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AIMS AND SCOPE

Turkish Journal of Surgery (Turk J Surg) is the official, peer reviewed, open access publication of the Turkish Surgical Society and Turkish surgical community. The journal is published quarterly on March, June, September and December and its publication language is English.

The aim of the Turkish Journal of Surgery is to publish high quality research articles, review articles on current topics and rare case reports in the field of general surgery. Additionally, expert opinions, letters to the editor, scientific letters and manuscripts on surgical techniques are accepted for publication, and various manuscripts on medicine and surgery history and ethics, surgical education and the field of forensic medicine are included in the journal.

As a surgical journal, the Turkish Journal of Surgery covers all specialties, and its target audience includes scholars, practitioners, specialists and students from all specialties of surgery.

The editorial and publication processes of the journal 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 (doaj.org/bestpractice).

The Turkish Journal of Surgery is currently abstracted/indexed by PubMed Central, Web of Science-Emerging Sources Citation Index, TUBITAK ULAKBIM TR Index, Scopus and EBSCO.

Processing and publication are free of charge. No fees are requested from the authors at any point throughout the evaluation and publication process. All expenses of the journal are covered by the Turkish Surgical Society.

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

Statements or opinions expressed in the manuscripts published in the journal reflect the views of the author(s) and not the opinions of the Turkish Surgical Society, editors, editorial board, and/or publisher; thus, the editors, editorial board, and publisher disclaim any responsibility or liability for such materials.

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INSTRUCTIONS TO AUTHORS

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

Manuscripts submitted to the Turkish Journal of Surgery will go through a doubleblind 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 the manuscripts submitted by the editors or the editorial board members of the journal. The Editor-in-Chief is the final authority in the decision-making process for all submissions.

An approval of research protocols by the Ethics Committee in accordance with international agreements (World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects," amended in October 2013, www.wma.net) is required for experimental, clinical, and drug studies and for some case reports. If required, ethics committee reports or an equivalent official document will be requested from the authors. For manuscripts concerning experimental research on humans, a statement verifying that written informed consent of the patients and volunteers was obtained following a detailed explanation of the procedures should be included. For studies carried out on animals, the measures taken to prevent pain and suffering of the animals should be stated clearly. Information on patient consent, name of the ethics committee, and the ethics committee approval number should also be stated in the Material and Methods section of the manuscript. It is the authors' responsibility to carefully protect patients' anonymity. For photographs that may reveal the identity of the patient, releases signed by the patient or his/herlegal representative should be enclosed.

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

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

Each individual listed as an author should fulfill the authorship criteria recommended by the International Committee of Medical Journal Editors (ICMJE - www.icmje.org). The ICMJE recommends that authorship be based on the following 4 criteria:

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work;
2. Drafting the work or revising it critically for important intellectual content;
3. Final approval of the version to be published; AND
4. Agreement to be accountable for all aspects of the work, and ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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

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

Turkish Journal of Surgery requires corresponding authors to submit a signed and scanned version of the authorship contribution form (available for download through www.turkjsurg.com) during the initial submission process in order to act appropriately on authorship rights and to prevent ghost or honorary authorship. If the editorial board suspects a case of "gift authorship," the submission will be rejected without further review. As part of the submission of the manuscript, the corresponding author should also send a short statement declaring that he/she accepts to undertake all responsibility for authorship during the submission and review stages of the manuscript.

The Turkish Journal of Surgery requires and encourages the authors and the individuals involved in the evaluation process of the submitted manuscripts to disclose any existing or potential conflicts of interests, including financial, consultant, and institutional. Any financial grants or other support received for a submitted study from individuals or institutions should be disclosed to the Editorial Board. To disclose a potential conflict of interest, the ICMJE Potential Conflict of Interest Disclosure Form should be filled in and submitted by all contributing authors. Cases of a potential conflict of interest of the editors, authors, or reviewers are resolved by the journal's Editorial Board within the scope of COPE and ICMJE guidelines.

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 cases that cannot be resolved internally. The Editor-in-Chief is the final authority in the decision-making process for all appeals and complaints.

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MANUSCRIPT PREPARATION

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 2017 - http://www.icmje.org/icmje-recommendations.pdf). Authors are required to prepare manuscripts in accordance with 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.turkjsurg.com. Manuscripts submitted via any other medium will not be evaluated.

Manuscripts submitted to the journal will first go through a technical evaluation process by the editorial office staff to 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 Transfer Form,
- Author Contributions Form, and
- ICMJE Potential Conflict of Interest Disclosure Form (should be filled in by all contributing authors)

INSTRUCTIONS TO AUTHORS

during the initial submission. These forms are available for download at www.turkjsurg.com.

Preparation of the Manuscript

Title page: A separate title page should be submitted with all submissions, which 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, and highest academic degree(s) of the author(s),
- Grant information and detailed information on the other sources of support,
- Name, address, telephone (including the mobile phone number) and fax numbers, and email 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: English abstract should be submitted with all submissions except for Letters to the Editor. The abstract of Original Articles should be structured with subheadings (Objective, 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 six 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).

Manuscript Types

Original Articles: This is the most important type of article since it provides new information based on original research. The main text of original articles should be structured with Introduction, Material and Methods (with subheadings), Results, Discussion, Conclusion subheadings. Please check Table 1 for the limitations for Original Articles.

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 provided with a separate subheading under the Material 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).

Expert Opinions: 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, Tables, Figures, Images, and other media are not included.

Review Articles: Reviews with high citation potential prepared by authors with extensive knowledge on a particular field and whose scientific background has already been proven by a high number of publications in the related field 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 main text should contain Introduction, Clinical and Research Consequences, and Conclusion sections. 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 constituting challenges in diagnosis and treatment, those offering new therapies or revealing insight not included in the literature, and interesting and educative case reports are accepted for publication. The text should include Introduction, Case Presentation, Discussion, and Conclusion subheadings. Please check Table 1 for the limitations for Case Reports.

Video Articles: We do encourage the submission of the video articles which report interesting cases and technical methods.

The details of the review process are below.

- All videos will be peer reviewed.
- All videos will be published on the journals official Web site.
- Article length: It should not exceed 500 words.
- Reference Number: Not to exceed 5 references

Diagnosis, surgical technique and outcome should be summarized. All important steps and aspects of the surgery should be mentioned in the video. If it is a new surgical technique, appropriately labeled and cited video materials may be used. Authors can use a rare case they have encountered, a surgical technique, or videos using modern technological devices.

The following items must be provided:

- The file of the video written in Word format.
- A completed copy of the online broadcast consent form (form will be prepared and linked), together with completed copies of patient consent forms, if appropriate.
- All videos must contain an English narration.
- All videos should also be in the highest resolution possible, more details on accepted file types and resolution are available at this link (authors' video article submission guidelines; https://turkjsurg.com/video-article-guidelines).
- The duration of the videos should not exceed five minutes and the maximum file size should be 300Mb.

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, Tables, Figures, Images, and other media should not be included. The text should be unstructured. The article being commented on must be properly cited within this manuscript.

Human Subjects Research

All research involving human participants must have been approved by the authors' Institutional Review Board (IRB) or by equivalent ethics committee(s) and must have been conducted according to the principles expressed in the Declaration of Helsinki. Authors should be able to submit, upon request, a statement from the IRB or ethics committee indicating approval of the research. The Journal reserves the right to reject work believed to have not been conducted in a high ethical standard, even when formal approval has been obtained.

Table 1. Limitations for each manuscript type

Type of manuscript	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
Original Article	5000	250 (Structured)	50	6	7 or total of 15 images
Review Article	5000	250	50	6	10 or total of 20 images
Case Report	1500	250	15	No tables	10 or total of 20 images
Surgical Methods	500	No abstract	5	No tables	10 or total of 20 images
Letter to the Editor	500	No abstract	5	No tables	No media

INSTRUCTIONS TO AUTHORS

Subjects must have been properly instructed and have indicated that they consent to participate by signing the appropriate informed consent paperwork. Authors may be asked to submit a blank, sample copy of a subject consent form. If consent was verbal instead of written, or if consent could not be obtained, the authors must explain the reason in the manuscript, and the use of verbal consent or the lack of consent must have been approved by the IRB or ethics committee.

Animal Research

All animal research must have approval from the authors' Institutional Animal Care and Use Committee (IACUC) or equivalent ethics committee(s), and the research must have been conducted according to applicable national and international guidelines. Approval must be received prior to beginning the research.

Manuscripts reporting animal research must state in the Methods section: The full name of the relevant ethics committee that approved the work, and the associated permit number(s). Where ethical approval is not required, the manuscript should include a clear statement of this and the reason why. The author should provide any relevant regulations under which the study is exempt from the requirement of approval.

Tables

Tables should be included in the main document, presented after the reference list, and 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.

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 the 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 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

While citing publications, preference should be given to the latest, most up-to-date publications. If an ahead-of-print publication is cited, the DOI number should be provided. Authors are responsible for the accuracy of references. Only references cited in the text should be included in the reference list. The reference list must be numbered according to the order of mention of the references in the text. In the main text of the manuscript, references should be cited using Arabic numbers in parentheses. 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." The reference styles for different types of publications are presented in the following examples.

Journal Article: Rankovic A, Rancic N, Jovanovic M, Ivanović M, Gajović O, Lazić Z, et al. Impact of imaging diagnostics on the budget - Are we spending too much? Vojnosanit Pregl 2013; 70: 709-11.

Book Section: Suh KN, Keystone JS. Malaria and babesiosis. Gorbach SL, Barlett JG, Blacklow NR, editors. Infectious Diseases. Philadelphia: Lippincott Williams; 2004. pp. 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 İndeksleri 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/ncidodlElD/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 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. 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.

Turkish Journal of Surgery

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FROM THE EDITOR'S DESK
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Respect for science and immorality

"Insanity is doing the same thing over and over again, but expecting different results."

from the novel "Sudden Death" by Rita Mae Brown

Dear readers of the Turkish Journal of Surgery,

Türkiye was literally shaken by a massive earthquake on February 6, 2023. The earthquakes, with epicenter city of Kahramanmaraş, affected 10 cities with a total population of around 13 million people and neighboring Syria. The official death toll has been rising every day, but as of the end of february it is approaching 50.000. However, the numbers of those injured, those receiving treatment and those suffering from post-traumatic psychological disorders are in the hundreds of thousands.

It is difficult to explain the fact that so many people have lost their lives, even though it is well known that Türkiye is an earthquake country, even though there are many experienced experts in this field and even though the finance needed has been already allocated to prevent earthquake damage with special taxes. It has been 24 years since the huge Marmara earthquake that struck Türkiye in 1999, but what we have experienced since February 6th reminds us of some painful truths.

Despite the painful experiences of the Marmara earthquake, Türkiye is perhaps even further behind than in 1999, both in preventing the devastation of the earthquake and in post-disaster organization. When I look at this issue as the editor of a scientific journal, I may see that these intolerable facts have many close relations with the science. First of all, we have to assume the fact that it is not earthquakes but rotten buildings and bad disaster organization that kill the people. If the rules of geology, geophysics, urban planning and engineering as dictated by science were respected, would our hearts be so heavy? Would it not have saved more of our people if trauma surgery and disaster organization had been guided by science? We saw in the most painful way what can happen when science and the objective facts of science are not respected.

But is it enough to respect the science? Unfortunately, not. After such a severe disaster, human morality must also be questioned and evaluated. How were those structures built, who built them, who turned a blind eye when the requirements of science are obvious? In the 24 years since the Marmara earthquake, where have the funds collected for the expected major earthquakes been spent? If we as a country do not see these as a general moral problem, I am afraid that we will always be talking about the same things when we experience new disasters.

Finally, my deepest condolences for those who passed away in the earthquake.

I wish courage and patience to our people who continue to live the sufferings of the earthquake. I would also like to thank the wonderful people from all over Türkiye and the world who rushed to the region after the earthquake, sent aid, and provided any kind of support they could. Seeing that both the people of that region and Türkiye were not alone, has relieved this pain awhile.

Sincerely,

Kaya SARIBEYOĞLU

Editor-in-Chief
Turkish Journal of Surgery

Turkish
Journal of Surgery

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10.47717/turkjsurg.2023.230102

IN MEMORY OF A VALIANT MAN

Turkish Surgery bid farewell to a very important and valuable name on December 5. As one of the founders of the Turkish Surgical Association and having served in this association for 20 years without interruption, Prof. Dr. Altan Tüzüner passed away, leaving behind significant services and valuable memories.

When we take a look at Prof. Dr. Altan Tüzüner's CV, it is understood that he was born in Ankara in 18.07.1940, attended primary school in Samsun Havza Primary School, secondary school in Edremit Secondary School and high school in Balıkesir High School.

His Academic Career (1):

He graduated from Ankara University Faculty of Medicine in 1964, which he entered in 1957. The same year, he started his specialization training at Ankara University Faculty of Medicine 1st Surgery Clinic. He completed his training in 1968 and became a specialist in the field of general surgery. The subject of his specialization thesis was "Complications After Goiter Surgeries and Their Treatment" (2).


Prof. Dr. Altan Tüzüner (1940-2022).

Following his specialization, he worked in the field of peripheral vascular surgery at Evangelishes Krakenhaus Mülheim-Ruth and Evangelishes Kra-kenhaus-Ratingen in West Germany. After having returned home, he completed his military service in Erzurum Marshal Çakmak Hospital in 1972-1973. He became an associate professor in 1975 at Ankara Medical Faculty 1st Surgery Clinic, which he returned to following his military duty. He continued working as a lecturer in this clinic and received the title of university professor in the field of general surgery in 1980 as an inactive and as an active member in 1982.

After having received the title of professor, he continued his teaching duties in the same clinic. Dr. Altan Tüzüner worked in the peripheral vascular surgery unit as of 1992 in line with the decision of the Faculty Board dated 14 December 1995 and numbered 32/95, which had been initiated by Prof. Dr. Semih Baskan, Dean of Medicine of Ankara University (3).

Prof. Dr. Altan Tüzüner served as the Head of the Department of General Surgery at Ankara Medical Faculty between 1997-2006 (4).

He made invaluable contributions to the training and expertise of many young general surgeons during his term as the head of the department and as a lecturer. Along with Prof. Dr. Ahmet Yaycıoğlu, Prof. Dr. İbrahim Ceylan, and Prof. Dr. Dikmen Arıbal, he contributed to many eye-opening works in the field of peripheral surgery. He retired in 2006 due to the age limit in Ankara University Faculty of Medicine, Department of General Surgery, where he had assumed important duties. He worked in the general surgery clinic for 42 years without interruption, where he started his life as a surgeon as a resident (4). Prof. Dr. Altan Tüzüner made invaluable contributions to the education and training of two of the previous presidents of the Turkish Surgical Society, Prof. Dr. Semih Baskan and Prof. Dr. Seher Demirer, and current President of Turkish Surgery Association, Prof. Dr. Serdar Karaca at Ankara Medical Faculty.

