	Rating	Description	Number	Percentage (%)
1	Excellent	Painless, stable hip; no limp; more than 15° internal rotation	39	88.7
2	Good	Painless, stable hip; slight limp or decreased motion; (-) Trendelenburg's sign	4	9
3	Fair	Minimum pain, moderate stiffness, (+) Trendelenburg's sign	1	2.3
4	Poor	Significant pain	-	-

DISCUSSION

This study revealed that satisfactory clinical (97.7%) and radiological (95.5%) outcomes were obtained in the early-term follow-up of one-stage combined surgical treatment in children aged over 18 months with DDH. In the literature, excellent and good outcomes according to McKay's clinical grading as well as class 1 and 2 outcomes according to Severin's radiological grading are interpreted as "satisfactory outcome". Many authors have reported satisfactory radiological and clinical outcomes of one-stage combined surgical treatment with varying rates in the past (Table 6).[4,5,18-21]

Among the studies conducted in similar mean age with the present study, Aly[12] detected radiologically 100% and clinically 80.5% satisfactory outcomes in the early-term follow-up. From studies with middle-term follow-up, Mazloumi et al.[20] reported radiologically 88.8% and clinically 75% satisfactory outcomes, whereas Zimri et al.[21] denoted radiologically 75.5% and clinically 90.6% satisfactory outcomes. Although the success rate of the combined surgical treatment of DDH reached 80-90% in the literature, this rate has decreased with longer duration follow-up. In a study with a long-term follow-up, the researchers reported radiologically 75.8% and clinically 72.7% satisfactory outcomes.[22] This study included early-term (25.6±11.6) follow-up, and we obtained radiologically 95.5% and clinically 97.7% satisfactory outcomes.

Table 4. Results of radiological assessments according to Severin's criteria

Class	Description	Number	Percentage (%)
1	Normal hips	29	66
2	Concentric reduction of the hips with moderate deformity of the femoral neck, head or acetabulum	13	29.5
3	Dysplastic hips without subluxation	2	4.5
4	Subluxation	-	-
5	Head articulating with a secondary acetabulum in the upper part of the original acetabulum	-	-
6	Redislocation	-	-

Table 5. Avascular necrosis of femoral head assessments according to the Kalamchi-MacEwen criteria

Grade	Description	Number	Percentage (%)
Type I	Changes affecting the ossific nucleus but resulting in an essentially normal head at final follow-up	5	11.4
Type II	Type I + Lateral physical damage resulting in coxa valga	-	-
Type III	Type I + Central physical damage resulting in coxa breva	3	6.8
Type IV	Total damage to the head and physis resulting in deformity of the femoral head and neck	-	-

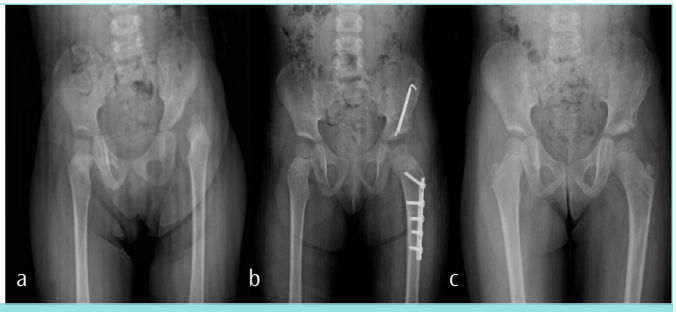

Figure 2. a) Pre-operative radiograph of a 23-month-old female patient, b) postoperative 6th month radiograph of the patient, and c) 26th month radiograph of the patient without AVN with excellent results.

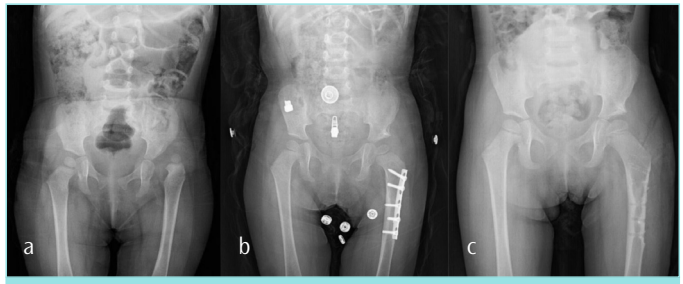

Figure 3. a) Pre-operative radiograph of a 19-month-old female patient with left DDH, b) postoperative 8th month radiograph of the patient who was treated with open reduction, PPO, and femoral shortening-derotation, c) 24-month radiograph of the patient with excellent results.

Table 6. Different rates of radiological and clinical results by many authors in the literature

Study	Hip number	Mean surgery age (year)	Follow-up time (year)	Severin (class 1+2)	Mckay's (excellent and good)	Complication
Vallamshetla et al.[18]	18	5.9	6.10	100%	100%	1 hip AVN, 1 hip redislocation
Umer et al.[19]	29	6.8	1.5	65.5%	86.2%	1 hip AVN
Mazloumi et al.[20]	36	3.8	7.6	88.8%	75%	3 hips with AVN, 2 hips subluxated, and 1 hip redislocated
Zimri et al.[21]	213	3.3	8	75.5%	90.6%	AVN and redislocation 3 cases (1.40%)
Aly[12]	20	3.8	3.8	100%	80.5%	1 hip AVN
Bhatti et al.[4]	82	-	3	85.4%	-	8 hip AVN, 2 hip subluxation

Salter, Pemberton, and Dega osteotomies are the most widely known of the various pelvic osteotomy methods for increasing the coverage of the femoral head in the surgical treatment of DDH.[23-27] Abdullah et al.[28] treated 34 hips with SIO and 8 hips with dega osteotomy out of 42 hips. In that study, the determination of the pelvic osteotomy type was based on AI values and the surgeon's experience. In addition, Mazloumi et al.[20] treated 29 hips with SIO and 7 hips with PPO in their series involving 36 hips, and they selected the type of pelvic osteotomy according to femoral head size and acetabular capacity. In this study, 12 (27.3%) hips were reconstructed with SIO, whereas PPO was applied in the reconstruction of 32 (72.7%) hips. The type of pelvic osteotomy was selected by evaluating the intraoperative acetabular morphology.

Abdullah et al.[28] performed femoral shortening and derotation in 40 of 42 hips (41 Tönnis type IV hips, 1 Tönnis type II hip) and detected subluxation in 2 hips and AVN in 1 hip. Ertürk et al.[29] performed femoral shortening and derotation in all the hips in their series involving 49 hips (33 Tönnis type IV hips, 16 Tönnis type III hips) and detected redislocation in 1 (2%) hip and AVN in 16 (32.6%) hips. According to Tönnis classification, 23 (52.3%) hips were type IV, 11 (25%) hips were type III, and 10 (22.7%) hips were type II in the present study. In this study, we performed shortening and derotation in all type IV and type III hips (except one type III hip). In contrast, we performed only derotation in all type II hips. We discovered no redislocation or subluxation in any of the cases according to our early-term follow-up.

The general consensus on the treatment of DDH is the necessity of absolute concentric reduction between the femoral head and acetabulum. The affected acetabulum in DDH has not normal acetabular anatomy; therefore, it is not like a normal acetabulum even after pelvic osteotomy. In addition, difficulties are experienced in achieving concentric reduction because the sphericity of the femoral head is lost (femoral head flattening) in high hip dislocations.[30,31] The contact area between the femoral head and acetabulum increases when pelvic osteotomy is performed.[32] This contact area between the femoral head and acetabulum is further increased with derotation osteotomy. The author's opinion is that femoral derotation should be performed even if there is no real increase in femoral anteversion to achieve maximum compliance between the dysplastic acetabulum with abnormal acetabular anteversion and the dysmorphic and aspheric femoral head.

AVN remains the most frequently observed complication for treating DDH. Many studies have demonstrated that the development of AVN depends on numerous factors such as patient age at presentation, treatment type, and severity of dysplasia. Ning et al.[27] reported AVN with a rate of 27.4% in a large case series including 864 hips in which they performed one-stage combined surgery and associated advanced age at surgery and high Tönnis grade with increased severity of osteonecrosis. In this study, AVN was in 8 (18.1%) of 44 hips according to the Kalamchi-MacEwen criteria. There was type I AVN in 5 hips and type III AVN in 3 hips. The rate of clinically significant AVN (Kalamchi-MacEwen type II, III, IV) was 6.8%. All hips with type III AVN consisted of Tönnis type IV hips. In addition, 2 hips were reconstructed with Pemberton osteotomy, and 1 hip was reconstructed with Salter osteotomy. The mean age was 43 months.

This study is different from other studies with respect to postoperative management. We preferred the spica cast in flexion, abduction, and neutral rotation because we derotated all the hips. Regardless of pelvic osteotomy type (Salter and Pemberton), we considered full-time immobilization for 12 weeks (6 weeks in spica cast, 6 weeks in brace) to be adequate. Bhuyan[30] performed spica cast in slight flexion, abduction, and internal rotation positions after open reduction, Salter osteotomy, and femoral shortening-derotation (range 20°-30°) on 30 hips and immobilized the hips for a total of 12 weeks (6 weeks in cast, 6 weeks in brace). On the other hand, Ertürk et al.[29] applied full-time immobilization for 12 weeks (6 weeks in spica cast, 6 weeks in brace) and part-time immobilization for 6 weeks on 49 hips in which open reduction, Salter osteotomy, and femoral shortening-derotation.

The author has attributed the radiological and clinical results obtained from this study as satisfactory and the absence of complications that require secondary surgery, such as redislocation and subluxation, to the selection of the pelvic osteotomy type according to the acetabular morphology, implementation of femoral derotation procedure with varying degrees (to achieve the maximum compliance of hip joint), and realization of the surgical procedure by a single experienced surgeon.

Study Limitations

This study has some limitations. First, this was a retrospective study with a relatively small number of patients. Second, only the early results of the surgical procedure were reported in the study. Mid- and long-term results should also be evaluated. Third, the study represents only one physician's experience without a comparative study.

CONCLUSION

Combined surgical procedures involving pelvic and femoral osteotomy with open reduction are effective in the management of DDH in children over 18 months of age. In addition, femoral derotation osteotomy is necessary for stable reduction in children after walking age.

MAIN POINTS

- Combined surgeries are an effective procedure in the treatment of DDH in children over 18 months of age.
- Femoral derotation osteotomy is required for stable reduction in children after walking age.
- There is no need for varus osteotomy for stable reduction.

ETHICS

Ethics Committee Approval: This study was approved by the Van Yüzüncü Yıl University Non-Invasive Clinical Research Ethics Committee (approval number: 2023/01-12, date: 20.01.2023).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

DISCLOSURES

Financial Disclosure: The author declared that this study had received no financial support.

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CYPRUS
JOURNAL OF MEDICAL SCIENCES

DOI: 10.4274/cjms.2023.2023-28
Cyprus J Med Sci 2023;8(5):334-338

Comparative Analysis of the Association Between Laparoscopic Peritoneal Dialysis Catheter Placement Methods and Anterior Abdominal Wall Complications

Necmi Bayraktar

Clinic of Urology, Dr. Burhan Nalbantoğlu State Hospital, Nicosia, North Cyprus

Abstract

BACKGROUND/AIMS: Peritoneal dialysis is a cost-effective treatment method which provides a high quality of life for patients. While laparoscopic peritoneal dialysis catheter placement is generally effective and safe, procedural complications can sometimes lead to therapy interruptions or modifications. This retrospective study aimed to investigate mechanical complications of the anterior abdominal wall associated with different laparoscopic approaches.

MATERIALS AND METHODS: We conducted a retrospective analysis of peritoneal dialysis patients who underwent laparoscopic catheter insertion between 2010 and 2023. The laparoscopic techniques were categorized into three groups, and their relationships with descriptive dependent and independent variables were examined. Additionally, comparisons were made between the different groups.

RESULTS: The complication rates of the anterior abdominal wall were found to be higher with the standard laparoscopic method. We concluded that age and body mass index (BMI) are influential factors for exit site leakage (ESL). Furthermore, being older than 50 years of age was found to be a contributing factor in hernia formation.

CONCLUSION: Our findings indicate that age, BMI, and surgical method are factors which contribute to the occurrence of anterior abdominal wall complications in peritoneal dialysis. The use of a minimally traumatic trocar in the percutaneous method shows promise in preventing hernia formation, while the utilization of a paramedian entry appears advantageous in preventing ESL. Nevertheless, comprehensive and multicentric studies are needed in order to determine the most appropriate patient-specific method.

Keywords: Abdominal wall complication, exit site leakage, laparoscopic catheter insertion, peritoneal dialysis

INTRODUCTION

Peritoneal dialysis is considered one of the most effective and reliable methods for renal replacement therapy. It offers a higher quality of life and is cost-effective compared to hemodialysis. Peritoneal dialysis patients do not experience the drawbacks associated with hemodialysis, such as adverse effects and prolonged hospital stays. However, mechanical dysfunctions relating to catheters in peritoneal dialysis patients can sometimes necessitate a change in treatment. Complications associated with catheter insertion can be categorized as either infectious or non-infectious (Table 1). One surgical complication which may arise following catheter placement is trocar-related hernia. Studies have revealed that 10-20% of peritoneal dialysis patients develop herniation during the course of their treatment.

Catheter entry site herniation and abdominal wall leaks, which involve the leakage of dialysate, are the most commonly observed mechanical complications, often associated with increased intra-abdominal pressure.[1] Exit site leakage (ESL) occurs when there is a disruption in the

To cite this article: Bayraktar N. Comparative Analysis of the Association Between Laparoscopic Peritoneal Dialysis Catheter Placement Methods and Anterior Abdominal Wall Complications. Cyprus J Med Sci 2023;8(5):334-338

ORCID IDs of the authors: N.B. 0000-0001-6449-9216.

Address for Correspondence: Necmi Bayraktar
E-mail: necmi.bayraktar@neu.edu.tr
ORCID ID: orcid.org/0000-0001-6449-9216

Received: 01.04.2023
Accepted: 06.07.2023

Table 1. Peritoneal dialysis catheter complications are summarized	
The infectious and mechanic complications of PD catheter insertion	
Infectious complications	Mechanic complications
Peritonitis	Malfunction of the catheters
Catheter exit site infections	Intestinal obstruction/perforation
Tunnel infections	Leakage of the dialysate*
	Hernia
*Exit site leakage.	

integrity of the peritoneal membrane. Factors contributing to leakage include the technique used for PD catheter insertion and weaknesses in the abdominal wall.[2] Since the first laparoscopic PD catheter placement was introduced in 1990, various surgical approaches and modifications have been implemented.[3] Over time, extensive studies have led to the development of international guidelines. However, it is important to note that some advanced techniques may require more complex surgeries and surgical expertise. The primary goal of these studies is to prevent complications arising from PD catheter placement and to enable longer-term peritoneal dialysis treatment.

Peritoneal dialysis has been widely practiced in North Cyprus for over 20 years, utilizing open, laparoscopic, and percutaneous techniques for catheter placement. Each technique has its own advantages and disadvantages, and they are evaluated independently and comparatively in order to enhance their effectiveness and reliability. Various precautions and recommendations have been proposed to prevent mechanical complications of the anterior abdominal wall, specifically trocar hernia (incisional) and exit site leaks. The primary cause of hernia formation in peritoneal dialysis patients is elevated intra-abdominal pressure, which leads to trocar (optical or working) and hernia formation at the entry point. Moreover, increased intra-abdominal pressure can also result in the development of inguinal or umbilical hernias.

Our retrospective study aimed to compare the outcomes of our modified laparoscopic techniques with the standard laparoscopic peritoneal dialysis catheter placement methods regarding anterior abdominal wall complications. Our objective was to evaluate and share the results of our experience.

MATERIALS AND METHODS

Study Design

We conducted a retrospective analysis of peritoneal dialysis patients who underwent laparoscopic peritoneal dialysis catheter insertion between 2010 and 2023. This study compared standard laparoscopic peritoneal dialysis catheter placements with modified techniques regarding anterior abdominal wall complications, specifically focusing on entry site hernia and ESL.

Inclusion and Exclusion Criteria

This study included patients between the ages of 18 and 80 who were deemed eligible for peritoneal dialysis and who underwent laparoscopic peritoneal dialysis catheter placement. Individuals with a history of hernia and previous extensive abdominal surgeries were excluded from this study. Furthermore, cases which necessitated advanced laparoscopic techniques, including omentectomy, omental fixation, catheter fixation, and adhesiolysis, were also excluded.

Sample Size and Sampling Technique

The patients were divided into three groups for evaluation: Group A consisted of patients before 2018 who had midline entry sites, group B consisted of patients after 2018 who had paramedian entry sites, and group C consisted of patients before 2018 who underwent the standard laparoscopic peritoneal dialysis catheter placement method.

In group A, the laparoscopic peritoneal dialysis procedure was combined with the percutaneous technique. Instead of using a trocar or another instrument, a pull-apart dilator was employed to create a tunnel in the rectus fascia, with only a skin incision made from the midline. Direct vision was facilitated using a 5 mm laparoscope.

In group B, the laparoscopic peritoneal dialysis procedure was combined with the percutaneous technique. However, unlike group A, the tunnel in the rectus fascia was created in the paramedian area instead of the midline.

In group C, the standard laparoscopic peritoneal dialysis catheter placement method was utilized.

Patients were provided with informed consent forms before the surgery in order to ensure understanding and agreement. Ethical approval for this study was obtained from the Ethics Committee of the TRNC Ministry of Health (approval number: YTK.1.01-EK25/22).

Statistical Analysis

Descriptive and characteristic features were analyzed using crosstabs, and the results of qualitative data are presented in terms of incidences and percentages [(n) and (%), respectively]. The independent variables included in the model were age, body mass index (BMI), operation time, hernia formation, and ESL. The association between the dependent and independent variables was determined using levels of significance and confidence intervals (CIs). Non-parametric tests were employed due to the non-homogeneous distribution of the data. The Independent-Samples Kruskal-Wallis test was utilized to compare differences between groups. Factors influencing any events were assessed using the Cox regression test. Statistical analysis of the obtained data was performed using the SPSS Windows version 24.0 statistical package program.

RESULTS

A total of 65 patients were included in this study. The mean age of the patients included in this study was 59.78 years (range: 18-80). Of the patients, 52 (80%) were male, and 13 (20%) were female. The mean operative time was 26 minute (range: 14-95). Group A comprised 22 patients, group B had 16 patients, and group C consisted of 27 patients. Twelve patients had a hernia at the catheter insertion site, with nine experiencing ESL complications. Age, gender, BMI, operation time, the presence of hernia, and ESL data are summarized according to the groups in Table 2.

In order to compare the occurrence of catheter insertion hernia formation between the groups, a non-parametric independent samples Kruskal-Wallis test was conducted. A p-value less than 0.05 was considered statistically significant. There was no difference between groups A and B, but a statistically significant difference was observed between group C and the other 2 groups (Table 3A, B).

Comparisons between the groups regarding ESL were made using the non-parametric independent samples Kruskal-Wallis test. A difference was found between groups B and C, but there was no significant difference between groups A and B or between groups A and C (Table 4A, B).

Cox regression analysis was performed in order to examine the relationship between various factors and the occurrence of hernia formation. The analysis revealed no statistically significant relationship between gender and hernia formation (p=0.79). Furthermore, no significant relationships were found between operation time (p=0.11) or BMI (p=0.84) and hernia formation. However, a statistically significant association was observed between age and hernia formation (p=0.01, 95% CI: 1.023-1.183).

In the Cox regression analysis for the occurrence of ESL, no statistically significant correlations were found between gender and ESL (p=0.83) or between BMI and ESL (p=0.057) (95% CI). However, age (p=0.02, 95% CI: 1.004-1.052) and operative time (p=0.07, 95% CI: 0.970-0.995) showed a statistical significance in relation to ESL.

DISCUSSION

Anterior abdominal wall complications are common in patients undergoing peritoneal dialysis.[4] Various factors contribute to the occurrence of these complications, including the surgical technique used, age, BMI, duration of surgery, time to start dialysis, presence of accompanying risk factors such as diabetes, and the causes of the chronic kidney disease. These complications can lead to treatment interruptions or even necessitate a switch in treatment modality.[4]

The peritoneal dialysis catheter is typically inserted into the peritoneal cavity using either a surgical technique (open surgery or laparoscopic-assisted) or a percutaneous technique (Seldinger or modified Seldinger techniques), with or without fluoroscopic guidance.[5] In laparoscopic procedures, placing the catheter by creating a rectus sheath tunnel helps prevent complications such as catheter migration and early leakage.

Cabtree and Fishman[6] provided a detailed description of creating a tunnel in the preperitoneal area. Rectus sheath tunneling (RST) has been shown to reduce hernia formation and ESL.[7] The standard laparoscopic method typically uses instruments such as a laparoscopic grasper or a 5 mm trocar to create the tunnel. Our modified approach uses a smaller and less traumatic pull-apart sheath/dilator. The smaller

Table 2. Descriptive statistics for study variables

		Group A		Group B		Group C	
		Mean ± SD	n (%)	Mean ± SD	n (%)	Mean ± SD	n (%)
Age		55.27±14.26		62.75±9.92		61.70±10.58	
Sex	Male		16 (72.7%)		13 (81.3%)		23 (85.2%)
	Female		6 (27.3%)		3 (18.8%)		4 (14.8%)
BMI (kg/m²)		29.16±4.75		26.12±4.53		27.44±4.21	
Operation time (min)		23.32±13.16		25.63±18.79		65.07±12.56	
Hernia	Yes		2 (9.1%)		1 (6.3%)		9 (33.3%)
	No		20 (90.9%)		15 (93.8%)		18 (66.7%)
	Total		22 (100.0%)		16 (100.0%)		27 (100%)
ESL	No		20 (90.9%)		16 (100.0%)		20 (74.1%)
	Yes		2 (9.1%)		0 (0.0%)		7 (25.9%)
	Total		22 (100.0%)		16 (100.0%)		27 (100%)

The study variables are shown as mean, standard deviation, and percentage. BMI: Body mass index, ESL: Exit site leakage, SD: Standard deviation.

Table 3A. Statistical comparison of the three groups in terms of hernia formation

Independent samples Kruskal-Wallis test summary	
Total, (n)	65
Test statistic	6.730
Asymptotic sig. (2-sided test)	**0.035***

*Bold and underlined numbers indicate statistical differences between groups.

Table 3B. Pairwise comparisons of groups in terms of hernia formation

Sample 1-sample 2	Test statistic	Standard error	Standard test statistic	Sig.
Group C-group A	7.879	3.650	2.159	**0.031***
Group C-group B	8.802	4.009	2.195	**0.028***
Group A-group B	-0.923	4.175	-0.221	0.825

Asymptotic significances (2-sided tests) are displayed. The significance level is 0.05.
*Bold and underlined numbers indicate statistical differences between groups.

Table 4A. Statistical comparison of the three groups in terms of exit site leakage

Independent samples Kruskal-Wallis test summary	
Total, (n)	65
Test statistic	6.194
Asymptotic sig. (2-sided test)	**0.045***

*Bold and underlined numbers indicate statistical differences between groups.

Table 4B. Pairwise comparisons of groups in terms of exit site leakage

Sample 1-sample 2	Test statistic	Standard error	Standard test statistic	Sig.
Group B-group A	2.955	3.717	0.795	0.427
Group B-group C	-8.426	3.569	-2.361	**0.018***
Group A-group C	-5.471	3.249	-1.684	0.092

-Asymptotic significances (2-sided tests) are displayed. The significance level is 0.05.
*Bold and underlined numbers indicate statistical differences between groups.

diameter of the pull-apart sheath/dilator used in our modified method may contribute to a lower incidence of hernia formation than the standard laparoscopic method. Additionally, the RST created in the modified method is shorter than in the standard method, reducing surgical trauma and defects during tunnel creation in the preperitoneal space and peritoneal entry site. Blitzkow et al.[8] used a similar pull-apart sheath/dilator in their modified method and reported similarly low rates of hernia formation.

Studies investigating the risk factors for hernia development provide conflicting information regarding gender and age. Some studies suggest that hernia is more common in older individuals (>40 years) or men, while others report no significant association between age, gender, and hernia formation.[4] Small body size and low weight (<60 kg) have been identified as risk factors for hernia development in some studies. However, in our study, we did not find a significant difference in terms of gender and BMI between those patients with and those without hernia. Nevertheless, we did observe that older age (over 50) was a risk factor for hernia formation.[9] Midline injury and hernia formation occur due to the weak support tissue of the midline, and paramedian access is often recommended. However, our study did not find any difference in hernia formation between midline and paramedian entrances. This may be attributed to using a low-diameter, bladeless trocar (pull-apart sheath/dilator) and the support provided by the distal cuff of the peritoneal catheter at the midline defect. In fact, our study and others have shown that surgical technique, in addition to other factors, plays a significant role in preventing or causing complications.[10] Complications are observed at higher rates in patients with compromised peritoneal integrity and in those who undergo multiple surgical procedures.[3,11]

The modified methods demonstrated lower rates of ESL compared to the standard method. This can be attributed to the use of a low-diameter and flexible trocar, as well as the creation of an exit area in compliance with international guidelines. The reduced ESL rates may be due to the ability to perform manipulations using a single trocar, which lowers the risk of leakage and infection compared to the standard technique involving multiple trocar entries. However, it should be noted that leakage is more commonly observed at midline entrances, highlighting the significance of surgical procedures and instrumentation. The results are influenced not only by changes in surgical technique, but also by the surgeon's experience, skill, and advancements in minimally invasive treatments.[6,10]

Study Limitations

One weakness of our study was the lack of homogeneous distribution and the absence of a randomized controlled evaluation of the patients. It is evident that assessing numerous variables in a small sample can result in statistically biased outcomes. Another limitation of this study was the restricted number of variables considered. Also, it should be noted that changes in surgical technique over time and the surgeon's increased experience could influence the results. While including North Cyprus data may introduce bias regarding changes in surgical technique and experience, the comparisons made between the groups and the identification of common factors affecting the outcomes helped mitigate this bias.

CONCLUSION

Our study found that the surgical technique plays a crucial role in the occurrence of anterior abdominal wall complications. Using atraumatic trocars in the percutaneous method, regardless of the point of entry into the rectus fascia, appears advantageous in preventing hernias. Paramedian abdominal access also seems beneficial in preventing ESL, regardless of the type of trocar used. However, it is important to note that complications in peritoneal dialysis are influenced by various factors beyond surgical technique. In conclusion, further multicenter controlled studies and standardization efforts are needed in order to obtain more specific findings and establish patient-specific treatment guidelines, particularly regarding surgical procedures.

MAIN POINTS

- Comparative analysis of the association between laparoscopic peritoneal dialysis catheter placement methods and anterior abdominal wall complications.
- Mechanical complications between minimally invasive peritoneal catheter insertion techniques.
- Impact of surgical modifications and experience on treatment outcomes.
- Complications associated with laparoscopic peritoneal dialysis catheter insertion.

ETHICS

Ethics Committee Approval: Ethical approval for this study was obtained from the Ethics Committee of the TRNC Ministry of Health (approval number: YTK.1.01-EK25/22).

Informed Consent: Patients were provided with informed consent forms before the surgery in order to ensure understanding and agreement.

Peer-review: Externally and internally peer-reviewed.

DISCLOSURES

Financial Disclosure: The author declared that this study received no financial support

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RESEARCH ARTICLE

CYPRUS
JOURNAL OF MEDICAL SCIENCES

DOI: 10.4274/cjms.2023.2023-97
Cyprus J Med Sci 2023;8(5):339-343

Could the Lactate-Albumin Ratio be Successful in Predicting Mortality due to COVID-19 Infection?

Ahmed Cihad Genç, Aysel Gürkan Toçoğlu

Clinic of Internal Medicine, Sakarya University Training and Research Hospital, Sakarya, Türkiye

Abstract

BACKGROUND/AIMS: High death rates are associated with coronavirus disease-2019 (COVID-19), particularly in severely ill hospitalized patients. Early detection of particularly severe cases will be beneficial for treatment decisions and clinical courses. Therefore, we aimed to discern the capacity of the lactate-albumin ratio (LAR) parameter in predicting the outcomes of patients admitted to the intensive care unit (ICU) to COVID-19 infection.

MATERIALS AND METHODS: The study comprised 535 COVID-19-diagnosed patients who were admitted to the ICU. The data of the patients were obtained by retrospectively scanning the patient files.

RESULTS: The study population consisted of 535 patients, 270 patients in the non-survival group and 265 patients in the survival group. In the non-survival group, the plasma lactate level was 2.3±1.4 mmol/L, whereas in the survival group, it was 1.74±0.8 mmol/L, and this difference was statistically significantly higher in the non-survival group ($p<0.001$). The plasma albumin level in the non-survival group was also 2.87±0.47 g/dL, whereas in the survival group, it was 3.36±0.55 g/dL. It was determined that this difference was statistically significant ($p<0.001$). The cut-off value of lactate in determining mortality in critically progressing COVID-19 patients was 1.725 [area under the curve (AUC): 0.637, %95 confidence interval (CI): 0.590-0.685] with 63% sensitivity and 60% specificity; albumin 3.03 (AUC: 0.763, 95% CI: 0.723-0.803) with 70% sensitivity and 66% specificity; and LAR 0.57 (AUC: 0.719, 95% CI: 0.676-0.763) with 68% sensitivity and 68% specificity.

CONCLUSION: LAR can be safely used as a sepsis-related mortality marker in the ICU. However, although LAR is a successful indicator in patients hospitalized in the ICU because of COVID-19, it has yet to be as successful as it was in patients with sepsis. Its routine use may facilitate more information about LAR and patient decision-making.

Keywords: COVID-19, albumin, lactate, mortality

INTRODUCTION

Severe acute respiratory syndrome-coronavirus-2, also known as coronavirus disease-2019 (COVID-19), was first identified in late 2019 in China. Despite strict quarantine practices, it has spread to all countries and has become a pandemic. Many scientific studies have been conducted to accelerate the diagnosis and find the treatment of COVID-19.[1] Infection with COVID-19 increases the risk of intensive care unit (ICU) admission and mortality in older persons, smokers, and patients with chronic diseases. The mortality rate in the ICU generally varies between 40% and 85%, which is higher than in the ward patients. The average cost per day or during hospitalization is higher for patients admitted to the ICU. Accurate mortality risk estimation can increase life expectancy and help more rational use of healthcare costs.[2] Numerous new molecules potentially serving as prognostic and mortality determinants for COVID-19 have been investigated. However, the cut-off values for these molecules have yet to be discovered for the newly defined COVID-19 condition, and efforts have been made to establish

To cite this article: Genç AC, Toçoğlu AG. Could the Lactate-Albumin Ratio be Successful in Predicting Mortality due to COVID-19 Infection? Cyprus J Med Sci 2023;8(5):339-343

ORCID IDs of the authors: A.C.G. 0000-0002-7725-707X; A.G.T. 0000-0002-9078-6996.