After his retirement, he continued his duties as chairman and lecturer in the Department of General Surgery, Ufuk University Faculty of Medicine until 2014.

Prof. Dr. Altan Tüzüner's valuable contributions and efforts to Turkish Surgery begin with his participation as a founding member in the establishment of Ankara Surgical Society in 1976 (5).

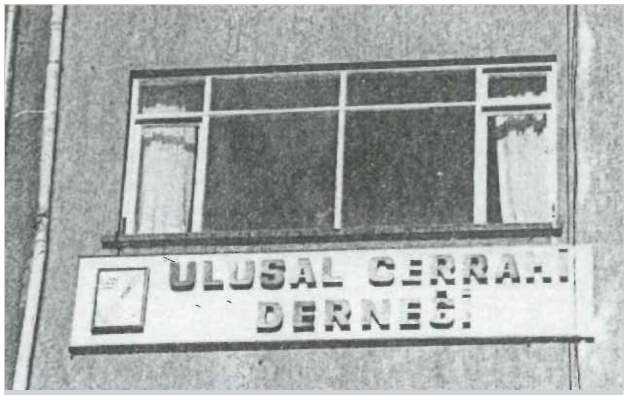
Prof. Dr. Altan Tüzüner's duties at the Turkish Surgical Society:

Member of the board of directors between 1990-1992, general secretariat for two terms between 1992-1996, chairman of the board of directors for two terms between 1996-2000, second chairman between 2002-2004, chairman of the board of directors between 2004-2006, second chairman between 2006-2008, and member of the board of directors between 2008 and 2010 (Table 1).

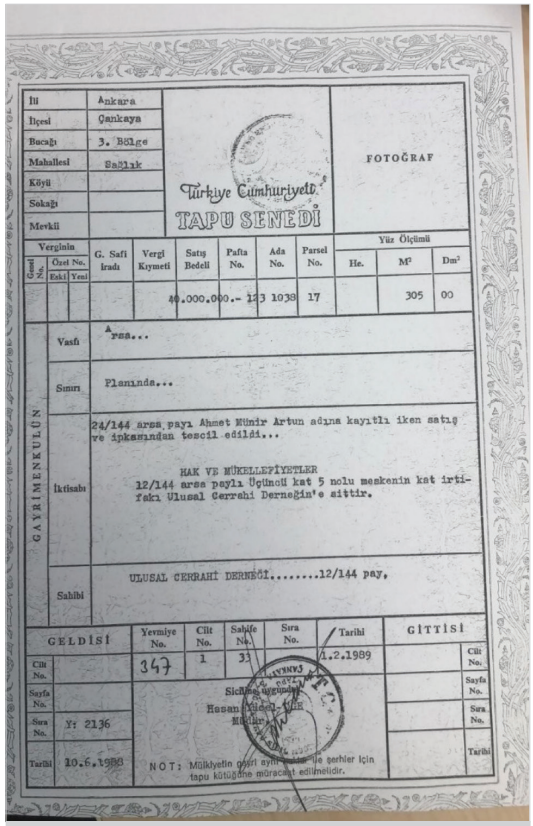
Table 1. Prof. Dr. Altan Tüzüner's duties at the Turkish Surgical Society (6)	
1990-1992	Member of the Board of Directors
1992-1994	General Secretary
1994-1996	General Secretary
1996-1998	Chairman of the Board of Directors
1998-2000	Chairman of the Board of Directors
2000-2002	Second Chairman
2004-2006	Chairman of the Board of Directors
2006-2008	Second Chairman
2008-2010	Member of the Board of Directors

The Turkish Surgical Society, which gathered in the offices of our colleagues who were members of the board of directors since the day it was founded, eventually found a headquarters in Ankara on Sağlık Street in 1989 with the authorization it received from the general assembly. This headquarters, which was purchased paying 40 million TL in 01.02.1989, was put into service in 20.11.1989 at Sağlık Street No: 11/5 (7).

Meeting of the Turkish Surgical Association Board of Directors in the new center, including Prof. Dr. Altan Tüzüner (8).



Our first headquarters on Sağlık Street.



The title deed of our first headquarters purchased by the Turkish Surgical Association in Ankara on Sağlık Street No: 11/5.

Prof. Dr. Altan Tüzüner served as the chairman of many congresses during his 20 years at the Turkish Surgical Society. To list them, he chaired the National Surgery Congress 1998, Eurosurgery 2000, National Surgery Congresses 2004 and 2006, Second Experimental Surgery Congress 2003, Third Experimental Surgery Congress 2005, 16th, 17th, 19th and 20th Regional Surgery Congresses (Table 2) (9).

Table 2. National Surgery Congresses, Experimental Surgery Congresses and Regional Surgery Congresses chaired by Prof. Dr. Altan Tüzüner

National Surgery Congress	6-10 May 1998, İzmir
Eurosurgery 2000	20-24 May 2000, İstanbul
National Surgery Congress	26-30 May 2004, Antalya
National Surgery Congress	24-28 May 2006, Antalya
2nd Experimental Surgery Congress	20-21 September 2003, Ankara
3rd Experimental Surgery Congress	18-20 November 2005, Ankara
16th Regional Surgery Congress	19-22 May 1999, Kuşadası
17th Regional Surgery Congress	21-23 October 1999, Edirne
19th Regional Surgery Congress	12-15 June 2003, Malatya
20th Regional Surgery Congress	10-12 June 2005, Sivas

Regional Surgery Congress, 15-17 October 1992, Trabzon. Prof. Dr. Altan Tüzüner and the Congress Organization Committee.

At the Eurosurgery 2000 Congress, under the chairmanship of Prof. Dr. Altan Tüzüner, a trail was blazed and the Executive Committee started its journey by having concluded the elections for the Turkish Surgical Society Competency Board. In this congress, the selected Proficiency Executive Board performed the written examination phase of the proficiency board exams for the first time. Those who were successful at this stage entered the Objective Original Clinical Examination stage in Ankara on March 17, 2001. Candidates who passed both stages were awarded the Turkish Surgery Association Competency Board Certificates. In this regard, Prof. Dr. Altan Tüzüner's intense efforts and encouragements should never be forgotten.

In order to explain the problems general surgeons faced especially in the field of malpractice following the implementation of the Turkish Penal Code No. 5237, which entered into force on September 26, 2004, Prof. Dr. Altan Tüzüner, former Minister of Interior and one of the former lecturers of our general surgery clinic, Assoc. Dr. Ülkü Güney, held meetings with Prof. Dr. Semih Baskan, Minister of Justice, Cemil Çiçek, and Speaker of the Grand National Assembly of Türkiye, Köksal Toptan.

As mentioned above, the contributions of Prof. Dr. Altan Tüzüner to the field of peripheral vascular surgery in our country should never be forgotten. He was among the founding members of the Vascular Surgery Society in Türkiye. He served as the Vice Chairman of the Board of Directors four times between 1986-1988, 1988-1990, 1990-1992, and 1992-1994 and as a Member of the Board of Directors between 1984-1996 and 2000-2002 (Table 3). (10).

Table 3. Duties of Prof. Dr. Altan Tüzüner in the Vascular Surgery Society

1986-1988	Vice Chairman of the Board of Directors
1988-1990	Vice Chairman of the Board of Directors
1990-1992	Vice Chairman of the Board of Directors
1992-1994	Vice Chairman of the Board of Directors
1994-1996	Member of the Board of Directors
2000-2002	Member of the Board of Directors

The most important and meaningful service Prof. Dr. Altan Tüzüner performed within the body of the Turkish Surgical Society was the construction and opening of the new headquarters of the Turkish Surgery Society, located on a green area of 1666 square meters with a closed area of 450 square meters, in Ümitköy, Ankara, with his personal efforts. This modern building has 2.5 floors, with a 120-person conference hall, kitchen and other support units on the ground floor. On the upper floor, there are rooms for the Chairman of the Board of Directors, the meeting room of the Board of Directors, secretariat and other administrative units. On the lower floor, there are rooms where polyclinic services would be provided and an archive room (11).

Turkish Surgical Society Moved to its New Headquarters

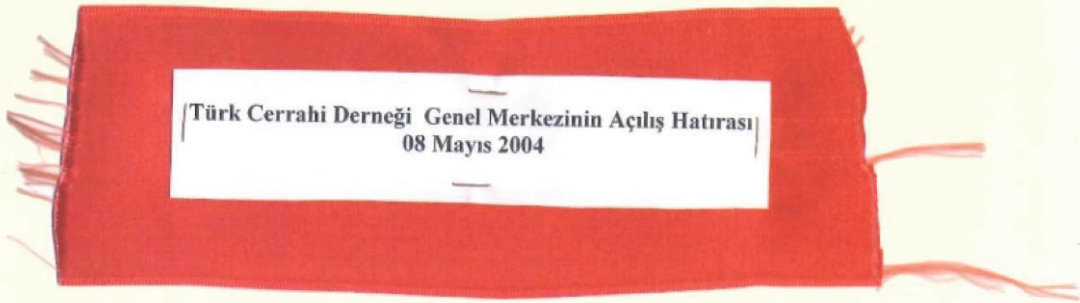
Turkish Surgical Society moved to its new center located inside Mesa Koru Building Complex in Ümitköy, Ankara in the past few days. Located on a green area of 1666 square meters with a closed area of 450 square meters, the building has 2.5 floors. While a conference hall for 120 people, a kitchen and other support units are found on the ground floor, the upper floor accomodates rooms for the Chairman of the Board of Directors, the meeting room of the Board of Directors, secretariat and other administrative units. On the lower floor, arrangements have been made with due regard the polyclinic to be opened in the upcoming days. The floor has a lead-room for radiological imaging, a separate room for laboratory purposes, and another room for internal and surgical procedures to be performed. Headquarters of the Turkish Surgical Society, which adds a different meaning to the environment with its contemporary appearance, is located right next to the park built in memory of Ahmet Taner Kışlalı, who was brutally murdered in the previous years.

Headquarters of the Turkish Surgical Society in Ümitköy.

At the ceremony held for this headqaurters, which was put into service on May 8, 2004, the Chairman of the Board of Directors of the Turkish Surgical Society, Prof. Dr. Altan Tüzüner, thanked our late Presidents Prof. Dr. Ahmet Yaycıoğlu, Prof. Dr. Şadan Eraslan, Prof. Dr. Yılmaz Sanaç and Board Member Operator Dr. Kemal Altay and showed an example of loyalty by having their wives cut the ribbons (12). Headquarters of the Turkish Surgical Society, which adds a different meaning to the environment with its contemporary appearance, is located right next to the park built in memory of Ahmet Taner Kışlalı, who was brutally murdered in 1999.

Chairman, Prof. Dr. Ahmet Tüzüner, addresses the attendees at the opening ceremony of the headquarters of the Turkish Surgical Society.

Wives of our late presidents cut the ribbon to open the headquarters.



A Souvenir from the Opening Ceremony of the Headquarters of the Turkish Surgical Society
8 May 2004

Prof. Dr. Altan Tüzüner and wives of our late presidents in the opening ceremony.

Title deed of the land we bought in Ümitköy.

Today, scientific meetings and courses for young surgeons are held in this contemporary center of the Turkish Surgical Society. Sixty-nine courses were held here between 2010-2022. Three courses are planned to be held this year. In addition to these activities, the second stage exams of the Turkish Surgical Society Proficiency Committee are also held here.

In the last general assembly held at Ankara University Faculty of Medicine in 12.06.2022, Prof. Dr. Altan Tüzüner served as the Chairman of the Council. At this general meeting, Prof. Dr. Altan Tüzüner was elected to the Honorary Board. Most recently, Prof. Dr. Altan Tüzüner was a member of the Turkish Surgery History Research Commission of the Turkish Surgical Society.

Prof. Dr. Altan Tüzüner's wife, Prof. Dr. Filiz Tüzüner, like himself, is a graduate of Ankara University Faculty of Medicine, received her specialization in the same faculty and served as the head of the anesthesia and reanimation department at the same faculty between 1994-2010. prof. Dr. After her retirement, Filiz Tüzüner started to work as a faculty member in the Department of Anesthesia and Reanimation, Faculty of Medicine, Ufuk University in Ankara. She is still working at the same faculty.

Prof. Dr. Altan Tüzüner had two children. Prof. Dr. Acar Tüzüner is a faculty member at Ankara University Faculty of Medicine, Department of General Surgery. His other child, Prof. Dr. Ayşegül Tüzüner, is a faculty member at Ankara University, Faculty of Dentistry, Department of Oral and Maxillofacial Surgery.

I would like to thank my esteemed professional elder and teacher Prof. Dr. Altan Tüzüner, who worked non-stop for 50 years as a faculty member and for 20 years since the establishment of the Turkish Surgical Society, trained hundreds of medical doctors and general surgeons and added them to the health army, and left us with countless beautiful memories and artifacts. I bow respectfully before the cherished memory of Prof. Dr. Altan Tüzüner.

Prof. Dr. Semih Baskan

Turkish Surgical Society

Chairman of the Board of Directors between

2006-2008

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ORIGINAL ARTICLE
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Level I axillary dissection in patients with breast cancer and tumor-involved sentinel lymph node after NAC is not sufficient for adequate nodal staging

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ABSTRACT

Objective: The purpose of the study was to investigate the oncological sufficiency of level I axillary dissection for adequate histological nodal staging (ypN) in patients with breast cancer and tumor-involved sentinel lymph node (SLN) after neoadjuvant chemotherapy (NAC).

Material and Methods: A prospective multicentre pilot study took place from 01.01.2018 to 30.11.2020 in three mammary centres in the Czech Republic in patients with breast cancer after NAC (NCT03556397). Patients in the cohort with positive histological frozen section of SLN were indicated to separate axillary dissection of levels I and II.

Results: Sixty-one patients with breast cancer after NAC were included in the study according to inclusion and exclusion criteria. Twelve patients with breast cancer and tumour involved SLN after NAC were further included in the analysis. Two (16.7%) patients had positive non-sentinel lymph nodes in level I only, one (8.3%) patient had positive lymph nodes in level II only, and seven (58.3%) patients had positive lymph nodes in both levels. Level I axillary dissection in a patient with tumour involved SLN after NAC would have resulted in understaging in five (41.7%) patients, mostly ypN1 instead of ypN2.

Conclusion: According to our pilot result, level I axillary dissection is not sufficient in terms of adequate histological nodal staging in breast cancer patients after NAC, and level II axillary dissection should not be omitted.

Keywords: Breast cancer, sentinel lymph node biopsy, neoadjuvant chemotherapy, axillary dissection, level I axillary dissection

INTRODUCTION

Implementation of neoadjuvant chemotherapy (NAC) in patients with breast cancer has brought new questions to axillary surgery. Changes in guidelines have allowed the use of less radical operations such as sentinel lymph node biopsy (SLNB) or targeted axillary dissection (TAD) instead of standard axillary dissection of levels I and II (ALND) even in patients with initially tumor infiltrated lymph nodes with regression after NAC (1-6). Less radical surgical methods have a lower incidence of complications such as seroma formation, lymphoedema, limitations of arm movement, loss of sensitivity. The complication rate of SLNB is significantly lower with 5% compared with up to 58.4% for ALND (7,8). However, in patients with residual nodal disease after NAC detected by SLNB or TAD, completion ALND of levels I and II still represents the standard procedure (1,9).

Correct histological nodal status after NAC is a determinant of long-term prognosis (10). The prognostic value of residual lymph node involvement may differ among breast cancer subtypes (11), and the number of metastatic lymph nodes can influence the decision about adjuvant systemic therapy (9). It could potentially also affect the indication of adjuvant radiotherapy (12).

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According to the recommendation of TNM Classification, adequate pathological nodal staging requires the resection and examination of at least low axillary lymph nodes (level I) with a minimum of six lymph nodes (13). It can be assumed that with a lower number of removed lymph nodes lower complication rate should occur (8), therefore the complication rate of level I axillary dissection should range between the complication rate of the standard level I and II axillary dissection and SLNB, but there are no studies on this topic in the literature.

This prospective pilot study investigated the sufficiency of axillary dissection of level I for adequate histological nodal staging (ypN) in patients with tumor-involved sentinel lymph nodes after NAC.

MATERIAL and METHODS

The presented analysis was one of the primary endpoints of the study "Sentinel Lymph Node Biopsy in Patients with Breast Cancer After Neoadjuvant Therapy." The study was designed as a prospective multicenter pilot trial and was conducted from 01.01.2018 to 30.11.2020 in three surgical departments specializing in breast cancer surgery (Silesian Hospital in Opava, University Hospital Ostrava, EUC Clinic Zlin). Inclusion criteria were diagnosis of breast carcinoma confirmed by biopsy, the indication of neoadjuvant chemotherapy, examination of axillary lymph nodes clinically and by ultrasound and surgical treatment after neoadjuvant chemotherapy. Exclusion criteria were incomplete neoadjuvant chemotherapy, inflammatory breast cancer, and the presence of distant metastases. Axillary nodal status before NAC was examined clinically, by ultrasound and in case of suspicious pathological lymph node by core-cut biopsy. Patients were informed about the suggested treatment and signed informed consent. The study was approved by the Ethics Committee of Faculty of Medicine, University of Ostrava, and by local ethics committees in each center. The study was registered on www.clinicaltrials.gov with code NCT03556397.

Patients included in the presented sub-analysis were patients with tumour involved SLN according to the histological frozen section in the form of micrometastases, micrometastases or isolated tumour cells (ITC) and separate axillary dissection of levels I and II (Figure 1).

Lymphatic mapping was performed by scintigraphy and patent blue. Sentinel lymph nodes were detected by gamma probe and visually tracked according to lymph vessels' blue coloring. Frozen section and definitive histological examination with immunohistochemical evaluation of the sentinel lymph node were performed. In case of finding tumor cells in perioperative frozen section of the sentinel lymph node, axillary dissection of levels I and II was further performed in each patient with perioperative in vivo division of levels and separate histological examination. Level I axillary lymph nodes were defined as lymph nodes below and laterally from the lateral edge of the pectoralis minor muscle, level II axillary lymph nodes as lymph nodes located behind the pectoralis minor muscle. Histological nodal status of axillary lymph nodes after NAC was classified according to the 8th edition of TNM Classification to ypN1 (under three tumor infiltrated lymph nodes), ypN2 (4-9 tumor infiltrated lymph nodes) and ypN3 (more than 10 tumor infiltrated lymph nodes).

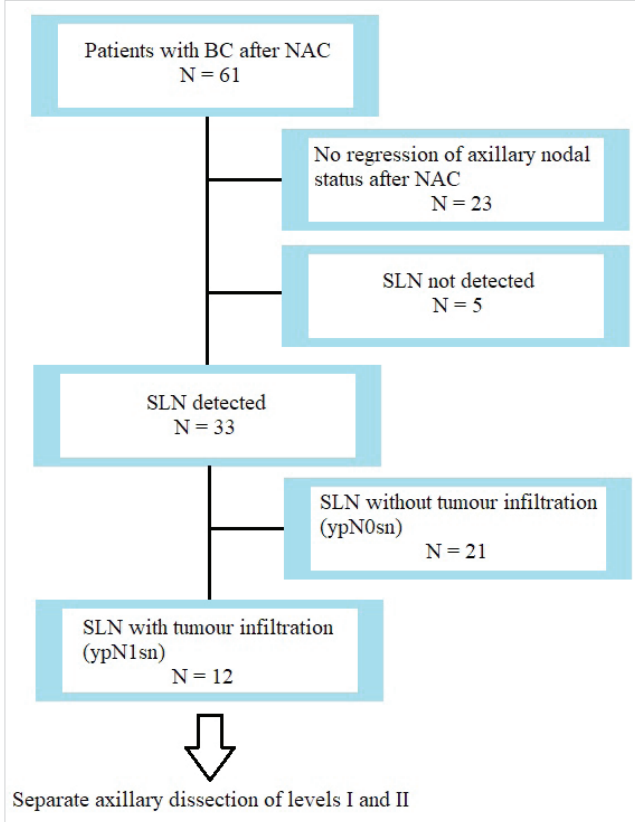

Figure 1. Study scheme.

Recorded patient and tumor characteristics included age, TNM classification, tumor typing and grading, the positivity of estrogen receptors (ER), progesterone receptors (PR) and HER2 receptors, type of surgery, type of tracer used for SLNB, number of harvested sentinel and non-sentinel lymph nodes, histological examination of lymph nodes. Mean values, percentages, and ranges were calculated.

RESULTS

Sixty-one patients with breast cancer after NAC were included in the study according to inclusion and exclusion criteria. The average age was 48.7 years, the stage of the primary tumor according to TNM classification was T1 in 13 (21.3%) patients, T2 in 33 (54.1%) patients, T3 in 10 (16.4%) patients and T4 in five (8.2%) patients. Axillary nodal status before NAC was N0 in 12 (19.7%) patients, N1 in 44 (72.1%) patients, N2 in two (3.3%) patients and N3 in three (4.9%) patients. Tumor types were

invasive carcinoma of no special type (NST) in 51 (83.6%) patients, invasive lobular carcinoma in six (9.8%) patients, medullary carcinoma in three (4.9%) patients and mucinous carcinoma in one (1.6%) patient. Tumor grade was G1 in four (6.6%) patients, G2 in 34 (55.7%) patients and G3 in 23 (37.7%) patients. According to molecular classification of breast tumours, the most common was triple-negative breast cancer (patients 20, 32.8%), luminal B was present in 18 (29.5%) patients, HER2+ in 16 (26.2%) patients, and luminal A in seven patients (11.5%).

Twelve patients with breast cancer and tumor involved SLN after NAC were further included in the analysis. The average age in the cohort was 52.1 years, with a minimum of 33 and a maximum of 77 years. The stage of the primary tumor was T1 in three (25.0%) patients, T2 in seven (58.3%) patients and T3 in two (16.7% patients). Axillary nodal status before NAC was N0 (16.7%) in one (8.3%) patient, N1 in seven patients (58.3%), N2 in two patients and N3 in two (16.7%) patients. The regression of axillary nodal burden after NAC was confirmed by clinical examination and USG in all patients in the analysis. The most common breast tumor type was invasive carcinoma of NST in eight (66.7%) cases, four (33.3%) patients had invasive lobular carcinoma. Breast conserving surgery was performed in one patient; in 11 patients, mastectomy was performed. The other patient characteristics are summarized in Table 1.

In seven cases, two tracers were used to detect sentinel lymph nodes-scintigraphy and patent blue, in other cases single tracer was used. The average number of harvested sentinel lymph nodes was 1.5, with a minimum one and maximum six nodes. Perioperative and definitive histological findings in SLNs are summarized in Table 2.

Table 1. Patient characteristics

Characteristic	Value	n (%)
T stage	T1	3 (25.0%)
	T2	7 (58.3%)
	T3	2 (16.7%)
N stage	N0	1 (8.3%)
	N1	7 (58.3%)
	N2	2 (16.7%)
	N3	2 (16.7%)
Tumor type	NST	8 (66.7%)
	Lobular	4 (33.3%)
Grading	G1	1 (8.3%)
	G2	7 (58.3%)
	G3	4 (33.3%)
Receptor positivity	ER positivity	9 (75.0%)
	PR positivity	6 (50.0%)
	HER2 positivity	1 (8.3%)
Tumor regression (Chevallier)	1	1 (8.3%)
	2	2 (16.7%)
	3	9 (75.0%)

In two (16.7%) patients, no tumor infiltrated non-sentinel levels I and II axillary lymph nodes were present. In two (16.7%) patients, tumor infiltrated non-sentinel lymph nodes were only found in level I axillary nodes. Levels I and II axillary lymph nodes infiltrated by tumor were present in seven (58.3%) patients (Table 2). Tumor infiltration of level II axillary lymph nodes only was present in one (8.3%) patient .

Performing level I axillary dissection would have only resulted in leaving tumour infiltrated lymph nodes in the axilla in eight (66.7%) patients. With the axillary dissection of levels I and II, upstaging of the pathological nodal status from ypN1 to ypN2 or from ypN2 to ypN3 occurred in five (41.7%) patients (Table 2).

DISCUSSION

The number of breast cancer patients after NAC has increased in the last decade (14), so questions about axillary staging in this subgroup are very topical. The primary outcome of our analysis was to evaluate the possibility of performing axillary dissection of level I only in patients with tumor involved sentinel lymph node after NAC without risk of understaging the axillary nodal status. To our knowledge, this is a first study focusing on the sufficiency of level I axillary dissection in breast cancer patients after NAC for staging purposes.

According to the 8th edition of TNM classification, axillary dissection of level I axillary lymph nodes can be performed with the condition of harvesting a minimum of six lymph nodes for adequate histological nodal staging (13). Five patients in the study achieved the number of lymph nodes in level I with six or more, other patients had a lower number of lymph nodes. On the other hand, TNM classification also states that one of the essential prognostic factors in breast cancer is the number and percentage of tumor infiltrated lymph nodes (13). In eight (66.7%) patients, other tumour infiltrated lymph nodes were found in level II of axillary lymph nodes, moreover, in five (41.7%) patients, an understaging would have occurred if only level I axillary dissection had been performed. According to the study results, the recommendation of TNM Classification about the axillary dissection of level I should not be interpreted as sufficient for adequate nodal staging.

Knowledge of the exact extent of nodal involvement in the axilla is key to determining optimal adjuvant treatment options. In patients with luminal A and luminal B breast cancer subtypes, the exact extent of nodal involvement may determine whether or not adjuvant chemotherapy is necessary (13). Patients with luminal B breast cancer at high risk of recurrence (involvement of four or more nodes, or one to three nodes and

Table 2. Overview of patients in the cohort (ypN = post-chemotherapy nodal status by final histological examination

Patient no.	Tumour type	Number of SLNs	Perioperative histological examination of SLN	Definitive histological examination of SLN	ypN acc. to level I dissection and SLNB	Number of affected LN in level I and SLN/ total number of LN in level I and SLN	ypN acc. to level I and II dissection and SLNB	Number of affected LN in level I and II and SLN/ total number of LN in level I and II and SLN
1	NST	1	micro	micro	N1	2/5	N1	2/11
2	NST	1	macro	macro	N2	7/15	N3	10/24
3	NST	1	micro	ITC	N1	1/2	N2	5/9
4	L	1	macro	macro	N1	2/8	N1	3/14
5	L	1	macro	macro	N1	2/4	N1	2/7
6	NST	1	micro	micro	N1	3/4	N2	4/6
7	L	1	ITC	ITC	N1	3/4	N2	5/10
8	NST	6	macro	macro	N3	10/13	N3	14/23
9	L	1	micro	macro	N1	3/3	N2	5/12
10	NST	1	macro	macro	N2	4/6	N2	5/10
11	NST	1	macro	macro	N1	1/6	N1	1/13
12	NST	2	macro	macro	N1	2/5	N1	2/11

LN: Lymph nodes, SLN: Sentinel lymph node, ITC: Isolated tumour cells, micro: micrometastasis, macro: macrometastasis, NST: Invasive carcinoma of no special type, L: Invasive lobular carcinoma.

either tumor size greater than five cm, histologic grade three, or Ki-67≥ 20%) may be offered adjuvant endocrine therapy with a combination of CDK 4/6 inhibitor abemaciclib (15). In the case of HER2 positive tumors, patients with nodal involvement or patients with the absence of steroidal receptor expression benefit most from the adjuvant dual anti-HER2 blockade (16). Patients with luminal B HER+ carcinoma with nodal involvement who did not achieve pathological complete remission after NAC administration benefit from sequential therapy of trastuzumab and neratinib (17).

In the past few decades, the trend in breast cancer surgery has been to reduce the radicality of operations performed (18). Few studies have documented replacing levels I and II axillary dissections with radiotherapy in patients with positive sentinel lymph node and without NAC (19,20). OTOASOR and AMAROS trials confirmed a lower morbidity rate in patients with radiotherapy compared to patients with ALND with the same oncosurgical safety (19,20). A study with a group of patients after NAC and positive sentinel lymph node with the indication of radiotherapy as an alternative to ALND is ongoing-Alliance study A011202, with the results in 2024 (21).

One of the most important factors in oncosurgical safety is the probability of locoregional relapses (22). Unfortunately, there are no studies in the literature regarding locoregional relapses in patients after level I axillary dissection after NAC. Graversen investigated locoregional relapses in three subgroups of patients without NAC-included were patients without axillary dissection, patients with level I axillary dissection and patients with level I and II axillary dissection (23). There were 3128 patients included in the study with five-year follow-up. Axillary relapse occurred in 19% of patients without ALND, 10% patients with level I axillary dissection, and 3% patients with level I and II axillary dissection (23). The incidence of axillary relapses in Graversen´s study from 1988 is much higher compared to the studies of AMAROS and OTOASOR with a published incidence of 2% and 0.43%, respectively, obviously due to the higher efficiency of current adjuvant therapy (19,20).

We foresee that in patients with positive sentinel lymph node after NAC, less radical procedures will be investigated as in patients without NAC. Few studies have already been published on this topic, but their results are inconsistent (24,25).