Address for Correspondence: Ahmed Cihad Genç
E-mail: genccihad@gmail.com
ORCID ID: orcid.org/0000-0002-7725-707X

Received: 11.09.2023
Accepted: 03.10.2023

these values.[3] Alternatively, existing scoring systems employed in non-COVID-19-related cases were utilized to predict patient mortalities. These datasets may encompass demographic characteristics, laboratory parameters, and mechanical ventilator modes employed by the patients.[4]

Sepsis and septic shock are global causes of mortality in the ICU.[5] Clinical and laboratory parameters were used to determine the mortality risk of sepsis or septic shock. Hyperlactatemia is considered a strong predictor of mortality in sepsis or septic shock.[6] Albumin, which is responsible for regulating plasma colloid oncotic pressure, plays a vital role in acid-base balance.[7] Decreased serum albumin levels are strong markers of mortality in patients with sepsis or septic shock.[8] The serum lactate-albumin ratio (LAR), which evaluates high lactate levels and low albumin levels together, is a good indicator that can be used to predict mortality in sepsis and septic shock in recent years.[9] LAR has been used as a sepsis-induced mortality marker in the ICU.[9]

Hence, there persists a requirement for assessing mortality rates among individuals admitted to the ICU because of COVID-19. In response to this exigency, we sought to scrutinize the efficacy of mortality prediction predicated on LAR value under ICU care for COVID-19. Our aim encompasses an inquiry into the efficacy of the LAR metric, recognized for its pertinence in appraising mortality tendencies in patients with sepsis and septic shock characterized by elevated mortality rates. Specifically, we aimed to discern the capacity of the LAR parameter in predicting the outcomes of patients admitted to the ICU due to COVID-19 infection.

MATERIALS AND METHODS

The population of the study consists of patients between 2020 and 2022. The study comprised 535 COVID-19-diagnosed patients who were admitted to the ICU between these periods. The data of the patients were obtained by retrospectively scanning the patient files. The lactate albumin value was checked from the blood taken during admission to the ICU. The data of the retrospective design study were conducted in accordance with the Declaration of Helsinki and after obtaining the approval of the Sakarya University Faculty of Medicine Ethics Committee (approval number: E-71522473-050.01.04-194690-334, date: 05.12.2022).

Statistical Analysis

To provide details on the general characteristics of the study population, descriptive analyses were performed. To evaluate whether they are regularly distributed or not, analytical and visual techniques (Kolmogrog-Simirlow/Shapiro-Wilk's test) were applied. For categorical data, % (percentage) values were used, whereas the mean and standard deviation were used for numerical variables. Student's t-test was used to examine whether continuous numerical variables differed between the two independent groups. Chi-square tests were used to examine whether there was a difference between the two categorical groups. The odds ratio was calculated for risk analysis, and the results were reported with confidential intervals. Receiver operating characteristic (ROC) analysis was performed to determine the cut-off value of the LAR in COVID-19 patients in the ICU. The area under the curve (AUC), sensitivity, and specificity values were determined. A p-value <0.05 was considered significant. Analysis was performed using the statistical program SPSS (IBM SPSS Statistics, version 21.0.). To determine the type II error value of the study, post-hoc analysis was performed using the G*Power application.

RESULTS

The study population consisted of 535 patients, 270 patients in the non-survival group and 265 patients in the survival group. The mean age of the non-survival group was 70.9±10.7 years, and that of the survival group was 59.7±16.3 years (Table 1). The mean age difference between

Table 1. Baseline characteristics and laboratory parameters of patients; survivors vs. non-survivors

	Non-survival, (n=270)	Survival, (n=265)	p
Age, years	70.9±10.7	59.7±16.3	**<0.001**
Gender			
Male, n (%)	174 (64.4%)	150 (56.6%)	0.064
Female, n (%)	96 (35.6%)	115 (43.4%)	
Comorbidities			
Diabetes mellitus, n (%)	100 (37.0%)	69 (26.1%)	**0.007**
Hypertension, n (%)	160 (59.3%)	123 (46.4%)	**0.003**
Coronary artery disease, n (%)	75 (27.8%)	44 (16.6%)	**0.002**
Labratory			
White blood cells, K/uL	12.1±10.1	7.5±3.9	**<0.001**
Hemoglobin, g/dL	12.1±2.1	12.5±1.9	**0.004**
Platelet, K/uL	200.6±94.2	207±86.7	0.416
Estimated glomerular filtration rate, mL/min/1.73 m^2	71.3±26.9	79.5±25.8	**0.006**
C-reactive protein, mg/L	140±97	70.5±70.46	**<0.001**
Procalcitonin, ng/mL	4.6±13.7	2.9±14.7	0.173
Erythrocyte sedimentation rate, 1 h, mmHg	63.6±27	51.2±28.7	**<0.001**
Lactate, mmol/L	2.3±1.4	1.74±0.8	**<0.001**
Albumin, g/dL	2.87±0.47	3.36±0.55	**<0.001**
Lactate-albumin ratio	0.82±0.5	0.55±0.38	**<0.001**
Intubation requirement, n (%)	230 (85.2%)	12 (4.6%)	**<0.001**

the non-survival and survival groups was statistically significant (p<0.001). There were 324 (60.6%) males and 211 (39.4%) females in the study population, and there was no statistically significant gender difference between the non-survival and survival groups (p=0.064). Comorbid conditions such as diabetes mellitus, hypertension, and coronary artery disease were investigated. These chronic conditions were more prevalent in the non-survival group (with p-values of 0.007, 0.003, and 0.002).

During ICU monitoring, 242 (45.6%) patients required intubation; among them, 230 (85.2%) patients had fatal outcomes. The number of patients who required intubation in the survival and non-survival groups differed statistically significantly (p<0.001). Odds ratios were calculated for mortality risk analysis. The mortality risk of a patient who developed the need for intubation in the ICU increased by 125 times (CI: 63-250).

The laboratory variables that significantly differed between the two groups, non-survival and survival, were as follows: white blood cell count (p<0.001), hemoglobin level (p=0.004), estimated-glomerular filtration rate (e-GFR) (p<0.001), and 1-h erythrocyte sedimentation rate (p<0.001).

In the non-survival group, the plasma lactate level was 2.3±1.4 mmol/L, whereas in the survival group, it was 1.74±0.8 mmol/L, and this difference was significantly higher in the non-survival group (p<0.001). The plasma albumin level in the non-survival group was also 2.87±0.47 g/dL, whereas in the survival group, it was 3.36±0.55 g/dL. It was determined that this difference was statistically significant (p<0.001).

We performed ROC analysis to determine the optimal cut-off values for albumin, lactate, and LAR to predict mortality. The cut-off value for lactate in predicting mortality in COVID-19 patients who were critically ill was 1.725 (AUC: 0.637, %95 CI: 0.590-0.685) with 63% sensitivity and 60% specificity; for albumin, it was 3.03 (AUC: 0.763, %95 CI: 0.723-0.803) with 70% sensitivity and 66% specificity; and for LAR, it was 0.57 (AUC: 0.719, 95% CI: 0.676-0.763) with 68% sensitivity and 68% specificity (Figure 1, Table 2). A post-hoc power analysis was performed to determine the type II error in the mortality prediction once the LAR cut-off value of 0.57 was approved. It was determined that the study had 99% power.

DISCUSSION

COVID-19 is a newly identified viral infection associated with high mortality rates, particularly in critically hospitalized patients. One of the main goals in managing these patients is to determine the prognosis and estimate the severity of the disease as soon as possible. It is known that early detection of particularly severe cases will be beneficial for treatment decisions and clinical courses. Although studies have been conducted on many laboratory parameters and scoring systems to predict the course of the disease, an ideal marker has yet to be determined. In this study, we aimed to determine the use of the LAR parameter in predicting the prognosis of patients admitted to the ICU due to COVID-19 infection.

Advanced age, male gender, concomitant diseases, and organ failure have been associated with poor prognosis in studies on COVID-19.[10,11] Similar to previous studies, patients who did not survival in our study were older and had more comorbidities (p<0.05). When the two groups were compared in terms of gender, the ratio of females to males was similar (p=0.064). In addition, increased C-reactive protein (CRP), procalcitonin, interleukin-6, creatinine, leukocyte, sedimentation levels, APACHE-II score, and low lymphocyte and albumin levels were found to be associated with severe disease and increased mortality in COVID-19 patients.[10-12] Similar to these results, in our study, significantly higher leukocyte, CRP, sedimentation, and lower hemoglobin, e-GFR, albumin, and lactate levels were obtained in those who did not survival (p<0.05). Contrary to expectations, there was no difference between the two groups in terms of procalcitonin levels (p=0.173).

Endothelial damage and increased permeability occur in patients with COVID-19 because of increased inflammation, causing albumin to accumulate in the interstitium and often causing hypoalbuminemia.[13] Low albumin levels were found to be an independent risk factor for mortality in studies conducted on these patients.[14] In a study of COVID-19 patients with sepsis and septic shock, low albumin levels were also associated with a higher risk of intubation.[15] In our study, albumin levels were lower in patients who did not survival, and the cut-off value in determining mortality was 3.03 (AUC: 0.763, 95% CI: 0.723-0.803) with 70% sensitivity and 66% specificity.

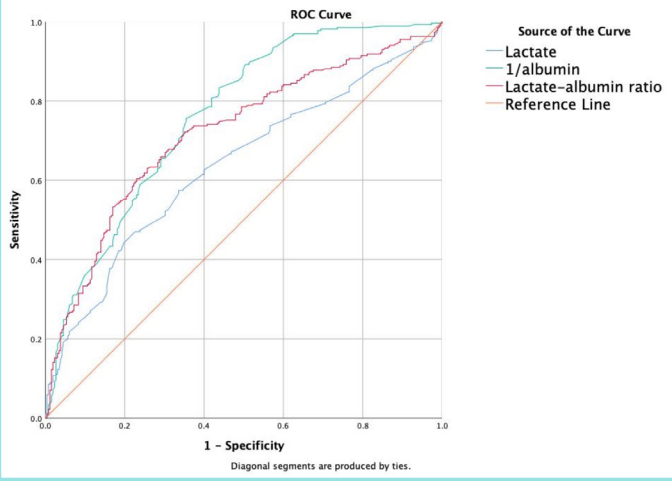

Figure 1. ROC curve of lactate, 1/albumin, and lactate-albumin ratio values for mortality.

ROC: Receiver operating characteristic.

Table 2. Values of AUC, sensitivity, and specificity of serum lactate level, serum albumin level, and lactate albumin ratio for predicting mortality

Risk factor	AUC	95% CI	Cut-off value	Sensitivity	Specificity	p
Lactate	0.637	0.590-0.685	1.725	63%	60%	**<0.001**
Albumin	0.763	0.723-0.803	3.03	70%	66%	**<0.001**
LAR	0.719	0.676-0.763	0.57	68%	68%	**<0.001**

AUC: Area under the curve, CI: Confidence interval, LAR: Lactate-albumin ratio.

Lactate has been reported to be a reliable biomarker for predicting the development of multiorgan dysfunction in septic patients.[16] Similarly, increased lactate levels were found to be associated with severe disease and mortality in COVID-19 studies.[17] The study by Velavan et al.[18] found that blood lactate levels were higher in COVID-19 pneumonia patients than in non-COVID-19 pneumonia patients. Contrary to the literature, although high lactate levels were found to be associated with a short survival time in the study of Gök et al.[13] in critically ill COVID-19 patients, they could not be identified as a risk factor for 30-day mortality. In our study, however, lactate levels were found to be higher in patients who did not survival, and the cut-off value in determining mortality in these patients was 1.725 (AUC: 0.637, 95% CI: 0.590-0.685) with 63% sensitivity and 60% specificity.

Although LAR is a well-known marker, especially in septic and critically ill patients, there have been few studies of LAR in COVID-19 patients.[1,9,13] When only albumin levels are evaluated, such as nutritionand chronic inflammation, and when only lactate levels are evaluated, such as cardiac arrest, trauma, burns, and thiamine deficiency could affect the measurements, and many studies focused on LAR. Patients with sepsis and septic shock who had higher LAR had multiorgan failure and died more frequently, and LAR's performance in predicting mortality was higher than that of albumin and lactate alone.[19,20] In a study of COVID-19 patients with sepsis and septic shock, serum lactate levels and LAR were shown to have the best diagnostic accuracy in predicting the need for mechanical ventilation and mortality.[15] In critically ill COVID-19 patients, Gök et al.[13] discovered that LAR is an independent risk factor for 30-day mortality. ROC analysis showed that LAR was superior to albumin (AUC: 0.644, $p<0.001$) and lactate levels (AUC: 0.795, $p<0.001$) in estimating 30-day mortality, with a cut-off value of 0.60 (AUC: 0.824, $p<0.001$).[13] Contrary to these studies, Özdemir and Altunok.[21] found that LAR is not a good predictor of mortality in COVID-19 patients. In our study, LAR levels were found to be higher in patients who did not survival, and the cut-off value in determining mortality in these patients was 0.57 (AUC: 0.719, 95% CI: 0.676-0.763) with 68% sensitivity and 68% specificity. In the meta-analysis of Yoon et al.[9] covering 4,723 patients with sepsis or septic shock, the LAR cut-off value for predicting mortality was calculated as 0.71 (95% CI: 0.54-0.84). If we accepted the mortality-determining cut-off LAR value of 0.71, we could accurately predict the mortality probability of our ICU with a sensitivity of 47% and specificity of 84%. The LAR value of 0.57 in our study was similar to the result in the meta-analysis. In our study, it was determined that the cut-off values of 3.03 (AUC: 0.763, 95% CI: 0.723-0.803) for albumin and 0.57 (AUC: 0.719, 95% CI: 0.676-0.763) for LAR were superior to lactate (AUC: 0.637, %95 CI: 0.590-0.685) in predicting mortality in critical COVID-19 patients.

Study Limitations

The most important limitations of our study were that it was a single-center, retrospective study that included patients with additional comorbidities that would affect the LAR level, patients with sepsis/septic shock were not identified, and a subgroup analysis was not performed. On the other hand, the high number of patients and the inclusion of only patients in the ICU, in terms of patient specificity, were the advantages of our study.

CONCLUSION

LAR is safely used as a sepsis-related mortality marker in the ICU. However, although LAR is a successful indicator in patients hospitalized in the ICU because of COVID-19, it has yet to be as successful as it was in patients with sepsis. Its routine use may facilitate more information about LAR and patient decision-making.

MAIN POINTS

- LAR is a successful indicator in patients hospitalized in the ICU due to COVID-19; however, it has yet to be as successful as it was in patients with sepsis.
- LAR and albumin values are superior to lactate in predicting mortality in critical COVID-19 patients.
- The cut-off value of LAR in predicting mortality in critical COVID-19 patients was 0.57 (AUC: 0.719, 95% CI: 0.676-0.763) with 68% sensitivity and 68% specificity.

Acknowledgment: We would like to thank Asst. Prof. Selçuk Yaylacı for sharing his clinical and academic knowledge with us.

ETHICS

Ethics Committee Approval: The data of the retrospective design study were conducted in accordance with the Declaration of Helsinki and after obtaining the approval of the Sakarya University Faculty of Medicine Ethics Committee (E-71522473-050.01.04-194690-334, date: 05.12.2022).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

DISCLOSURES

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

Financial Disclosure: The authors declared that this study had received no financial support.

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CYPRUS
JOURNAL OF MEDICAL SCIENCES

DOI: 10.4274/cjms.2021.2021-71
Cyprus J Med Sci 2023;8(5):344-353

Assessment of Continuous Care Based on the Roy Adaptation Model in Patients Undergoing Total Knee Replacement: A Quasi-Experimental Study

Ayşegül Savcı[1], Özlem Bilik[2]

[1]Department of Surgical Nursing, Kütahya Health Sciences University Faculty of Nursing, Kütahya, Türkiye
[2]Department of Surgical Nursing, Dokuz Eylül University Faculty of Nursing, İzmir, Türkiye

Abstract

BACKGROUND/AIMS: To assess the effectiveness of continuous care based on the Roy Adaptation Model (RAM) in patients undergoing total knee replacement (TKR) surgery.

MATERIALS AND METHODS: This quasi-experimental study included 83 patients in a university hospital. The intervention group was offered continuous care based on RAM. The research data were collected using a Patient Identification Form, the Western Ontario and McMaster Universities Osteoarthritis Index, and the Hospital Anxiety and Depression Scale.

RESULTS: Except for the pain score, no statistically significant difference in the pre-discharge and 3rd month was found for the patients in the intervention and control groups. It was determined that the pain scores of patients in the intervention group in the pre-discharge period were lower than those in the control group (p=0.022) A significant difference was found between the anxiety score averages in time in the intervention group in terms of the group time interaction (p=0.009). Because of further analysis, a statistically significant difference was determined that the anxiety scores of patients in the intervention group in the 3rd month were lower than those in the control group (p=0.032). A significant difference was found between the depression score averages in time in the intervention group in terms of the group x time interaction (p=0.037).

CONCLUSION: The functional status and pain of patients improve over time. In this process, continuous care based on RAM was effective in developing effective adaptation behaviors of patients, and a positive effect on pain, anxiety, and depression was determined.

Keywords: Total knee replacement, roy adaptation model, continuous care

INTRODUCTION

Osteoarthritis (OA) is a primary indication for total knee replacement (TKR) surgery. OA can develop in different joints, but it is most commonly seen in the knee joints as an outcome of the increase in the number of overweight individuals and decreases in people's social activities.[1-3] Worldwide, OA is the joint most commonly affected by with an estimated prevalence of 15% in persons aged 56 to 84 years.[4]

In the United States, OA was the justification for 95% of TKA procedures performed.[5] OA in the knees leads to limitations in movement,

*A doctoral thesis published in 2015 contained data from this study. The manuscript presented as poster at 24th National Congress of Orthopedics and Traumatology & 7th Orthopedic and Traumatology Nursing Congress between 29 October and 3 November 2015 in Türkiye, and the first and first prize was awarded taken.

To cite this article: Savcı A, Bilik Ö. Assessment of Continuous Care Based on the Roy Adaptation Model in Patients Undergoing Total Knee Replacement: A Quasi-Experimental Study. Cyprus J Med Sci 2023;8(5):344-353

ORCID IDs of the authors: A.S. 0000-0002-9176-7420; Ö.B. 0000-0002-8372-8974.

Address for Correspondence: Ayşegül Savcı
E-mail: aysegul.savci@ksbu.edu.tr
ORCID ID: orcid.org/0000-0002-9176-7420

Received: 24.03.2021
Accepted: 07.06.2021

deformities, and a disruption of the knee structure, which in turn become barriers to daily living and social activities, resulting in both physical and psychosocial disability.[1,6] TKR surgery is a successful treatment for eliminating pain and allowing recovery of movement in the joints.[7-9] However, patients undergoing TKR surgery experience various circumstances that affect their quality of life before and after surgery. While patients hope to be relieved of their pain on the one hand, they also become fearful of becoming dependent on others. Pain, weakness, activities of daily living (ADL) limitations, becoming dependent, and a change in customary roles may result in social isolation, anxiety, and depression, especially in the early postoperative period.[2,10-13] Successful recovery and adaptation to the prosthesis depends on the adaptation of patients to the care and rehabilitation provided, successful management of additional illnesses, and the presence of sufficient psychological and social support.[12,14] The recent decrease in hospital stay duration has made continuous care a requirement.[11] Continuous care refers to the establishment of a continuous and consistent interaction between patient and caregiver.[12,15-18] This process encompasses the period before hospitalization and after discharge and requires a multidisciplinary team equipped to handle issues arising in different areas of specialization.[12,17] Nurses play key roles in helping patients adapt to daily life by determining patients' levels of knowledge, care, and needs and by interacting with other health professionals.[16,19] This study used the Roy Adaptation Model (RAM) in patients undergoing TKR to enhance nurses' understanding of caregiving theories and their skills at incorporating these theories into the care they provide. Using continuous care based on RAM may provide insight into evaluating the adaptation process that patients undergo and relevant factors, and may be a useful example of providing integrated care.

Continuous Care

The concept of continuous care in healthcare services was introduced in 1960 in the United States.[18] Continuous care is specifically planned for the individual patient and relates to a specific time. This period can cover as short a time as the hospitalization period of a patient or it can apply to long-term care that starts with the individual's first-line healthcare. Continuous care has three components: *informational continuity*, *relational continuity*, and *management continuity*.[16] Various methods may be used in the implementation of continuous care. These methods encompass *discharge instructions, periodic patient follow-ups,* case conferences among team members in which patients and their families are also included, and *telephone follow-ups*.[18] In the continuous care of TKR patients, emphasis is placed on the importance of a multidisciplinary team that includes a case management nurse, nurse anesthetist, occupational therapist, orthopedist, physiotherapist, dietician, and a psychiatrist when necessary. While the case management nurse is in charge of managing care, support from other healthcare disciplines is enlisted when needed.[12,15,18,20] In this study, the researcher performed the duties of a case management nurse.

Roy Adaptation Model

Sister Callista Roy defined the model as a "continuously growing and developing adaptive system of conditions, circumstances, and influences that surround and affect the development and behavior of a person".[19] Various *focal*, *contextual, and residual stimuli* change the environment and affect the open system of the human being. Focal stimuli are those that are extrinsic to which the individual immediately responds with the reflex of adjustment. Contexual stimuli are all those that are not directly caused by behavior but have an effect on behavior and arise from the individual's internal and external worlds. Residual stimuli are internal or external factors that have a continuous effect on the individual but whose impact cannot be fully explained. The model describes two coping subsystems of individuals-the regulator and cognator systems-that are present at birth or later acquired. If environmental impacts are greater than what the individual can cope with, the system cannot function and a deviation from health is the result. The observable behaviors of individuals comprise the RAM's *physiological*, *self-concept*, *role function*, and *interdependence* adaptive modes. Behaviors in the physiological domain consist of functions that maintain physical integrity. Roy classified behavioral responses in the domain of adaptation as adaptive or non-adaptive. The objective of nursing is to develop adaptive responses.[19]

Aim

The aim of this study sough to evaluate the effects of RAM-based continuous care given to post-operative TKR patients. The hypotheses of the study were (primary outcomes): (1) The intervention group's pain, anxiety, and depression levels will be lower than the control group levels. (2) The intervention group's functional state will be higher than in the control group. (3) There is a difference between the mean scores of pain, anxiety, and functional status between the intervention and control groups, and between group x time (Baseline, Pre-discharge, 3rd month) interactions.

MATERIALS AND METHODS

Design: This study had a quasi-experimental design.

Sample: The study was completed with TKR patients treated from October 2012 to July 2014 at the orthopedic and traumatology unit of a university hospital situated in western Türkiye. A convenience sample was selected from patients admitted to the orthopedic unit for TKR surgery. The inclusion criteria were being a first-time TKR patient, age 18 or older, oriented, and able to speak and understand Turkish. The exclusion criteria included a confirmed neurological or psychiatric medical diagnosis. Eighty-three patients participated, and seven patients were excluded from the study (Figure 1). The first 44 patients were designated as the control group, and the next 39 patients were recruited into the intervention group (n=76). After the study data were collected, the data were applied to the G*power package program for power analysis. The sample size for each group was taken as an average of 36, and the two-way analysis of variance was used in the power analysis on repeated measures. The power analysis employed the mean scores for anxiety and depression, the study's dependent variables, and it was found that the power was above 80%.[21] At the end of the study, the power was 0.86, and when the effect size was 0.37, the p values were 0.05.

Procedure: Informational booklets and telephone follow-ups provided during this period were part of the continuous care intervention. The patients were provided with education "preoperatively," "postoperatively" and "pre-discharge" based on the informational booklet drawn up by the researcher. In the follow-ups after discharge, the information was repeated according to the patients' needs (Figure 2). The educational booklet contained updated information considering evidence-based applications on: preoperative preparation with the TKR patient, difficulties that the patient may encounter postoperatively, relevant pre-discharge and post-discharge

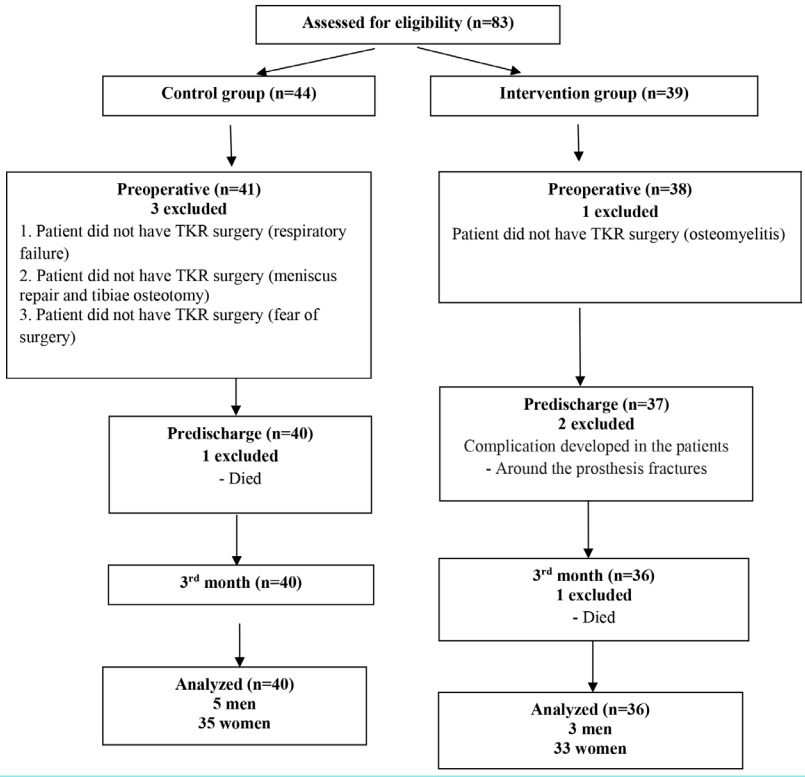

Figure 1. Sample flow diagram.

TKR: Total knee replacement.

Education period	Content	Intended to be affected RAM modes
Preoperatively 1. Interview (When the decision TKR in the outpatient clinic is taken or the first-time patient enters the clinic)	Preoperative education - Total knee replacement. - Medical instruments that may be encountered at the hospital (urinary catheter, drain, spirometer, compression socks) and how to use them. - Pain management. - Venous thromboembolism and routine thrombophilaxy. - Respiratory exercises and spirometry use. - Possible complications and initiatives to prevent. - Exercises (quadriceps strengthening exercise, foot exercise). - Changes to be made at home planned. - Questions of patients and families answered.	Physiological Self-concept Interdependence
Postoperatively Discharge 2.-3. Interviews	Postperative education - Advancement of early mobilization (foot exercises were shown and if possible, the first experience of standing up was done together). - Discussions about home care after discharge (transition from hospital to home, rehabilitation exercises, drug use, wound care, bathing, traveling, sexual life, driving, check-in times. - Questions related to the above topics were answered and their experiences shared.	Physiological Self-concept Interdependence
First 3 months 4.-12. Interviews	Questions answered	Physiological Self-concept Role function Interdependence

Figure 2. Content of education and affected RAM* modes.

*RAM: Roy Adaptation Model.

information, and guidance for caretakers post-discharge.[3,7,13,20,22,23] The opinions of four academic nurses, a physician, an academic physiotherapist, two orthopedic nurses, and three patients who had undergone TKR were included in the booklet. Over the study period, the patients were allowed to call the researcher whenever they wanted to ask a question and receive advice on any topic they wanted. In addition, the patients' recovery processes were assessed, and patients who needed more follow-ups were called once a week.

The control group was provided with routine care at the clinic during the study period. When TKR was planned for a patient, the physician provided the patient with information about "the diagnosis, risks of the surgery, and surgical procedure." Before discharge, patients were given informational brochures about the period after discharge. Any question that patients had throughout the process, from admittance until discharge, were answered during nursing interventions. The data for the intervention group were collected after the completion of data collection for the control group. Following the collection of initial information from the patients, the researcher implemented continuous care based on RAM (Figure 3). Data were collected from the patients "preoperatively," "pre-discharge," and in "the 3rd month." The application of instruments was completed in 20-30 min for each measurement. Phone calls lasted 20-40 minutes on average. A researcher collected the data (A.S.).

Instruments: The research data were collected using (1) a Patient Identification Form, (2) the Western Ontario and McMaster Universities Osteoarthritis Index, and reliable scale for the evaluation of pain, stiffness, and functional state in patients with OA.[24,25] Scores are based on a scale of 20 points for pain, 8 points for stiffness, and 68 points for functional state; the higher the points, the worse the individual's condition.[24] The Cronbach's alpha coefficients (baseline, 1st follow-up and 2nd follow-up) were: 0.77, 0.78, 0.82, respectively for pain; 0.82, 0.96, 0.90, respectively for stiffness, and 0.93, 0.91, 0.93, respectively, for functionality. The Cronbach's alpha coefficient indicates whether items measure the same characteristics and whether the items are related to what is being measured. Cronbach's alpha coefficients less than 0.40 indicate that the instrument is not reliable; coefficients between $0.40 \leq \alpha < 0.60$ indicate low reliability, $0.60 \leq \alpha < 0.80$ good reliability, and $0.80 \leq \alpha < 1.00$ high reliability.[21]

The Hospital Anxiety and Depression Scale developed by Zigmond and Snaith[26] consists of subscales for anxiety and depression. This is a commonly used, valid, and reliable scale.[27] The scale is made up of 14 items: 7 symptoms of depression and 7 symptoms of anxiety. The results of the receiver operating characteristic analysis determined that the cut-off points on the Turkish questionnaire were 10 for the anxiety subscale and 7 for the depression subscale. Individuals scoring above these points are identified as a risk group.[27] The Cronbach's alpha coefficients (baseline, 1st follow-up, 2nd follow-up) for this study were 0.83, 0.74, 0.87 for anxiety and 0.59, 0.59, 0.70 for depression.

Ethics

Written informed consent was approved by the Dokuz Eylül University Hospital Ethical Committee (approval number: 30-GOA2011/13-09-2011). In addition, written permission was obtained from the University Hospital. The researcher obtained the patients' written and verbal consents after explaining to them the purpose of the research, the process of data collection, and the study's implementation, informing them that they may withdraw from the study at any time and that their names would be kept confidential. The studies comply with the Declaration of Helsinki.

Statistical Analysis

The Statistical Package for the Social Services SPSS version 15.0 (SPSS®, IBM® Corp., Armonk, NY, USA) program was used in the data analysis in the second stage of the study. Data analysis included descriptive statistics of numbers (i.e. percentages, means, standard deviation), χ^2, t-tests, a 2-factor repeated-measures analysis of variance, and a paired t-test with Bonferroni correction.