Lymph nodes in axillary levels I and II are not anatomically separated. A surgeon performing level I dissection orients by using the lateral border of pectoral minor muscle as a boundary of the axillary levels. But some borderline lymph nodes cannot be clearly identified as belonging to level I or II. Level I axillary dissection may contain a few lymph nodes from level II, or some lymph nodes of level I may remain in the axilla. This could be a slight limitation in the reproducibility of the study. Another apparent limitation is the low number of included patients. However, the study was designed as a pilot trial. Based on the results, we conclude that level I axillary dissection seems insufficient for adequate nodal staging in patients with tumour involved sentinel lymph node after NAC.

CONCLUSION

Although TNM classification recommends the axillary dissection of level I with at least six lymph nodes as a minimum for adequate nodal staging in patients with breast cancer, our study revealed that this procedure is not sufficient after NAC due to the risk of understaging. Since nodal staging after NAC is an essential prognostic factor and could affect the indication of further treatment, we do not consider axillary dissection of level I only as an adequate method, and we recommend a standard axillary dissection of levels I and II.

Ethics Committee Approval: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee of Faculty of Medicine, University of Ostrava (12/2018, 26.3.2018), by the Ethics Committee of University Hospital Ostrava (1031/2017, 23.11.2017), by the Ethics Committee of Silesian Hospital in Opava (298/2017, 14.11.2017) and by the Ethics Committee of EUC Clinic Zlín (13/2020, 27.4.2020). All patients participating in the study signed consent to participate.

Peer-review: Externally peer-reviewed.

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ORİJİNAL ÇALIŞMA-ÖZET
Turk J Surg 2023; 39 (1): 1-6

Meme kanseri ve tümör tutulumlu sentinel lenf nodu olan hastalarda, neoadjuvan kemoterapi sonrası seviye 1 aksiller diseksiyon, uygun bir nod evrelemesi için yeterli değildir

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ÖZET

Giriş ve Amaç: Çalışmanın amacı, neoadjuvan kemoterapi (NAC) sonrası meme kanseri ve tümör tutulumlu sentinel lenf nodu (SLN) olan hastalarda yeterli histolojik nodal evreleme (ypN) için seviye I aksiller diseksiyonun onkolojik yeterliliğini araştırmaktır.

Gereç ve Yöntem: 01.01.2018 ve 30.11.2020 tarihleri arasında Çek Cumhuriyeti'ndeki üç meme merkezinde NAC sonrası meme kanseri olan hastalarda prospektif çok merkezli bir pilot çalışma gerçekleştirildi (NCT03556397). SLN'nin histolojik frozen kesiti pozitif olan kohorttaki hastaların, seviye I ve II'de ayrı aksiller diseksiyon yapması belirtildi.

Bulgular: NAC sonrası meme kanseri gelişen 61 hasta dahil edilme ve dışlanma kriterlerine göre çalışmaya dahil edildi. NAC'den sonra SLN'ye dahil olan meme kanseri ve tümörü olan 12 hasta ayrıca analize dahil edildi. İki (%16,7) hastada sadece seviye I'de pozitif sentinel olmayan lenf nodu vardı, bir (%8,3) hastada sadece seviye II'de pozitif lenf nodu vardı ve yedi (%58,3) hastada her iki seviyede de pozitif lenf nodu vardı. NAC sonrası SLN tutulmuş tümörü olan bir hastada seviye I aksiller diseksiyon beş (%41,7) hastada çoğunlukla ypN2 yerine ypN1 olarak düşük evreleme ile sonuçlanacaktı (%41,7).

Sonuç: Pilot sonuçlarımıza göre meme kanseri hastalarında NAC sonrası yeterli histolojik nodal evreleme açısından seviye I aksiller diseksiyon yeterli değildir ve seviye II aksiller diseksiyon ihmal edilmemelidir.

Anahtar Kelimeler: Meme kanseri, sentinel lenf nodu biyopsisi, neoadjuvan kemoterapi, aksiller diseksiyon, seviye I aksiller diseksiyon

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ORIGINAL ARTICLE
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Protective role of vitamin B12 on acetic acid induced colitis in rats

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ABSTRACT

Objective: Inflammatory bowel disease (IBD) is a chronic, relapsing, and remittent inflammatory disease of the gastrointestinal tract. Nutritional deficiency may be instrumental in and attributable to this disease. We examined the effect of VitB12 supplementation on acetic acid (AA)-induced colitis in rats.

Material and Methods: Five minutes after the application of acetic acid to the rats to create a colitis model, VitB12 was administered 1 mg/kg, i.p concentration, then the application continued for three consecutive days. Control groups were included for colitis and VitB12. After 4d, the rats were sacrificed, and colonic tissues were harvested for macroscopic and microscopic examination of colonic damage. TNF-α, IL-1β, IL-6, MDA, GSH and SOD values were measured biochemically.

Results: There was statistically significant macroscopic improvement in damage to the colon tissues ($p< 0.05$). The severity of inflammation reduced in the VitB12 treated rat group compared with the control group, but was not significantly. The levels of TNF-α, IL-1β, MDA, and SOD did not differ between AA control and VitB12 treated AA colitis group. However, the levels of IL-6 and GSH were statistically significant different in rats with AA-induced colitis after VitB12 injection ($p< 0.05$).

Conclusion: Nutritional deficiencies might contribute to the pathogenesis of IBD, and the efficacy of VitB12 supplementation has controversial effects on the intestinal mucosa.

Keywords: Vitamin B12, inflammatory bowel disease, inflammation, acetic acid

INTRODUCTION

Inflammatory bowel disease (IBD), which has two major typical forms, ulcerative colitis (UC) and Crohn's disease (CD), is a chronic, relapsing and remitting inflammatory disease of the gastrointestinal (GI) tract. The relationship between individual genetic factors that regulate the innate and adaptive immune system, enteric microbiota, the enteric immune system, and environmental factors, particularly nutritional factors, are key determinants of IBD pathogenesis, and it has been suggested that these factors cause an excessive enteric immune response to gut flora or nutritional antigensis (1). Since multiple factors can contribute to inflammation of the intestinal mucosa, and nutritional deficiencies may occur due to malabsorption, inflammation, and resection, it has been postulated that nutritional deficiencies may actually evoke or influence colitis. The deficiencies in vitamin D, folate (vitamin B9), and VitB12 are among the most prevalent in IBD patients (2).

Vitamin B12 (VitB12), referred to as cobalamin, belongs to the B vitamin family. It is a critical coenzyme in various important metabolic processes that take place during the synthesis of nucleic acids, erythrocyte biogenesis, and the metabolism of amino acids and folate (3). Clinical medicine encounters VitB12 insufficiency frequently as a result of intestinal inflammation brought on by diarrhea, which impairs VitB12 absorption (4). For the diagnosis of VitB12 deficiency in healthy people, minimum serum values of 200 pg/mL have been established (5,6). Vitamin deficiencies in patients with IBD may cause clinical, biochemical, and inflammatory damage. For instance, anaemia in IBD has been linked to VitB12 deficiency (7).

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Additionally, a VitB12 deficiency prevents the pro-oxidant and pro-inflammatory homocysteine from being converted to methionine, causing homocysteine to build up in the blood and intestinal mucosa of IBD patients (8). As a result, VitB12 inadequacy is frequently present in patients with ileal dysfunction (2).

Deficiency of folate and VitB12 may be involved in the pathogenesis of IBD by modulating TNF-α mediated cytotoxicity and inducing the production of inflammatory cytokines and chemokines, such as monocyte chemoattractant protein (MCP-1) and IL-8 (9-11). Although several experimental and cohort studies have shown evidence of an association between the pathogenesis of IBD and VitB12 and folate deficiency (5,6), it is still not clear whether VitB12 deficiency leads to IBD. The aim of the present study was to assess the effect of VitB12 in acetic acid (AA)-induced colitis in rats. Additionally, our goal was to determine the protective role of VitB12 in colitis with biochemically inflammatory indices and markers of oxidative damage.

MATERIAL and METHODS

Animals

A total of 28 male Wistar-Albino rats weighing between 250 and 350 g were included, and were kept in separate cages in groups of two or three, at a constant temperature of 23°C and in a 12-hour light/dark cycle. They were fed a standard diet, and food and water were available ad libitum. All animals were maintained under fasting conditions for 24 h before undergoing surgical procedures, and no antibiotics were given before or after the procedures. Approval for the study protocol was granted by the Experimental Animals Ethics Committee of Gaziosmanpaşa University Medical Faculty. All experimental, surgical, and laboratory procedures were applied in Gaziosmanpaşa University Medical Faculty Experimental Research Centre and Gaziosmanpaşa University Medical Faculty Biochemistry and Histology Laboratories.

Induction of Acetic Acid (AA)-Colitis

The colitis model was induced by inserting a soft 6 mm pediatric-feeding catheter into the anus of each rat, and advancing the tip by 8 cm. One mL of 4% AA (pH 2.3) solution was slowly transrectally injected. In order to spread AA into the colon lumen, 2 mL of air was put into the catheter. Physical trauma was reduced by withdrawing the catheter slowly, and the rats were held upside down by the tail for 30 s to prevent any leakage of the administered substance. The experimental procedures were carried out under general anesthesia via an intramuscular administration of 75 mg/kg ketamine hydrochloride (Ketalar 500 mg flacon; Pfizer, İstanbul, Türkiye) and 10 mg/kg xylazine hydrochloride (Rompun 2% flacon; Bayer, İstanbul, Türkiye).

Experimental Group

The total 28 rats were randomized into four groups of seven. Group 1 (Control saline) was the control group, in which the rats received transrectal injections of saline; group 2 (AA colitis control) was the control colitis group, in which AA was administered into the colon of the rats; group 3 (VitB12) was the VitB12 treatment group, in which 1 mg/kg of VitB12 was intraperitoneally administered five minutes after saline injection, with treatment then continuing for three consecutive days; group 4 (VitB12 treatment in AA colitis) was the AA-induced colitis group in which 1 mg/kg VitB12 was intraperitoneally administered five minutes after colitis induction, with treatment then continuing for three consecutive days. All rats were sacrificed on day four after the induction of colitis by cervical decapitation (Figure 1). Before the procedure, 30 mg/kg hydrochloride and 5 mg/kg xylazine were administered as anesthesia. Intracardiac blood samples were drawn via making an incision of the abdomen and accessing the heart through the diaphragm. All blood samples were stored at -80°C until the day of analysis.

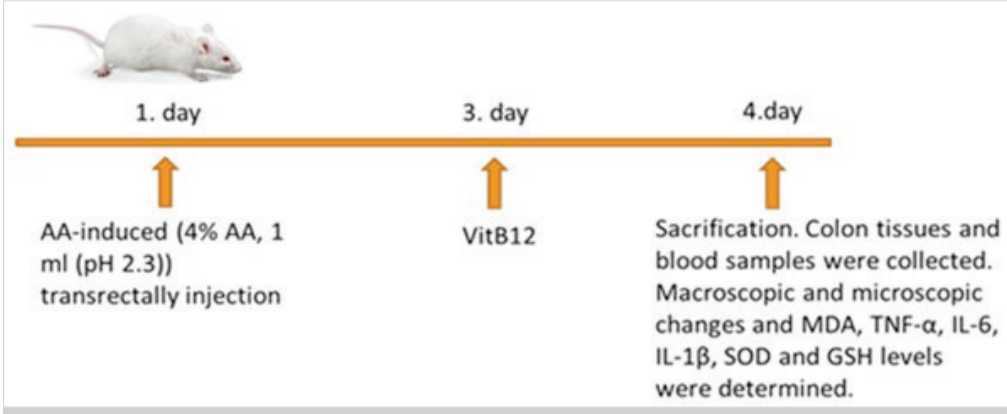

Figure 1. Experimental procedure.

Clinical Changes After AA Administration and Macroscopic Findings

Body weights were obtained before and after the colitis induction procedure. A new parameter, weight change (WC) was obtained according to the formula "body weight after the procedure-body weight before the procedure". Macroscopic assessment of the colon was made after the rats had been sacrificed. The longitudinally removed colon was opened and washed with saline. Mucosal lesions were then macroscopically scored, according to the Morris scoring system (12), as shown in Table 1.

Microscopic Changes

Colonic samples were chosen according to the Morris scoring system. The colon of each rat was macroscopically assessed, and samples of the region with the highest macroscopic score were obtained. These samples were then fixed in 10% buffer-neutral formaldehyde solution for 36 h. The fixed samples were embedded in paraffin, and 5 µm sections were obtained by cutting the paraffin blocks. Hematoxylin and eosin were used for staining after melting the paraffinized samples. Histologic assessment was carried out by a researcher blinded to the group information. A total of 10 sections from the seven rats in each group were considered, and an average of 20 microscopic views was assessed for each group. These views were analyzed via a computer-assisted light microscope (Nikon Eclipse 200, serial no: T1al 944909, Japan) with an integrated camera (Nikon Ds-Fi1, Japan), and transferred to the monitor for analysis using a Nis element program. Inflammation score (IS) was reported by the researcher, using a coding system that evaluates the intensity of inflammation in the colon strata. The four-level grading system is shown in Table 2 (13).

Biochemical Measurement

The blood samples were centrifuged at 4.000 rpm for 10 min at 4°C, and the removed plasma was stored at -80°C. Glutathione (GSH; item no: 7003002; Cayman Chemical, Estonia) and malondialdehyde (MDA; item no: 10009055; Cayman Chemical, Estonia) levels were measured with the colorimetric method, in accordance with the manufacturer's instructions, and superoxidismutase (SOD; cat no: YHB2870Hu;YH-Biosearch, China), TNF-a (cat no: YHB1098Ra; YH-Biosearch, China), interleukin (IL)-6 (cat no: YHB0630Ra; YH-Biosearch, China), and IL-1β (cat no:YHB0616Ra; YH-Biosearch, China) levels were measured using the enzyme-linked immunosorbent assay (ELISA) method.

Statistical Analysis

All statistical analyses were conducted by using SPSS (Version 22.0, SPSS Inc., Chicago, IL, USA). Descriptive statistics were presented as mean ± standard deviation and median (min-max). Normality distributions of the data were assessed by Shapiro-Wilk test. The significance of the difference between two paired groups was evaluated using Wilcoxon signed rank test. The significances of the difference between more than two groups were evaluated by using Kruskal-Wallis test (non-parametric analysis of variance) since data did not meet the assumptions of a parametric analysis of variance (ANOVA) test. Post-hoc test conducted after Kruskal-Wallis test in order to determine significant differences among the multiple groups with pairwise comparison. p value <0.05 was considered statistically significant.