RESULTS

Sociodemographic Characteristics

Of all patients participating in the study, 89.5% (68) were women, 84.2% were married, 64.5% were housewives, 30.1% were retired, 71.1% lived with their spouses, and 15.8% lived at their children's homes. Of the patients, 69.7% had a chronic illness, 51.3% had tried physical therapy, 76.3% underwent surgery because of pain and loss of function, 31.3% had been suffering from knee pain for more than 4 years, 50.0% had bilateral surgery, and 41.8% required the support of a cane, crutches, or someone's assistance before the surgery. Of the patients, 58.2% could walk without a helping vehicle. The mean age of the intervention group was 66.77±8.3, mean body mass index (BMI) was 32.6±7.03, the average stay at the hospital was 9.5±2.9 days; in the control group, the mean age was 65.57±6.5, mean BMI was 30.5±4.71, and the average stay at the hospital was 9.2±3.2 days. The distribution of the features of the intervention and control groups is shown in Table 1.

Effects of RAM-Based Continuous Care on Pain, Stiffness and Functional State

No significant difference was found in the intervention group in pain, stiffness, and functional state scores in terms of the group time interaction (Baseline, pre-discharge, 3rd month) (Table 2). Except for the pain score, no statistically significant difference in the pre-discharge and 3rd month was found for the patients in the intervention and control groups. It was determined that the pain scores of patients in the intervention group in the pre-discharge period were lower than those in the control group (t=2.343 p=0.022). No statistically significant difference in the pre-discharge and 3rd month was found for stiffness scores for the patients in the intervention and control groups (pre-test t=0.633, p=0.528; post-test t, time 1=0.933, p=0.354; post-test t, time 2=0.102; p=0.919). No statistically significant difference in the pre-discharge and 3rd month was found between functional state scores for the patients in the intervention and control groups (pre-test t=1.836, p=0.071; post-test t, time 1=1.533, p=0.130; post-test t, time 2=0.178; p=0.859) (Table 2).

Effects of RAM-Based Continuous Care on Anxiety and Depression

A significant difference was found between the anxiety score averages in time in the intervention group in terms of the group x time interaction (Baseline, pre-discharge, 3rd month) (F=4.892) (p=0.009) (Table 3). Because of further analysis, a statistically significant difference was determined that the anxiety scores of patients in the intervention group in the 3rd month were lower than those in the control group (t=2.201; p=0.032). No statistically significant difference was determined between

	Domains of Adaptation	Evaluating Stimuli Focal stimulus: Osteoarthritis, TDP Continuous Care Interventions	Nursing Diagnoses	Continuous Care Nursing Interventions	Evaluation
Pre-operative	***Physiological mode***	***Contextual stimuli:*** - Severity of osteoarthritis - Weakness of knee muscles and tendons - *Additional* illnesses - Obesity ***Residual stimuli:*** - Genetic characteristics - Sedentary life	**Pain,* **Reduced physical activity* **Disruption of sleep patterns* **Loss of positive body image*	***Management:*** *- Taking the patient's detailed history* *- Determining the patient's capabilities with regard to managing additional illnesses* *- Creating a healthcare program jointly with other healthcare disciplines* *- Determining the patient's needs* *- Controlling pain (the patient's methods of coping with pain are queried, appropriate nonpharmacological methods are taught, patient is informed about the use of analgesics, etc.)* *- Ascertaining the patient's functionality, determining and controlling the factors causing the reduction in physical activity, supporting the patient in exercising* *- Evaluating the patient's sleep patterns, reviewing how the patient copes with any changes in sleep patterns and ensuring effective coping* *- Evaluating the patient's perception of his/her own body, developing strategies to cope with the change in body image* *- Determining the causes and the level of the patient's anxiety, ensuring that this anxiety is expressed and eradicated* *- Determining the patient's coping strategies, giving support in the use of those that are effective* *- Evaluating the patient's self-esteem and improving reduced self-esteem* *- Ascertaining how the patient has been affected by the role change* *- Evaluating the capacity of the patient to carry out ADL* *- Evaluating the opinions and expectations of the patient and the patient's family members regarding prostheses* *- Making arrangements at home (ergonomic arrangements appropriate to the prosthesis)* *- Preventing infections (guiding the patient into treatment if there is infection)* *- Eliminating the fears and anxieties of the patient and family* *- Determining risk factors related to social isolation and taking the necessary precautions* ***Information-based:*** *- Sharing information gathered from the patient with the doctor, physiotherapist and dietician* *-Evaluating the treatment methods and their effectiveness prior to the surgery*	***Effective adaptive behavior:*** *- Effectively managing additional illnesses* *- Effective pain management* *- Doing the recommended exercises to strengthen knee muscles and tendons* *- Having the patient confirm that he/she gets enough sleep and is not tired* *- Having the patient express an acceptance of the change in body image or confirm a positive body image* *- Having patient be aware of the reasons for his/her anxiety and be able to define his/her emotional state* *- Having the patient use coping strategies that will eliminate/solve issues* *- Paying attention to the diet plan* *- Losing weight* *- No finding related to infection* *- Making the necessary arrangements at home* *- Building up realistic expectations* *- Being willing to fulfill life's roles* *- Making an effort to carry out ADL* *- Moving about feeling safe and without a fear of falling* *- The patient's accepting the present situation and that there will be a need for someone else's support during the recovery period and then gradually reducing the use of this support* *- Gaining independence steadily and being strong enough to live one's life* *- Socializing appropriate to the patient's condition and participating in activities* ***Ineffective adaptive behavior:*** *- Continuing to be obese* *- Developing an infection* *- Building up high expectations* *- Experiencing anxiety* *- Experiencing pain* *- Steady increase of functional limitations/strain* *- Existence of/continued sleep problems* *- Patient feeling weak* *- Continuing to live out the role of passive or dependent patient/Being dependent on others* *- Not exercising regularly/avoiding exercising* *- Unwilling to carry out ADL/Waiting for or wanting someone else to do the activities* *- Experiencing social isolation* *- Not consulting health professionals when there is a problem*
	Self-concept mode	***Contextual stimuli:*** *- Being dependent on someone else* *- Fear (fear of surgery, fear of becoming disabled)* *- Unrealistic expectations* *- Negative experiences* *- Anxiety about becoming dependent* ***Residual stimuli:*** *- Postponement of surgery* *- Feeling of being a burden on caregivers*	**Weakness* **Anxiety* **Ineffective individual coping* **Reduced self-esteem*		
	Role function mode	***Contextual stimuli:*** *- Reduced physical activity* *- Insecurity* *- Being dependent on someone else* *- Not engaging in ADL* ***Residual stimuli:*** *- Postponement of surgery* *- Losing control over life decisions*	**Loss of role/function* **Not engaging in ADL*		
	Interdependency mode	***Contextual stimuli:*** *- Weakness,* *- Being dependent on someone else* ***Residual stimuli:*** *- Losing control over life decisions* *- Feeling of being a burden on caregivers*	**Inadequacy in coping within the family* **Social isolation*		
				- Cooperating with the doctor, physiotherapist and nurses to inform the patient and family about the different prostheses, the treatment applied and the exercise protocol ***Relational:*** *- Cooperating with the dietician to set up an appropriate scheme for weight loss* *- Cooperating with the doctor to develop realistic expectations about the different prostheses and treatment* *- Cooperating with the physiotherapist with regard to setting up appropriate exercises recommended to strengthen knee muscles and tendons*	*- Negative sense of self-esteem*
Post-operative (early stage)	***Physiological mode***	***Contextual stimuli:*** *- Pain/Inadequate pain control* *- Other effects of surgery (weakness, loss of appetite, constipation)* *- Edema/swelling* *- Weakness of knee muscles and tendons* *- Fear (fear of falling)* *- Additional illnesses* *- Anesthesia* *- Narcotic analgesics* *- Bilateral application of prostheses,* etc. *- Insufficient knowledge* ***Residual stimuli:*** *- Intraoperative process* *- Obesity* *- Not being ready for replacement surgery*	**Pain* **Reduced tissue perfusion* **Restricted movement* **Loss of appetite* **Constipation* **Activity intolerance* **Disruption of sleep patterns* **Hypovolemia* **Dehydration risk* **Risk of peripheral neurovascular function disorder*	***Management:*** *- Creating a healthcare program jointly with other healthcare disciplines* *- Determining the patient's needs* *- Eliminating the fears and anxieties of the patient and family* *- Preparing for the surgery* *- Continuing with treatment and care* *- Ensuring that ADL are carried out* *- Ensuring pain control* *- Ensuring that the patient's additional illnesses are under control* *- Preventing infection* *- Ensuring/encouraging early mobilization* *- Ensuring eating plan is appropriate to body needs* *- Improving activity tolerance* *- Restoring sleep patterns* *- Preventing constipation* *- Preventing dehydration* *- Determining and managing needs related to restricted movement* *- Setting up a discharge plan* *- Supporting the patient's caregivers* *- Ensuring that the patient achieves the planned range of joint motion* *- Supporting and restoring the ability to achieve personal hygiene* *- Ensuring that the patient is able to express and effectively cope with weakness, anxiety, despair, lowered self-esteem, dependency, being a burden and being afraid* ***Information-based:*** *- Sharing of the information obtained from the patient by doctors, physiotherapists and other nurses in the clinic with the anesthesiologist* ***Relational:***	***Effective adaptive behavior:*** *Having normal vital signs, all systems functioning appropriate to the recovery process, stabilization of neurovascular condition, able to tolerate food as much as is needed, sufficient sleep, rest, looking relaxed, no complications (infections, bleeding, DVT, fluid-electrolyte imbalance, etc.), able to breathe deeply--able to use a spirometer--and adapt to rehabilitation exercises, early mobilization, normal intestinal sounds/no elimination problems, effective pain management, expressing preparedness for discharge, reaching at least a 90- (110 if possible) degree joint range of motion, able to tend to personal hygiene, cooperating with the team in the care stage, willing to take on the responsibility of own care, having a positive body image, effective role integration in response to role changes, taking responsibility in the context of roles, able to express emotions and cope with feeling weak, anxious, despair, reduced self-esteem, feelings of dependency, being a burden and being fearful* ***Ineffective adaptive behavior:*** *Disruptions in system functions, surgery-related tissue damage and anesthesia-related reduced arteriovenous circulation, loss of appetite, constipation, numbness of fingertips, feeling cold, reduced movement, insomnia, loss of knee joint function, activity intolerance, pain, late mobilization, developing complications (bleeding, infection, DVT, fluid-electrolyte imbalance), lack of personal hygiene, reduced self-esteem, weakness, anxiety, not being able to fulfill sexual and adult rules, not being able to return to work, social isolation, disruption of the family routine, inadequacy in support systems, feeling like a burden, fear of falling or becoming disabled, prolonging of recovery period,*
	Self-concept mode	***Contextual stimuli:*** *- Fear (fear of harming the prosthesis)* *- Fear (fear of becoming disabled)* *- Being dependent on someone else* *- Feeling of being a burden on caregivers* *- Unrealistic expectations* ***Residual stimuli:*** *- Losing control over life decisions*	**Weakness,* **Anxiety* **Despair* **Ineffective individual coping,* **Reduced self-esteem*		
	Role function mode	***Contextual stimuli:*** **Restricted movement* *- Being dependent on someone else* ***Residual stimuli:*** *- Prolonging of recovery period*	**Inability to fulfill roles* **Inability to practice personal hygiene*		
	Interdependency mode	***Contextual stimuli:*** *- Being dependent on someone else* *- Feeling of being a burden on caregivers* ***Residual stimuli:*** *- Losing control over life decisions* *- Prolonging of recovery period*	**Interruption of family processes* **Inadequacy in coping within the family*		
				- Cooperating with the physiotherapist to increase and encourage the performance of rehabilitation exercises *- Achieving effective pain control through cooperation with the doctor and anesthesiologist*	*increased dependency on another person in the post-operative period*

Figure 3. Continuous care interventions based on the RAM. Nursing diagnoses and continuous care interventions according to RAM domains and evaluation of effective-ineffective adaptive behaviors.

RAM: Roy Adaptation Model, ADL: Activities of daily living

Figure 3. Continued

Post-discharge (late period)	***Physiological mode***	***Contextual stimuli:*** *- Pain* *- Weakness of knee muscles and tendons* *- Fear (fear of falling)* *- Additional illnesses* *- Restricted movement* *- Bilateral application of prostheses,* etc. ***Residual stimuli:*** *- Obesity*	**Pain* **Constipation* **Activity intolerance* **Disruption of sleep patterns* **Risk of developing complications (infections, DVT, etc.)*	***Management:*** *- Creating a healthcare program jointly with other healthcare disciplines* *- Providing information and continuing with advisory services (telephone monitoring, polyclinic controls)* *- Determining the patient's needs* *- Ensuring pain control* *- Improving activity tolerance* *- Making arrangements at home (ergonomic arrangements appropriate to the prosthesis)* *- Assessing the symptoms of possible complications* *- Preventing constipation* *- Preventing infection* *- Preventing DVT* *- Restoring sleep patterns* *- Eliminating the fears and anxieties of the patient and family* *- Determining the patient's home care needs, preparing and educating the patient for discharge* ***Information-based:*** *- Sharing information gathered from the patient with the doctor, physiotherapist* ***Relational:*** *- Ensuring that the patient is able to get in contact when he/she has a need* *- Cooperating with the physiotherapist with regard to setting up appropriate exercises recommended to strengthen knee muscles and tendons* *- Cooperating with the doctor to guide patient with regard to complications that may develop* *- Directing the patient to a psychologist when there is a need for psychological support*	***Effective adaptive behavior:*** *Performing rehabilitation exercises and continuing the joint range of motion with the prosthesis, avoiding complications, becoming less and less dependent on others in activities of daily life, effectively keeping pain under control, being willing to be engaged in social activities, resuming interrupted roles, making arrangements at home to suit new situation, living life without fear or anxiety* ***Ineffective adaptive behavior:*** *- Symptoms and findings of complications* *inability to continue joint range of motion that had been reached with the prosthesis,* *being unwilling to perform the rehabilitation exercises, avoiding activity, fear of falling,* *prolonging of dependency period, social isolation,* *increasing responsibility on part of caregivers, disruption in familial relations*
	Self-concept mode	***Contextual stimuli:*** *- Fear of harming prosthesis* *- Being dependent on someone else* *- Unrealistic expectations* *-Fear (fear of falling)* *-Being discharged without being ready* *- Feeling of being a burden on caregivers* ***Residual stimuli:*** *- Prolonging of recovery period*	**Weakness* **Fear of falling* **Ineffective individual coping* **Reduced self-esteem*		
	Role function mode	***Contextual stimuli:*** *-Restricted movement* *- Being dependent on someone else* ***Residual stimuli:*** *- Prolonging of recovery period*	**Inability to fulfill roles*		
	Interdependency mode	***Contextual stimuli:*** *- Being dependent on someone else* *- Feeling of being a burden on caregivers* ***Residual stimuli:*** *-Fear (fear of falling)*	**Inadequacy in coping within the family* **Losing one's job* **Inadequate in resuming social responsibilities* **Social isolation*		

Figure 3. Continuous care interventions based on the RAM. Nursing diagnoses and continuous care interventions according to RAM domains and evaluation of effective-ineffective adaptive behaviors.

RAM: Roy Adaptation Model, ADL: Activities of daily living

Table 1. Demographic and clinical features of the patients

Clinical features	Intervention group, (n=36)	Control group, (n=40)	Test	p*
Age (X† ± SD‡)	6.77±8.3	65.57±6.5	t§=0.703	0.484
BMI (X† ± SD‡)	32.6±7.03	30.5±4.71	t§=1.503	0.138
Gender				
Female	33 (91.7)	35 (87.5)	-	0.715
Male	3 (8.3)	5 (12.5)		
Duration of stay				
(X†± SD‡)	9.5±2.9	9.2±3.2	t§=0.465	0.643
Chronic disease‖				
Yes	24 (66.7)	29 (72.5)	$\chi^{2¶}$=0.092	0.762
No	12 (33.3)	11 (27.5)		
Receiving physical therapy				
Yes	18 (50.0)	19 (47.5)	$\chi^{2¶}$=0.000	1.000
No	18 (50.0)	21 (52.5)		
Reason for the surgery				
Pain	5 (13.9)	8 (20.0)	$\chi^{2¶}$=2.565	0.277
Function loss	4 (11.1)	1 (2.5)		
Pain + function loss	27 (75.0)	31 (77.5)		
When the problem began				
Less than a year ago	10 (27.8)	3 (7.5)	$\chi^{2¶}$=8.081	0.18
1-3 years ago	13 (36.1)	11 (27.5)		
4 years ago or more	13 (36.1)	26 (65.0)		
Surgery site				
The right knee	14 (38.9)	7 (17.5)	$\chi^{2¶}$=5.988	0.50
The left knee	9 (25.0)	8 (20.0)		
The bilateral knee	13 (36.1)	25 (62.5)		
Needing assistance in walking				
Someone's help	4 (11.1)	2 (5.0)	$\chi^{2¶}$=3.061	0.382
Cane	8 (22.2)	10 (25.0)		
Crutches/walker	5 (13.9)	2 (5.0)		
On his/her own	19 (52.8)	26 (65.0)		

*: P-value, †: Mean, ‡: Standard deviation, §: T-test for independent samples, ‖Chronic disease: Hypertension, diabetes mellitus, hypo/hyperthyroidism, chronic heart disease, asthma, chronic obstructive pulmonary disease, osteoporosis, hyperlipidemia, ²¶: Chi-square test.

Table 2. Comparison of patients' WOMAC* scores

WOMAC	Baseline (X† ± SD‡)		Pre-discharge (X† ± SD‡)		3rd month (X† ± SD‡)		Group/time effects	
	The intervention group, (n=36)	The control group, (n=40)	The intervention group, (n=36)	The control group, (n=40)	The intervention group, (n=36)	The control group, (n=40)	F§	p‖
Pain	14.41±4.76	13.75±3.09	4.17±2.51	5.6±3.13	2.1±2.36	2.3±2.37	1.175	0.312
t¶	0.715		2.343		0.378			
p‖	0.478		**0.022**		0.707			
Stiffness	5.05±2.26	4.72±2.27	1.33±1.72	1.70±1.69	0.47±1.02	0.45±0.87	0.858	0.426
t¶	0.633		0.933		0.102			
p‖	0.528		0.354		0.919			
Functional state	48.38±13.72	43.35±9.59	21.69±9.14	8	8.38±6.70	8.12±6.20	1.936	0.148
t¶	1.836		1.533		0.178			
p‖	0.071		0.130		0.859			

*: Western Ontario and McMaster Universities Osteoarthritis Index, †: Mean, ‡: Standard deviation, §: Repeated-measures ANOVA with two between-group factors, ‖: P-value, ¶: T-test for independent samples.

Table 3. Comparison of patients' HAD* scores by group and time

HAD*	Baseline (X† ± SD‡)		Pre-discharge (X† ± SD‡)		3rd month (X† ± SD‡)		Group time interaction effects	
	The intervention group, (n=36)	The control group, (n=40)	The intervention group, (n=36)	The control group, (n=40)	The intervention group, (n=36)	The control group, (n=40)	F§	p‖
Anxiety	9.30±5.13	7.97±3.72	7.38±3.39	8.00±3.44	4.91±4.68	6.30±3.25	4.892	0.009
t¶	1.055		1.532		2.201			
p‖	0.259		0.130		0.032			
Depression	7.52±4.00	6.87±2.94	6.19±2.79	6.22±2.89	4.97±4.28	6.12±3.16	3.359	0.037
t¶	0.815		0.047		1.322			
p‖	0.418		0.963		0.191			

*: Hospital Anxiety and Depression Scale, †: Mean, ‡: Standard deviation, §: Repeated-measures ANOVA with two between-group factors, p‖: P-value, ¶: T-test for independent samples.

pre-test (t=1.355; p=0.259) and post-test t, time 1 (t=1.532; p=0.130). A significant difference was found between the depression score averages in time in the intervention group in terms of the group time interaction (Baseline, Pre-discharge, 3rd month). (F=3.359) (p=0.037). As a result of further analysis, no statistically significant difference in the pre-discharge and 3rd month depression scores was found between the patients in the intervention and control groups (pre-test t=0.815, p=0.418; post-test t, time 1=0.047, p=0.963; post-test t, time 2=1.322, p=0.191) (Table 3).

DISCUSSION

Total knee surgery is a choice that leads to a welcomed increased quality of life. The improvement in the postoperative pain-stiffness-functionality variables of all patients was consistent with the literature. Reduced pain, decreased stiffness, improved functioning, and an increased quality of life are the most fundamental outcomes of TKR surgery.[9,22,28] Another study with female patients undergoing TKR surgery reported reduced pain along with improved functioning.[29] In long-term studies that followed up on patients, pain and functionality were reported to be good.[8,9,30] However, orthopedic surgery can cause serious pain in the early postoperative period.[31,32] One study determined that among patients undergoing TKR surgery, 12% experienced severe pain in the early postoperative period.[3] In this study, it was determined that the pain scores of patients in the intervention group in the pre-discharge period were lower than those in the control group. This result was related to effective pain control in the intervention group. The results of this study may be considered effective adaptive behaviors in the physiological adaptation domain. In particular, the fact that the pain scores were better in the intervention group may be associated with how the patients in the intervention group developed effective adaptive behavior to cope with pain, which was included in the self-concept adaptation domain.

The tendency toward anxiety and depression decreased with time in the intervention group compared with the control group. At the same time, the anxiety scores in the intervention group in the 3rd month were significantly lower than those in the control group. All of these findings are consistent with the literature. Before the operation, the pain associated with the condition generally leads to increasing restrictions in movement as well as to deformities and instabilities, which impede ADL, make adaptation to home and work life difficult, and cause the patient to feel handicapped.[2,6] Because surgical prosthesis is an elective procedure, these interventions are postponed because of patients' experience with severe pain. This causes fear and avoidance of chronic pain and leads to patients adopting negative thought patterns. With fear comes hypervigilance or avoidance.[10] On the other hand, while patients undergoing TKR surgery hope that they will be relieved of their pain and will be able to prevent their immobility, they also live in fear that their problems will increase.[28,33] In the early postoperative period, patients

are faced with pain and other adverse effects of the surgery, additional illnesses, anesthesia, narcotic analgesics, fear (i.e. falling, becoming handicapped, becoming a burden), and other factors.[13] Following discharge from the hospital, patients face pain, restricted movement, and fears (i.e. of falling, of hurting the prosthesis, of dependency, of being discharged before being fully prepared, of a lack of information, and of being a burden). Throughout the process, patients have to cope with social isolation, weakness, anxiety, an inability to cope, an inability to fulfill one's role, and a loss of self-respect, among other negative factors.[2,11] In a study, 41.5% of patients undergoing orthopedic surgery experienced psychological changes in the post-operative period. These changes were feeling discouraged, feeling ill and handicapped, crying, feeling low, apathy, changes in sleep patterns, fatigue, irritability, nervousness and despair, and helplessness.[17] In another study, 20% of patients undergoing TKR were found to experience a sizable amount of post-operative stress in the first and third months.[10] However, postoperatively, patients may be confronted with symptoms such as a lack of energy, a loss of balance, and a fear of falling.[28] In our study, patients said that they felt crippled in the early period and were anxious that they would never walk again. At the same time, the patients experienced a fear of falling and perceived themselves as dependents that were a burden on their families. A study reported that 21% of their patients felt the need for some sort of social or psychological support.[17] In another study, also reported that telephone follow-ups were effective because this method provided the opportunity to evaluate the patient's environmental factors and support systems.[34] The low anxiety and depression scores in the patients in our intervention group indicated that individuals were able to display effective adaptive behavior in the self-concept, interdependency, and role function adaptation domains.

Patients are faced with many problems after TKR surgery. Education and follow-up protocols have been devised to improve TKR surgery outcomes and to help patients adapt to life with prostheses.[35,36] Education and subsequent follow-ups are of great importance because patients have to spend more time recovering at home due to shortened hospital stays.[14] Follow-ups are particularly important for evaluating the condition of patients who do not come in for routine visits.[37] In our study, it was found that patients, especially those living in other provinces, had difficulty coming in for their check-ups and were happy with telephone follow-ups. On the other hand, it is recommended that the topics covered in the education of patients are repeated because patients may be sleepy, irritated, in pain, stressed, and may not be able to concentrate on the information given to them pre-discharge.[8,37] A study discovered that patients and their families who were provided with a brief education did not learn much. Therefore, patients encountered problems at home because of gaps in their knowledge and had no opportunity to ask questions.[38] In another study where 207 patients with total joint prostheses were followed over the course of a year, it was found that patients were able to feel free to ask any questions they might have.[14]

Study Limitations

The lack of randomization in the study was one of its limitations. In addition, because a large majority of the patients lived in different cities, their coming in for a checkup and being examined by the same healthcare professionals was problematic. This was a limitation because maintaining continuity in caregivers is an important factor in continuous care. Another limitation was that the patients' health insurance did not cover their additional rehabilitation needs.

Moreover, the system of working on a multidisciplinary platform is a structure that has not yet become well established in the Turkish healthcare system. The researcher acted as a bridge between disciplines to facilitate continuous care interventions. The study's foundation on a nursing model is a strength of the research. The use of a nursing model not only helped to generate new knowledge for nursing researchbut also facilitated a holistic approach to the patient/individual/group and provided the means to determine realistic goals that were tailored to consider individual differences and ensure the maintenance of continuous care. The model acts as a bridge between theory and practice in the nursing profession and contributes to the evaluation of care.

CONCLUSION

Evaluation in RAM depends on the question, "Did the individual adapt?" This requires analyzing and deciding whether the targeted behavioral change was achieved. When the nurse evaluates the adaptation of patients with TKR, the change processes must be assessed, and it must be determined whether there has been effective adaptation. Changes in pain, stiffness, and functional status of patients affect their physiological, self-concept, and role function adaptive modes according to RAM. Anxiety and depression situations affect their self-concept, role function, and interdependence adaptive modes according to RAM. Moreover, all these adaptive modes affect each other. The lower levels of pain, anxiety, and depression in the patients in the intervention group indicated that they were better at showing more effective adaptive behavior. The outcome revealed that RAM-based continuous care prepared patients for better adaptation to living life with their prosthesis.

Relevance to Clinical Practice

In our study, as in the literature, the patients experienced stress for many reasons preoperatively, postoperatively, at pre-discharge, and at home, and for this reason sought support. RAM-based continuous care prepared patients for the process with education, advice, and telephone follow-ups; offered them the chance to become familiar with and adapt to their prosthesis, express their distress, identify problems at an early stage, and be encouraged to participate in social activities. Continuous care enables early identification and prevention of possible complications, thereby increasing the success of TKR surgery and easing the economic burden caused by revision surgery and other costs. Continuous care based on a model may provide integrated care that will serve as a guide for nursing interventions. Continuous care structured around RAM, which will be used in orthopedic nursing in TKR patients for the first time, will serve as a guide for nursing regarding patient care, carrying the dimensions of care to another level and enabling a more humanistic and holistic approach.

MAIN POINTS

- This study used the Roy Adaptation Model in patients undergoing total knee replacement surgery to enhance nurses' understanding of caregiving theories and their skills at incorporating these theories into the care they provide.
- Basing the continuous care provided to patients undergoing knee replacement surgery on the RAM may provide insight into evaluating the adaptation process patients go through and influencing factors, and it may be a useful example of integrated care.

- The use of a nursing model in this study contributed to strengthening the philosophy of nursing science.

Acknowledgments: The authors wish to thank the participants who voluntarily participated in the study.

ETHICS

Ethics Committee Approval: Written informed consent was approved by the Dokuz Eylül Hospital Ethical Committee (approval number: 30-GOA2011/13-09-2011).

Informed Consent: The researcher obtained the patients' written and verbal consents after explaining to them the purpose of the research, the process of data collection, and the study's implementation, informing them that they may withdraw from the study at any time and that their names would be kept confidential.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.S., Ö.B., Design: A.S., Ö.B., Supervision: Ö.B., Resources: A.S., Materials: A.S., Ö.B., Data Collection and/or Processing: A.S., Analysis and/or Interpretation: A.S., Ö.B., Literature Search: A.S., Writing: A.S., Critical Review: Ö.B.

DISCLOSURES

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

Financial Disclosure: The authors declared that this study had received no financial support.

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RESEARCH ARTICLE

CYPRUS
JOURNAL OF MEDICAL SCIENCES

DOI: 10.4274/cjms.2020.2849
Cyprus J Med Sci 2023;8(5):354-359

Role of Parental Attitudes Towards Rational Drug Use in Predicting Fever Management Practices

Aslı Akdeniz Kudubeş, İlknur Bektaş, Dijle Ayar, İsa Çelik, Murat Bektaş

Department of Nursing, Dokuz Eylül University Faculty of Nursing, İzmir, Türkiye

Abstract

BACKGROUND/AIMS: This study was conducted in a descriptive cross-sectional type to investigate the prediction of parental attitudes toward rational drug use on fever management practices.

MATERIALS AND METHODS: The study was conducted between March and May 2019 with 150 parents whose children were receiving treatment at the pediatric units. The study data were collected using a Parental Data Form, the Parental Attitude Scale Toward Rational Drug Use (PASTRDU), and the Parent Fever Management Scale (PFMS). Percentage calculations, mean scores, Pearson's correlation analysis, linear regression analysis, and multiple correlation analysis were employed for data analysis.

RESULTS: Three models were formed according to the relationship between variables in multiple regression analysis. According to the models developed, the PFMS was found to increase as the overall score and sub-dimension scores of the PASTRDU increased ($p<0.001$).

CONCLUSION: It is thought that parents who develop positive attitudes toward rational drug use and manage their child's fever appropriately will experience less anxiety, their quality of life will improve, their self-confidence in child care will increase, and their satisfaction with the care that they receive from health professionals will increase.

Keywords: Parents, drug, attitude, fever

INTRODUCTION

Rational drug use reduces social and financial burdens and prevent biopsychosocial damages stemming from the misuse of drugs in society.[1,2] The most common misapplications when parents administer drugs to their children involve the application of excessive or inadequate doses, incorrect adjustment of time intervals, improper storage conditions, the combination of the drug with other drugs and substances, and premature quitting of the normal course.[3,4] The concept of rational drug use in children has become even more important because of height, weight, and body surface area differences by the developmental period of the child. The responsibilities of the pediatric nurse regarding rational drug applications include providing parental education and making necessary observations on the side effects of drugs. The nurse should first interrogate the current knowledge of parents and then inform them about the indications, doses, correct time, and points to be considered.[5] Due to the physiological and developmental characteristics of children, the likelihood of harm caused by drug errors in children is three times higher than that in adults.[6,7] According to the reports in the literature about common misapplications about drug use, parents use antipyretics without prescription, they do not apply drugs in appropriate doses, they have difficulty giving drugs to their children, they give drugs one after another in the case of multiple drug prescription, they give the drug when the child wakes up if it is sleeping, they keep using the drug until the child has recovered, they stop using the drug in the case of side effect development, and they quit the normal course of the drug when the child has vomited.[8-11] Therefore, it is important to increase

To cite this article: Akdeniz Kudubeş A, Bektaş İ, Ayar D, Çelik İ, Bektaş M. Role of Parental Attitudes Towards Rational Drug Use in Predicting Fever Management Practices. Cyprus J Med Sci 2023;8(5):354-364

ORCID IDs of the authors: A.A.K. 0000-0002-0911-8182, İ.B. 0000-0001-8048-9501, D.A. 0000-0001-5196-2355, İ.Ç. 0000-0003-3381-2286, M.B. 0000-0003-3327-8204.