Table 1. Macroscopic evaluation scale

Score	Criterion
0	No damage
1	Focal hyperemia without ulceration
2	Hyperemia or linear ulceration without thickening of colonic wall
3	Linear ulceration with inflammation in one area
4	Ulceration or inflammation in two or more areas
5	Two or more areas of major ulceration and inflammation, one or more sites of damage to the colon segment longer than 1 cm
6-10	The ulcer and inflammation area longer than 2 cm in the colon (the score is increased by 1 unit for every 1 cm damage)

Table 2. Inflammation grading scale

Score	Inflammation grade
0	No inflammatory cells
1	Giant cells, scattered few lymphocyte and plasma cell
2	Giant cells, increased amount of plasma cell, eosinophil, neutrophil
3	A great number of mixed inflammatory cells, microabscess formation

RESULTS

The Effect of VitB12 on AA-Induced Colitis

The body weights of the rats in all four groups were measured pre-experiment and post-experiment. The control saline group rats gained weight after saline injection, while the AA colitis control group rats lost weight following AA injection; the statistically difference was significant in both groups (p= 0.028; p= 0.018, respectively) (Table 3, Figure 2). There was no significant weight change in the other two groups. The new WC parameter was obtained by subtracting the post-experiment weight from the pre-experiment weight. A post-hoc analysis showed that the WC differences between the AA colitis control and control saline, AA colitis control and VitB12, control saline and VitB12 treatment in AA colitis groups were significant (p= 0.002, p= 0.027, and p= 0.03, respectively). There was no statistically difference between the AA colitis control and VitB12 treatment in AA colitis groups. Post-hoc analyses revealed significantly different mean macroscopic scores between the control saline group vs. the VitB12 treatment in AA colitis group and the control saline groups vs. the AA colitis control and VitB12 and AA colitis control groups (p= 0.032, p< 0.001, and p= 0.001, respectively) (Table 4, Figure 3). Post-hoc analysis showed mean

Table 3. Comparison of pre-post experiment weight and weight change means according to rat groups

			Pre-post weight changes			Pre-post weight differences			
		n	Mean ± SD	Median (min-max)	p	Mean ± SD	Median (min-max)	p	Post-hoc p
Control	Pre	7	277.86 ± 12.17	272 (265-300)	**0.028***	28.14 ± 25.07	24 (-4, 70)	**0.001****	**0.030[a]**
	Post	7	306.00 ± 34.33	294 (276-370)					
AA colitis	Pre	7	288.43 ± 35.86	270 (255-336)	**0.018***	-34.42 ± 20.65	-26 (-66, -13)		**0.002[b]**
	Post	7	254.00 ± 23.69	252 (232-302)					
VitB12	Pre	7	314.57 ± 48.60	308 (242-390)	0.176	14.57 ± 24.01	14 (-18, 48)		**0.027[c]**
	Post	7	329.14 ± 43.51	310 (290-388)					
VitB12 + AA colitis	Pre	7	352.86 ± 28.86	336 (324-392)	0.108	-18.00 ± 23.00	-22 (-46, 12)		
	Post	7	334.86 ± 32.30	336 (290-376)					

SD: Standard deviation, Min: minimum, Max: maximum.
*Statistically significant (p< 0.05), **Statistically significant (p< 0.01),
[a]Control - VitB12 + AA colitis, [b]Control - AA colitis, [c]AA colitis - VitB12.

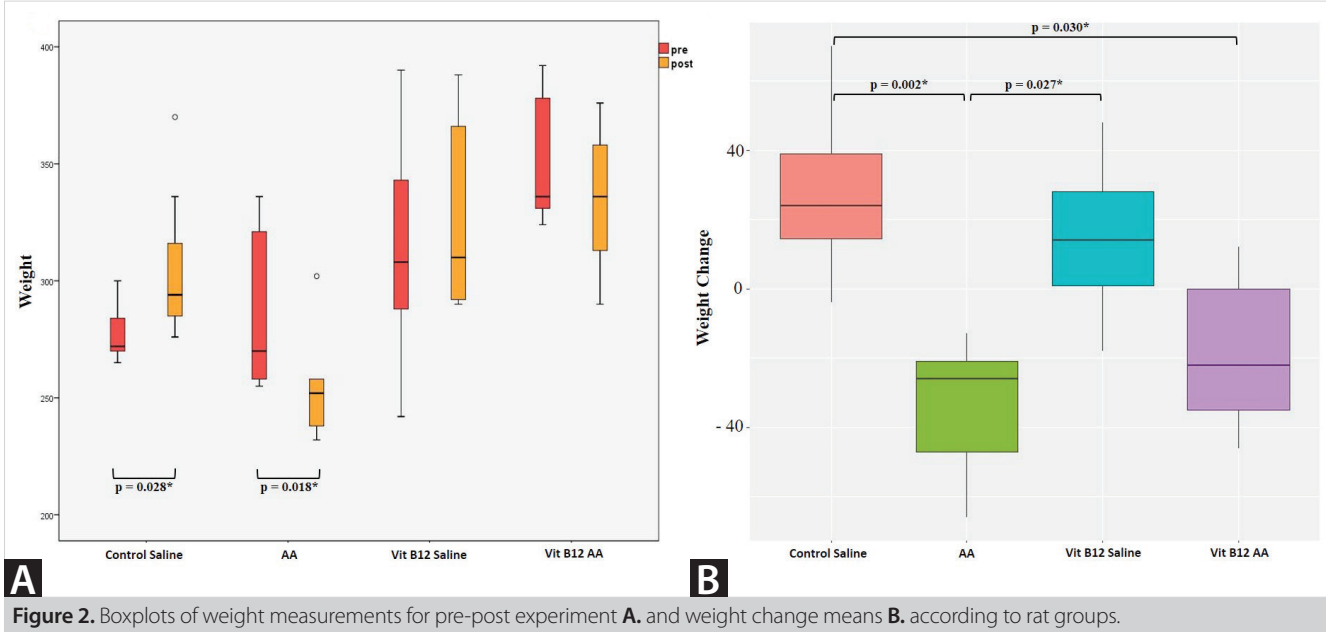

Figure 2. Boxplots of weight measurements for pre-post experiment **A.** and weight change means **B.** according to rat groups.

A. The control group and AA colitis group were significantly statistically different in pre-experimental and post-experimental weight loss (p= 0.028, p= 0.018, respectively). **B.** The control group was significantly statistically different when compared with the AA colitis and VitB12 + AA colitis groups (p= 0.002, p= 0.03, respectively). The AA colitis was significantly statistically different when compared with the VitB12 group (p= 0.027).

Table 4. Comparison of macroscopic damage score means according to rat groups

	n	Mean ± SD	Median (min-max)	p	Post-hoc p
Control	7	0.14 ± 0.37	0 (0-1)	<0.001*	**<0.001[a]**
AA colitis	7	6.57 ± 1.13	7 (5-8)		**0.001[b]**
VitB12	7	0.57 ± 0.53	1 (0-1)		
VitB12 + AA colitis	7	3.14 ± 0.90	3 (2-4)		**0.032[c]**

SD: Standard deviation, Min: Minimum, Max: Maximum.
*Statistically significant (p< 0.001).
[a]Control - AA colitis, [b]AA colitis - VitB12, [c]Control - VitB12 + AA colitis.

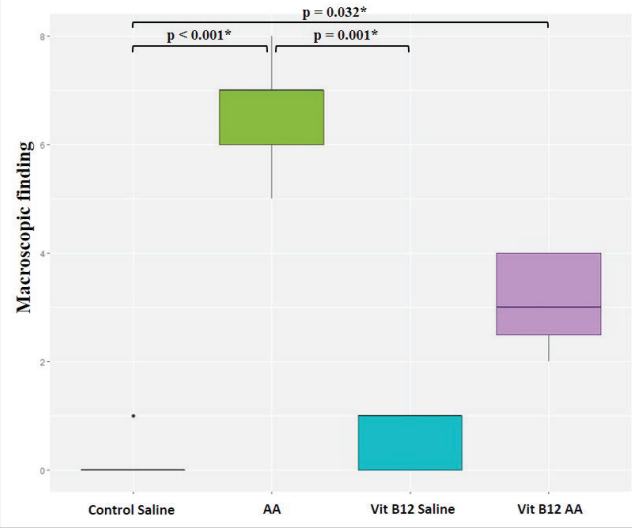

Figure 3. Boxplot for macroscopic finding according to rat groups. There were statistical differences between the control group vs. the VitB12 + AA colitis group and the control vs. the AA colitis groups, and the VitB12 and AA colitis groups (p= 0.032, p< 0.001, and p= 0.001, respectively).

differences in inflammation average between the VitB12 treatment in AA colitis and VitB12 groups, the AA colitis control and VitB12 groups, and the AA colitis control and control saline groups (p= 0.016, p< 0.001, and p= 0.005, respectively), as shown in Table 5 (Figure 4). Hematoxylin and eosin stained paraffin sections of four groups can be seen Figure 5. AA colitis control group has the greatest intensity of inflammatory cells. Control saline group appears to be normal colon tissue. The intensity of inflammation treatment decreased with VitB12 treatment in VitB12 and VitB12 treatment in AA colitis group but the only difference between VitB12 and AA colitis control is significant. There is no statistically significant difference between AA and VitB12 treatment in AA colitis groups.

Changes of Biochemical Measurement After VitB12 Administration in AA-Induced Colitis

All biochemical parameters and mean values are shown in Table 6. Different mean IL-1β values were observed between the VitB12 treatment in AA colitis and control saline groups, and the VitB12 treatment in AA colitis and VitB12 groups (p= 0.006, and p= 0.001, respectively), as shown in Table 6. Significantly different mean plasma IL-6 values were shown between the VitB12 treatment in AA colitis and control saline groups, the VitB12 treatment in AA colitis and the AA colitis control groups, and the VitB12 treatment in AA colitis and VitB12 groups (p= 0.048, p= 0.023, and p= 0.009, respectively). Significant differences in the mean serum TNF-α values between the VitB12 treatment in AA colitis and VitB12 groups and the control saline and VitB12 treatment in AA colitis groups (p= 0.025 and p= 0.021, respectively) were observed. There was a statistically significant difference between the VitB12 treatment in AA colitis and VitB12 groups (p= 0.001) in mean SOD values (Table 6, Figure 6). Post hoc analysis revealed a statistically significant difference in the mean GSH between the VitB12 treatment in AA colitis and VitB12 groups, and the VitB12 treatment in AA colitis and AA colitis control groups (p= 0.028 and p= 0.003, respectively). Significantly different mean serum MDA levels between the VitB12 treatment in AA colitis and VitB12 alone

Table 5. Comparison of inflammatory score means according to rat groups

	n	Mean ± SD	Median (min-max)	p	Post-hoc p
Control	7	0.32 ± 0.12	0.31 (0.21-0.57)	<0.001*	0.005[a]
AA colitis	7	2.02 ± 0.61	1.98 (1.17-2.86)		<0.001[b]
VitB12	7	0.26 ± 0.11	0.24 (0.14-0.48)		
VitB12 + AA colitis	7	1.31 ± 0.56	1.38 (0.70-2.24)		0.016[c]

SD: Standard deviation, Min: Minimum, Max: Maximum.
*Statistically significant (p< 0.001).
[a]Control - AA colitis, [b]AA colitis - VitB12, [c]VitB12 - VitB12 + AA colitis.

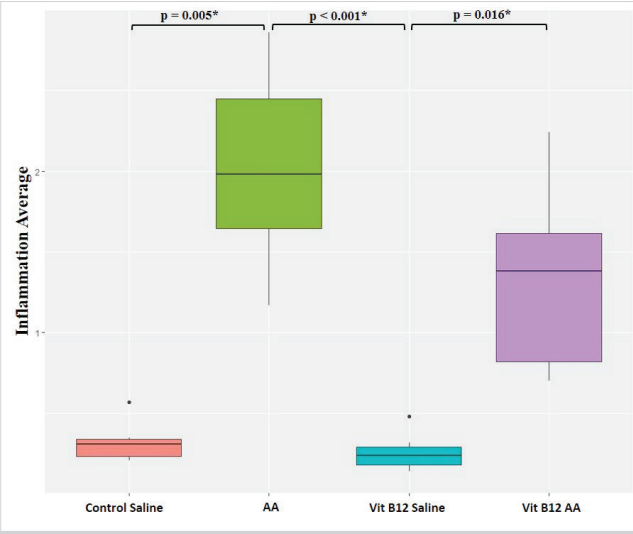

Figure 4. Boxplot for the inflammation score average according to rat groups. There were statistical differences between the control and AA colitis groups, the AA colitis and VitB12 groups, and the VitB12+AA colitis and VitB12 groups (p= 0.005, p< 0.001, and p= 0.016, respectively).

groups and the AA colitis control and VitB12 groups were observed (p= 0.002 and p= 0.010, respectively).

DISCUSSION

In the present study, we evaluated the effect of VitB12 administration on a rat model of AA-induced colitis under the hypothesis that VitB12 supplementation is essential in the prevention of IBD. As per results, VitB12 treatment in AA colitis group's values of IL-6, TNF- α, MDA, IL-1β, SOD, GSH were lower than AA colitis control group, but only IL-6 and GSH parameters reached the significant level. Furthermore, inflammation score and a macroscopic score of VitB12 treatment in AA colitis group were also lower than AA colitis control group. Few studies have investigated the association between VitB12 and colitis pathogenesis, and, to the best of our knowledge, the present study is the first and only experimental model that examined the effect of VitB12 supplementation modulating inflammation in a colitis rat model. Our results signified that although VitB12 can influence colitis, their influences seemed to be marginal and supplementary.

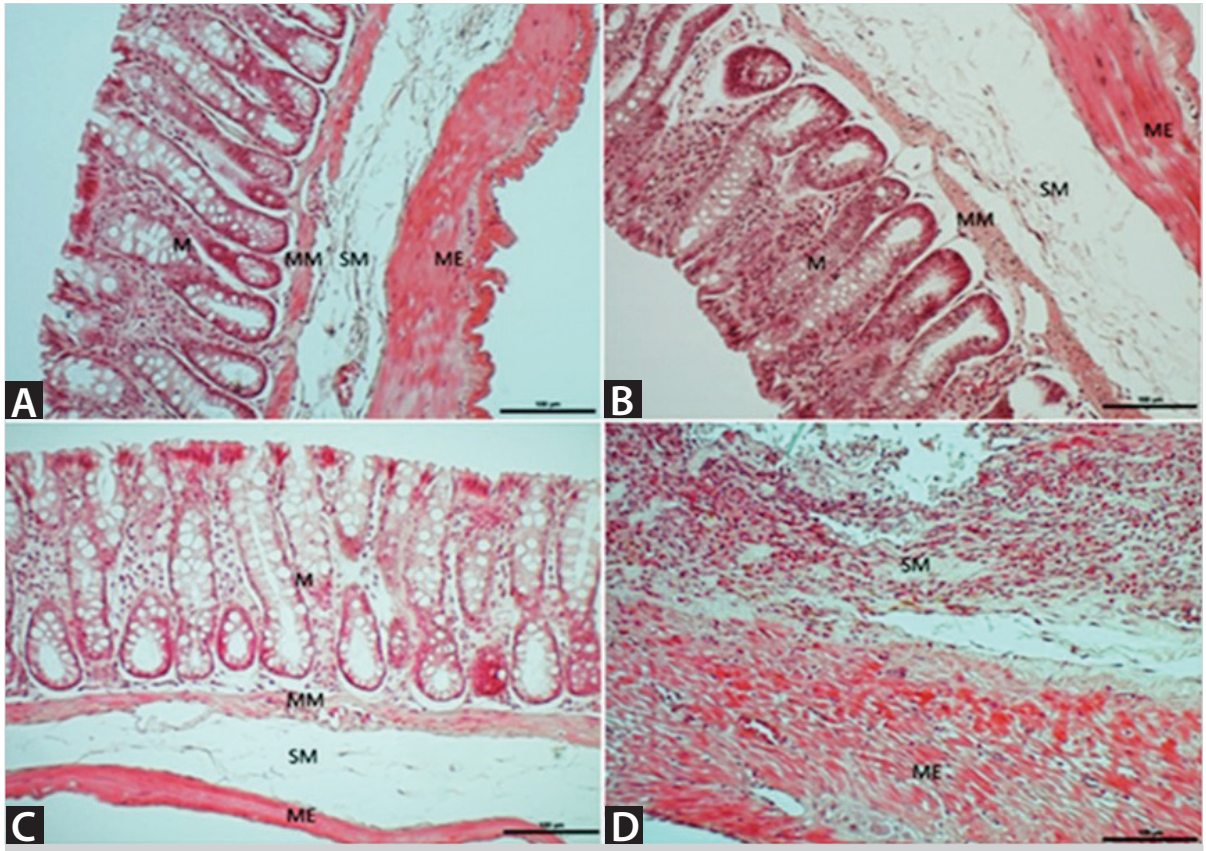

Figure 5. Photomicrographs of H&E stained paraffin sections of the colonic tissues of rats. **A.** Colon saline group showing normal mucosa with intact epithelial surface and normal tissue inflammatory cells. **B.** VitB12 + AA colitis group. **C.** VitB12 group seen to be generally similar to the control group. **D.** AA group showing destruction in all layers and severe crypt and MM damage, SM edema, significant epithelium loss, diffuse inflammatory cells infiltration and necrosis.
M: Mucosa, ME: Muscularis externa, MM: Muscularis mucosa, SM: Submucosa (hematoxylene and eosin, bar 100 µm).

Table 6. Mean comparisons for biochemical parameters

	G	N	Mean ± SD	Median (min-max)	p	Post-hoc p
IL-1β (pg/mL)	1	7	16.67 ± 0.96	16.73 (15.01-17.73)	**0.001****	**0.006**[a]
	2	7	16.24 ± 0.84	16.18 (15.26-17.35)		
	3	7	17.05 ± 0.46	17.05 (16.27-17.72)		**0.001**[b]
	4	7	12.83 ± 0.54	12.57 (12.40-13.96)		
IL-6 (ng/L)	1	7	224.66 ± 8.67	226 (210.66-233.33)	**0.005****	**0.048**[c]
	2	7	226.38 ± 8.26	226 (213.66-238.00)		**0.023**[d]
	3	7	227.14 ± 7.88	224 (217.66-237.00)		**0.009**[e]
	4	7	205.42 ± 9.98	201 (192.00-217.33)		
TNF α (ng/L)	1	7	209.65 ± 6.83	209 (199.33-218.33)	**0.011***	**0.021**[f]
	2	7	204.00 ± 12.64	195 (192.33-221.66)		
	3	7	209.09 ± 7.68	209 (199.00-219.00)		**0.025**[g]
	4	7	188.14 ± 10.40	186 (173.66-201.00)		
SOD (U/L)	1	7	624.86 ± 17.71	625 (604-647)	**0.002****	
	2	7	626.43 ± 27.38	627 (591-661)		
	3	7	642.29 ± 5.93	640 (634-651)		**0.001**[h]
	4	7	583.00 ± 23.55	587 (552-615)		
GSH (uM)	1	7	1.31 ± 0.28	1.25 (0.95-1.75)	**0.003****	
	2	7	1.56 ± 0.25	1.57 (1.29-2.02)		**0.003**[i]
	3	7	1.46 ± 0.49	1.32 (0.94-2.07)		**0.028**[k]
	4	7	0.72 ± 0.18	0.64 (0.57-1.01)		
MDA (uM)	1	7	3.63 ± 0.14	3.61 (3.44-3.85)	**0.002****	
	2	7	3.44 ± 0.33	3.41 (2.95-3.85)		**0.010**[l]
	3	7	4.31 ± 0.39	4.24 (3.84-4.85)		**0.002**[m]
	4	7	3.35 ± 0.34	3.34 (3.00-4.00)		

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

*Statistically significant p< 0.05, **Statistically significant p< 0.01.

G: Groups (1= Control, 2= AA colitis, 3= VitB12, 4= VitB12 + AA colitis).

[a]Control - VitB12 + AA colitis, [b]VitB12 - VitB12 + AA colitis, [c]Control - VitB12 + AA colitis, [d]AA colitis - VitB12 + AA colitis, [e]VitB12 - VitB12 + AA colitis, [f]Control - VitB12 + AA colitis, [g]VitB12 - VitB12 + AA colitis, [h]VitB12 - VitB12 + AA colitis, [i]AA colitis - VitB12 + AA colitis, [k]VitB12 - VitB12 + AA colitis, [l]AA colitis - VitB12 , [m]VitB12 - VitB12 + AA colitis.

Clinical trials that aimed to find an association between the pathogenesis of IBD and vitamin B status have also been published, as they are observational prospective trials that investigated the effect of vitamin B on the course of IBD. As the studies that assessed the serum folate and VitB12 levels of patients with IBD have produced inconsistent results, meta-analyses have been conducted. The first meta-analysis, determined that people with CD have significantly higher levels of plasma homocysteine than do control groups. There was no difference between UC and CD patients (8). A recently published meta-analysis compared serum folate and VitB12 levels in people with IBD and healthy individuals. Interestingly, it found no difference in the mean of VitB12, but the folate levels did differ; people with UC patients had significantly lower serum folate levels than control group, but people with CD did not have different levels of folate from the control group (14).

Antioxidant mechanisms are essential for protecting the colonic mucosa from the harmful effect of inflammation (15). Increasing antioxidant defense mechanisms in the colon mucosa, via pharmacologic therapies, may be beneficial in IBD treatment. Excessive inflammatory response to oxidative stress exacerbates chronic inflammation including intestinal inflammation (16). The release of pro-inflammatory cytokines, such as IL-6, IL-1, and TNF-α, which are crucial to the start and progression of intestinal inflammation, is a major indicator of this disease (17). Padmanabhan et al. (2019) suggested that folate and VitB12 supplementation decreased the level of oxidative stress and ameliorated the cytotoxic effects of carsinogenesis in a rat

Figure 6. Boxplots for IL6 **A.** and TNF α **B.**, MDA **C.**, IL1β **D.**, SOD **E.**, GSH **F.** measurements according to rat groups.
A. The control group vs the VitB12 + AA group (p= 0.048); the AA group vs the VitB12+AA group (p= 0.023); the VitB12 group vs the VitB12 + AA colitis group (p= 0.009). **B.** The control group vs the VitB12 + AA colitis group (p= 0.021); the VitB12 group vs the VitB12+AA colitis group (p= 0.025). **C.** The AA group vs the VitB12 group (p= 0.010); the the VitB12 group vs the VitB12 + AA colitis group (p= 0.002). **D.** The control group vs the VitB12+AA group (p= 0.006); the VitB12 group vs the VitB12 + AA colitis group (p= 0.001). **E.** The VitB12 group vs the VitB12+AA colitis group (p= 0.001). **F.** The AA group vs the VitB12+AA group (p= 0.003); the VitB12 group vs the VitB12 + AA colitis (p= 0.028).

model of colon cancer (18). Moreover, it was demonstrated that the deficit in VitB12 and folate increased plasma level of IL-1β ve IL10 in rats subjected to dextran sodium sulphate (DSS) as an experimental colitis model (19). Similarly, VitB12-producing *Lactobacillus* (CLAB) attenuated colitis damage as well as inflammation and antioxidant markers [myeloperoxidase (MPO), malondialdehyde (MDA), interleukin 6 (IL-6), IL-1β and tumour necrosis factor-α (TNF-α)] in the mice colitis model formed with dextran sodium sulfate (DSS) (20). TNF-α mRNA levels and protein levels of p38, cytosolic phosphopolypase A2, and cyclooxygenase 2 were decreased in an experimental model of colitis induced by VitB12-treated DSS (21).

The present study investigates VitB12 as an antioxidant therapy for IBD, although many antioxidant compounds have yielded promising results as such treatment (22). Our study demonstrated that VitB12 supplementation decreased the levels of IL-6 and GSH in an AA-induced colitis rat model as similar to other studies. Although other biomarkers of inflammation (TNF-α and IL-1β) and oxidative stress (SOD and MDA) were reduced by VitB12, no significant results were observed. The experimental colitis models and the method and duration of administration of VitB12 to animals may differ. Evaluating specific markers of intestinal mucosa on an experimental colitis model that uses antioxidant supplementation may be more beneficial. Additionally, we used a standard diet, not a methyl-deficient diet.

According to Lurz et al. (2020), there were no appreciable variations in body weight between deficient and sufficient VitB12 diets in mice. Colon lengths in VitB12-deficient and VitB12-supplemented mice exposed to DSS were found to differ. In all treatment groups, an increase in the colonic expression of the anti-inflammatory cytokine IL-10 and in the pro-inflammatory cytokine TNF-α in post-DSS has been observed (23). Furthermore, a decrease in colonic tissue damage has previously been reported in the context of DSS. The increase in IL-10 is likely to be responsible for the reduction in tissue damage in VitB12-deficient mice (24). Similarly, in our study, IS and macroscopic score decreased in VitB12 treatment in AA colitis group. However, prior research has shown that VitB12 deficiency causes decreased populations of both CD8+ cell and NK cells, which could possibly account for the decrease in tissue-specific damage (25). Despite these results, multiple studies show that IBD patients have lower VitB12 levels than healthy controls (14). Although more research is required to completely understand the underlying mechanisms, the malabsorption of VitB12 in

colitis likely contributes to inflammation and tissue damage in the intestine.

CONCLUSION

We assessed the effect of VitB12 on AA-induced colitis and expected to see an anti-inflammatory benefit of giving VitB12. Our study demonstrated the benefit of VitB12 via the mean of inflammatory markers, such as IL-6, and the indirect oxidative stress marker GSH. These findings shed important light on the relationships between intestinal inflammation and VitB12. There are several limitations, however, that must be taken into account. The use of AA as a model of colitis is but one of many models of IBD (23). Local inflammatory and oxidative markers were limited in this study. Inflammation and oxidative markers in serum samples were analyzed, but these markers were not tested in colon tissue. Lastly, because only male rats were used, sex-related differences could not be distinguished. In conclusion, our results suggest that changing dietary VitB12 levels may affect conditions of intestinal health. The fact that the anti-inflammatory effect of VitB12 has been demonstrated in this study increases the scientific value of VitB12 for inflammatory diseases. If VitB12 is asserted as an anti-inflammatory, it will be valuable in terms of leading to new studies with vitamin B derivatives. Thus, delivering VitB12 supplements to IBD patients may enhance their healthier lives and prevent other illnesses.

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Ethics Committee Approval: This study was approved by Gaziosmanpaşa University Rectorate Animal Experimentation Local Ethics Committee (Decision no: 51879863-183, Date: 08.05.2014).

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Conflict of Interest: The authors have no conflicts of interest to declare.

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ORİJİNAL ÇALIŞMA-ÖZET
Turk J Surg 2023; 39 (1): 7-16

Sıçanlarda asetik asit ile oluşturulmuş kolit üzerine vitamin B12'nin koruyucu etkisi

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ÖZET

Giriş ve Amaç: Enflamatuvar bağırsak hastalığı (IBD), gastrointestinal sistemin kronik, tekrarlayıcı ve remitan enflamatuvar bir hastalığıdır. Beslenme eksikliği bu hastalıkta katkıda bulunabilir. Biz çalışmamızda, VitB12 takviyesinin sıçanlarda asetik asit (AA) kaynaklı kolit üzerindeki etkisini incelemeyi amaçladık.

Gereç ve Yöntem: Kolit modeli oluşturmak için sıçanlara asetik asit uygulamasından beş dakika sonra VitB12 1 mg/kg, i.p üç gün süreyle uygulandı. Kolit ve VitB12 için kontrol grupları dahil edildi. Dört gün sonra, sıçanlar sakrifiye edildi ve kolon hasarının makroskopik ve mikroskobik incelemesi için kolon dokuları toplandı. Sıçanlardan alınan kan örneklerinde TNF-α, IL-1β, IL-6, MDA, GSH ve SOD değerleri biyokimyasal olarak ölçüldü.

Bulgular: Kolon dokularında iyileşme makroskopik olarak istatistiksel olarak anlamlıydı (p< 0,05). Kontrol grubu ile karşılaştırıldığında VitB12 ile tedavi edilen sıçan grubunda enflamasyonun şiddeti azaldı. AA ile indüklenmiş kolitli grupta VitB12 ile tedavi sonucu TNF-α, IL-1β, MDA ve SOD seviyeleri azalmıştı, fakat istatistiksel olarak anlamlı farklılık görülmedi. Ancak, B12 vitamini enjeksiyonundan sonra AA ile indüklenen kolitli sıçanlarda IL-6 ve GSH seviyeleri önemli ölçüde anlamlı azaldı (p< 0,05).

Sonuç: Beslenme eksiklikleri IBD patogenezine katkıda bulunabilir ve VitB12 takviyesi bağırsak mukozası üzerinde yararlı etkilere sahiptir.

Anahtar Kelimeler: Vitamin B12, enflamatuvar bağırsak hastalığı, enflamasyon, asetik asit

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ORIGINAL ARTICLE
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The evaluation of morbidity in gastrointestinal tumor patients underwent cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (HIPEC)

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ABSTRACT

Objective: In this study, we aimed to determine the postoperative morbidity rate and identify demographic, clinical, and treatment-related variables that may be potential risk factors for morbidity in gastrointestinal tumor patients undergoing hyperthermic intraperitoneal chemotherapy (HIPEC) with or without cytoreductive surgery (CRS).

Material and Methods: In this retrospective study, 60 patients who had undergone HIPEC due to gastrointestinal tumor between October 2017 and December 2019 were included. Systemic toxicities were graded and evaluated according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 criteria.