Address for Correspondence: Aslı Akdeniz Kudubeş
E-mail: asliakdeniz@hotmail.com
ORCID ID: orcid.org/0000-0002-0911-8182

Received: 02.06.2020
Accepted: 03.12.2020

parental knowledge regarding rational drug use in the management of fever, which is an important symptom in children.

One of the symptoms of many diseases in children, fever, is a condition that requires rapid intervention and is critical in terms of possible complications. 20-30% of pediatric emergency department visits are reported to be due to reasons related to high fever.[12,13] Although the treatment of fever cases in children is easy, irrational, improper, and untimely interventions can lead to undesirable consequences.[13,14] The lack of adequate knowledge about fever and its treatment in parents and the low educational level of the parents are reported as factors affecting the approach to the child with fever.[15,16] Studies report that parents' fear of fever decreases and wrong interventions are prevented when healthcare workers train parents on the definition of fever, its causes, symptoms of high fever, home care of the child with fever, primary home interventions, and correct time to visit a health institution.[14,17,18] One of the most effective ways to lower fever in children is to use antipyretic drugs. Parents should take care not to overdose when administering antipyretic drugs to their children. This can be achieved by raising the rational drug use attitudes of parents.[18,19]

Providing health education to parents on the importance and necessity of fever management in children can help reduce fever-related complications.[16] Informing parents about rational drug use and fever management will ensure adopting the right approach for the child with fever. In addition, when parents become knowledgeable about unnecessary and incorrect drug use, negative practices for lowering a high fever will be prevented.[20] In the literature, rational drug use and fever management in children have been studied as separate variables.[6-8,11,14,15] On the other hand, no studies have investigated the effects of rational drug use attitudes of parents on fever management practices. Therefore, studies investigating the prediction of the Parental Attitude Scale Toward Rational Drug Use (PASTRDU) on the Parent Fever Management Scale (PFMS) are needed.

MATERIALS AND METHODS

Aim

This study used a descriptive cross-sectional design and was conducted to investigate the prediction of PASTRDU on PFMS.

Population and Sample

The study was planned to be conducted between March and May 2019 with the parents of children treated at the pediatric surgery, pediatric emergency clinic, and children's examination-infection clinic of children's hospital. The sampling required for the study was calculated using GPOWER 3.1 statistical analysis software based on a 0.05 significance level, 80% power, and 0.15 effect size (medium effect size). As a result, the sample size required for regression analysis was determined to be 68 subjects. Considering the likelihood of a 10% drop, the sample size was 75 subjects. The study was conducted between March and May 2019 with 150 parents whose children were receiving treatment at the pediatric units of a university hospital. Participants in this study included parents whose children were admitted to the university hospital pediatric unit, and the parents were over 18 years of age and willing to participate in the study.

Data Collection Tools

Data collection tools included a Parental Data Form, PASTRDU, and PFMS.

Parental Data Form

The form consists of 12 questions. The first three items ask about the sociodemographic characteristics of the parents (age, gender, and educational status), and the rest include questions for determining parents' knowledge about the body temperature of their children.

The Parental Attitude Scale Toward Rational Drug Use

The scale developed by Çelebi and Çelebioğlu[21] consists of 40 items. It has two sub-dimensions: Suitable and Rational Use (29 items) and Effective and Safe Use (11 items). It is a five-point Likert-type scale, and each item is scored from 1 to 5. Increased scores obtained from the scale indicate increased positive parental attitudes towards rational drug use. Cronbach's alpha co-efficient for the overall scale is 0.887. In addition, Cronbach's alpha co-efficients for the Suitable and Rational Use and Effective and Safe Use sub-dimensions are 0.894 and 0.771, respectively. Item-total correlation values are 0.32-0.61.[21] Cronbach's alpha value of the scale in this study was determined as 0.954.

The Parent Fever Management Scale

This 8-item scale was developed by Walsh et al.[22], and its validity and reliability studies were conducted by the same authors. A validity and reliability study of the Turkish version of the scale was performed by Cinar et al.[23]. It is a five-point Likert-type scale, in which each item is scored between 1=never, 2=rarely, 3=sometimes, 4= often, and 5=always. The minimum and maximum scores that can be obtained from the scale range from 8 to 40 points. Increased scores obtained from the scale indicate increased parent fever management practices. Cronbach's alpha coefficient of the overall scale is 0.79.[23] Cronbach's alpha value of the scale in this study was determined as 0.855.

Data Collection

For this study, the researchers collected data during daily visits to the clinic and interviews with parents who met the criteria. The researchers asked the parents to complete the data collection forms in the clinic's single patient rooms. Before beginning the research, the participants were informed about the objective of the study, and the parents who agreed to participate in the research were included in the research. The researchers obtained both written and oral consent from the parents. The data collection forms were filled out by the parents in approximately 10 min. One family did not want to participate in the study because they thought that their child might be adversely affected. The participation rate was 99.5%.

Ethical Considerations

This study was approved by the Institutional Review Board of the University (approval number: 4709GOA-2019/10-04). Institutional permissions were obtained to carry out the study. In addition, written and verbal consent of the parents were obtained by meeting them face-to-face and informing them about the aim of the study.

Statistical Analysis

Mean and percentage calculations were employed in the descriptive data analyzes. The Shapiro-Wilks test was used to determine if the

dataset was well-modeled by a normal distribution. The relationship between PASTRDU and PFMS was analyzed using Pearson's correlation analysis. The extent to which PASTRDU predicts PFMS was analyzed using linear regression analysis. VIF and tolerance analysis were employed to determine whether there was multicollinearity between PASTRDU and PFMS. A VIF value <10, a tolerance value <0.02, and a condition index value <15, which are independent variables, were included in the regression analysis. The significance level was set at 0.05.

RESULTS

The mean age of the parents who participated in the study was 34.25±7.50. 78% of them were femalesand 52% were high school graduates. The average number of children was 2.10±1.22. 52% of the participants were found to learn fever-management related issues from healthcare workers and 51% were determined to follow their child's body temperature with a thermometer. 56.7% of the parents stated that they considered 38 °C and over as fever, 50% measured their child's body temperature from the child's armpit, 43.3% took the child to a health institution before giving antipyretic medication to the child, and 51.2% used antipyretics to lower the child's fever and gave a lukewarm bath to the child. In addition, 58.7% of the parents stated that their physician decided the dose of the antipyretics. On the other hand, 75.3% of the respondents were found to not use non-prescription medication for their child. There was a statistically significant relationship between PFMS and the gender of the parents. There was a statistically significant relationship between PFMS and PASTRDU according to the educational background of parents ($p<0.05$). There was no statistically significant relationship between PASTRDU and the gender of the parents ($p>0.05$) (Table 1).

The evaluation of the prediction of sociodemographic characteristics of the parents on their PFMS in the multiple regression analysis indicated that age, gender, education level, and the number of children affected PFMS by 14.1%. All factors except for the number of children were found to significantly affect PFMS ($p<0.05$). The analysis of the prediction of parents' socio-demographic characteristics on their PASTRDU indicated that age, gender, education level, and the number of children affected PASTRDU use by 18.7%. All factors except for the number of children and gender were found to significantly affect PASTRDU ($p<0.05$). The number of children and female gender positively affects PASTRDU (Table 2).

A moderate, positive, and highly significant relationship was found between PASTRDU and PFMS ($p<0.01$). In addition, a moderate, positive, and highly significant relationship was found between PFMS and the suitable and rational use sub-dimension of PASTRDU and a moderate, positive, and highly significant relationship was found between PFMS and the effective and safe use sub-dimension of PASTRDU ($p<0.01$) (Table 3).

Table 1. Rational drug use attitudes and fever management status according to parents' gender and education

		Parental attitudes towards rational drug use			Fever management practices		
		Mean ± SD	Z	p	Mean ± SD	Z	p
Gender	Female, (n=117)	193.21±1.47	1,236	0.216	39.76±0.22	2,251	0.024
	Male, (n=33)	190.06±2.93			37.78±0.68		
Educational status	Before high school, (n=31)	183.83±3.85	3,253	0.001	37.96±0.65	2,328	0.020
	High school and after, (n=119)	194.78±1.25			39.14±0.23		

SD: Standard deviation.

Table 2. Predicting parents' socio-demographic characteristics on their attitudes toward rational drug use and fever management practices

Parents' socio-demographic characteristics	Fever management practices	Attitudes towards rational drug use
	β	β
Age	0.207*	0.353*
Gender	0.201*	0.075
Educational status	0.210*	0.217*
Number of children	0.022	0.058
R	**0.376**	**0.432**
R^2	**0.141**	**0.187**
F	**5,973**	**8,334**
DW** (1.5-2.5)	**2,201**	**1,908**

*p<0.05, **Durbin-Watson.

Table 3. Relationship between parental attitudes towards rational drug use and fever management practices

	1	2	3	4
1. Parent Fever Management Scale (PFMS)	1			
2. Parental Attitude Scale for Rational Drug Use (PASTRDU)	0.641*	1		
3. PASTRDU suitable and rational use sub-dimensions	0.647*	0.951*	1	
4. PASTRDU effective and safe use sub-dimensions	0.497*	0.868*	0.672*	1

*p<0.01 level significant.

Three models were created according to the relationship between variables in the multiple regression analysis. Each of the subdimensions of PASTRDU was specified as a separate model. In the last model, the prediction of the total score of PASTRDU on PFMS was determined. Accordingly, as the total score obtained from the PASTRDU increased, positive attitudes toward PASTRDU increased. On the other hand, as the total score obtained from the PFMS increased, the PFMS were determined to increase. In the first model, the Suitable and Rational Use sub-dimension of PASTRDU was found to affect 41.8% of PFMS, whereas the increase in suitable and rational use augmented PFMS by 0.647 (β=0.647). In the second model, the Effective and Safe Use sub-dimension of PASTRDU was determined to affect 24.7% of PFMS, whereas the increase in effective and safe use increased PFMS by 0.497 (β=0.497). In the third model, PASTRDU together with suitable/rational use and effective/safe use subdimensions was found to influence PFMS by 41.1%, whereas PASTRDU was determined to affect PFMS by 0.641 (β=0.641). All factors were found to statistically significantly affect PFMS ($p<0.05$) (Table 4).

DISCUSSION

This study investigated the prediction of parents' socio-demographic characteristics on PASTRDU and PFMS. In this study, it was determined that the educational status of the parents affected rational drug use and fever management, and that parental gender affected fever management. The education level of parents is important when accessing information about PFMS and PASTRDU. Parents with high levels of education are eager to access and apply knowledge about fever management and rational drug use.[15,24,25] In addition, parents can recognize fever-lowering practices with low reliability. Parents who have a high level of education understand the importance of the fact that using non-prescription drugs and can pose risks for their children. As the age of parents increases, their knowledge and experience about child care increases, so they can manage fever properly and develop positive attitudes toward rational drug use. In addition, mothers play a greater role in fever management practices because of their primary role in child care compared with fathers.[15,24,25] As most parents who participated in our study were female (78%) and had a high school education (52%), they are thought to have better fever management skills. In addition, since the parents participating in our study had 2 children on average, the number of children was thought to not have an effect on increasing PFMS and their PASTRDU. The literature supports the finding of this study that age, gender, and education level of the parents increased their PFMS.[15,16,23-25]

The findings show the prediction of PASTRDU on their PFMS. In this study, three models were formed by considering the correlations between the variables. The relationships investigated in these models were as follows: the relationship between the means of the total scores obtained from the suitable and rational use sub-dimension of PASTRDU and PFMS in Model 1; the relationship between the means of the total scores obtained from the effective and safe use sub-dimension of PASTRDU and PFMS in Model 2; and the relationship between the means of the total scores obtained from PASTRDU and PFMS in Model 3.

Model 1 showed that as the scores obtained from the suitable and rational use sub-dimension of PASTRDU increased, PFMS increased. The timely and right-dose administration of antipyretics is critical for reducing a child's fever or keeping it under control. Although it is easy to control fever in children, irrational, improper, and untimely practices may lead to negative consequences.[16] Information given by nurses to parents will create positive results in increasing the correct and rational practices of parents. The content of parent training by nurses should include the definition of fever, its symptoms, home care, first aid, and criteria for taking the child to a health institution. In addition, information about antipyretics to be administered provides support for parents regarding suitable and rational drug use. In case of fever in the child, the parent developing positive attitudes towards rational drug use can refer to suitable practices, administer antipyretics properly, reduce their fear of fever, and reduce misapplications. Knowing the suitable drug approach and time to visit a health institution is thought to increase fever management practices in mothers who exhibit suitable and rational drug use attitudes. The literature supports the finding in Model 1.[4-7]

Model 2 indicated that as the scores obtained from the effective and safe use sub-dimension of PASTRDU increased, PFMS increased. Because of the physiological properties of children, effective and safe drug use is critical in eliminating the possibility of improper drug use in children.[24] Parents who exhibit negative attitudes towards effective and safe drug use are observed to use antipyretics at excessive or inadequate doses, to give drugs one after another in the case of multiple drug prescriptions, to store drugs under inappropriate conditions, to not administer the drug during sleep time, and to quit the normal course of the drug when the child has vomited or a side effect has developed.[26] Such mismanagement adversely affects parents' fever management practices. Parents who develop positive attitudes towards effective and safe drug use are reported to not use non-prescription antipyretics in the case of fever in their child, to obtain information about the use of antipyretics from health professionals, and to know the side effects of

Table 4. Predicting parental attitudes towards rational drug use on fever management practices

	Fever management practices		
	Model 1	Model 2	Model 3
	β	β	β
Parental attitudes towards rational drug use	0.647*	0.497*	0.641*
R	0.647	0.497	0.641
R^2	0.418	0.247	0.411
F	106,504	48,657	103,422
p	0.001	0.001	0.001
DW** (1.5-2.5)	2,369	2,129	2,299

*P<0.01 level significant, **Durbin-Watson.

these drugs. Therefore, increasing parental knowledge about rational drug use is of significance in the management of fever, an important symptom in children. Thus, the fever management practices of parents who have a high level of discriminating skill for improper practices and wrong drug use and who are aware of the importance of safe drug use are thought to increase. The literature supports the finding of Model 2.[12,23,27]

Model 3 revealed that as the total scores obtained from the PASTRDU increased, the PFMS increased. Providing parent education on rational drug use and making necessary observations about the side effects of drugs are among the responsibilities of nurses. Parental education on the indications of antipyretics, their doses, correct application time, and points of attention is important. It is possible to reduce fever-bound complications through education on both antipyretic use and other applications in fever management.[24,26,28] Parental education on rational drug use and antipyretics allows parents to appropriately approach child fever. Parents who develop positive attitudes toward rational drug use are observed to be successful in fever management. In addition, inappropriate and wrong drug use by parents who are aware of how to lower fever is actually prevented. Due to the high educational status received from health professionals, parents are thought to develop attitudes toward rational drug use, manage their child's fever appropriately, and have a high level of healthcare satisfaction. The literature supports the finding in model 3.[12,23,24,28]

Study Limitations

Despite the many study strengths, it is limited by the use of a convenience sample, which may affect the generalizability of the study.

CONCLUSION

Positive attitudes of parents towards rational drug use were determined to affect fever management practices. In this study, PFMS was found to increase as the overall score and sub-dimension scores of PASTRDU increased. In addition, it was determined that some sociodemographic characteristics of nurses, such as gender and educational status, affected the average scores of rational drug use and fever management. Pediatric nurses have a great deal of responsibility for parental education. Therefore, it is thought that the sociodemographic characteristics and rational drug attitudes of nurses should be considered while increasing the knowledge and skills of nurses regarding fever management.

Nurses who have significant roles in rational drug use and fever management education should be aware of their responsibilities and update their knowledge regularly regarding the matter in question. In in-service training programs given to pediatric nurses, providing information particularly about rational drug use and the responsibilities of nurses and performing regular revisions of this information will contribute to parental education carried out by nurses and prevent many problems related to patient safety.

MAIN POINTS

- The fever management practices of the parents increased as the overall score and sub-dimension scores of the parental attitude scale towards rational drug use increased.
- Positive attitudes of parents towards rational drug use were determined to affect fever management practices.
- Providing health education to parents on the importance and necessity of fever management in children can help reduce fever-related complications.

ETHICS

Ethics Committee Approval: This study was approved by the Institutional Review Board of the University (approval number: 4709GOA-2019/10-04).

Informed Consent: In addition, written and verbal consent of the parents were obtained by meeting them face-to-face and informing them about the aim of the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.A.K., Design: A.A.K., Supervision: A.A.K., Materials: A.A.K., Data Collection and/or Processing: A.A.K., İ.B., D.A., İ.Ç., Analysis and/or Interpretation: A.A.K., M.B., Literature Search: A.A.K., İ.B., D.A., İ.Ç., Writing: A.A.K., İ.B., Critical Review: A.A.K., D.A., M.B.

DISCLOSURES

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

Financial Disclosure: The authors declared that this study had received no financial support.

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CYPRUS
JOURNAL OF MEDICAL SCIENCES

DOI: 10.4274/cjms.2021.3213
Cyprus J Med Sci 2023;8(5):360-364

The Relationship Between Grip Strength and Reaction Time in Different Age Groups

Kansu Kanlı[1], Tuba Yerlikaya[1], Salih Angın[2]

[1]Department of Physiotherapy and Rehabilitation, Near East University Faculty of Health Sciences, Nicosia, North Cyprus
[2]Department of Physiotherapy and Rehabilitation, Cyprus International University Faculty of Health Sciences, Nicosia, North Cyprus

Abstract

BACKGROUND/AIMS: Hand grip strength (HGS) and reaction time are crucial functions to maintain daily activities. They are also a sign of general physical health. The aim of this study was to determine the relationship between grip strength and reaction time in children, adults and older adults.

MATERIALS AND METHODS: The study included a total of 120 subjects, comprising 40 children, 40 adults and 40 older adults. The Jamar Hydraulic Hand Dynamometer (Sammons Preston, Bolingbrook, Illinois) was used to evaluate HGS and the Nelson Hand Reaction Ruler was used for the upper extremity reaction time.

RESULTS: A statistically significant difference was determined between the three age groups with respect to grip strength ($p<0.001$) and reaction time ($p<0.001$). No statistically significant correlation was found between grip strength and reaction time of children ($r=-0.27$, $p=0.09$) and adults ($r=-0.22$, $p=0.18$). A statistically significant, negative, and strong correlation was found between grip strength and reaction time in older adults ($r=-0.53$, $p<0.001$).

CONCLUSION: The results of the study showed no relationship between the grip strength and reaction time of children and adults, whereas the grip strength levels of the older adults were seen to increase as reaction time decreased.

Keywords: Hand grip strength, reaction time, aging, older adult, adult

INTRODUCTION

The hand, which is a complex and highly differentiated organ, plays an important role in the sustainability of daily life activities.[1] The number and size of muscle fibres decrease as a result of age-related loss of spinal motor neurons, leading to impaired mechanical muscle performance that translates into reduced functional capacity for daily living activities.[2] Hand grip strength (HGS) and reaction time are the key factors during all functions of the upper extremity. The normative values of HGS and reaction time alone will provide more objective information about functional status.[3-6] However, the relationship between these two parameters has not yet been fully clarified.

HGS can be seen as a general indicator of the integrity of the central nervous system associated with cognitive variables.[7-9] Although there are studies reporting that the decrease in HGS is related to cognitive decline, it has also been reported that individual differences have an impact.[10,11] It can therefore be understood that there are conflicting views on the relationship between HGS and reaction time, and there are several different studies in litterature on this subject.[12-15] Several studies have examined a specific age group or either HGS or reaction time.[8,16] To the best of our knowledge, there are no studies that have examined the relationship between the reaction time and HGS of children. Most such studies have reported the relationship between HGS and cognition in older adults and thus, data related to adults and

To cite this article: Kanlı K, Yerlikaya T, Angın S. The Relationship Between Grip Strength and Reaction Time in Different Age Groups. Cyprus J Med Sci 2023;8(5):360-364

ORCID IDs of the authors: K.K. 0000-0003-1623-2845; T.Y. 0000-0002-5968-0384; S.A. 0000-0003-1623-2845.

Address for Correspondence: Tuba Yerlikaya
E-mail: tuba.yerlikaya@neu.edu.tr
ORCID ID: orcid.org/0000-0002-5968-0384

Received: 17.11.2020
Accepted: 17.03.2021

children are still lacking.[7,17,18] The aim of this study was to determine the relationship between grip strength and reaction time in children, adults and older adults.

MATERIALS AND METHODS

This study was conducted in the Physical Therapy and Rehabilitation Department of the Near East University Medical Faculty Hospital, North Cyprus, between January 2018 and April 2018. Approval for the study was granted by the Scientific Research Ethics Committee of the Near East University (approval number: YDU/2018/54-490).

Participants

The study sample was selected from the relatives of patients who presented at the Near East University Hospital, students at the Near East Primary School and Secondary School, and individuals residing in the provinces of North Cyprus. Participants were chosen from healthy children aged 6 to 14, healthy adults aged 18-65 years and older adults aged 66-79 years, who had not presented at the clinic with any health-related problems within the last six months. While the children group was selected randomly from children at school, the other groups were selected randomly according to the hospital registration list.

Exclusion criteria for all groups were defined as:

- A history of mobility limiting musculoskeletal or neuromuscular disease, or upper extremity abnormalities,

- A history of upper extremity surgery,

- The presence of any communication problems.

Written informed consent for participation in this cross-sectional study was obtained from all the subjects, or from the parent or legal guardian of children below the age of majority. Personal information and anthropometric data of the participants were collected in face-to-face interviews. The demographic record form consisted of age, gender, height, weight, body mass index and dominant hand (Table 1).

Hand Grip Strength: Jamar Hydraulic Hand Dynamometer (Sammons Preston, Bolingbrook, Illinois)

The HGS evaluation of the participants was performed according to the standard measurement of the American Society of Hand Therapists: The subject is seated with the elbow positioned in 90º flexion and the hand positioned centrally with the thumb pointing upwards. The participants were instructed to squeeze the handles of the dynamometer as strongly as possible.[19] The Jamar dynamometer has five different handle positions: I-3.5 cm; II-4.8 cm; III-6.1 cm; IV-7.3 cm; and V-8.6 cm. The handle position was adjusted according to the hand size of the child, adult and older participants, and three different measurements were taken with a rest time of at least 30 seconds between each measurement. The mean value of the three measurements was calculated and recorded as kilogram units.[20]

Reaction Time: Nelson Hand Reaction Test

Each subject was placed in a sitting position on a chair, with the forearms and hands placed on the table in a comfortable position for the Nelson Hand Reaction Test. The hand was positioned so that the thumb and index fingers were 8 to 10 cm above the table, with the upper parts of the thumb and index fingers in a parallel position. The test supervisor placed and held a ruler between the thumb and index finger of the participants. The participants were instructed to look directly at the centre point of the ruler and then to catch the ruler when it was released by the supervisor. The value written on the upper part of the ruler, at the point where it was caught by the participant was recorded. Five measurements were recorded, and after exclusion of the best and worst values, the average of the other three measurements was calculated, and recorded as the distance to which the ruler fell. For each measurement, the value on the ruler was calculated according to the formula below and the reaction time of the participants was calculated. The formula: reaction time = $\sqrt{2}$ x Fall Distance of Ruler/ Gravity Related Speed Reaction Time = $\sqrt{2}$ x distance (cm)/980 sec.[21,22]

Statistical Analysis

Data obtained in the study were analysed statistically using SPSS version 24.00 software (IBM SPSS Statistics for Windows, IBM Corp., Armonk, NY, USA). As a result of the power analysis applied, it was calculated that when 120 participants were included in this study (40 subjects in each group), 80% power with 95% confidence interval would be obtained. The distribution of participants regarding the characteristic features of child, adult and older adult participants were defined by frequency analysis. Definitive statistics of age and anthropometric measurements were stated as mean, standard deviation, minimum and maximum values. The standard distribution compatibility of the data set, which was used to determine the hypothesis tests of the research was evaluated using the Kolmogorov-Smirnov and Shapiro-Wilk tests in respect of skewness-kurtosis values. As the data set was not compatible with normal distribution, non-parametric hypothesis tests were used.

Table 1. Descriptive features of the study groups

	Children, (mean ± SD)	Adults, (mean ± SD)	Older adults, (mean ± SD)
Gender (n, %)			
Female	21 (52.50%)	20 (50.00%)	19(47.50%)
Male	19 (47.50%)	20 (50.00%)	21(52.50%)
Age (years)	9.95±2.62	42.63±14.34	71.38±4.14
Height (m)	1.42±0.19	1.69±0.09	1.64±0.09
Weight (kg)	38.16±15.74	74.68±14.16	76.08±15.03
BMI (kg/m^2)	18.22±3.31	26.13± 4.57	28.47±5.51
Dominant hand (n, %)			
Right/Left	38 (95%)/2 (5%)	38 (95%)/2 (5%)	39 (97.50%)/1 (2.50%)

BMI: Body mass index, SD: Standard deviation.

The Kruskal-Wallis H test was used for the comparisons of grip strength and reaction time of the child, adult and older adult participants. Bonferroni correction was applied for the evaluation of the results. Correlations between grip strength and reaction time were evaluated using the Spearman's test. The statistical significance level was accepted as $p<0.05$

RESULTS

The comparison of grip strength in three groups are shown in Table 2. The average grip strength results were found to be 14.97±8.55 kg for children, 34.96±12.63 kg for adults and 26.57±9.80 kg for the older adults. A statistically significant difference was determined between the three age groups in respect of grip strength ($p<0.001$). When the differences were evaluated between the groups, the grip strength of adults was determined to be higher than that of children and older adults, and the grip strength of older adults was higher than that of the children.

The average reaction time was determined as 0.16±0.01 sec for children, 0.18±0.02 sec for adults and 0.19±0.02 sec for older adults. A statistically significant difference was determined between the three age groups in respect of reaction time values ($p<0.001$). The reaction time values of the children were lower than those of the adults and older adults, and the reaction time values of the adults were significantly lower than those of the older adults.

The correlation of grip strength values of the child, adult and older adult subjects are shown in Figure 1. No statistically significant correlation was determined between the grip strength and reaction time of the child ($p=0.09$) and adult subjects ($p=0.18$). A statistically significant, negative rotative, and moderate correlation was observed between grip strength and reaction time of the older adult subjects ($r=-0.53$, $p<0.001$).

DISCUSSION

The most important finding of this study was that the grip strength levels of older adults increased as reaction time decreased while the grip strength and reaction time of the children and adults showed no correlation. Reaction time and grip strength are essential measures to evaluate an individual in respect of both cognitive and physical function.[23] When literature was investigated regarding studies based on grip strength and reaction time, no study could be found which evaluated these two variables simultaneously within three different age groups. According to best of our knowledge this study is the first study showing the relationship between grip strength and reaction time in children, adults and older adults, the level of change in these variables and a map of the process.

With inevitable irreversible neuron losses, the ageing process causes movements to slow down and reaction time to be prolonged, while the decrease in type II muscle fibers required for force generation causes loss of muscle strength-mass with the increase of adipose tissue in the muscle fibers.[24-26] These two factors have a positive effect

Table 2. Comparison of grip strength and reaction time between the groups

Parameter	Group	Mean ± SD	Min.-Max.	Median	χ^2 (p)	η^2	Difference
Grip strength (kg)	Children[a]	14.97±8.55	2.33-34.00	12.15	46,210		[a-b]
	Adult[b]	34.96±12.63	18.00-62.60	31.80	<0.01	0.361	[a-c]
	Older adults[c]	26.57±9.80	8.33-48.00	26.65			[b-c]
Reaction time (sec)	Child[a]	0.16±0.01	0.10-0.19	0.16	48,199		[a-b]
	Adult[b]	0.18±0.02	0.13-1.21	0.18	<0.01	0.377	[a-c]
	Older adults[c]	0.19±0.02	0.15-0.21	0.19			[b-c]

SD: Standard deviation, Min.: Minimum, Max.: Maximum.

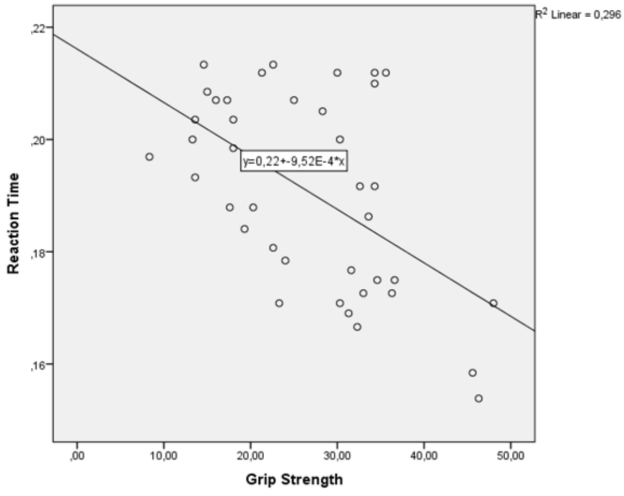

Figure 1. Correlations between merged grip strength and reaction time of three groups.

Table 3. Correlation between grip strength and reaction time of participants

			Grip strength (kg)			
			Children, (x̄14.97±8.55)	Adults, (x̄34.96±12.63)	Older adults, (x̄26.57±9.80)	Total, (x̄25.50±13.24)
Reaction time (sec.)	Children, (x̄1.81±0.32)	R	-0.27			
		P	0.09			
	Adults, (x̄2.31±0.46)	R		-0.22		
		P		0.18		
	Older adults, (x̄2.59±0.46)	R			-0.53	
		P			<0.001	
	Average, (x̄2.24±0.54)	R				0.07
		P				0.47

on the prevention of cardiovascular mortality in particular, while also increasing cognitive function and physical function.[27]

Age-related reductions in muscle mass have consistently been shown to be linked to changes in muscle activation and muscle recruitment characteristics, which have an impact on hand dexterity.[28] Age-related changes include slower muscle contraction speed, which slows neural conduction velocity, and increased muscle antagonist co-activation required to stabilize or restrict the joint during movement.[29,30]

Martin et al.[31] evaluated the relationship between hand dexterity and grip strength, and evaluated the reaction time of hand dexterity in individuals aged 18-93 years. All hand dexterity tasks were reported to have significantly declined with decreased strength in older adults whereas no relationship between strength and steadiness of hand dexterity was seen in younger adults. Those findings were similar to the results of the current study, although a child age group was not included.[31]

Bucsuházy and Semela[16] examined the difference between reaction times of child and adult groups and similar to the results of the current study, no significant difference was found. Choudhary et al.[23] reported a significant negative correlation between HGS in the dominant hand and visual reaction time in a study of adult kitchen workers. The results were contrary to the current study findings of our study, which can be considered to be due to increased function of the hand in occupational use.[23]

Reduction of grip strength and prolonged reaction time cause important secondary risks in older adults. Prolonged reaction time creates a more extended period in which to correct the balance and as a result of the decrease in muscle strength, the risk of falling increases with the insufficiency of muscle strength required to correct the balance. HGS measurements can be a useful part of clinical evaluations in older adults to identify individuals with reduced functional and cognitive health. Exercise and activities to improve muscle strength and to reduce reaction time are essential for older adults to reduce the risk of falls. There is also a need for further long-term research to determine whether regular sports activity during childhood and adulthood have any continued effect into old age.