Results: Mean age of the patients was 60.43 ± 12.83. Primary tumor localization was the stomach in 33 patients (55%), colon in 21 (35%), rectum in five (8.3%), and appendix in one patient (1.7%). PCI mean value was 9.51 ± 10.92. CC-0 was applied in 37 (61.7%) patients, CC-1 in 11 (18.3%), CC-2 in 6 (10%), and CC-3 in six patients (10%). Morbidity was observed in 50 (83.33%) of the 60 patients participating in the study according to NCI-CTCAE v3.0 classification. Mild morbidity rate was 46.6%, severe morbidity rate was 36.6%, and mortality rate was 11.66%. Enteric diversion application, length of stay in the ICU, and length of hospital stay were shown to have a statistically significant effect on the NCI-CTCAE morbidity score ($p= 0.046$, $p= 0.004$, $p< 0.001$).

Conclusion: With proven beneficial effects on survival in patients with locally advanced gastrointestinal tumors, CRC and HIPEC are acceptable in these patients despite their increased morbidity and mortality rate. With new studies on this subject, morbidity and mortality rates may be reduced.

Keywords: Gastrointestinal tumor, cytoreductive surgery, hyperthermic intraperitoneal chemotherapy, morbidity, HIPEC

INTRODUCTION

Peritoneal spread that occurs in primary gastrointestinal cancers (such as the stomach, colon, rectum and appendix) is a common cause of treatment failure (1). The effectiveness of chemotherapy and immunotherapy alone in the treatment of peritoneal carcinomatosis (PC) is limited. Therefore, effective treatments have been sought. Methods such as various combinations of systemic chemotherapy and hyperthermic intraperitoneal chemotherapy (HIPEC) with or without cytoreductive surgery (CRS) have been studied to improve survival and prevent complications. CRS/HIPEC has been used since the 1980s to treat peritoneal malignancy caused by colorectal adenocarcinoma, appendix mucinous carcinoma, and gynecological malignancies (2).

Combined CRS/HIPEC therapy performed in specialized centers has been shown to be an effective treatment option for selected patients with primary and secondary PC. In this dual combination, CRS is used to treat macroscopic disease and HIPEC is used to treat microscopic residual disease. This combination method has slowly become the accepted standard treatment for diseases such as pseudomyxoma peritonei and peritoneal mesothelioma (3-5). In addition, the best long-term results for PC from colorectal cancer have been reported with CRS/HIPEC (6,7). Although there has been quite a bit of research showing that CRS/HIPEC is beneficial, some oncologists remain uncertain of this therapeutic approach due to its high toxicity (8).

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For peritoneal metastases, the benefit of CRS-HIPEC is well defined, and the toxicities associated with treatment are well known. Major morbidity rates of 24-34% and mortality rates of 2-4% have been reported following CRS/HIPEC in large patient series (5,9-13). The most commonly used morbidity and mortality classification systems that assist surgeons in characterizing postoperative complications are Clavien, Feldman, Elias, Bozetti and the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE) (14-22). In our study, we chose NCI-CTCAE version 3.0 to classify surgical morbidity, HIPEC toxicity, and mortality (14). The aim of our study was to determine the postoperative morbidity rate and identify demographic, clinical, and treatment-related variables that may be potential risk factors for morbidity in gastrointestinal tumor patients undergoing HIPEC with or without CRS.

MATERIAL and METHODS

This retrospective study was held in the General Surgery Clinic of Trakya University Faculty of Medicine Hospital, Türkiye between October 2017 and December 2019. Institutional human study review committees of Trakya University Faculty of Medicine (2019/397) approved the study which was conducted in accordance with the tenets of the Declaration of Helsinki, and written informed consent was obtained from all subjects. Data of 60 patients (41 males, 19 females) that had undergone HIPEC were evaluated. Patients under the age of eighteen, who were pregnant, who were unable to give their consent to the procedure, or whose data could not be accessed were excluded from the study.

Age, sex, comorbidities, primary tumor focus (cecum, ascending colon, hepatic corner, transverse colon, splenic corner, descending colon, sigmoid colon tumors in a single group; colon tumors), the operation performed, PCI and complete cytoreduction score (CC), whether they received neoadjuvant therapy or not, duration of hospital stay, intensive care unit (ICU) stay, operation time and data of side effects, morbidity and complications that occurred during the follow-up of the patients were collected after obtaining consent from the patients. The CC score was calculated over the residual tumor in the patient after cytoreduction was complete. In this study, scoring was assessed as CC-0, no residual disease; CC-1, minimal residual disease (0-2.5 mm residual); CC-2, residual disease between 2.5 mm and 2.5 cm; and CC-3, residual disease above 2.5 cm. PCI scores were further divided into three groups, No PC: PCI= 0; Mild PC: 0< PCI< 13; and Severe PC: PCI> 13. The number of patients was determined according to Bozzetti, Elias, Feldman and NCI-CTCAE v.3 scoring. NCI-CTCAE scores were also grouped into no morbidity: grade 0, mild morbidity: grade 1 and 2, and severe morbidity: grade 3, 4 and 5. NCI-CTCAE v.3 scores and groups formed according to these scores, age, sex, PCI score and the groups formed from this score, CC score, primary tumor focus, whether neoadjuvant was taken or not, splenectomy or enteric diversion performed during the surgery, hypertension, type II diabetes, coronary artery disease, previous cerebrovascular disease, surgery time, length of stay in the hospital and ICU were evaluated. Similarly, the duration of surgery, length of hospital stay, and length of stay in the ICU were compared with the CC score and PCI score and the groups formed from this score.

Statistical Analysis

Normal distribution was evaluated by Shapiro-Wilk test. For comparisons of more than two groups, one-way analysis of variance was used for normally distributed variables, and Kruskal-Wallis test was used for variables that were not normally distributed. The relations between qualitative variables were evaluated using Pearson Chi-square test, and the relations between quantitative variables were evaluated with Spearman correlation analysis. As descriptive statistics for quantitative variables, mean and standard deviation were used for normally distributed variables, and medians and quartiles were used for variables that were not normally distributed. Frequency and percentage were given for qualitative variables. The level of significance was set at 0.05 in all statistical analyses. All statistical analyses were performed using the TURCOSA (www.release.turcosa.com.tr) statistical package program.

RESULTS

Demographic characteristics of the patients included in the study are given in Table 1. Mean of the patients was 60.43 ± 12.83 (range, 23-83). Twenty-nine patients (48%) had hypertension, 13 (22%) type II diabetes mellitus, 10 (17%) coronary artery disease and two (3.3%) previous cerebrovascular disease as comorbidity. Thirty-three of the patients (55%) underwent operation for gastric tumor, 21 for colon originated tumor (35%), five for rectal tumor (8.3%) and one for appendix origin tumor (1.7%). Ten of the patients (16.6%) received neoadjuvant therapy. While 12 of the patients did not have PC, 30 patients had mild PC and 18 patients had severe PC. The PCI mean value was 9.51 ± 10.92. Complete cytoreductive surgery (CC-0) for 37 (61.7%) patients, CC-1 for 11 (18.3%), CC-2 for 6 (10%), and CC-3 cytoreductive surgery for 6 (10%) was applied. Median surgery time of the patients was 292.5 (range, 115-555) minutes, and median length of hospital stay was 14 (10-47) days. Splenectomy was performed in eight (13.34%) patients, and enteric diversion was performed in eight (13.34%) patients during surgery.

Morbidity classification of the patients according to Feldman, Bozzetti, Elias and NCI-CTCAE v3.0 is shown in Table 2. According to the new classification of NCI-CTCAE v3.0, 10 patients had no morbidity, 28 patients had mild morbidity, and 22 patients had severe morbidity. Morbidity was observed in 50 (83.33%) of the 60 patients participating in the study according to NCI-CTCAE v3.0 classification. Mild morbidity rate was 46.6%, severe morbidity rate was 36.6%, and mortality rate was 11.66%.

Table 1. Demographic characteristics and perioperative characteristics of the patients included in the study

Variables	n (%)
Age, (years) Mean ± SE (min-max)	60.43 ± 12.83 (23-83)
PCI, Mean ± SE (min-max)	9.51 ± 10.92 (0-39)
Surgery time (minutes) Median (min-max)	313.51 ± 86.55 (115-555)
Length of hospital stay (days) Median (min-max)	15.61 ± 6.89 (10-47)
Receiving neoadjuvant therapy	10 (16.7%)
Splenectomy	8 (13.34%)
Enteric diversion	8 (13.34%)
Length of ICU stay (days) Median (min-max)	2.05 (0-33)
Gender	
Female	19 (31.7%)
Male	41 (68.3%)
PC	
Mild PC (PCI score between 0 and 13)	42 (40%)
Severe PC (PCI score 13 and above)	18 (30%)
CC Scores	
CC-0	37 (61.7%)
CC-1	11 (18.3%)
CC-2	6 (10%)
CC-3	6 (10%)
Primary Tumor Origin	
Stomach	33 (55%)
Colon	21 (35%)
Rectum	5 (8.3%)
Appendix	1 (1.7%)
Comorbidities	
Hypertension	29 (48%)
Type II diabetes mellitus	13 (22%)
Coronary artery disease	10 (10%)
Cerebrovascular disease	2 (3.3%)

CC: Complete cytoreduction, ICU: Intensive care unit, PC: Peritoneal carcinomatosis PCI: Peritoneal carcinomatosis index.

Morbidities observed in patients are shown in Table 3. Ninety-six morbidities were observed in total. The most common morbidity was pneumonia. Of the seven patients who died, four died due to pneumonia, one due to sepsis following esophagojejunostomy leakage in the ICU, one patient due to hemotoxicity concurrent with nephrotoxicity, and one patient because of cerebrovascular disease. Following surgery, a total of three patients had leakage: one esophagojejunostomy anastomotic leak, one duodenal stump leak, and one ileotransverostomy leakage. Pancreatic-cutaneous fistula developed in one patient. It was observed that one patient developed acute myocardial infarction on the 27th day of hospitalization following surgery.

Predictive factors that may affect the NCI-CTCAE morbidity score are shown in Table 4. It was observed that age, sex, primary tumor origin, neoadjuvant therapy, having hypertension, having Type II Diabetes Mellitus, presence of coronary artery disease, had a cerebrovascular disease, having had splenectomy, surgery time, PCI scores, and CC scores did not affect the NCI-CTCAE morbidity score. It was observed that the application of enteric diversion, the length of stay in the ICU, and the length of hospital stay had a statistically significant effect on the NCI-CTCAE morbidity score ($p= 0.046$, $p= 0.004$, and $p< 0.001$, respectively).

The relation of PC distribution of the patients with other parameters is shown in Table 5. A statistically significant correlation was observed between the PCI scores and surgical time ($p= 0.017$, $p= 0.017$). There was a weak correlation between the PCI score and surgical time (correlation coefficient= 0.31). There was no significant relation between PCI scores and PC subgroups and in the length of ICU stay ($p = 0.484$) and length of hospital stay ($p= 0.383$).

The relation between CC scores and other parameters is shown in Table 6. It was observed that there was a statistically significant relation between CC scores and surgery time, and this relationship was due to the difference between CC-0 and CC-2 ($p= 0.004$). As the CC score increases, so does the average duration of surgery; but in CC-3, the average duration fell below CC-0. There was no statistically significant relationship between CC scores and length of stay in the ICU ($p= 0.735$) and length of hospital stay ($p= 0.270$).

Table 2. Number of patients according to Feldman, Bozzetti, Elias and NCI-CTCAE v.3 morbidity classification systems

	Feldman	Bozzetti	Elias	NCI-CTCAE v.3
Grade 0			10	10
Grade 1	13	10	4	7
Grade 2	32	35	31	21
Grade 3	8	8	2	7
Grade 4	7	7	6	8
Grade 5			7	7

Table 3. Morbidities and patient numbers according to the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v.3

	Grade 1-2	Grade 3-4-5		Grade 1-2	Grade 3-4-5
Wound infection	5		Bradycardia	1	
Evisceration		2	Atrial fibrillation	1	
Fever	6		Supraventricular tachycardia	1	
Ileus	2		Myocardial infarction		1
Atelectasis	7		Hypertension		2
Pleural effusion	8	8	Cerebrovascular disease		1
Pneumonia	16	5	Encephalopathy	2	1
Urinary tract infection	3		Duodenal stump leak		1
Central catheter infection	1		Esophagojejunostomy leakage		1
Abdominal abscess	1	1	Pancreatic fistula	1	
Intraabdominal bleeding		2	Ileotransverostomy leakage		1
Diarrhea	1		Nephrotoxicity	1	7
Hematochezia		1	Hematotoxicity	3	2

DISCUSSION

In this study, we retrospectively examined morbidity after HIPEC with or without CRS and the factors that may affect morbidity. According to the NCI-CTCAE morbidity score, total morbidity rate was 83.33%, light morbidity rate was 46.6%, severe morbidity rate was 36.6%, and mortality rate was 11.66%. It was observed that the application of enteric diversion, length of stay in the ICU, and length of stay in the hospital had a statistically significant effect on the NCI-CTCAE morbidity score. In addition, it was determined that the operation time was significantly correlated with CC scores and PCI.

Previously, patients with peritoneal metastases were considered to have an incurable disease. With the addition of CRS/HIPEC to the treatment protocol, however, there has been increasing evidence that this treatment modality is effective in treating selected patients with peritoneal metastases from the appendix (7,23), colon and rectum (8,14,24), small intestine (25,26), ovarian (27) and peritoneum (mesothelioma) cancers (28). Still, the association of this procedure with significant morbidity makes patient selection more important than anything else.

Park et al. (24) have reported a mean operative time of 9.4 hours (range 3.4-19.6) and hospital stay of 20.2 days (8-70). In another study of 420 patients undergoing HIPEC/CRS, they have observed a mean operative time of 563 minutes and a hospital stay of 22 days (25). Polanco et al. (8) have reported that median operative time was 430 minutes and hospital stay was 15.86 days in their study with 370 patients. In our study, median operative time of the patients was 292.5 (range, 115-555) minutes and median hospitalization was 14 (10-47) days. These results are similar to the results of previous studies.