Study Limitations

A limitation of this study was that a sufficient number of participants could not be reached to allow evaluation of all age groups according to decades. Another limitation was that although the ASHT protocol was followed, different postures during testing of the children may have affected the results.

CONCLUSION

The results of this study, which evaluated the relationship between grip strength and reaction time of children, adults and older adults, demonstrated that HGS was not associated with reaction time in children and adults, but a correlation was determined in older adults, with an increase in grip strength values as reaction time shortened. Thus, the reaction time was seen to be affected by age rather than strength, and the reaction time was affected by grip strength in old age.

MAIN POINTS

- Handgrip strength was not associated with the reaction time in children and adults.
- Reaction time was seen to be affected by age rather than strength, and the reaction time was affected by grip strength in old age.
- Handgrip strength is considered a meaningful measure of current physical health and future outcome in older adults.

ETHICS

Ethics Committee Approval: Approval for the study was granted by the Scientific Research Ethics Committee of the Near East University (approval number: YDU/2018/54-490).

Informed Consent: Informed consent was obtained from all individual participants included in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: S.A., Design: S.A., Supervision: S.A., Materials: K.K., Data Collection and/or Processing: K.K., Analysis and/or Interpretation: K.K., Literature Search: T.Y., Writing: T.Y., Critical Review: T.Y.

DISCLOSURES

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

Financial Disclosure: The authors declared that this study had received no financial support.

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RESEARCH ARTICLE

CYPRUS
JOURNAL OF MEDICAL SCIENCES

DOI: 10.4274/cjms.2023.2023-73
Cyprus J Med Sci 2023;8(5):365-371

Validity and Reliability Study of the Turkish Version of the Michigan Revised Diabetes Knowledge Test and Its Relationship with the Turkish Health Literacy Scale-32 Scores

Ülkem Şen Uzeli[1], Dilek Yapar[2], Nihal Aydemir[3], Ferit Kerim Küçükler[4]

[1]Clinic of Internal Medicine, Osmancık State Hospital, Çorum, Türkiye
[2]Muratpaşa District Health Directorate, Antalya, Türkiye
[3]Department of Nephrology, Hitit University Faculty of Medicine, Çorum, Türkiye
[4]Clinic of Endocrinology, Medinverse Clinic, İstanbul, Türkiye

Abstract

BACKGROUND/AIMS: Education is essential in patients with diabetes to prevent acute and/or chronic complications that may develop over time due to diabetes. This studyaimed to examine the relationship between diabetes knowledge level and health literacy (HL) level of patients by testing the validity and reliability of the Turkish version of the revised Diabetes Knowledge Test-2 (Tr-DKT2).

MATERIALS AND METHODS: A total of 148 patients with insulin-using diabetes were included in our study. Türkiye Health Literacy Scale-32 (THLS-32) and after the determination of the validity of the language and content of the Michigan revised DKT2, it was applied to the patients. The internal consistency of DKT2 was calculated using the Kuder-Richardson-20 (KR-20) formula. The construct validity of DKT2 was examined by testing the validity of known groups and the relationship between it and the THLS-32 score.

RESULTS: A moderate, positive correlation was found between the mean scores on the total THLS-32 and DKT2 (r=0.378). Regarding the test-retest reliability, the intraclass correlation co-efficient value for the total score was found to be 0.893 (95% confidence interval: 0.841-0.928), which was evaluated to be a high value. The internal consistency co-efficient was found to be 0.70 for DKT2. The KR-20 value was calculated as 0.72 for the general test dimension and 0.68 for the insulin use dimension.

CONCLUSION: The Turkish version of DKT2 is a valid and reliable measurement tool. We think that as the HL levels of the patients increase, the diabetes patients will manage diabetes well as their diabetes knowledge level increases.

Keywords: Diabetes education, diabetes mellitus, health literacy

INTRODUCTION

Diabetes mellitus (DM) is a chronic disease that develops because of insulin deficiency or defects in insulin action and requires constant medical care. According to the data of the International Diabetes Federation, there were 463 million individuals with diabetes worldwide in 2019, and this number is estimated to rise to 700 million by 2045.[1] The prevalence of diabetes is increasing in our country as well as in the world. It is necessary to raise awareness among people about the causes of diabetes, facilitating factors, and early diagnosis and treatment.

To cite this article: Şen Uzeli Ü, Yapar D, Aydemir N, Küçükler FK. Validity and Reliability Study of the Turkish Version of the Michigan Revised Diabetes Knowledge Test and Its Relationship with the THLS-32 Scores. Cyprus J Med Sci 2023;8(5):365-371

ORCID IDs of the authors: Ü.Ş.U. 0009-0006-6479-7858; D.Y. 0000-0001-7656-1152; N.A. 0000-0003-2430-8280; F.K.K. 0000-0002-9277-0584.

Address for Correspondence: Ülkem Şen Uzeli
E-mail: ulkem_sen@hotmail.com
ORCID ID: orcid.org/0009-0006-6479-7858

Received: 04.07.2023
Accepted: 22.07.2023

The most important step in raising awareness is education. Diabetes can be prevented or delayed by lifestyle changes. Society will be more easily guided to lifestyle changes through education programs after this awareness has been achieved. Good control and education are essential to prevent complications that may develop over time in DM.

Health literacy (HL) is the ability of an individual to acquire, understand, evaluate, and apply health-related information so that he or she can make effective and appropriate health decisions.[2,3] Seeing the course of chronic diseases such as diabetes, preventing negative health outcomes, and helping patients develop self-care skills are closely related to patients' health and diabetes literacy.[4,5] Achieving positive results throughout the illness of patients with diabetes is largely achieved through effective communication related to the treatment of the disease. It is necessary to evaluate both patients' diabetes and their general HL to strengthen their communication with patients.

This study was conducted to create a Turkish version of the Revised Diabetes Knowledge Test-2 (DKT2), test its validity and reliability, and examine the relationship between patients' diabetes knowledge and HL levels.

MATERIALS AND METHODS

The Type and Sample of the Study

This is a cross-sectional and methodological study. The study was conducted between November 2018 and December 2018 in the endocrinology polyclinic of Hitit University Çorum Erol Olçok Training and Research Hospital. Permission from Dr. James T. Fitzgerald, who is a Professor at the University of Michigan Medical School Geriatric Research Education and Clinical Center and who developed the original form of the DKT2, was obtained via e-mail to evaluate the Turkish validity and reliability of the scale. At the outset, the approval of the Hitit University Non-interventional Research Ethics Committee (approval number: 2019-14, date: 04.01.2019) was obtained. Patients who were aged >18 years, were literate, spoke Turkish as their mother tongue, used insulin, and had been followed for at least 1 year because of type 1 or type 2 diabetes were included in the study. The study included 148 patients who met the inclusion criteria. The retest procedure was applied to 100 patients in the sample who agreed to undergo the test for a second time. All patients signed a voluntary consent form and completed the descriptive information form.

Data Collection Tools and Implementation of the Study

The data collection form consisted of three parts. The first part had 20 questions about descriptive characteristics, such as gender, age, educational status, and diabetes-related data, such as chronic complications, hemoglobin A1c (HbA1c) levels, and the status of having received diabetes education. The second part consisted of the Turkish version of the 23-item DKT2, and the third part consisted of the Turkish Health Literacy Scale-32 (THLS-32), whose Turkish validity and reliability study had been previously tested.

Turkish Health Literacy Scale-32

The Turkish validity and the reliability study of the THLS-32 was conducted based on the European Health Literacy Scale. This scale consists of 32 items, and the Cronbach's alpha co-efficient was found to be 0.927. Scores on the scale range between 0 and 50, and high scores indicate a high level of HL. The relationship of scores with literacy levels is interpreted as follows: 0 and 25, "inadequate"; 26-33, "problematic (limited)"; 34-42, "adequate"; 43-50, "excellent".

Diabetes Knowledge Test-2

Revised by the Michigan Diabetes Research Education Center, this test consists of 23 questions that measure diabetes knowledge. The first 14 questions of the scale were designed for patients with diabetes using oral antidiabetic drugs (OAD); however, the entire scale can be applied to patients who use insulin. The test includes the following topics: the first 14 questions are about diet, metabolic tests, complications of diabetes, and exercise. The last nine questions are about insulin and insulin administration. Each question has only one correct answer. The scale score can be obtained by calculating the percentage of correct answers given to the sub-dimensions and the total scale or by summing the scores assigned to each correct response. The alpha reliability co-efficient was 0.77 for the general knowledge test and 0.84 for the insulin use sub-dimension.[6]

Evaluation of the Turkish Validity and Reliability of the Diabetes Knowledge Test-2

First, the Turkish version of DKT2 (Tr-DKT2) was created to evaluate the level of diabetes knowledge in the study. In the process of translating and culturally adapting DKT2 into Turkish, translation-back translation and expert opinion methods defined in the language and cultural adaptation guidelines of Beaton et al.[7] were used. A committee of experts, consisting of two education scientists with an endocrinology background who had a good command of English, evaluated the translated texts and finalized the Turkish version of the scale. To test the intelligibility of the Turkish version, Tr-DKT2 was administered to 20 volunteer patients who presented to the outpatient clinic and met the inclusion criteria, under the observation of the researcher. The patients were asked to evaluate the intelligibility of the scale items by responding with one of the following options: "intelligible", "unintelligible", or "undecided". The responses obtained in the pilot study indicated that none of the items required any changes. In this study, the scale score was obtained by calculating the percentage of correct answers. Reliability was evaluated using internal consistency and test- retest reliability. Internal consistency was tested by calculating the reliability co-efficient Kuder-Richardson-20 (KR-20).[8-10] Test- retest reliability was evaluated using the intraclass correlation co-efficient (ICC). The construct validity of the scale was evaluated using criterion validity, and the Spearman correlation level between education levels and scale scores was calculated.

Statistical Analysis

Study data were analyzed using the SSPS 23.0 statistical software package. Descriptive statistics were presented using numbers and percentages for categorical variables and mean ± standard deviation and median (minimum-maximum values) values for continuous variables. The normality of continuous variables was evaluated using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). It was determined that the Tr-DKT2 scores did not show a normal distribution. The relationship between the scale scores was evaluated using the Spearman correlation test. In this study, $p<0.05$ was considered statistically significant.

RESULTS

Turkish Validity and Reliability Results of the Diabetes Knowledge Test-2

To test the Turkish intelligibility of Tr-DKT2, which was created according to the language and cultural adaptation guidelines of Beaton et al.[7], it was applied to 20 volunteer patients in the outpatient clinic, and then it was finalized. Afterward, the questionnaire, which was applied to 148 patients in the first test, was applied to 100 patients in the sample for the second time with an average of 15.9±5.3 (minimum: 7-maximum: 30) days interval. Test- retest reliability was calculated as ICC 0.893 (95% CI: 0.841-0.928) for the total DKT2, ICC 0.826 (95% CI: 0.741-0.883) for the general knowledge test, and ICC 0.801 (95% CI: 0.704-0.866) for the insulin use sub-dimension. The internal consistency co-efficient was found to be 0.70 for DKT2, KR-20=0.72 for the general test, and KR-20=0.68 for the insulin use sub-dimension. Education levels and the Spearman correlation co-efficient were evaluated for the construct validity of the scale, and a moderate correlation was found (r=0.364; p<0.001). There was a weak, statistically significant relationship between education level and the general test and insulin use sub-dimension scores (r=0.286 p=0.004 and r=0.292 p<0.001, respectively). The median DKT score was 65.2 (34.7-95.6) for primary school graduates, 73.9 (43.4-100) for secondary school graduates, and 78.2 (43.4-95.6) for university graduates, and there was a statistically significant difference between them (p<0.001). Considering these results, it was shown that DKT2 is a valid and reliable scale. The Turkish version, which was found to be valid and reliable after the analyzes, is presented in Figure 1.

Demographic Data and Clinical Characteristics of the Patients

A total of 148 patients with diabetes, 86 males and 62 females, were included in the study, and their mean age was 47.5±13.8 (minimum: 18; maximum: 77) years. The mean body mass index was 30.7±6.89 (19.4-54.9) kg/m^2, and only 29 (19.6%) patients had a normal weight. The examination of patients' distribution according to their education level indicated that 74 (50%) were primary school graduates, 39 (26.4%) were secondary school graduates, and 35 (23.6%) were university graduates. Of the patients, 96.0% did not live alone, and 13 patients (8.8%) stated that they lived with a healthcare worker (Table 1). The mean duration of diabetes diagnosis was 11.7±7.5 (1-35) years, and 46.6% of the patients had been diagnosed with hypertension. The examination of diabetes-related complications showed that 60.8% of the patients had at least one minor or macrovascular complication. The most common complication was neuropathy (with; 34.5%), followed by coronary artery disease (23.6%), nephropathy (22.3%), and retinopathy (7.4%). While 66.9% of the patients had been using OAD and insulin, 33.1% had been using only insulin. It was observed that patients using insulin had been using it for an average of 7.74±6.77 (1-30) years and 45 patients (30.4%) for more than 10 years. Hospitalizations were mostly due to hyperglycemia (Table 2). In Table 3, the laboratory values of the patients' last controls are presented. As seen in the table, the patients' mean creatinine level was 1.01±1.08 (0.2-7.8) mg/dL, and the mean HbA1c level was 8.6±2% (5-17.6). The HbA1c level was <7.5 in 45 patients (30.4%), 7.5-9 in 54 patients (36.5%), and ≥9 in 49 patients (33.1%). The low-density lipoprotein cholesterol level was <100 mg/dL only in 37.6% of patients. The triglyceride level was <150 mg/dL in 54.1% of patients, 150-499 mg/dL in 43.9%, and ≥500 mg/dL in 2%.

Relationship between Patients' Health Literacy and Diabetes Knowledge Levels

In this study, patients scored an average of 31.4±7.95 (11-49) on the T-HLS-32. Accordingly, HL levels were inadequate in 23% of patients, limited problematic in 39.2%, adequate in 26.4%, and excellent in 11.4%. The DKT2 scores comprised two parts: general test and insulin use. Patients were found to correctly answer an average of 10.1±2.06 (5-14) questions from the general test, an average of 6.16±1.61 (2-9) questions from the insulin use section, and an average of 16.3±3.08 (8-23) questions from the total test. It was determined that patients' knowledge was 72.3±14.7 percent (35.7-100%) on the general test, 68.4±17.9 percent (22.2-100%) on insulin use, and 70.8±13.4 percent (34.7-100) on the total test (Table 4). A moderate-level, positive correlation was found between THLS-32 and DKT2 scores (r=0.378). Accordingly, patients with a high THLS-32 score also had high DKT2 scores (Table 5). In addition, patients with inadequate/problematic limited HL levels had a median DKT score of 67.3 (34.7-100), and those with adequate/excellent HL levels had a median DKT score of 76.1 (52.1-95.6). Accordingly, a statistically significant difference was found between the groups (p<0.001).

DISCUSSION

In this study, we tested the Turkish validity and reliability of the DKT2 and evaluated the correlation between HL and diabetes knowledge level in patients with diabetes. The findings showed that patients with high HL levels also had high diabetes knowledge levels. This result shows the notion that diabetes education and HL are significant factors in improving patients' ability to manage their health conditions.

The DKT2 is a quick and cost-effective method to assess the general diabetes and diabetes self-care knowledge of patients with diabetes.[6] The results of the study indicated that the Turkish DKT2 scale is an appropriate, valid, and reliable test for patients with diabetes living in Türkiye. It is also a short and intelligible test in terms of application. The first 14 questions of the test were used to measure the general diabetes knowledge level of all patients with diabetes. When previous validity and reliability studies in the literature were examined, it was seen that only the validity and reliability of this 14-item general dimension were tested in some countries.[11-13] The internal consistency value calculated for the general knowledge dimension in these studies ranged from 0.6 to 0.75. In the revision study of DKT2 by Fitzgerald et al.[6], this value was found to be 0.77 for the general test dimension and 0.84 for the insulin use dimension. In our study, the internal consistency co-efficient was 0.72 for the general test sub-dimension, 0.68 for the insulin use sub-dimension, and 0.7 for the total scale. These internal consistency levels were found to be adequate. The reliability level of the Turkish version that we created was consistent with the literature in terms of internal consistency.

This study was initiated on November 2018. Since there was no DKT developed to measure the diabetes knowledge of patients in Türkiye or published in a Turkish validity-reliability study until the start of the study, the author of the test, Fitzgerald, was contacted via e-mail, and the necessary permission was obtained to use the test in the study and to test the validity and reliability of the Turkish version. During this process, İdiz et al.[14] also tested the Turkish version of the revised DKT2, which was created for their sample, and published the results in 2020.

Michigan Diyabet Araştırma ve Eğitim Merkezi Revize Diyabet Bilgisi Testi Türkçe Versiyonu (Tr-DBT-2)

1. Diyabet diyeti:
   a. Çoğu insanın yemek yeme şeklidir.
   b. Çoğu insan için sağlıklı bir diyettir.*
   c. Çoğu insan için çok fazla karbonhidrat içerir.
   d. Çoğu insan için çok fazla protein içerir.
2. Aşağıdakilerden hangisinin karbonhidrat içeriği en yüksektir?
   a. Fırında tavuk
   b. Kaşar peyniri
   c. Fırında patates*
   d. Fıstık ezmesi
3. Aşağıdakilerden hangisinin yağ içeriği en yüksektir?
   a. Düşük yağlı (%2) süt*
   b. Portakal suyu
   c. Mısır
   d. Bal
4. Aşağıdakilerden hangisi bir "besin değeri düşük yiyecektir?
   a. Herhangi bir şekersiz yiyecek
   b. Etiketinde "yağsız" yazan herhangi bir yiyecek
   c. Etiketinde "şekersiz" yazan herhangi bir yiyecek
   d. Kalorisi, porsiyon başına 20 kaloriden az olan yiyecekler*
5. A1C, geçtiğimiz ……. için ortalama kan şekeri düzeyinizin ölçüsüdür.
   a. Bir gün
   b. Bir hafta
   c. 6-12 hafta*
   d. 6 ay
6. Evde şeker testi için en iyi yöntem hangisidir?
   a. İdrar testi
   b. Kan testi*
   c. Her ikisi de eşit derecede iyidir.
7. Şeker ve benzeri madde içermeyen meyve suyunun kan şekeri üzerindeki etkisi nedir?
   a. Düşürür.
   b. Yükseltir.*
   c. Etkisi yoktur.
8. Hangisi düşük kan şekeri tedavisinde kullanılmamalıdır?
   a. 3 adet küp şeker
   b. ½ bardak portakal suyu
   c. 1 bardak alkolsüz diyet içecek*
   d. 1 bardak yağsız süt
9. Diyabeti iyi seviyede kontrole sahip bir kişi için egzersizin kan şekeri üzerindeki etkisi nedir?
   a. Kan şekerini düşürür.*
   b. Kan şekerini yükseltir.
   c. Etkisi yoktur.
10. Kan şekeriniz düşmeye başlıyorsa hangisini yapmanız gerekir?
    a. Egzersiz
    b. Yatmak ve dinlenmek
    c. Biraz meyve suyu içmek*
    d. Hızlı etki gösteren insülin almak
11. Enfeksiyonun kan şekeri üzerindeki en olası etkisi nedir?
    a. Kan şekerini düşürür.
    b. Kan şekerini yükseltir.*
    c. Etkisi yoktur.
12. Hangisi ayak bakımı yapmanın en iyi yoludur?
    a. Her gün ayaklarınıza bakmak ve yıkamak.*
    b. Her gün ayaklarınıza alkolle masaj yapmak.
    c. Her gün bir saat suda bekletmek.
    d. Normalden bir numara büyük ayakkabı almak.
13. Az yağlı yiyecekler yemek hangi riski azaltır?
    a. Sinir hastalıkları
    b. Böbrek hastalıkları
    c. Kalp hastalıkları*
    d. Karaciğer hastalıkları
14. Uyuşma ve karıncalanma hangisinin semptomları olabilir?
    a. Böbrek hastalıkları
    b. Sinir hastalıkları*
    c. Göz hastalıkları
    d. Karaciğer hastalıkları
15. Hangisi genellikle diyabetle ilişkili değildir?
    a. Görme problemleri
    b. Böbrek problemleri
    c. Sinir problemleri
    d. Akciğer problemleri*
16. Hangisi ketoasidoz (DKA) belirtisidir?
    a. Titreme
    b. Terleme
    c. Kusma*
    d. Düşük kan şekeri
17. Eğer gribe yakalanmışsanız, yapmanız gereken
    a. Daha az insülin almaktır.
    b. Daha az sıvı almaktır.
    c. Daha fazla proteinli yemektir.
    d. Kan şekerinizi daha sık ölçmektir.*
18. Hızlı etki gösteren insülin aldıysanız, kan şekeri düşmesini en olası hangi zamanda yaşarsınız?
    a. 2 saatten daha kısa sürede*
    b. 3-5 saat arasında
    c. 6-12 saat arasında
    d. 13 saatten fazla bir zamanda
19. Tam öğle yemeğinden önce, kahvaltıda insülin almayı unuttuğunuzu fark ettiniz. Şimdi ne yapmalısınız?
    a. Kan şekerinizi düşürmek için öğle yemeğini atlamalısınız.
    b. Genellikle kahvaltıda aldığınız insülini almalısınız.
    c. Genellikle kahvaltıda aldığınız insülinin iki katı kadar insülin almalısınız.
    d. Ne kadar insülin almanız gerektiğine kara vermek için kan şekerinizi kontrol etmelisiniz.*
20. Kan şekerinin düşmesi hangisinden kaynaklanıyor olabilir?
    a. Çok fazla insülin*
    b. Çok az insülin
    c. Çok fazla yiyecek
    d. Çok az egzersiz
21. Eğer sabah insülininizi alır fakat kahvaltıyı atlarsanız, kan şekeri düzeyiniz genellikle
    a. Yükselir.
    b. Düşer.*
    c. Aynı kalır.
22. Kan şekerinin yükselmesi hangisinden kaynaklanıyor olabilir?
    a. Yetersiz insülin*
    b. Yemekleri atlamak
    c. Ara öğünü geciktirmek
    d. Egzersizinizi atlamak
23. Kan şekerinin düşmesi hangisinden kaynaklanıyor olabilir?
    a. Ağır egzersiz*
    b. Enfeksiyon
    c. Aşırı yeme
    d. İnsülininizi almama

Figure 1. The Turkish version of Tr-DKT-2, which was found valid and reliable.

DKT-2: Diabetes Knowledge Test-2.

In this study, the reliability co-efficient calculated with ∝ for the first part of DKT2 was 0.60 for the general test sub-dimension, ∝=0.59 for insulin use, and ∝=0.70 for the total scale.[14] It is noteworthy that the internal consistency level was below the critical value of 0.6 for the insulin use dimension.

Diabetes education is effective in improving the clinical outcomes and quality of life of patients.[15] The role of patient education in diabetes has been emphasized in many studies.[16-18] Therefore, patients with diabetes need to be aware of the disease and its management to achieve good metabolic control. However, some studies have shown that approximately 50-80% of patients with diabetes have a significant lack of knowledge and skills.[19] In the study by Fitzgerald et al.[6], the mean test score in patients with type 1 diabetes was 84.7±20% for the general test and 84.9±24.1% for insulin use, and the scores in patients with type 2 diabetes were 71.7±24.7% and 64.3±28.4%, respectively.[11] In our study, the scores were 72.3%±14.7% and 68.4%±17.9% in all patients This finding shows that the education levels and diabetic education levels of the patients in the two study groups were similar.

According to the data obtained in the study, the HL level was inadequate or limited in 62.2% of the patients. This indicated that patients' ability to effectively use health services and health-related information was limited. On the other hand, when patients' diabetes knowledge level was examined, the mean correct knowledge level was 72.3% for the

Table 1. Some demographic characteristics of the patients

Parameters, (n=148)	
Gender, n (%)	
Male	86 (58.1)
Female	62 (41.9)
Age, year	
Mean ± SD	47.5±13.8
Median (minimum-maximum)	48.5 (18-77)
BMI, kg/m²	
Mean ± SD	30.7±6.8
Median (minimum-maximum)	29.3 (19.4-54.9)
BMI classification, n (%)	
18.5-24.9 (normal weight)	29 (19.6)
25-29.9 (overweight)	55 (37.2)
30-34.9 (class 1 obesity)	32 (21.6)
35-39.9 (class 2 obesity)	17 (11.5)
≥40 (class 3 obesity)	15 (10.1)
Level of education, n (%)	
Primary education	74 (50.0)
Secondary education	39 (26.4)
University and above	35 (23.6)
Marital status, n (%)	
Married	124 (83.8)
Single	16 (10.8)
Widowed	8 (5.4)
Households, n (%)	
None	6 (4.1)
Spouse and children	124 (83.8)
Other	18 (12.2)
Living with a healthcare worker, n (%)	
No	135 (91.2)
Yes	13 (8.8)
Monthly family income, n (%)	
Low	69 (46.6)
Middle	74 (50.0)
High	5 (3.4)

*: Row percentage, SD: Standard deviation, BMI: Body mass index.

Table 2. Patient characteristics related to DM

Parameters, (n=148)	
Duration of DM, year	
Mean ± SD	11.7±7.5
Median (minimum-maximum)	10 (1-35)
Duration of DM, n (%)	
≤5 years	31 (20.9)
6-10 years	52 (35.2)
11-20 years	48 (32.4)
≥21 years	17 (11.5)
Complications of DM, n (%)	
No	58 (39.2)
Yes	90 (60.8)
Complications of DM, n (%)*	
Nephropathy	33 (22.3)
Neuropathy	51 (34.5)
Retinopathy	11 (7.4)
Coronary artery disease	35 (23.6)
Foot ulcers	3 (2.0)
Amputation	2 (1.4)
Treatment for DM, n (%)	
OAD + insulin	99 (66.9)
Insulin	49 (33.1)
Duration of insulin use, year	
Mean ± SD	7.7±6.7
Median (minimum-maximum)	6 (1-30)
Duration of insulin use, n (%)	
<10 years	103 (69.6)
≥10 years	45 (30.4)
Hospitalization in the past year, n (%)	
No	135 (91.2)
Once	13 (8.8)
Length of hospitalization (n=13), day	
Mean ± SD	6.1±4.8
Median (minimum-maximum)	5 (1-20)
Indiciations for hospitalization (n=13), n (%)	
Hyperglycemia	11 (84.6)
Hypoglycemia	1 (7.7)
Diabetic ketoacidosis	1 (7.7)

*: Multiple options were marked, DM: Diabetes mellitus, SD: Standard deviation, BMI: Body mass index, OAD: Oral antidiabetic drugs.

general test and 68.4% for insulin use. These rates suggested that patients had basic knowledge about diabetes but needed more detailed health knowledge and skills. In the study by Bains and Egede[20], a moderate correlation was found between HL and diabetes knowledge (r=0.44). Similarly, a moderate correlation was found in our study. In addition, similar correlations have been found between limited HL and poorer disease knowledge in the literature.[21-23]

When the patients' education level was examined, it was seen that 50% of them were primary school graduates, 26.4% were secondary school graduates, and 23.6% were university graduates. In this study, it can be said that the level of diabetes knowledge increased with the increase in education level (r=0.364; p<0.001). In a study conducted in Saudi Arabia, similar to our study, it was found that the level of diabetes knowledge increased as the education level increased.[24]

Study Limitations

DKT2, the validity and reliability of which was tested in our study in Turkish, was designed to measure the knowledge level of patients with diabetes. The scale was created by focusing on knowledge areas related to the general management of diabetes and insulin use. However, dimensions such as long-term effects, nutrition, exercise, and blood sugar control, which are other important issues of diabetes, are not included in the scale. There may be some questions about these issues, but they are not considered among the main dimensions of the scale. While this underlines that we found the Turkish version of DKT2 to be valid and reliable in our study, it also reveals a limitation that we should pay attention to in its use. We may need to use a more comprehensive scale or other assessment methods besides DKT2 to accurately measure the general level of diabetes knowledge when evaluating our patients.

CONCLUSION

In conclusion, healthcare providers should pay more attention to diabetes education so that patients can take necessary precautions

Table 3. Characteristics of patients' laboratory values

Parameters, (n=148)	
Creatinine, mg/dL	
Mean ± SD	1.01±1.08
Median (minimum-maximum)	0.70 (0.20-7.80)
eGFR, mL/minutes/1.73 m²	
Mean ± SD	97.8±29.5
Median (minimum-maximum)	105 (6-148)
HbA1c	
Mean ± SD	8.6±2
Median (minimum-maximum)	8.2 (5-17.6)
HbA1c, n (%)	
<7.5	45 (30.4%)
7.5-9	54 (36.5%)
≥9.5	49 (33.1%)
LDL cholesterol, mg/dL	
Mean ± SD	111.8±35.8
Median (minimum-maximum)	110 (40-219)
LDL cholesterol level, n (%)	
<100	53 (37.6)
100-129	44 (31.2)
130-159	35 (24.8)
≥160	9 (6.4)
Triglyceride, mg/dL	
Mean ± SD	175±109
Median (minimum-maximum)	139.5 (5-626)
Triglyceride level, n (%)	
<150	80 (54.1)
150-499	65 (43.9)
≥500	3 (2)

*: Multiple options were marked. SD: Standard deviation, e-GFR: Epidermal growth factor receptor, HbA1c: Hemoglobin A1c, LDL: Low-density lipoprotein.

Table 4. Patient scores from THLS-32 and DKT2

Parameters, (n=148)	
THLS-32 score	
Mean ± SD	31.4±7.95
Median (minimum-maximum)	30.7 (11-49)
Level of HL according to THLS-32	
Inadequate (0-25)	34 (23.0)
Problematic/limited (>25-33)	58 (39.2)
Adequate (>33-42)	39 (26.4)
Excellent (>42-50)	17 (11.4)
Count of correct responses to the DKT2 general test	
Mean ± SD	10.1±2.06
Median (minimum-maximum)	10 (5-14)
Correct responses to the DKT2 - general test (%)	
Mean ± SD	72.3±14.7
Median (minimum-maximum)	71.4 (35.7-100)
Correct responses to DKT2 - insulin use	
Mean ± SD	6.16±1.61
Median (minimum-maximum)	6 (2-9)
Correct responses to DKT2 - insulin use (%)	
Mean ± SD	68.4±17.9
Median (minimum-maximum)	66.6 (22.2-100)
Correct responses to total DKT2	
Mean ± SD	16.2±3.08
Median (minimum-maximum)	17 (8-23)
Correct responses to the total DKT2 (%)	
Mean ± SD	70.8±13.4
Median (minimum-maximum)	73.9 (34.7-100)

*: Multiple options were marked. THLS-32: Turkish Health Literacy Scale-32, SD: Standard deviation, HL: Health literacy, DKT2: Diabetes Knowledge Test-2.

Table 5. Correlation between DKT2 and THLS-32

	THLS-32
	r (p)
DKT2 general	0.318 (<0.001)
DKT2 insulin use	0.311 (<0.001)
DKT2 total	0.378 (<0.001)

DKT2: Diabetes Knowledge Test-2, THLS-32: Türkiye Health Literacy Scale-32.

regarding self-care or the development of complications during the treatment process. Unfortunately, providing diabetes education alone is not enough to increase patients' knowledge levels. The general HL level of the society also needs to be improved. Providing diabetes education at regular intervals, measuring patients' knowledge levels, and closely following patients with inadequate diabetes knowledge are significant approaches to disease management.

MAIN POINTS

- Education is of great importance for preventing acute and chronic complications that may develop in diabetes.
- For diabetes education, scales for the evaluation of both diabetes and health literacy of patients should be developed.
- With the help of scales to be used for diabetes, the treatment processes of patients can be performed much easier.

ETHICS

Ethics Committee Approval: This study was approved by by Hitit University Non-interventional Research Ethics Committee (approval number: 2019-14, date: 04.01.2019).

Informed Consent: All patients signed a voluntary consent form and completed the descriptive information form.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Ü.Ş.U., D.Y., N.A., F.K.K., Design: Ü.Ş.U., D.Y., N.A., F.K.K., Data Collection and/or Processing: Ü.Ş.U., D.Y., N.A., F.K.K., Analysis and/or Interpretation: Ü.Ş.U., D.Y., N.A., F.K.K., Literature Search: Ü.Ş.U., D.Y., N.A., F.K.K., Writing: Ü.Ş.U., D.Y., N.A., F.K.K.

DISCLOSURES

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

Financial Disclosure: The authors declared that this study had received no financial support.

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CYPRUS
JOURNAL OF MEDICAL SCIENCES

DOI: 10.4274/cjms.2021.3530
Cyprus J Med Sci 2023;8(5):372-377

Investigation of the Relationship Between Care Dependency and Self-Care Behaviors in Chemotherapy Patients

Naciye Esra Koyuncu[1], Serpil Su[2]

[1]Havva and Memiş Koçak Family Health Center, Konya, Türkiye
[2]Department of Fundamental Nursing, Necmettin Erbakan University Faculty of Nursing, Konya, Türkiye

Abstract

BACKGROUND/AIMS: The symptoms experienced by patients receiving chemotherapy reduce their ability to perform daily life activities, adversely affect their quality of life, and make them dependent on care to meet their care needs. This study was conducted to examine the relationship between care dependency and self-care behaviors in patients undergoing chemotherapy.

MATERIALS AND METHODS: This descriptive and correlational study was conducted with 100 patients in Türkiye between November 2018 and February 2019. Ethics committee approval, institution permit, and patient consent were obtained to conduct the study. Data were collected by face-to-face interviews using the Patient Information Form, Care Dependency Scale, and Self-care Behavior Scale according to Self-Care Inability Theory in Patients Receiving Chemotherapy. In the analysis of the data, t-test, Mann-Whitney U test, Kruskal-Wallis test, Pearson correlation test, and regression analysis were used in independent groups.

RESULTS: It was found that 74% of the patients who participated in the study were male, 48% were between 39 and 58 years old, 38% were diagnosed with lung cancer, and 63% received 2-4 cycles of chemotherapy. The mean scores of "Care Dependency Scale" (68.98±15.89) and "Self-care Behavior Scale According to Self-Care Inability Theory in Patients Receiving Chemotherapy" (69.54±13.20) were at a moderate level. It was determined that the patients' care dependency scores accounted for the change in the total score of self-care behaviors at a rate of 21%.

CONCLUSION: As a result, the study found that self-care behavior increased as the care dependency of chemotherapy patients decreased, and self-care behaviors were affected by care dependency at a low rate.

Keywords: Care dependency, chemotherapy, self-care

INTRODUCTION

The incidence of cancer, which ranks second among the causes of death in the world, is 225.1 per hundred thousand based on 2018 data published by the International Agency for Cancer Research.[1] Based on the Turkish Health Statistics Annual report for 2015, this rate was 247.6 per hundred thousand in men and 177.5 per hundred thousand in women in Türkiye, while it increased to 259.9 in men and increased to 183.2 in women based on the report published in 2016.[2,3] These data show that the need for chemotherapy, which is considered an important part of cancer treatment, has also increased.[4] Because of the large number of patients today, chemotherapy treatment is carried out on an outpatient basis or in a hospital for a short time. Patients experience many symptoms that develop after treatment at home without the support of health professionals. Therefore, it is essential to develop self-care in order for patients to cope with the symptoms.[5,6]

Care dependency, a dynamic process that is directly affected by illness or defectiveness, is defined as "a process in which a patient who has reduced self-care and is dependent on another person in meeting care

To cite this article: Koyuncu NE, Su S. Investigation of the Relationship Between Care Dependency and Self-Care Behaviors in Chemotherapy Patients. Cyprus J Med Sci 2023;8(5):372-377

ORCID IDs of the authors: N.E.K. 0000-0002-2879-8873; S.S. 0000-0001-9263-6046.

Address for Correspondence: Serpil Su
E-mail: suserpil@gmail.com
ORCID ID: orcid.org/0000-0001-9263-6046

Received: 03.12.2020
Accepted: 15.05.2021

needs is professionally supported".[7] The main objective of this support is to restore the independence of an individual in self-care practices.[8,9] The symptoms experienced by patients receiving chemotherapy reduce their ability to perform daily life activities, adversely affect their quality of life, and make them dependent on care to meet their care needs. Therefore, patients have difficulty meeting their self-care needs.[9] There are studies that report low and moderate levels of self-care in patients receiving chemotherapy.[10,11]

It is known that nurses have important roles in restoring self-care abilities in patients.[7] Nurses help manage this process better by developing individualized care strategies by reducing patients' anxiety before and during treatment, providing information about expected symptoms, and following the treatment process.[4] In a study conducted by Breen et al.[12] in hematologic cancer patients in Australia, a remote healthcare application controlled by nurses was used to allow patients to manage the side effects of chemotherapy, and the authors concluded that patients managed their symptoms better. In a study that used the customized Chemo-Support application to reduce chemotherapy-associated symptoms, patients' symptom severity and distress were reduced.[13] In the study of Wang et al.[14], self-care education was provided to breast cancer patients who underwent chemotherapy, and the authors found that the education reduced the frequency of symptoms significantly.

Patients who receive chemotherapy often develop care dependency in relation to cancer, chemotherapy, and additional diseases.[15] In the literature, patients who have care dependency are often reported to have problems in providing self-care.[16] Accordingly, as patients who undergo chemotherapy become care-dependent, their self-care can be affected.[11] However, no study investigating this relationship was found in the literature. Therefore, the purpose of this study was to examine the relationship between care dependency and self-care behaviors in patients undergoing chemotherapy. Findings of this study can contribute to better identification of patients' needs and planning appropriate nursing interventions.

Study Questions

1. What are the mean scores of patients on the Self-care Behavior Scale according to Self-Care Inability Theory in Patients Receiving Chemotherapy?

2. What are the mean scores of patients on the Care Dependency Scale?

3. What is the relationship between "Self-care Behavior Scale According to Self-Care Inability Theory in Patients Receiving Chemotherapy" and "Care Dependency Scale" scores and other independent variables?

MATERIALS AND METHODS

Design and Sampling

This descriptive and correlational study was conducted in an outpatient chemotherapy unit of a university hospital located in Central Anatolia, Türkiye, between November 2018 and February 2019. The sample of the study consisted of 100 patients who were receiving chemotherapy. Data were collected from 30 patients to determine the sample size, and it was determined that the sample size should be at least 100 patients with 5% alpha margin of error and 80% power in the G*Power software. The sample size was sufficient based on the post-hoc power analysis conducted at the end of the study (100%). Patients aged 18 years and older who were capable of self-feedback and received at least one course of chemotherapy were included in the study, whereas patients receiving chemotherapy and radiotherapy simultaneously were not included.

Data Collection

Data for the study were collected using a face-to-face interview method. Prior to the initiation of drug treatment in patients who arrived at the chemotherapy unit, the investigator explained the purpose of the study to the patients, and written and verbal consents were obtained. "Patient Information Form", "Care Dependency Scale" and "Self-care Behavior Scale According to Self-Care Inability Theory in Patients Receiving Chemotherapy" were used in the data collection. Filling out the forms took approximately 20 min.

Patient Information Form

It was created by investigators based on a literature review.[4,17] The form consisted of a total of 16 questions, including 11 questions on the descriptive characteristics of the patients and 5 questions related to the disease.

Care Dependency Scale

"Care Dependency Scale" was developed by Dijkstra in 1998 to assess the level of care dependency of patients, and a validity and reliability study of the scale in Türkiye was conducted by Yönt et al.[8] in 2010. "Care Dependency Scale" is rated based on a 5-point Likert scoring system and consists of 17 items that include daily life activities. The rating is as follows: 1 "completely dependent", 2 "Quite dependent", 3 "partially dependent", 4 "very little dependent" and 5 "nearly/completely independent". The lowest score on the scale is 17, and the highest score is 85. Higher scores on the scale indicate that the patient is independent in meeting self-care needs, and lower scores indicate that the patient is dependent on others in meeting self-care needs. The Cronbach's alpha value of the scale was 0.91.[8] In this study, the Cronbach's alpha value was 0.97.

Self-Care Behavior Scale According to the Self-Care Inability Theory in Patients Receiving Chemotherapy

Developed by Karadağlı and Alpar[9], the scale is a 5-point Likert scale consisting of 24 items. The scale is a Likert scale based on scoring between 5 "always" and 1 "never". The highest score on the scale is 120, and the lowest score is 24. As the score on the scale increases, the self-care behaviors of individuals increase positively. The scale questions consisted of six factors: individual care, sleep pattern, maintaining respiration, activity and movement, dietary habits, and coping with problems. Cronbach's alpha coefficient of the scale was calculated as 0.88.[9] In this study, Cronbach's alpha reliability coefficient was 0.83 for the entire scale.

Ethical Considerations

Ethics committee approval was obtained from the Ethics Committee for Non-Drug and Medical Device Research of a university hospital (approval number: 2018/1391). Institutional permission was obtained from the hospital where the study was conducted, and permission was obtained from the authors to use the scales. In addition, the participants were informed about the study, and verbal and written consent was obtained.

Table 1. Distribution of description and disease characteristics of patients (n=100)

Features	n	%
Gender		
Woman	26	26.0
Male	74	74.0
Age		
19-38 years old	11	11.0
39-58 years old	48	48.0
59-69 years old	27	27.0
≥70 years old	14	14.0
Marital status		
Single	12	12.0
Married	88	88.0
Educational status		
Elementary school	87	87.0
High school and above	13	13.0
Evaluation of monthly income		
Low	31	31.0
Middle	69	69.0
Working status		
Working	40	40.0
Not working	60	60.0
Place of residence		
Provincial	49	49.0
County/village-town	51	51.0
Health insurance		
Yes	85	85.0
No	15	15.0
Medical diagnosis		
Lung cancer	38	38.0
Stomach cancer	13	13.0
Breast cancer	10	10.0
Colon cancer	7	7.0
Other*	32	32.0
Presence of chronic diseases		
No	61	61.0
Yes	39	39.0
Received cure		
2-4 cycles	63	63.0
5-7 cycles	19	19.0
≥8 cycles	18	18.0
Presence of metastases		
No	37	37.0
Yes	63	63.0

*Other cancers: adenocarcinoma, lymphoma, larynx, bladder, mesenchymal, multiple myeloma, colon, pancreas, cervix, testis.

Statistical Analysis

SPSS 22 software was used to evaluate the data. Number, percentage, mean, and standard deviation were used as descriptive statistics, and variables were found to have a normal distribution according to Skewness and Kurtuosis. The t-test, Mann-Whitney U test, Kruskal-Wallis test, and simple multiple regression analysis were used to compare the mean scores of independent groups in the Self-Care Behavior Scale according to the Self-Care Inability Theory in patients receiving chemotherapy according to demographics and disease characteristics. The relationship between scale scores was analyzed with Pearson correlation analysis. $P<0.05$ level was considered statistically significant.

RESULTS

74% of the patients undergoing chemotherapy were male, 48% were in the age range of 39-58 years, 88% were married, 87% were primary school graduates, 69% had a middle-income level, 60% did not work in any job, 51% lived in county/village-town, 85% had health insurance, 38% were diagnosed with lung cancer, 61% had no other chronic disease, 63% received 2-4 cycles of chemotherapy, and 63% had metastases (Table 1).

Table 2 presents the total mean scores of patients on the scales. Patients scored 68.98±15.89 points in the "Care Dependency Scale" and 69.54±13.20 in "Self-care Behavior Scale According to Self-Care Inability Theory in Patients Receiving Chemotherapy" (Table 2). When examining the relationship between total scale scores, there was a moderate, positive, and highly significant relationship between them ($r=0.46$), ($p<0.001$) (Table 3).

In the primary analysis, it was determined that educational status, presence of chronic disease, and mean score of the Care Dependency Scale had an effect on the total score of "Self-Care Behavior Scale According to Self-Care Inability Theory in Patients Receiving Chemotherapy". In the multiple regression analysis conducted to assess the effect of these three independent variables together, two independent variables, the presence of chronic disease and educational status, were excluded from the regression analysis as they did not have an adequate effect ($p>0.05$). Regression analysis results showing the effect of the "Care Dependency Scale" mean score variable ($p<0.001$) are provided in Table 4. The analysis was started with the multiple regression model, and the analysis was concluded with a simple regression model because there was only one variable left in the model. It was determined that the care dependency mean scores of the patients accounted for the change in the total score of self-care behaviors at a rate of 21% (Table 4).

DISCUSSION

Symptoms that develop because of chemotherapy cause physical, mental, and social problems and affect self-care behaviors.[5] The purpose of this study was to examine the relationship between care dependency and self-care behaviors in patients undergoing chemotherapy. The results are discussed below.

In the study, it was found that patients' dependency on care was moderate (Table 2). We believe that this result is associated with the fact that the mean number of chemotherapy cycles was 2-4 for 63% of the sampled patients who were included in the sample because the presence of symptoms and dependency on care increase as

the number of cycles increases in chemotherapy. Consistent with these study results, Bilgin et al.[18] found in their study with patients hospitalized in the oncology clinic that the patients' care dependency was moderate. In the study by Piredda et al.[15] investigating the perception of care dependency in patients with advanced-stage cancers, care dependency was mostly negatively perceived by patients, but this was seen as a natural phenomenon.

The study found that the patient's self-care behavior was moderate (Table 2). In a similar study conducted by Koç and Şener[19], they found that oncology patients had a moderate level of self-care strength scale mean scores. Furthermore, in a study conducted by Küçükkaya and Erçel[11] in gynecological oncology patients, it was reported that the patients' self-care power was at a moderate level. In a similar study, the self-care power of patients was found to be moderate.[10] Unlike these study results, there are studies reporting high self-care power in cancer patients.[20,21] We believe that this difference was caused by factors such as age, educational status, presence of chronic diseases, number of cycles, and culture of patients in the sample group.

The study found that as the care dependencies of patients decreased, self-care behavior increased (Table 2). There has been no study in the literature comparing care dependency and self-care behaviors in patients undergoing chemotherapy. However, based on this result, it can be concluded that the care needs of patients with fewer complications are fewer, and therefore their self-care is better. Cancer patients are most afraid of losing control and being dependent during chemotherapy.[20] In these patients, the quality of care, self-sufficiency, and quality of life are increased by reducing the dependency on care by meeting basic requirements such as bathing, dressing, nutrition, mobility, and communication.[22,23] In the pilot study by Shams et al.[5] in Pakistan, as a result of the attempts to support self-care behavior in the patient group receiving chemotherapy, it was observed that the physical and mental side effects decreased and the quality of life increased. In studies with chemotherapy patients, it has been noted that providing information and training about side effects before treatment facilitates the management of side effects and increases patient self-care.[4,10,12]

In this study, it was found that self-care behaviors were affected by care dependency at a low rate (21%) (Table 4). However, in the literature, patients who have care dependency are often reported to have problems in providing self-care.[16] Because of prolonged cancer treatment processes in cancer patients and the presence of comorbidities, development of care dependency is highly likely.[15] Patients in this study had medium-level dependencies, which may have led to different results. This may be due to the moderate dependency of patients. In addition, this result may have been affected by Türkiye's sociocultural structure. Taking care of the sick, looking after them, and helping them is part of Turkish culture. We may have come to this conclusion because the patient's relatives met the needs that were not met by the patients.

Table 2. Distribution of scores in "Care Dependency Scale" and "Self-Care Behavior Scale According to the Theory of Self-Care Disability in Patients Receiving Chemotherapy" and the relationship between them (n=100)

Scale and sub-dimensions	Minimum-maximum	$\bar{x} \pm SD$	Cronbach's alpha
"Care Dependency Scale" total score	**26-85**	**68.98±15.89**	**0.97**
"Self-Care Behavior Scale" total score	**38-101**	**69.54±13.20**	**0.83**
1. Individual care	6-19	12.24±2.87	
2. Sleep pattern	5-20	10,65±3.75	
3. Maintaining respiration	4-20	10.86±3.82	
4. Activity and movement	4-18	9.10±2.73	
5. Dietary habits	8-25	17.87±4.70	
6. Coping with problems	3-15	8.82±2.73	

SD: Standard deviation.

Table 3. Relationship between the "Care Dependency Scale" and "Self-Care Behavior Scale According to the Theory of Self-Care Disability in Patients Receiving Chemotherapy" scores of patients (n=100)

	"Self-Care Behavior Scale" total score; (69.54±13.20)	
	r	**p**
"Care Dependency Scale" total score; (68.98±15.89)	0.46	**0.001**

r: Pearson correlation analysis.

Table 4. Effect of independent variables on the "Self-Care Behavior Scale According to the Theory of Self-Care Disability in Patients Receiving Chemotherapy" scores: results of regression analysis (n=100)

Independent variables	B	S.E.	β	T	p	95% CI for (B)	
"Self-Care Behavior Scale" total score							
(Fixed)	43.04	5.26		8,179	0.001	32.60	53.48
Care Dependency Scale Score	0.38	0.07	0.46	5,167	0.001	0.24	0.53

R=0.46, R^2=0.21, F=26.70, p=0.001, Durbin-Watson: 0.64, S.E.: Standard error, CI: Confidence interval.

Study Limitations

The study had the following limitations: People over 65 years of age were included in the study, chemotherapy complications varied from person to person, and there were differences in chemotherapy processes (diagnosis, cancer stage, treatment protocol, and number of chemotherapy sessions).

CONCLUSION

This study found that care dependency and self-care behaviors of patients undergoing chemotherapy were moderate, self-care behaviors increased as care dependency decreased, and self-care behavior was affected by care dependency at a low rate. In line with these results, it is recommended to evaluate care dependency as well as self-care in patients who receive chemotherapy who have a high level of dependency and are supported more with education and monitored, and that studies with larger samples should be conducted and experimental studies should be conducted on this subject.

MAIN POINTS

- Care dependency and self-care behaviors of patients undergoing chemotherapy were moderate.
- The care dependencies of patients decreased and self-care behavior increased.
- Self-care behavior was affected by care dependency at a low rate.

ETHICS

Ethics Committee Approval: Ethics committee approval was obtained from the Ethics Committee for Non-Drug and Medical Device Research of a university hospital (approval number: 2018/1391).

Informed Consent: The participants were informed about the study, and verbal and written consent was obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: N.E.K., S.S., Design: N.E.K., S.S., Supervision: N.E.K., S.S., Fundings: N.E.K., S.S., Materials: N.E.K., S.S., Data Collection or Processing: N.E.K., Analysis or Interpretation: N.E.K., S.S., Literature Search: N.E.K., S.S., Writing: N.E.K., S.S., Critical Review: S.S.

DISCLOSURES

Conflict of Interest: The authors declared that they have no conflict of interest.

Financial Disclosure: The authors declared that this study received no financial support.

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CYPRUS
JOURNAL OF MEDICAL SCIENCES

DOI: 10.4274/cjms.2023.2023-15
Cyprus J Med Sci 2023;8(5):378-384

The Effect of the Frequency of Vaginal Examination During the Birth Process on Birth Comfort and Maternal-Fetal Outcomes

Fatma Kayabaşı[1], Zümrüt Yılar Erkek[2]

[1]Department of Midwifery, Tokat Gaziosmanpaşa University Graduate Education Institute, Tokat, Türkiye
[2]Department of Midwifery, Tokat Gaziosmanpaşa University Faculty of Health Sciences, Tokat, Türkiye

Abstract

BACKGROUND/AIMS: This study was conducted to determine the effect of the frequency of vaginal examination (VE) during labor on pregnant women's birth comfort and maternal-fetal outcomes.

MATERIALS AND METHODS: This descriptive study was conducted with 178 pregnant women who presented to the delivery room of Gaziosmanpaşa University Training, Research, and Application Hospital. A Descriptive Data Form and the Childbirth Comfort Questionnaire (CCQ) were used to collect data.

RESULTS: It was determined that the median value of the number of VEs performed on pregnant women was two times in the latent phase, three times in the active phase, two times in the transitional phase, and eight times during the total labor period. The median value of the latent phase CCQ of pregnant women was significantly higher than that of the transitional phase CCQ ($p<0.05$). It was determined that spontaneous rupture of membranes developed in most pregnant women, maternal and fetal birth complications developed in the remainder, and fetal distress was the most common complication. The number of VEs of pregnant women who developed fetal birth complications with rupture of membranes during the VE was significantly higher ($p<0.001$). A positive, significant correlation was found between the frequency of VE, duration of delivery, and total hospital stay ($p<0.001$).

CONCLUSION: It was found that the frequency of VE was above the World Health Organization criteria but had a negative effect on mothers' birth comfort and maternal and fetal outcomes.

Keywords: Birth comfort, frequency of vaginal examination, maternal-fetal outcomes, normal birth

INTRODUCTION

Vaginal examination (VE) is a significant midwifery intervention that is routinely performed to evaluate the progress of birth, detect risks, and intervene in risks earlier. In midwifery care, a woman in the birth process undergoes at least one VE, which can be repeated every 4 h or more often depending on the course of birth or the requirements of the maternity unit. Because the average birth time is between eight and twelve hours, most women undergo VE at least two or three times during birth.[1,2] A VE that is performed in accordance with the procedures can be a superb compass for the birthing process. When it is not performed carefully, it can be perceived as a negative experience that causes psychological and physical pain as well as disrupts natural body rhythms and leads to psychological consequences. For this reason, VE should be questioned very well in terms of its significance in midwifery practices and its harms and benefits to women and labor.[3-6] Doctors and midwives must

To cite this article: Kayabaşı F, Yılar Erkek Z. The Effect of the Frequency of Vaginal Examination During the Birth Process on Birth Comfort and Maternal-Fetal Outcomes. Cyprus J Med Sci 2023;8(5):378-384

ORCID IDs of the authors: F.K. 0000-0002-6376-0280; Z.Y.E. 0000-0002-0495-9003.

Address for Correspondence: Zümrüt Yılar Erkek
E-mail: zumrut.yilar@gop.edu.tr
ORCID ID: orcid.org/0000-0002-0495-9003

Received: 21.02.2023
Accepted: 28.06.2023

understand women's feelings and experiences during VE and perform it diligently only when necessary, without causing pain and discomfort. Contrary to these evaluations, some studies in the literature have shown that midwives are not careful about the frequency of VE, pain and stress management, provision of information for pregnant women, and their wishes.

The World Health Organization (WHO) recommends that vaginal was examined by the same practitioner every four hours. However, this number varies in clinics depending on the instructions of the institution and the person performing the VE. Although it is a widely used practice, evidence-based outcomes regarding its benefits/harms seem inadequate. According to existing research findings, there is a weak recommendation level and a very low quality of evidence.[7-10]

Childbirth is an unforgettable life experience for women. Having a positive experience of childbirth can strengthen women's self-confidence and satisfaction with the birth. The increase in women's satisfaction with birth is related to their perception of comfort during birth.[11] Comfortable birth may be achieved by overcoming physiological complaints and providing effective care during the birth process.[12,13] Midwives play an important role in providing and maintaining comfort during the birth process. Midwives must perform interventions in accordance with the procedures so that they can increase women's comfort during birth. Therefore, midwives and doctors should understand women's feelings and experiences during VE. When VE is needed to improve their own practices, healthcare professionals should perform the examination with care and minimal discomfort to women by encouraging them and preventing pain. Adhering to the best evidence includes performing VE at birth only when necessary and by the best practitioner possible.[14]

A review of the national literature indicated that there was no study investigating the frequency and requirement of cervical dilatation evaluation with vaginal touch at birth, its effect on maternal-fetal outcomes, and the opinions of women about VE. A systematic review of the Cochrane database showed that there was not much data on the duration of birth, maternal infections, and general views of women Reflecting on these needs, this study was conducted to make an important contribution to the literature in the field of midwifery.

MATERIALS AND METHODS

A descriptive research method was used.

Sample

The universe of the study consisted of pregnant women admitted to the birthing room of Gaziosmanpaşa University Training, Research, and Application Hospital, where the research data were collected between July 10, 2020 and May 10, 2021. No sample calculation was performed in the study, and 178 pregnant women who met the research criteria and volunteered to participate were included in the study between the research dates. According to sampling criteria, pregnant women who had a gestational age of >37 weeks, were expected to have a normal birth, could speak and understand Turkish, had a low-risk or risk-free pregnancy, had a single fetus, were aged between 18 and 35 years, had no presentation-position anomaly, volunteered to participate in the study, and submitted a written consent form were included in the study. Pregnant women who developed complications during the birth process were not included in the study.

Data Collection Tools

A descriptive data form and the Childbirth Comfort Questionnaire (CCQ) were used to collect the study data.

Descriptive Data Form

This form was prepared by the researchers following a review of the literature.[1-4,11,14,15] It consists of three parts.

The first part has 15 questions about the sociodemographic and obstetric characteristics of pregnant women. Socio-demographic data include women's age, education level, occupation, residence, income status, etc., and obstetric data include the gestational week of the woman, number of pregnancie, births, miscarriages, mode of birth, etc.

The second part consists of records about the frequency and time of VE and the number of people who perform it.

The third part comprises data on fetal- maternal outcomes of pregnant women during and after birth. These data include the duration of birth, mode of birth, rupture status of membranes, maternal complications (bleeding, infection, laceration, etc.), fetal complications (meconium aspiration, cephalohematoma, fetal asphyxia, etc.), length of hospital stay, and status of antibiotic use. Data for evaluating the fetal- maternal outcomes of pregnant women during and after birth were collected using hospital records during birth and the early postpartum period (first 2 h postpartum).

Childbirth Comfort Questionnaire

This scale comprises items about the views of pregnant women on their birth comfort during VE. The original name of the scale is "Childbirth Comfort Questionnaire." It was developed by Schuiling in 2003 inspired by Kolcaba's comfort theory. A Turkish validity and reliability study of the scale was conducted by Coskuner Potur et al.[11] in 2015. The Cronbach's alpha coefficient of the scale was found to be 0.75. This coefficient was calculated to be 0.72 in this study. The scale consists of 9 questions and has a five-point Likert-type evaluation structure. Responders are expected to evaluate the items on the scale considering their comfort in the birthing room. Each expression relates to a particular feeling of comfort (relaxation, relief, or superiority) and its dimensions (physical, environmental, psychospiritual, or social). Scores on the scale range between 9 and 45. High scores on the scale show an increase in comfort levels, whereas low scores show a decrease in the level of comfort.[11]

Implementation of the Study

The study data were collected using the face-to-face interview technique after the researcher informed the pregnant women about the purpose of the research and the questionnaire. The first and second parts of the questionnaire form were applied by the researcher after the written and verbal consent of pregnant women was obtained during their admission to the maternity ward. The data about the frequency and time of VE and the person who performed it, which were in the second part of the questionnaire, were collected using the records of the "Birth and Labor Form" that was used for the monitoring of pregnant women during birth in the birthing room. The data of the third part of the questionnaire were collected from the hospital records by the researchers during birth and early postpartum (first 2 h postpartum) The CCQ was applied at the beginning of the latent phase of birth (1-3 cm cervical dilatation)[11,16] and during the transition phase of birth (8-10

cm cervical dilatation).[17] The scale was applied between contractions when the pregnant woman did not experience pain. To determine the functionality of the data collection forms, they were applied to the sample group after they had been piloted on 10 pregnant women who met the research criteria.

Statistical Analysis

Study data were analyzed using the SPSS for Windows 25.0 software package. Numbers, percentages, and minimum, maximum, median, mean, and standard deviation (SD) values were used in the analysis of descriptive data. The Kolmogorov-Smirnov test was used to determine the normality of data, and independent samples t-test and one-way analysis of variance (ANOVA) were used to evaluate these data. Mean and SD values were presented for data showing a normal distribution, and median, minimum, and maximum values were presented for data with non-normal distribution. Mann-Whitney U, Kruskal-Wallis variance, and Wilcoxon analyses were used to evaluate data that did not show a normal distribution. The chi-square test was used to determine the relationship between qualitative data, and Spearman correlation analysis was used to examine the relationship between two variables. In statistical tests, the confidence interval was taken as 95% and the significance level was taken as $p<0.05$.

RESULTS

Table 1 shows the distribution of some sociodemographic characteristics of pregnant women. Table 2 shows the distribution of people who underwent VEs according to phases during the birth process and the count and total count of VEs. As shown in the table, 1,185 (77.1%) VEs were performed by midwives and 351 (22.9%) by physicians during the birth process. Examination of the frequency of VEs during birth indicated that the median value of the count of VEs was two in the latent phase of birth, three in the active phase, and two in the transition phase. The median value of the total count of VEs performed during the birth process was eight. In addition, it was determined that VE was performed 421 times in the latent phase, 679 times in the active phase, and 436 times in the transition phase, and a total of 1,536 VEs were performed.

Table 3 shows a comparison of the median values of pregnant women's scores on the childbirth comfort scale at the beginning of the latent phase and the end of the active phase. Accordingly, it was determined that the median value of CCQ scores at the beginning of the latent phase (median: 32) was significantly higher than that of CCQ scores at the transition phase (median: 30) ($p<0.05$).

Table 4 shows a comparison of the frequency of VEs and maternal- fetal birth outcomes in pregnant women. Accordingly, the median value (median: 10) of the count of VEs during which a membrane rupture occurred was statistically significantly higher than the median value (median: 7) of the count of VEs during which a spontaneous membrane rupture occurred ($p<0.001$). Likewise, it was determined that the median value of the count of VEs (median: 10) performed on those who developed fetal birth complications was statistically significantly higher than the median value of the count of VEs (median: 7) performed on those who did not ($p<0.001$).

Table 5 presents the relationship between the frequency of VE and CCQ scores (transition phase), length of hospital stay during birth, and newborn Apgar scores. A significant positive relationship was found between the frequency of VE and the duration of birth and total hospital stay. Accordingly, it was determined that as the number of VEs increased, the duration of birth increased ($r=0.798$; $p<0.001$) and the total length of hospital stay increased ($r=0.479$; $p<0.001$), as well. However, there was no statistically significant relationship ($p>0.05$) between the number of VEs and CCQ scores (transition phase), length of postpartum hospital stay, and Apgar scores.

Table 1. Distribution of some socio-demographic characteristics of pregnant women (n=178)

Variables	Median (minimum-maximum)	
Age (year)	25.97±4.24	
Length of marriage (year)	4.24±3.69	
	n	**%**
Age groups		
20-24	72	40.5
25-29	67	37.6
30-34	31	17.4
35-39	8	4.5
Level of education		
Primary school	76	42.7
High school	48	27.0
University and higher	54	30.3
Working status		
Working in a paid job	35	19.7
Not working in a paid job	143	80.3
Marital status		
Married	169	94.9
Single	9	5.1
Education level of the spouse		
Primary school	67	37.7
High school	51	28.7
University and higher	60	33.6
Working status of the spouse		
Working in a paid job	157	88.2
Not working in a paid job	21	11.8
Health insurance		
Yes	28	15.7
No	150	84.3
Place of residence		
Province	82	46.1
County	61	34.3
Town	10	5.6
Village	25	14.0
Evaluation of the economic status		
Income < expenses	47	26.4
Income = expenses	112	62.9
Income > expenses	19	10.7
Family type		
The core family	139	78.1
Extended family	39	21.9

Table 2. Distribution of persons who underwent vaginal examinations and the number of VEs performed according to phases in the birth process

Phases	The person performing VE	Total, n (%)	Median (min.-max.)	Mean ± SD
Latent phase, (n=421)	Physician	159 (37.8)	1 (1-3)	1.22±0.49
	Midwife	262 (62.2)	2 (1-8)	2.28±1.59
Active phase (n=679)	Physician	115 (16.9)	1 (1-9)	1.67±1.43
	Midwife	564 (83.1)	3 (1-12)	3.22±1.97
Transition phase, (n=436)	Physician	77 (17.7)	1 (1-3)	1.49±0.72
	Midwife	359 (82.3)	2 (1-9)	2.23±1.23
Total, (n=1536)	Physician	351 (22.9)	1 (1-9)	1.39±0.90
	Midwife	1185 (77.1)	2 (1-12)	2.60±1.68
	Total count of VEs (1536)		**Median (min.-max.)**	**Mean ± SD**
Latent phase	421		2 (1-9)	2.37±1.69
Active phase	679		3 (1-13)	3.84±2.29
Transition phase	436		2 (1-9)	2.48±1.20
Total	1536		8 (4-16)	8.63±2.97

min.: Minimum, max.: Maximum, SD: Standard deviation, VE: Vaginal examination.

Table 3. Distribution of the median values of pregnant women's scores on the CCQ

CCQ application	n	Median (minimum-maximum)	Z	p
Latent phase (1-3 cm)	178	32 (22-41)	-7.450	0.001
Transition phase (8-10 cm)	178	30 (20-39)		

Z: Wilcoxon test, CCQ: Childbirth Comfort Questionnaire.

Table 4. Comparison of the frequency of VEs and postpartum maternal and fetal outcomes (n=178)

	n	Frequency of VEs median (min.-max.)	Test and p-value
Episiotomy application			
Yes	122	8 (4-16)	KW=5.490 p=0.064
No	34	7 (4-16)	
Laceration	22	7.50 (4-16)	
Rupture of the membranes			
Spontaneous	118	7 (4-16)	U=2396.500 **p=0.001**
During VE	60	10 (5-16)	
Maternal birth complications			
Yes	12	9.50 (5-13)	U=796.500 p=0.244
No	166	8 (4-16)	
Fetal birth complications			
Yes	38	10 (4-16)	U=1885.500 **p=0.006**
No	140	7 (4-16)	

KW: Kruskal-Wallis test; U: Mann-Whitney U test, CCQ: Childbirth Comfort Questionnaire, VE: Vaginal examination.

Table 5. Relationship between the frequency of VE performed on pregnant women and their CCQ scores (transition phase), duration of birth, length of hospital stay, and newborn Apgar scores

Variable		CCQ scores (transition phase)	Duration of birth	Length of postpartum hospital stay	Total length of hospital stay	Apgar score (1st minute)	Apgar score (5th minute)
Frequency of the VE	**r**	-0.006	0.798*	-0.099	0.479*	-0.008	-0.005
	p	0.931	**0.001**	0.189	**0.001**	0.911	0.943

*r= Spearman correlation analysis, CCQ: Childbirth Comfort Questionnaire, VE: Vaginal examination.

DISCUSSION

This study was conducted to determine the effect of the frequency of VE performed during birth on birth comfort and maternal and fetal outcomes. The findings of this study were discussed in line with the results of similar studies in the literature.

The WHO and NICE recommend that the VE of a pregnant woman should be performed by the same health personnel during birth.[18,19] In this study, VEs were performed by two practitioners, including a midwife and a physician, and mostly by midwives (Table 2). This result shows that normal births are managed by midwives in the hospital where the research was conducted because most women in our country receive reproductive health services such as pregnancy, childbirth, and puerperium from a physician. Only 28.6% of births in health institutions and 15.9% of births in other places are performed by midwives.[20] There are findings in the literature similar to ours. For example, Küçük and Çalık[21] reported that pregnant women were mostly evaluated by two to three different healthcare professionals. Hatamleh et al.[22] stated that more than half of the women in their study were examined by both a midwife and a doctor. EL-Moniem and Mohamady[2] stated that as the duration of birth increased, both the number of examinations and the number of staff who performed them increased. Hassan et al.[14] reported that only 12% of pregnant women were examined by one person and that 41% were examined by "many" healthcare professionals during birth. It is thought that many VEs cause inconsistency between findings on the progression of birth and that women lose their confidence in healthcare providers. Tuffnell et al.[23] argued that an inaccuracy rate of more than 50% in cervical measurements increased cesarean section rates.[1] Therefore, it is recommended that examinations should be performed as carefully as possible, when necessary, and by the same person. VE is an extremely necessary application for monitoring the progress of birth and detecting and intervening in high-risk situations earlier. However, frequent VEs and lack of care during this application cause pain, discomfort, anxiety, and feelings, such as fear, shame, guilt, and powerlessness, and decrease the satisfaction of women with childbirth.[3-6] It is recommended that VEs should be routinely performed at fixed 4-h intervals in the first stage of birth.[18,24] The duration of birth is expected to be last 6-12 h in the first stage and 7-15 h in total.[25,26] Considering the duration of birth and the frequency of VE that is deemed appropriate, it is expected that VEs will be performed two to three times in the first stage and four to six times in total. The median value of the birth time was found to be 150 min in the latent phase in the first stage, 180 min in the active phase, and 30 min in the transition phase, with the total time being 685 min. According to these data, the count of VEs performed was higher than that suggested by the WHO. A review of the relevant literature indicated that the average number of VEs during birth varied between 2.8 and 5.6 (1-15 times).[2,14,22,27-30] Shepherd and Cheyne[30] found that approximately half of the women had three or more VEs during birth, and almost 70% of them had more VEs than expected when the WHO every four hours criterion was considered. They stated that data, as in this study, were obtained from the records of the midwives using the routine practice hours recorded in the case files. Similarly, EL-Moniem and Mohamady[2] reported that vaginal was examined very frequently.[5-12] Hassan et al.[14] found the average number of VEs performed during childbirth to be 4.24 and stated that approximately 36% of women said that they had a "potentially high" number of VEs during childbirth. Stuart emphasized that there was little research evidence to determine the average rate of vaginal exams in normal birth or what it really needed to be.[30] The results of the study by Bergstrom et al.[31] were quite remarkable. They reported that the number of VEs performed during birth was between 2 and 17 and that women were given a VE after each contraction. On the other hand, Küçük and Çalık[21] determined that VE was mostly performed 1 to 4 times and that an average of 4.05±1.721 VEs (1-12 times) was performed during birth. The frequency of VE was higher than the count recommended by international organizations in this study, which is thought to be because women often presented to the birthing service in the latent phase and therefore the time spent in birth was prolonged. In addition, more than half of the pregnant women (50.6%) were found to give birth for the first time, which can be counted among the factors that may cause this situation because the duration of birth differs between primiparous and multiparous pregnant women. While the first phase lasts for 8-12 h in primiparas, this period decreases to 6-8 h in multiparas.[32]

It is crucial that midwifery practices support birth comfort. It is thought that especially positive birth experiences can break the negative thoughts and prejudices of women about birth and help gain positive opinions on normal birth. Therefore, birth comfort should be considered during the birth process. It was determined that the median value of pregnant women's scores on the CCQ at the beginning of the latent phase was significantly higher than the median value of their scores in the transition phase (Table 5). In the literature, it is stated that non-pharmacological methods applied to relieve pregnant women's pain during birth increase birth comfort.[17,33,34] In this study, nothing was applied to reduce the pain experienced by pregnant women. Accordingly, it is thought that there was no change in the pregnant women's comfort related to the frequency of VE. Although the count of VEs was higher than the count recommended by the WHO, it was a pleasing finding that pregnant women's birth comfort was above the average (Table 3). This can be attributed to the high-quality care provided by midwives to pregnant women in the hospital environment during birth. Midwifery practices, which are performed in physical, sociocultural, psychospiritual, and environmental dimensions and are especially aimed at relieving pregnant women's pain, increase comfort by providing relief and relaxation and helping overcome their problems.[11,17]

Although there is no research providing evidence on the relationship between the frequency of VE performed during childbirth and maternal and neonatal infection, it has been stated that VEs performed more frequently than four-hour intervals may increase the risk of infection for both the mother and newborn.[10] In addition, frequent VEs can cause genital puerperal infection, postop-endomyometritis, and chorioamnionitis.[3] As a result of this study, it was determined that although the count of VEs was high, this situation did not cause infection in either the mother or the newborn. In the study of Küçük and Çalık[21], similar to the results of this study, it was determined that the frequency of VE was within normal standards and that it did not cause any infection in the mother and newborn. The WHO recommends the rate of episiotomy to be 20% at most.[21] In this study, it was determined that episiotomy was performed in most pregnant women and that this situation was not related to the frequency of VE. In studies conducted in our country, the rates of episiotomy vary between 50% and 75%.[35] This difference can be attributed to the fact that hospitals do not meet the criteria for mother-friendly hospitals and that the majority of pregnant women in the study were nulliparous. In the study, it was determined that membrane rupture developed spontaneously in most pregnant

women, maternal and fetal birth complications developed in very few of them, and that most complications were fetal distress.

Although the frequency of VE performed on pregnant women was high in the study, it was observed that this situation did not adversely affect postpartum maternal and fetal outcomes to a large extent. This pleasing situation can be attributed to the skills of practitioners and the fact that VEs were carefully performed in the hospital when necessary, with minimal discomfort to pregnant women, and by encouraging them and preventing them from suffering pain. On the other hand, in the present study, it was determined that the count of VEs in pregnant women who developed membrane rupture and fetal birth complications during VE was significantly higher ($p<0.001$) (Table 4). When the application of vaginal touch every 2 h and every 4 h was compared, no difference was found in terms of birth time, epidural analgesia administration, cesarean section, spontaneous vaginal birth, and surgical vaginal birth.[7-9] In a review in which four studies were analyzed, it was reported that VEs administered every 4 h increased the number of vaginal deliveries, had little or no effect on chorioamnionitis, neonatal infection, or admission rates to the neonatal intensive care unit, and that outcomes such as positive birth experience or maternal pain had not been evaluated at all.[36] The findings of this study are consistent with those in the literature. The frequency of VE that is seven times and above raises concerns about the increased risk of infection, and it has been reported that it is related to chorioamnionitis, which occurs in 8-12 women per 1000 births.[4,14] In another study, it was stated that five or more VEs during delivery were associated with an increased risk of intrapartum and peripartum febrile morbidity and severe perineal trauma and that the increase in the number of staff performing VE was a risk factor for the development of neonatal infection.[37]

A significant positive relationship was found between the frequency of VE and the duration of birth and total hospital stay. Accordingly, it was determined that as the number of VEs increased, the duration of birth and the total length of hospital stay also increased (Table 5). This was an expected result. The prolongation of the birth period also increases the frequency of VEs performed during the follow-up of birth.

CONCLUSION

In conclusion, VE was applied to pregnant women eight times by two practitioners, including midwives and physicians, mostly by midwives, during birth in the present study. This frequency is above the standards. It was observed that the frequency of VE did not affect birth comfort, maternal and fetal birth complications developed in a few pregnant women, and that the majority of these complications were fetal distress. It was determined that the count of VEs in pregnant women who developed fetal birth complications due to rupture of membranes during VE was high and that the length of hospital stay was prolonged as the number of VEs increased. In line with these results, it is recommended that VE performed during birth should be performed only when necessary or routinely every 4 h and, if possible, by the same health personnel, and that the study should be repeated in a larger population.

MAIN POINTS

- Vaginal examinations during birth should be applied in accordance with the criteria of the World Health Organization.
- The frequency of vaginal examination does not affect birth comfort.
- The high number of vaginal examinations may adversely affect maternal (rupture of membranes, prolonged hospital stay) and fetal (fetal distress) outcomes.

Acknowledgments: This study was published as a Master's thesis. We would like to thank all pregnant women who participated in this study.

ETHICS

Ethics Committee Approval: This study was approved by the University of Health Sciences Türkiye, Gaziosmanpaşa University Faculty of Medicine Non-Interventional Ethics Committee (approval number: 83116968/437-20 KAEK-061).

Informed Consent: Verbal and written consent was obtained from all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: F.K., Z.Y.E., Concept: F.K., Z.Y.E., Design: F.K., Z.Y.E., Data Collection and/or Processing: F.K., Z.Y.E., Analysis and/or Interpretation: F.K., Z.Y.E., Literature Search: F.K., Z.Y.E., Writing: F.K., Z.Y.E.

DISCLOSURES

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

Financial Disclosure: The authors declared that this study had received no financial support.

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RESEARCH ARTICLE

CYPRUS
JOURNAL OF MEDICAL SCIENCES

DOI: 10.4274/cjms.2023.2023-84
Cyprus J Med Sci 2023;8(5):385-389

Research on the Relationship Between Breast Cancer and General Female Deaths Related to the Disease

İsmail Özsan[1], Kadir Yılmaz[2]

[1]Department of General Surgery, Okan University Faculty of Medicine, İstanbul, Türkiye
[2]Department of Statistics, İstanbul Commerce University Institute of Science, İstanbul, Türkiye

Abstract

BACKGROUND/AIMS: This research aimed to examine the relationship of breast cancer (BC) with general female deaths related to the disease.

MATERIALS AND METHODS: In the research, data collected from the World Health Organization-International Agency for Research on Cancer (IARC), the World Bank, and the Turkish Ministry of Health were used for 1998-2017 period. BC diagnostic incidence, all female mortality, and disease female mortality parameters were used as research parameters with controlling variables such as number of physicians and private-government health expenditures.

RESULTS: BC diagnosis incidence was negatively correlated with female mortality ($r=-0.988$; $p<0.01$), disease related female mortality ($r=-0.990$; $p<0.01$) and private health expenditure ($r=-0.815$; $p<0.01$). BC diagnosis incidence was positively correlated with physicians ($r=0.992$; $p<0.01$) and government health expenditure ($r=0.815$; $p<0.01$). Year-controlled partial correlation analysis results showed that BC diagnosis incidence was positively correlated with disease female mortality ($r=0.473$; $p<0.05$) and private health expenditure ($r=0.551$; $p<0.05$) whereas BC diagnosis incidence was negatively correlated with physicians ($r=-0.681$; $p<0.05$) and government health expenditure ($r=-0.551$; $p<0.05$). The effects of all female mortality ($B=-243.37$; $p<0.05$), disease female mortality ($B=3160.37$; $p<0.01$), and number of physicians ($B=-59611.22$; $p<0.01$) were significant at the multivariate level.

CONCLUSION: With the increase in the diagnosis of BC, there is a decrease in female deaths in the society, while helping to decrease female deaths due to other diseases. In addition to the diagnosis of BC, it is possible to follow-up for other conditions with a high mortality level.

Keywords: Breast cancer, diagnosis, mortality

INTRODUCTION

Breast cancer (BC) is one of the leading causes of cancer-related deaths in women, and it causes many women to die worldwide every year.[1-3] Although there are still studies on the risk causes of the disease, the risks of other cancer types, especially the family, are also valid for BC. Today, many methods have been developed for the early treatment of BC, including chemotherapy, surgical removal of the mass, and breast prosthesis. Although BC has a high mortality rate, early diagnosis is vital in BC and significantly reduces mortality rates.[4-7] However, early diagnosis requires not only individual awareness but also social and public awareness.

Female deaths have a different place in society than deaths in general. Due to patriarchal structures or social norms, women have more difficulty accessing health services than men.[8-10] As a result, diseases in women have a higher mortality value and can negatively affect both public health and the health and quality of life of individuals. In the process that starts with the mother's qualifications of the woman and birth and continues with the raising of the child, mothers are more prone to diseases, both psychologically and physically.[11-14]

To cite this article: Özsan İ, Yılmaz K. Research on the Relationship Between Breast Cancer and General Female Deaths Related to the Disease. Cyprus J Med Sci 2023;8(5):385-389

ORCID IDs of the authors: İ.Ö. 0000-0001-7570-4174; K.Y. 0000-0003-2568-3015.

Address for Correspondence: İsmail Özsan
E-mail: dr_ozsanozsan@yahoo.com
ORCID ID: orcid.org/0000-0001-7570-4174

Received: 27.08.2023
Accepted: 13.10.2023

Local and international struggle is important in monitoring the statistics of women's deaths and public health throughout the world. Therefore, many international institutions, especially organizations such as the World Health Organization (WHO) and World Bank (WB), organize studies to prevent female deaths. However, despite these studies, it is necessary to investigate whether sufficient results have been obtained. In the literature research conducted for this purpose, it is seen that this subject has not been adequately examined. The fact that the WHO-International Agency for Research on Cancer (IARC) data were provided until 2012, the data of the Ministry of Health of Türkiye until 2017, and the fact that they do not distinguish between mortality and incidence confirms this. Therefore, the relationship between BC-related deaths and other female deaths needs to be elucidated. In this study, we aimed to examine the relationship of BC with general female deaths related to the disease.

MATERIALS AND METHODS

In the research, a dataset collected from the WHO-IARC, the WB, and the Turkish Ministry of Health was used for 1998-2017 period. Cancer incidence values were collected from the WHO-IARC from 1998 to 2012 and the Ministry of Health Cancer Reports from 2013 to 2017. The most recent report of the Ministry of Health on cancer was published in 2021. In this report, and in the National Statistics Agency, the latest BC deaths are given until 2017. In the IARC reports compiled by WHO for the whole world, incidence data were given for Türkiye only between 1998 and 2012.

Dependent Variable

BC diagnosis incidence.

Independent Variables

Mortality rate, adult, female (per 1,000 female adult).

Mortality from CVD, cancer, diabetes, or CRD between the exact ages of 30 and 70 years, female (%).

Controlling Variables

Physicians (per 1,000 people).

Domestic private health expenditure (% of current health expenditure).

Domestic general government health expenditure (% of current health expenditure).

Ethical Concern

Because the research is based on public data and excludes private information, no ethical approval or informed consent is needed. Data provided by the WHO-IARC, the WB, and the Turkish Ministry of Health were open to the public, and no written or any permission, registration is needed.

Statistical Analysis

Research parameters are described with means and standard deviations with ranges. Since the data set is under 30 years, non-parametric tests were used. Spearman's rho correlation analysis and year-controlled partial correlation analysis were used for the correlation analysis. Since all regression linearizations include deviations,[15] the Generalized Linear Model (Logit) was used for multivariate analysis. SPSS 25.0 for Windows was used at 95% confidence interval and 0.05 significance level.

RESULTS

The minimum BC incidence was 707 and the maximum value was 11,851 with 2506.40±4118.58 mean value. The mean female mortality was 68.02±11.09, and the mean disease-related female mortality was 12.77±1.39 (Table 1).

According to Spearman's rho correlation analysis, BC diagnosis incidence was negatively correlated with female mortality ($r=-0.988$; $p<0.01$), disease related female mortality ($r=-0.990$; $p<0.01$) and private health expenditure ($r=-0.815$; $p<0.01$). BC diagnosis incidence was positively correlated with physicians ($r=0.992$; $p<0.01$) and government health expenditure ($r=0.815$; $p<0.01$) (Table 2).

Table 1. Minimum, maximum values, means, and standard deviations of the research parameters

	Minimum	Maximum	Mean	SD
BC diagnostic incidence	707.00	11851.00	3506.40	4118.58
All female mortality (per 1,000 female adult)	51.58	93.73	68.02	11.09
Disease female mortality (female, %)	11.00	15.20	12.77	1.39
Physicians (per 1,000 people)	1.22	1.85	1.58	0.19
Private health expenditure (% of current health expenditure)	19.50	38.32	27.49	6.38
Government health expenditure (% of current health expenditure)	61.68	80.50	72.51	6.38

BC: Breast cancer, SD: Standard deviation.

Table 2. Spearman's rho and year-controlled correlation analysis results for the relationship between BC mortality and research parameters

	Spearman's rho	Year-controlled partial
All female mortality (per 1,000 female adult)	-0.988**	0.013
Disease female mortality (female %)	-0.990**	0.473*
Physicians (per 1,000 people)	0.992**	-0.681**
Private health expenditure (% of current health expenditure)	-0.815**	0.551*
Government health expenditure (% of current health expenditure)	0.815**	-0.551*

*p<0.05, **p<0.01, BC: Breast cancer.

Year controlled partial correlation analysis results showed that BC diagnosis incidence was positively correlated with disease female mortality (r=0.473; p<0.05) and private health expenditure (r=0.551; p<0.05) whereas BC diagnosis incidence was negatively correlated with physicians (r=-0.681; p<0.05) and government health expenditure (r=-0.551; p<0.05) (Table 2).

Although the correlation of private health expenditure with BC diagnosis incidence was significant at the univariate level (p<0.01), its effect on BC diagnosis incidence was insignificant at the multivariate level (p>0.05). The effects of all female mortality (B=-243.37; p<0.05), disease female mortality (B=3160.37; p<0.01), and number of physicians (B=-59611.22; p<0.01) were significant at the multivariate level (Table 3).

The BC incidence rate has been increasing between 1998 and 2017. However, there was a shift in 2013 (Figure 1).

DISCUSSION

Female mortality is an issue that is emphasized all over the world, and research to be carried out by many international organizations is supported because health is seen as a global public good.[16,17] Among female deaths, BC is important both because it is specific to women and because it is easier to treat with early diagnosis. However, official data, statistical shares, and literature studies indicate that there is not enough work on this subject[18,19]. This study aimed to examine the relationship of BC with general female deaths and female deaths related to the disease.

Studies on the incidence and mortality level of BC are in an increasing trend because of the reflection of communication and health services all over the world[20-25]. In fact, it is still unclear whether this increase is due to the increase in the incidence of the disease itself or to the increase in the possibilities of examination and diagnosis. The general opinion on this subject shows that with the increase in diagnostic possibilities, unexplained deaths have decreased gradually in the past, and the diagnosis of cancer types, especially BC, is made more frequently. In the data compiled for Türkiye, which we examined in the study, it is seen that the incidence of BC has increased over time. Especially since 2013, there has been a more serious increase.

At this point, it should be noted that although BC is important in terms of cancer types and mortality in women, it is not sufficiently followed up by the WHO and the Ministry of Health. WHO has not followed the data since 2013, and the Ministry of Health does not follow or share the data after 2017 or before 2013. These disruptions experienced according to other cancer types or WHO data from other countries show that both institutions are not sufficiently effective and successful in data sharing.

According to the results of the correlation analysis, there was a statistically significant and negative relationship between all female deaths, female deaths due to disease, and incidence of BC diagnosis. This shows that as the diagnosis rate increases, the number of deaths decreases. In fact, the success rate in treatment and early diagnosis is increasing day by day. On the other hand, the year-controlled analysis shows that this situation is not significant with the temporal effect.

Table 3. Generalized linear model (Logit) for BC incidence and research parameters

Parameter	B	S.E.	95% CI wald		Hypothesis test		
			Lower	Upper	Wald chi-square	df	p
(Intercept)	-5553566.51	881820.11	-7281902.17	-3825230.86	39.66	1	0.001
All female mortality rates	-243.37	112.59	-464.05	-22.69	4.67	1	0.031
Disease female mortality	3160.86	765.54	1660.43	4661.29	17.05	1	0.001
Physicians	-59611.22	14748.35	-88517.46	-30704.97	16.34	1	0.001
Private health expenditure	73.85	134.94	-190.62	338.33	0.30	1	0.584
Government health expenditure	0	.	.	.	.	.	.
Year	2802.08	447.58	1924.83	3679.33	39.19	1	0.001
(Scale)	1579698.79	499544.62	849964.37	2935944.54			

BC: Breast cancer, S.E.: Standard error, CI: Confidence interval.

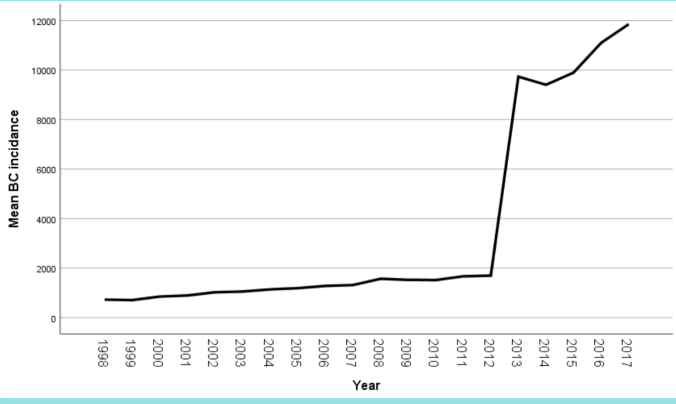

Figure 1. BC diagnostic incidence according to year.

BC: Breast cancer.

There is a statistically significant relationship between disease-related deaths and the prevalence of BC diagnosis. Therefore, rather than the effect of population increases, it should be stated that newly diagnosed diseases also have an effect on this relationship.

In the study, the number of physicians (per 1,000 people) and the effect of private and public health expenditures was examined as a control variable. Correlation analysis results show that private health expenditures have a reducing effect on BC diagnostic incidence, whereas government health expenditures play an increasing role. Making private health expenditures mostly for cosmetic, esthetic, and sanitation reasons may be effective in achieving this result. government spending on health is more planned, aimed at reducing deaths from BC and increasing early detection.

According to the results of the multivariate GLM logit model, the decreasing effect of all female deaths on BC diagnosis prevalence and the increasing effect of female deaths due to disease are significant. At this point, it is possible to state that the increase in women's deaths draws attention to women's deaths in the social sense, and BC is one of the most striking issues. It is possible to explain the inverse proportion of female deaths caused by other diseases as a decrease in attention to BC-related deaths when looking at other fields.

Study Limitations

The most important limitation of this research is that although BC is an important mortality and cancer type, data sharing in this area is very limited. Both the WHO and the Ministry of Health show serious deficiencies in sharing these data. Another important limitation of this study is that clinical studies in this area are quite limited and, more generally, population-based studies are not conducted.

Contribution to the Literature

The most important contribution of this research to the literature is the examination of a subject that is important to mortality in women and is common among cancer types. Another important contribution of the research is that it aims to examine and reveal women's deaths in a holistic framework by bringing a different perspective to the studies conducted in this field from the past to the present. In this respect, this study is important in terms of reducing the death rate of women, increasing the level of public health, and improving our understanding of BC.

CONCLUSION

As a result, with the increase in the diagnosis of BC, there is a decrease in female deaths in the society, while helping to decrease female deaths due to other diseases. In addition to the diagnosis of BC, it is possible to follow-up for other conditions with a high mortality level.

Although BC-related deaths and prevalence are serious problems, both official studies and international solidarity and data sharing on this subject are quite inadequate. Therefore, it is necessary to increase cooperation between institutions with larger budgets and to carry out larger-scale screening and diagnostic studies.

MAIN POINTS

- Breast cancer is an important global public health problem for females.
- Increase in the diagnosis of breast cancer decreases female deaths.
- Undiagnosed female deaths may be related to undiagnosed breast cancer.
- Female mortality reasons may be more understandable with the diagnosis of breast cancer.
- The number of physicians has a positive effect on the diagnosis of breast cancer.

ETHICS

Ethics Committee Approval: Because the research is based on public data and excludes private information, no ethical approval or informed consent is needed. Data provided by the WHO-IARC, the WB, and the Turkish Ministry of Health were open to the public, and no written or any permission, registration is needed.

Informed Consent: It wasn't obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: İ.Ö., Concept: İ.Ö., Design: İ.Ö., Data Collection or Processing: İ.Ö., Analysis or Interpretation: K.Y., Literature Search: İ.Ö., Writing: İ.Ö.

Conflict of Interest: The authors declared that they have no conflict of interest.

Financial Disclosure: The authors declared that this study received no financial support.

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CYPRUS
JOURNAL OF MEDICAL SCIENCES

DOI: 10.4274/cjms.2023.2023-108
Cyprus J Med Sci 2023;8(5):390-396

Protective Effects of *Citrus* Flavonoid Hesperidin in Enterocytes After Induction with TNF-α and IFN-ɣ Which Mimic the COVID-19 Disease

Uğur Özgürbüz[1], Seda Vatansever[2], Eda Becer[3], Hilal Kabadayı Ensarioğlu[2], Damla Akoğulları Çelik[2]

[1]Clinic of Anesthesiology and Reanimation, İzmir Atatürk Research and Training Hospital, İzmir, Türkiye
[2]Department of Histology and Embryology, Manisa Celal Bayar University Faculty of Medicine, Manisa, Türkiye
[3]Eastern Mediterranean University Faculty of Pharmacy, Gazimağusa, Cyprus

Abstract

BACKGROUND/AIMS: Coronavirus disease (COVID-19) is caused by a virus and exhibits various symptoms such as cough, fever, and chills. Flavonoids have a potential inhibitory effect on coronaviruses. In this study, we determined the effects of hesperidin on enterocyte cells (IEC) after tumor necrosis factor (TNF)-α and interferon (IFN)-γ induction which mimics the severe acute respiratory therapy-coronavirus-2 (SARS-CoV-2) infection.

MATERIALS AND METHODS: The IEC-6 were treated with 50 ng/mL of TNF-α and 100 ng/mL of IFN-ɣ for 48 h to mimic inflammatory shock similar to COVID-19 disease. IEC-6 cells were cultured as control, COVID-19 disease mimic, hesperidin prophylactic, or treated groups. The cytotoxicity effect of hesperidin was analyzed using an MTT assay. Serum levels of TNF-α and interleukin (IL)8 were evaluated using ELISA. The distributions of TNF-α, IFN-ɣ, IL-1ß, Insulin-like growth factor-I, and caspase-3 were analyzed by indirect immunoperoxidase staining.

RESULTS: Both TNF-α and IL8 levels were higher in TNF-α and IFN-ɣ induction of enterocyte culture medium than in the control. Lesser immunoreactivity of TNF-α was detected in the treatment group which hesperidin applicate after TNF-α and IFN-ɣ combination. While IL-1 immunoreactivity was similar in both the hesperidin prophylactic and treatment groups, lesser immunoreactivity of TNF-α was observed in the hesperidin treatment group. Both IFN-ɣ and vascular endothelial growth factor A immunoreactivities were also decreased in the hesperidin treatment group.

CONCLUSION: We found that hesperidin had anti-inflammatory and cell protection effects in IEC after TNF-α and IFN-γ induction which mimics the model of SARS-CoV-2 infection. Therefore, hesperidin could be used to reduce gastrointestinal system symptoms in COVID-19 disease.

Keywords: COVID-19 disease, hesperidin, enterocytes, gastrointestinal tract, immunregulatory

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected millions of people worldwide, and its variant remains at risk of infection. There has been a lot of research against diagnostic kits for viruses, eradication and inactivation of them, control of the pandemic, and prevention of cellular damage in all organs. Because of the high mortality rate and easy spread of the viruses, there is still need for new treatment strategies to prevent the cells from attacking SARS-CoV-2.[1]

Angiotensin-converting enzyme 2 (ACE2) is the functional receptor of SARS-CoV-2, and its receptors have been demonstrated on alveolar epithelial cells, which are responsible for acute respiratory distress syndrome.[1] The intestinal epithelial cells, especially the enterocytes of

To cite this article: Özgürbüz U, Vatansever S, Becer E, Kabadayı Ensarioğlu H, Akoğulları Çelik D. Protective Effects of Citrus Flavonoid Hesperidin in Enterocytes After Induction with TNF-α and IFN-ɣ Which Mimic the COVID-19 Disease. Cyprus J Med Sci 2023;8(5):390-396

ORCID IDs of the authors: U.Ö. 0000-0002-8268-464X; S.V. 000-0002-7415-9618; E.B. 0000-0002-2378-128X; H.K.E. 0000-0001-7429-1478; D.A.Ç. 0000-0001-9778-8532

Address for Correspondence: Eda Becer
E-mail: edabecer@yahoo.com
ORCID ID: orcid.org/0000-0002-2378-128X

Received: 03.10.2023
Accepted: 24.10.2023

the small intestine, also express ACE2 receptors. Rather than respiratory symptoms, coronavirus disease 2019 (COVID-19) patients also had gastrointestinal symptoms after 4,243 patients' meta-analysis.[2] ACE2 expression was more frequently observed in the ileum and colon than in the lung and was mainly expressed in the absorptive enterocytes of the ileum and colon, which offers a potential explanation for diarrhea observed in many COVID-19 patients.[3] It can explain gastrointestinal tract complaints such as diarrhea, nausea, vomiting, etc. and the formation of SARS-CoV-2 RNA in the feces of infected patients. The presence of ACE2 receptor in many organs such as the lung, small intestine, colon, kidney, spleen, brain, oral and nasal mucosa, etc. may explain the risk and multiorgan failure after SARS-CoV-2 infection.[1,4]

To protect the cells, including the lung, brain, bowel, etc., is also important to reduce cellular death and protect the cells from the effect of the viruses as well as SARS-CoV-2. The regeneration capacity of cells in all organs should be maintained during COVID-19 disease. Therefore, to treat or eliminate the viruses, a treatment needs to be developed.[5]

Natural products can be used to prevent infected cells with viruses, bacteri, etc. Therefore, they should be used as antiviral medicines, either directly or indirectly. A major functional flavanone in flavonoids, hesperidin (HD; 3,5,7- trihydroflavanone 7-rhamnoglucoside), can be isolated from lemons and other citrus fruits.[6] Anti-carcinogenic, anti-atherogenic, anti-hyperlipidemic, anti-diabetic, anti-inflammatory, anti-hypertensive, cardioprotective, membrane integrity agonist, caspase-3 and caspase-8 stimulant, apoptosis agonist, antibacterial, antiviral, etc. actions of hesperidin were also demonstrated.[7]

Hesperidin is one of the common compounds that interact with ACE2, TMPRSS2, GRP78, and AT1R, which are the most important receptors for SARS-CoV-2.[8,9] In addition, the antiviral activity of hesperidin demonstrated binding affinity to various SARS-CoV-2 protease domains.[10] Therefore, hesperidin may be a specific compound that binds both ACE2 and the receptor binding domain region of the spike protein of SARS-CoV-2.[11] In addition, hesperidin, baicalin, glycyrrhizic acid, and hyperoside were suggested to be key molecules related to traditional Chinese medicine formula.[9]

After SARS-CoV-2 infection, the release of cytokines, such as interleukin (IL)-1ß, IL-6, IL-12, IL-18, IL-33, tumor necrosis factor (TNF)-α, interferon (IFN)-γ, transforming growth factor-ß, is triggered and causes damage to many organs, including the gastrointestinal system.[12] Kawaguchi et al.[13] demonstrated that hesperidin controls inflammatory and proinflammatory cytokine secretion in *in vitro* and *in vivo* studies. More recently, hesperidin has been shown to bind to cellular ACE2 and respond to anti-SARS- CoV-2 infection activity in an *in vitro* cell line model.[10,14] However, the mechanism of action of hesperidin against SARS-CoV-2-infected enterocytes remains unknown. In this study, we analyzed the effects of hesperidin on enterocytes cells after TNF-α and IFN-γ induction which mimic SARS-CoV-2 infection. This was an experimental study.

MATERIALS AND METHODS

Cell Line and Cell Culture

The enterocyte cell line (IEC-6, CRL-1592, ATCC) was grown in Dulbecco's Modified Eagle Medium containing 90% of fetal bovine serum and 1% streptomycin at 37 °C in a humidified 5% CO_2/95% incubator until 80% confluency. This study is an *in vitro* model and does not require the approval of the ethics committee or informed consent.

Measurement of 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium Bromide

Cell viability was measured using an MTT assay as described previously.[15] The IEC-6 cell line (3,000 cells) in 96-well plates was treated with hesperidin in a dose-dependent manner for 24 or 48 h and then subjected to MTT assay (Sigma-Aldrich, Cat. No. M2003).

In vitro COVID-19 Mimic Model Consideration

To mimic inflammatory shock similar to COVID-19 disease, 3,000 IEC-6 cells per well in 96-well plates were treated with 50 ng/mL of TNF-α (315-01A-50UG, PetroTech) and 100 ng/mL of IFN-ɣ (315-05-100UG, PetroTech) for 48 h. Subsequently, the culture medium level of TNF-α (201-12-0083, SunRedBio) and IL8 (SRB-T-83151, SunRedBio) were evaluated with ELISA according to the manufacturer's protocol. Also, distributions of TNF-α and IL8 were also analyzed using indirect immunoperoxidase staining (see below).

Study Groups

IEC-6 cells were cultured in culture medium and used as the control group. Rest of the cells were other applicate with TNF-α and IFN-ɣ that was COVID-19 disease mimic group, or hesperidin applicate before or after TNF-α and IFN-ɣ combination and they were accepted prophylactic or treated groups, respectively. All culture experiments were performed in triplicate.

Indirect Immunoperoxidase Staining

The cells from all groups were fixed with 4% paraformaldehyde (1.04004.0800, Merck) at room temperature for 30 min, after washing with phosphate-buffered saline (PBS, PBS404.100, Bioshop) 0.1% Triton X-100 (A4975,0100, Applichem) for permeabilization at 4 °C for 15 min. The cells from all groups were incubated with 3% H_2O_2 (1.08597.2500, Merck, Germany) for 5 min and then with blocking solution (TA-125-UB, ThermoFisher Scientific, USA) for 1 h at room temperature. Primary antibodies against TNF-α (rabbit polyclonal, BT-AP09103, BT-LAB), IFN-ɣ (rabbit polyclonal, 15365-1-AP, Proteintech), IL-1ß (rabbit polyclonal, ABP51611, Abbkine), insulin-like growth factor (IGF)-I (rabbit polyclonal, sc-9013, Santa Cruz), VEGFA (rabbit polyclonal, sc-152, Santa Cruz), and caspase-3 (rabbit polyclonal, BT-AP01199, BT-LAB) were incubated at 4 °C overnight. After washing with PBS, biotinylated goat anti-rabbit/mouse IgG (TP-125-UB, ThermoFisher Scientific) and then peroxidase-conjugated streptavidin (TS-125-UB, ThermoFisher Scientific, USA) were incubated for 30 mi. Diaminobenzidine (DAB, TA-125-HD, ThermoFisher Scientific) was applied to the cells for 5 min, and Mayer's hematoxylin (TA-125-MH, ThermoFisher Scientific) was used for counterstaining. Slides were covered with mounting medium (DMM-125, Spring Bioscience) and viewed under a light microscope (BX43, Olympus, Japan).

Statistical Analysis

The data are expressed as mean ± standard deviation in the assay. Additionally, the Graph Pad Prism 7 software was used for analysis, and $p<0.05$ was considered statistically significant. Mann-Whitney U tests were used for data analyzes

RESULTS

The inhibitory effect of hesperidin on the proliferation of IEC-6 cells was determined using the MTT assay in our study. After the MTT assay, IEC-6 cell viability was similar to or without hesperidin application in a dosage-dependent manner. The double cell proliferation level was detected 100 µM dosage for 48 h, and this concentration was used for the rest of the study (Figure 1). After the MTT data analysis, we found no significant differences between the groups.

The levels of TNF-α and IL8 in the culture medium were measured using ELISA. TNF-α and IL8 levels were higher in the model culture medium than in the control. Therefore, a 48-h incubation of enterocytes with TNF-α and IFN-ɣ combination was used (Figure 2).

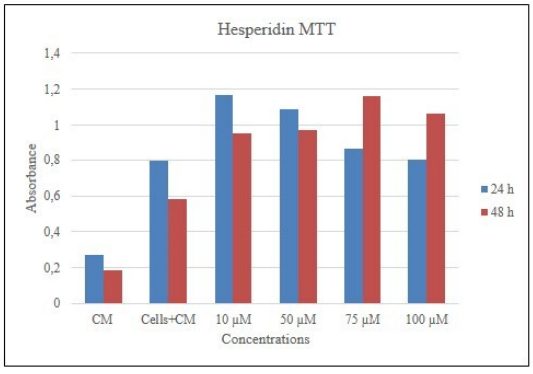

Figure 1. Cytotoxicity of hesperidin on IEC-6 cells. Hesperidin was not inhibiting cell proliferation of IEC-6 cells at all concentrations (10 µM, 50 µM, 75 µM and 100 µM) for 24 and 48 h. Cytotoxicity was determined in MTT assays. CM: culture medium.

IEC: Enterocyte cells

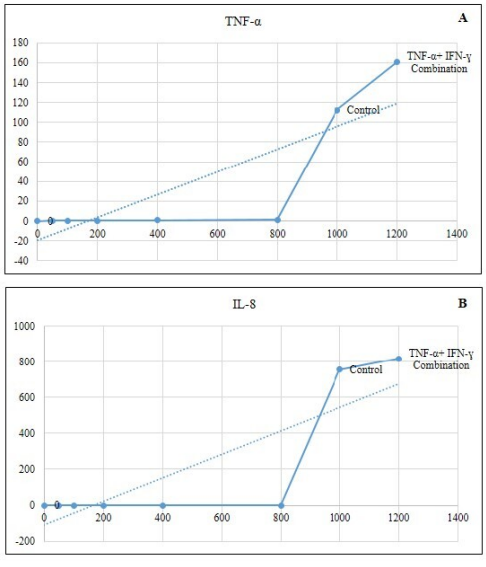

Figure 2. ELISA results from control and TNF-α + IFN-ɣ combination application IEC-6 cell culture mediums. Both TNF-α (A) and IL8 (B) levels were higher after TNF-α + IFN-ɣ combination application than in the culture mediumof control cells. The level of standards is shown as dotted lines.

IEC: Enterocyte cells, TNF: Tumor necrosis factor, IFN: Interferon

Lesser TNF-α immunoreactivity was detected in the treatment group which hesperidin applicate after TNF-α and IFN-ɣ combination (Figure 3). Moreover, with hesperidin application after TNF-α + IFN-ɣ combination, the IFN-ɣ immunoreactivity was moderate and distributions of IFN-ɣ was less than that in the hesperidin prophylactic group (Figure 4).

Immunoreactivity of IL-1ß was similar in both the hesperidin prophylactic (Figure 5C) and hesperidin treatment (Figure 5D) groups. However, strong IL-1 immunoreactivity was detected TNF-α + IFN-ɣ combination group (Figure 5B). In our study, cytoplasmic precipitation of IGF-1 was detected in the hesperidin prophylactic group (Figure 6C); this precipitation was not detected in other hesperidin treatment groups (Figure 6).

The immunoreactivity of VEGFA was decreased in hesperidin application after TNF-α + IFN-ɣ combination (treatment) group (Figure 7D) when compared with the other groups' VEGFA immunoreactivity

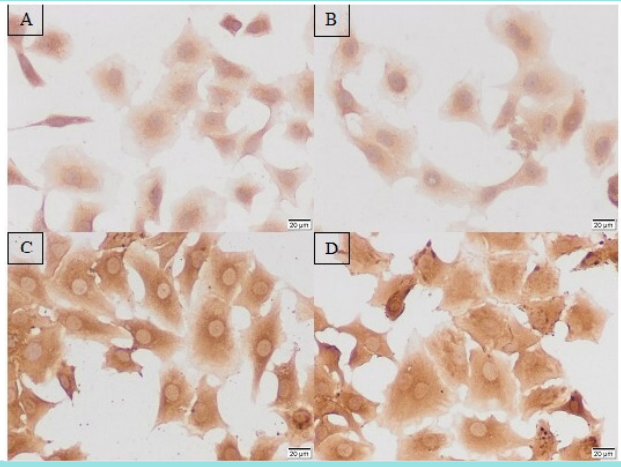

Figure 3. Distributions of TNF-α immunoreactivity on control (A), TNF-α + IFN-ɣ combination (B), hesperidin prophylactic (C), and hesperidin treatment (D) groups. Scale bars: 20 µm.

TNF: Tumor necrosis factor, IFN: Interferon

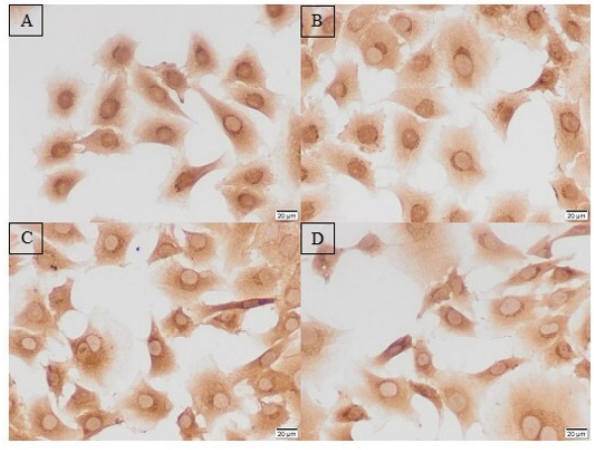

Figure 4. Distributions of IFN-ɣ immunoreactivity on control (A), TNF-α + IFN-ɣ combination (B), hesperidin prophylactic (C), and hesperidin treatment (D) groups. Scale bars: 20 µm.

TNF: Tumor necrosis factor, IFN: Interferon

(Figure 7). In our study, cellular damage of the IEC-6 cells was analyzed by the distribution of caspase-3. Weak immunoreactivity of caspase-3 was detected in all groups (Figure 8). Because similar caspase-3 immunoreactivity was observed in all groups, it was thought that apoptotic cell death was triggered in IEC-6 cells after TNF-α + IFN-ɣ application, but hesperidin had no effect on the control of caspase-3 secretion (Figure 8).

DISCUSSION

SARS-CoV-2 is responsible for millions of infections and deaths worldwide. Research has shown that ACE2 is a crucial functional SARS-CoV-2 receptor for gaining cellular entry into target cells. In addition, the ACE2 receptor is widely found in various organs such as the lung, small intestine, liver, and oral and nasal mucosa.[3,16] Therefore, blocking the ACE2 receptor can decrease the infection risk and protect cells against SARS-CoV-2. However, curative treatment is not available against viruses.

Hesperidin is a bioactive polyphenolic compound that displays numerous biological activities such as anti-inflammatory and antioxidant properties.[17] It has been used as an herbal medicine for a long time because of its high safety profile after oral intake.[18] Recently, Cheng et al.[19] showed that hesperidin suppressed the infection by blocking SARS-CoV-2 binding to the ACE2 receptor and inhibiting ACE2 protein expression. Additionally, Kandeil et al.[14] reported a hesperidine inhibitory effect on the viral replication of SARS-CoV-2 at the early stage of virus infection. On the other hand, to the best of our knowledge, there is no study regarding the effects of hesperidin on SARS-CoV-2 infection-related digestive symptoms.

Immune system hyperactivation in COVID-19 patients increases proinflammatory cytokines that induce inflammatory cell death, tissue damage, and multi-organ failure.[20] According to the Karki et al.[21] protocol, to analyze the model after incubation with TNF-α and IFN-ɣ, the levels of TNF-α and IL8 were investigated in culture media after 48 h of incubation. In our study, both TNF-α and IL8 levels were higher in the model culture medium than in the control; therefore, 48 h incubation of enterocytes with TNF-α and IFN-ɣ combination was decided.

TNF-α, IFN-γ and IL-1ß are crucial cytokines that play a critical role in SARS-CoV-2 infection-related organ damage. Case studies have shown that patients who have chronic, immune-inflammatory diseases such as inflammatory bowel disease (IBD) or Crohn's disease and are

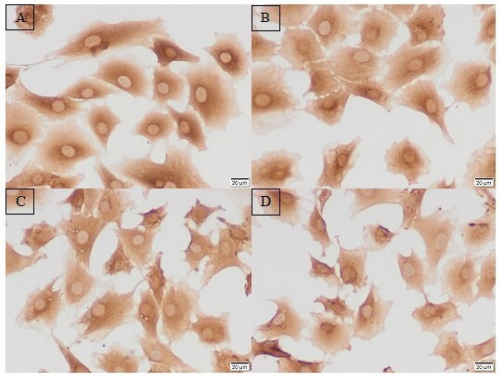

Figure 5. Distributions of IL-1 immunoreactivity in the control (A), TNF-α + IFN-ɣ combination (B), hesperidin prophylactic (C), and hesperidin treatment (D) groups. Scale bars: 20 µm

TNF: Tumor necrosis factor, IFN: Interferon, IL: Interleukin

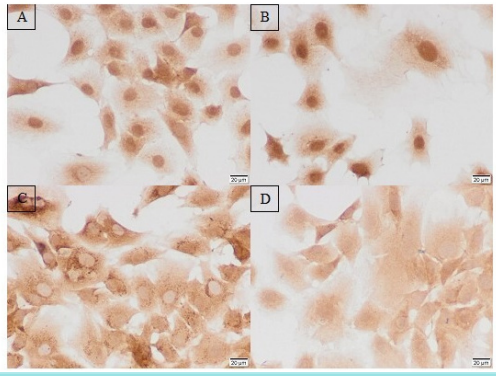

Figure 7. Distributions of VEGFA immunoreactivity in the control (A), TNF-α + IFN-ɣ combination (B), hesperidin prophylactic (C), and hesperidin treatment (D) groups. Scale bars: 20 µm.

TNF: Tumor necrosis factor, IFN: Interferon, VEGFA: Vascular endothelial growth factor-A

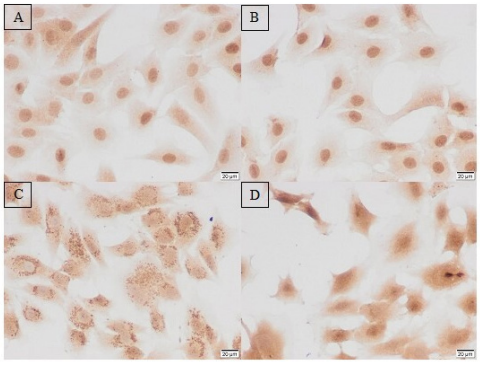

Figure 6. Distributions of IGF-I immunoreactivity in the control (A), TNF-α + IFN-ɣ combination (B), hesperidin prophylactic (C), and hesperidin treatment (D) groups. Scale bars: 20 µm.

TNF: Tumor necrosis factor, IFN: Interferon

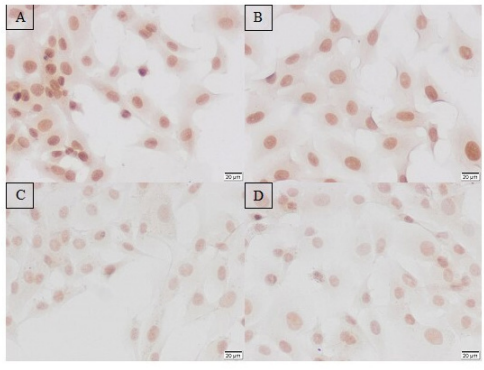

Figure 8. Distributions of caspase immunoreactivity in the control (A), TNF-α + IFN-ɣ combination (B), hesperidin prophylactic (C), and hesperidin treatment (D) groups. Scale bars: 20 µm.

TNF: Tumor necrosis factor, IFN: Interferon,

on anti-TNF-α therapy tends to have a mild course after SARS-CoV-2 inflammation.[22,23] These results suggest that prophylactic anti-cytokine therapy may also be beneficial in SARS-CoV-2 infection.

The anti-inflammatory properties of hesperidin are due to its inhibition of different pro-inflammatory mediators.[24] It was reported that hesperidin significantly reduced inflammatory mediators IL-1ß and TNF-α in various studies.[25] Therefore, distributions of the TNF-α, IFN-ɣ, IL-1ß was investigated. In our study, lesser immunoreactivity of TNF-α was detected in the treatment group which hesperidin applicate after TNF-α and IFN-ɣ combination.

Recent studies have demonstrated that higher expressions of IFN-γ in serum is an important predictor of the severity and prognosis of SARS-CoV-2-infected patients.[5,21] In addition, anti-SARS-CoV-2 plant-derived phenolic compounds such as hesperidin, which decrease inflammatory cytokines, were reported. Hesperidin is a natural compound that could target the binding interface between the ACE2 receptor and SARS-CoV-2 Spike.[11] It has been reported that hesperidin strongly binds to the RNA-dependent RNA polymerase active site, which catalyzes the replication of SARS-CoV-2 RNA.[26] In our study, with hesperidin application after TNF-α + IFN-ɣ combination, the IFN-ɣ immunoreactivity was moderate and distributions of IFN-ɣ was less than that in the hesperidin prophylactic group.

SARS-CoV-2 infection activates the NLRP3 inflammasome, leading to the secretion of active IL-1ß and IL-18 and the initiation of a cytokine storm.[27] IL-1ß stimulates Th-17 and IL-6 immune response, however IL-18 induces IFN-γ producing by Th-1 lymphocytes.[28] In this study, the immunoreactivity of IL-1ß was similar in both the hesperidin prophylactic and hesperidin treatment groups. Strong IL-1ß immunoreactivity was detected TNF-α + a IFN-ɣ combination group. IL-1ß is activated after SARS-CoV-2 infection then TNF-α and IFN-ɣ secretion are stimulated. For this reason, hesperidin may affect different steps of infection.

According to the immunocytochemistry results, application of hesperidin after TNF-α + IFN-ɣ combination, which was a COVID-19 disease mimic model, controlled the secretion of TNF-α and IFN-ɣ. Application of hesperidin either before or after TNF-α + IFN-ɣ combination, the secretion of IL-1ß was also controlled. Cheng et al.[19] demonstrated that hesperidin was proven to prevent cytokine storm by inhibiting the expression of proinflammatory cytokines. Our results also indicated that application of hesperidin after TNF-α + IFN-ɣ shock, secretion of cytokines, which were especially responsible for the SARS-CoV-2 cytokine storm, was controlled on IEC-6 enterocytes. The inhibitory effect of hesperidin on viral replication of SARS-CoV-2 was demonstrated at the early stage of virus infection.[14] In this study, we demonstrated the prophylactic and treatment role of hesperidin in enterocytes after inflammatory shock, which is similar to COVID-19 disease.

Immune gut homeostasis plays an important role in determining the course of IBD and infection caused by SARS-CoV-2. The improvement of colitis after hesperidin treatment is related to the inhibition of pro-inflammatory cytokines TNF-α, IL-6, IL-1ß, and IL-33 in the colon.[29] The regulatory balance of inflammatory cytokines in the gut is important for lung commensal microorganisms. Therefore, treatment or preventive therapy that controls cytokine diversity in the gut should be considered in COVID-19 disease. Hesperidin may be used for this purpose.

Bioinformatics data analyzes demonstrated that the immunoregulatory effects of hesperidin or glucosyl hesperidin in treating COVID-19 were targeting TNF-α, IGF-I, vascular endothelial growth factor (VEGF) A, etc.[12,30] IGF-1 can stimulate inflammatory cytokine secretion, and IGF-1 level is one of the possible immune system regulators. Hazrati et al.[31] showed that IGF-1 was suspected to modulate inflammation and was related to COVID-19 infection in a severe form. In fact, higher IGF-1 concentrations were associated with a lower risk of COVID-19 infection mortality.[31] In our study, cytoplasmic precipitation of IGF-1 was detected in the hesperidin prophylactic group, but this precipitation was not detected in the hesperidin treatment group.

VEGFA is a pro-nociceptive and angiogenic factor. It has been shown that VEGFA levels increase in bronchial alveolar lavage fluid from SARS-CoV-2-infected patients.[32] The immunoreactivity of VEGFA was decreased in the hesperidin application after TNF-α + IFN-ɣ combination (treatment) group when compared with the other groups VEGFA immunoreactivity.

Trigger of inflammation and failure of immune response are the most common side effects of SARS-CoV-2. Therefore, understanding the biological process that controls homeostasis is important for controlling cellular damage after virus infection. Our study demonstrated that IGF-I and VEGFA distribution decreased after hesperidin application on IEC-6 cells. Therefore, hesperidin, other than cytokine controlling in enterocytes, may also regulate the secretion of growth factors.

The cellular death and other side effects of SARS-CoV-2 viruses. The apical enterocyte membrane and epithelial tight junctions are the barrier of the intestinal epithelium. After alterations or destruction of the intestinal epithelium induce enterocyte apoptosis.[33] In our study, cellular damage of the IEC-6 cells was analyzed by the distribution of caspase-3. Weak immunoreactivity of caspase-3 was detected in all the groups. Because similar caspase-3 immunoreactivity was observed in all groups, it was thought that apoptotic cell death was triggered in IEC-6 cells after TNF-α + IFN-ɣ application, but hesperidin had no effect on the control of caspase-3 secretion. After inflammatory shock, caspase-1-dependent cell death is observed by inflammatory shock; therefore, in our study, cell death by caspase-3 may not have been triggered.

Study Limitations

The main limitation of this study was that more infection-related antibodies could have been studied to investigate the protective effects of hesperidin against the SARS-CoV-2 infection model. The protective effects of hesperidin are also needed in *in vivo* models.

CONCLUSION

The genetic diversity of SARS-CoV-2 results in a higher rate of widespread infection. After infection with SARS-CoV-2, the cytokine storm responds to the uncontrolled overproduction of soluble markers of inflammation. Therefore, therapeutic strategies and control of the side effects of the viruses are needed.

During the pandemic, it has been observed that patients might present or develop various GI symptoms during COVID-19. The detection of SARS-CoV-2 in fecal samples is essential for clinical practice, particularly for patients with atypical symptoms, and should be performed when COVID-19 patients are leaving the hospital to confirm viral clearance. The relationship between the digestive system and COVID-19 should be further explored in future related studies. The composition of balanced

gut microbiota has a major influence on the effectiveness of lung immunity.[34]

Hesperidin, diosmin, and rutin are widely available in pharmaceutical stores under various trade names and can be derived from various natural nutritive foods reported to have antiviral properties. The GO biological process result showed that the 45 targets of hesperidin were involved in a series of biological process which are mainly involved in the regulation of immune response, inflammation and virus infection, such as the regulation of production of molecular mediator of immune response, positive regulation of leukocyte migration, cytokine production involved in immune response, production of molecular mediator involved in inflammatory response, and virion attachment to the host cell.[30] Both hesperidin and glucosyl hesperidin had a great impact on immune, inflammation, and viral infection induced by COVID-19 according to systematic pharmacological analysis.[12] On the basis of *in silico* screening, hesperidin was also predicted to target the interaction site between SARS-CoV-2 Spike and ACE2 receptors, thus blocking the entry of the virus into human lung cells. Therefore, hesperidin could be a promising prophylactic drug against COVID-19.[35] According to the research aimed to screen drugs with high affinity to bind ACE2 and SARS-CoV-2 proteins, hesperidin was always at the top of the bioactive antiviral com-pounds.[8,10] Consistently, the present research concluded the remarkable immunoregulatory effects of hesperidin in treating COVID-19.

MAIN POINTS

- Hesperidin had anti-inflammatory and cell protection effects in enterocyte cells after tumor necrosis factor (TNF)-α and interferon (IFN)-γ induction which mimics the model of severe acute respiratory therapy-coronavirus-2 infection.
- IGF-I and vascular endothelial growth factor-A (VEGFA) distribution decreased after hesperidin application to enterocyte cells-6 cells. Hesperidin, other than cytokine control in enterocytes, may also regulate the secretion of growth factors.
- The immunoreactivity of VEGFA was decreased in hesperidin application after the TNF-α + IFN-ɣ combination (treatment) group.

ETHICS

Ethics Committee Approval:

Informed Consent: This study is an in vitro model and does not require the approval of the ethics committee or informed consent.

Peer-review: Externallay and internally peer reviewed.

Authorship Contributions

Surgical and Medical Practices: U.Ö., H.K.E., D.A.Ç., Concept: H.S.V., Design: U.Ö., H.S.V., D.A.Ç., Data Collection and/or Processing: U.Ö., H.S.V., E.B., H.K.E., Analysis and/or Interpretation: H.S.V., H.K.E., Literature Search: H.S.V., E.B., D.A.Ç., Writing: U.Ö., H.S.V., E.B., H.E.K., D.A.Ç.

DISCLOSURES

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

Financial Disclosure: The authors declared that this study had received no financial support.

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