The rate of severe morbidity (class 3 and 4) calculated according to NCI-CTCAE scoring after CRS/HIPEC varies between 20.8% and 53.3% in various sources (26-28). Park et al. (24) have reported that 74.2% of the patients had postoperative complications in the short-term and 10.6% in the long-term. Hematological abnormalities [neutropenia (15.2%) and thrombocytopenia (6.1%)] have been reported as the most common complications of grade II in the same study (24). Baumgartner et al. (29) have reported that 148 (59.9%) of 247 patients experienced complications in the first 60 days after CRS/HIPEC. Among 20 patients (8.1%) with Grade 1 complications, the most common complication has been found as superficial wound infection in five patients and postoperative blood product transfusion in 87 patients (35.2%) with grade 2 complications (29 patients). They have observed grade 3-4 complications in 41 (16.6%) patients (29). In another study, it has been found that the overall complication rate was 42% and the incidence of severe complications (grade III +) in the entire study cohort of patients undergoing CRS/HIPEC was 24% (30). Several studies have established that the incidence of 3/4 grade pulmonary complications was 10-16% (3,25,31,32), hematological toxicity was 4-39%, renal failure was 2-4% (33,34), and venous thromboembolism was 4-4.4% (6,35). In our study, morbidity was observed in 50 (83.33%) of the 60 patients who participated in the study according to NCI-CTCAE v3.0 classification. Mild morbidity rate was 46.6%, severe morbidity rate was 36.6%, and mortality rate was 11.66%. A total of 96 morbidities were observed in 26 different ways. The most common morbidity was pneumonia. Chua et al. (36) have observed that morbidity rates in colorectal patients with CRS/HIPEC varied between 12% and 52%, and mortality rates varied between 0.9% and 5.8%. Fujimura et al. (37) have reported 50% morbidity and

Table 4. Analysis of potential risk factors for NCI-CTCAE scores. According to the NCI-CTCAE scoring grade 0; no morbidity, grade 1 and 2; mild morbidity, grade 3, 4 and 5; severe morbidity

Variables	No morbidity (grade 0) n= 10	Mild morbidity (grade 1-2) n= 28	Severe morbidity (grade 3-4-5) n= 22	p	Test statistic
Age, mean ± SE	64.4 ± 3.77	60.89 ± 2.02	58.04 ± 3.30	0.423	0.8731
Sex					
Male (n= 41)	6 (14.64%)	20 (48.78%)	15 (36.58%)	0.800	0.4451
Female (n= 19)	4 (21.06%)	8 (42.10%)	7 (36.84%)		
Primary tumor origin					
Stomach (n= 33)	7 (21.22%)	16 (48.48%)	10 (30.30%)		
Colon (n= 21)	2 (9.52%)	8 (38.10%)	11 (52.38%)	0.240	7.9691
Rectum (n= 5)	1 (20%)	4 (80%)	0		
Appendix (n= 1)	0	0	1 (100%)		
Neoadjuvant therapy					
No (n= 50)	7 (14%)	24 (48%)	19 (38%)	0.463	1.5397
Yes (n= 10)	3 (30%)	5 (50%)	2 (20%)		
Hypertension					
No (n= 31)	3 (9.68%)	16 (51.61%)	12 (38.71%)	0.318	2.2891
Yes (n= 29)	7 (24.15%)	12 (41.37%)	10 (34.48%)		
Type II diabetes mellitus					
No (n= 47)	7 (14.90%)	23 (48.93%)	17 (36.17%)	0.718	0.6632
Yes (n= 13)	3 (23.08%)	5 (38.46%)	5 (38.46%)		
Coronary artery disease					
No (n= 50)	8 (16%)	22 (44%)	20 (40%)	0.485	1.4462
Yes (n= 10)	2 (20%)	6 (60%)	2 (20%)		
Cerebrovascular disease					
No (n= 58)	10 (17.25%)	27 (46.55%)	21 (36.20%)	0.798	0.4501
Yes (n= 2)	0	1 (50%)	1 (50%)		
Splenectomy					
No (n= 52)	10 (19.23%)	25 (48.07%)	17 (32.70%)	0.184	3.3847
Yes (n= 8)	0	3 (37.5%)	5 (62.5%)		
Enteric diversion					
No (n= 52)	10 (19.23%)	26 (50%)	16 (30.77%)	0.046	6.1663
Yes (n= 8)	0	2 (25%)	6 (75%)		
CC scores					
CC-0 (n= 37)	7 (18.92%)	19 (51.35)	11 (29.73%)		
CC-1 (n= 11)	2 (18.18%)	5 (45.46%)	4 (36.36%)	0.675	4.0119
CC-2 (n= 6)	0	2 (33.33%)	4 (66.66%)		
CC-3 (n= 6)	1 (16.67%)	2 (33.33%)	3 (50%)		
PCI, median (min-max)	3.50 (0-39)	4.00 (0-32)	9.00 (0-39)	0.185	3.3724
PC					
Mild PC (n= 42)	7 (16.66%)	22 (52.38%)	13 (30.96%)	0.329	2.2263
Severe PC (n= 18)	3 (16.66%)	6 (33.34%)	9 (50%)		
Surgery time (minute) Median (min-max)	255 (225-375)	300 (210-555)	312 (115-495)	0.166	3.5976
Length of ICU stay (day) Median (min-max)	0 (0-3)	0 (0-3)	1.5 (0-33)	0.004	10.8360
Length of hospital stay (day), Median (min-max)	12 (10-14)	14 (10-17)	18.5 (10-47)	<0.001	17.4415

CC: Complete cytoreduction, ICU: Intensive care unit, PC: Peritoneal carcinomatosis PCI: Peritoneal carcinomatosis index.

Table 5. Analysis of potential risk factors for peritoneal carcinomatosis index (PCI) scores. PCI scores were divided into three groups, No PC: PCI= 0, Mild PC: 0< PCI< 13, Severe PC: PCI> 13

Variables	No PC (n= 12)	Mild PC (n= 30)	Severe PC (n= 18)	p	Test statistic
Length of ICU stay (day) Median (min-max)	0 (0-3)	0 (0-33)	0 (0-20)	0.484	1.4506
Surgery time (minute) Median (min-max)	270 (210-420)	270 (220-495)	375 (115-555)	**0.017**	**8.2079**
Length of hospital stay (day), median (min-max)	14 (10-18)	14 (10-47)	14 (10-33)	0.383	1.9185

Table 6. Analysis of potential risk factors for Complete cytoreduction (CC) scores. CC-0; no residual disease, CC-1; minimal residual disease (0-2.5 mm residual), CC-2; residual disease between 2.5 mm and 2.5 cm and CC-3; residual disease above 2.5 cm

Variables	CC-0 (n= 37)	CC-1 (n= 11)	CC-2 (n= 6)	CC-3 (n= 6)	p	Test statistic
Length of ICU stay (day) Median (min-max)	0 (0-33)	0 (0-20)	0 (0-6)	1 (0-8)	0.735	1.275
Surgery time (minute) Median (min-max)	270 (210-420)	335 (220-495)	382 (375-495)	255 (115-555)	**0.004**	**13.371**
Length of hospital stay (day), median (min-max)	14 (10-47)	14 (10-27)	13.5 (11-28)	17 (12-33)	0.270	3.925

33.3% reoperation rate in gastric cancer patients with CRS/HIPEC. It has been suggested that higher mortality observed with CRS and HIPEC for gastric cancer may be associated with gastrectomy (38). Our morbidity rates are similar to some studies (24,29), and higher than others (27,30). In our study, we think that 55% of the patients had gastric cancer, contributing to high mortality and morbidity. In addition, significant variations among the reported studies may be related to a variety of factors such as heterogeneity in data collection and reporting, differences in the rating and recording of major complications (such as Clavien scoring, NCI-CTCAE scoring and NSQIP definitions), institutional practices, experience of centers, and differences in patient populations or surgical techniques (8).

Many factors such as sex, age, number of visceral resections, number of peritonectomy procedures, disruption of umbilical fissure, primary colon anastomosis, number of anastomoses, incomplete cytoreduction, chemotherapeutic agent dose, and histopathological classification have been reported as predictive factors of morbidity following CRS/HIPEC (3,25,39-41). Simkens et al. (42) have identified patient's recent smoking history, surgical history, physical performance status, and the extent of cytoreduction as important prognostic factors for severe morbidity. In another study, only the CC score has been found to be a risk factor (29). Saxena et al. (43) have defined operative time greater than 10 hours and ASA greater than 3 as independent risk factors for complications of grade 3/4 in patients with pseudomyxoma peritonei. However, we did not observe most of these factors in our study. Furthermore, we observed that the application of enteric diversion, length of stay in the ICU, and length of stay in the hospital had statistically significant effects on the NCI-CTCAE morbidity score. However, based on this result, it would not be scientifically correct to say that the length of hospitalization and length of stay ICU directly increase morbidity. Patients with high morbidity scores will stay longer in the hospital to treat the associated morbidity as needed. The way to test this hypothesis is to prolong the non-indicative hospitalization periods of patients with lower morbidity scores and determine whether these patients will experience different or severe morbidities. However, this is not possible within the framework of general medical rules.

CONCLUSION

Studies have shown that there is a direct relationship between PCI and grade 3/4 morbidity and mortality. As a result of extending the PC, more extensive surgery, more blood loss, and consequently higher complication rates have been observed. High PCI (PCI> 17 for colorectal and PCI> 12 for stomach) in peritoneal metastases originating from stomach and colorectal has also been associated with poorer overall survival (44,45). In addition, it has been reported that both PCI and CC scores are prognostic factors affecting clinical and oncologic outcomes after HIPEC and CRS according to some study results (4,10,31). High CC-0 rates were observed in patients with low PCI, low CC-0 rates, and high CC-2 rates in patients with high PCI. These correlations suggest that incomplete resections and poor prognosis can be observed in cases of extensive peritoneal seeding (46). The necessity of obtaining complete cytoreduction has been emphasized in a number of publications in order to increase the chances of success of the treatment (47,48). It was

agreed that the PCI threshold value for CRS + HIPEC application in gastric cancer patients should be below 12 points (49). Coccolini et al. (47) have reconfirmed in their last meta-analysis that the PCI score threshold should be below 12 points. In our study, the mean value of PCI was 9.51 ± 10.92 and was below the reported value of 12. However, we did not observe any relationship between PCI rates and the NCI-CTCAE morbidity score in our study. Similarly, Verwaal et al. (50), using the same PCI scores as our study, have not found a relation between PCI scores and morbidity. Similar to PCI, CC scores did not affect the NCI-CTCAE morbidity score. There are studies (26,50) showing that CC scores affect the NCI-CTCAE morbidity score as well as those (25,28) showing that they do not. In our study, there was a statistically significant relation between CC scores and the duration of the surgery, which was due to the difference between CC-0 and CC-2. The mean surgery time increased as the CC score increased; but in CC-3, the mean time fell below CC-0. Therefore, it is thought that in patients with CC-3, the extent of peritoneal tumor spread, and possible resection is at a level that will increase the risk of perioperative mortality. Therefore, the operation time may be shortened because there is no resection attempt.

The limitations of the present study are the nuances of a single-center series and its evaluation of short-term results following HIPEC with or without CRS. However, this study is still valuable as we show the short-term clinical consequences of HIPEC with or without CRS used to treat peritoneal metastasis from gastrointestinal cancer.

In the literature, it has been shown that the addition of cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy to modern chemotherapy regimens significantly prolongs survival in patients with locally advanced cancer of the gastrointestinal tract. The morbidity rate of the current procedure is higher than conservative surgical techniques. However, this rate is expected considering the size of the surgery and the chemotherapeutic cytotoxic effect. Presenting different clinical experiences on this subject will be effective in determining the factors associated with unexpected events that may occur following operation and for reducing morbidity rates by better managing complications.

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ORİJİNAL ÇALIŞMA-ÖZET
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Hipertermik intraperitoneal kemoterapi (HIPEC) ile sitoredüktif cerrahi uygulanan gastrointestinal tümör hastalarında morbiditenin değerlendirilmesi

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ÖZET

Giriş ve Amaç: Çalışmada, sitoredüktif cerrahi (CRS) ile veya CRS olmaksızın hipertermik intraperitoneal kemoterapi (HIPEC) uygulanan gastrointestinal tümör hastalarında postoperatif morbidite oranını belirlemeyi ve morbidite için potansiyel risk faktörleri olabilecek demografik, klinik ve tedavi ile ilgili değişkenleri belirlemeyi amaçladık.

Gereç ve Yöntem: Çalışmaya Ekim 2017 ile Aralık 2019 tarihleri arasında gastrointestinal tümör nedeniyle opere edilen ve HIPEC uygulanan 60 hasta dahil edildi. Postoperatif morbiditeler retrospektif olarak, Ulusal Kanser Enstitüsü (NCI) Advers Olaylar için Ortak Terminoloji Kriterleri (CTCAE) sürüm 3.0 kriterlerine göre derecelendirildi ve değerlendirildi.

Bulgular: Hastaların yaş ortalaması 60,43 ± 12,83 idi. Primer tümör lokalizasyonu 33 hastada (%55) mide, 21'inde kolon (%35), beşinde rektum (%8,3) ve bir hastada apendiks (%1,7) idi. PCI ortalama değeri 9,51 ± 10,92 idi. 37 (%61,7) hastaya CC-0, 11'ine (%18,3) CC-1, 6'sına (%10) CC-2 ve altısına (%10) CC-3 uygulandı. NCI-CTCAE v3.0 sınıflamasına göre çalışmaya katılan 60 hastanın 50'sinde (%83,33) morbidite gözlendi. Hafif morbidite oranı %46,6, şiddetli morbidite oranı %36,6 ve mortalite oranı %11,66 idi. Enterik diversiyon uygulaması, yoğun bakımda kalış süresi ve hastanede kalış süresinin NCI-CTCAE morbidite skoru üzerinde istatistiksel olarak anlamlı bir etkisi olduğu gösterildi (p= 0,046, p= 0,004, p< 0,001).

Sonuç: Lokal-ileri gastrointestinal tümör hastalarında sağkalım üzerinde kanıtlanmış faydalı etkileri olan CRC ve HIPEC, artan morbidite ve mortalite oranlarına rağmen bu hastalar için kabul edilebilirdir. Bu konuda yapılacak yeni çalışmalarla morbidite ve mortalite oranları düşürülebilir.

Anahtar Kelimeler: Gastrointestinal tümör, sitoredüktif cerrahi, hipertermik intraperitoneal kemoterapi, morbidite, HIPEC

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ORIGINAL ARTICLE
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The risk factors for failure and recurrence of LIFT procedure for fistula in ano

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ABSTRACT

Objective: Fistula in ano (FIA) is a common anorectal problem. There are several techniques that have been used for treatment; however, all of them carry risks of recurrence and incontinence. Ligation intersphincteric fistula tract (LIFT) is a type of treatment with a promising result of preserving the anal sphincter function. This study aimed to evaluate the outcome and risk factor of LIFT failure and to demonstrate the pattern of recurrence. The research funding was supported by Rajavithi Hospital.

Material and Methods: From January 2015 to January 2020, there were 250 cases of fistula in ano operations. A total of 148 patients underwent LIFT operation. The patients' average age was 39.72 ± 10.55 years and the average follow-up period was 111.86 ± 79.73 days. The average time to diagnose the recurrence was 99.12 ± 30.08 days. In addition, average time to perform a surgery after the diganosis was 64.67 ± 25.76 days. The study's analyses used data on age, sex, type of fistula, operative intervention, healing time, reinterventions, and recurrence.

Results: There were 22.97% of recurrence among 148 LIFT patients. Half of the patients who underwent the operation had a preoperative imaging study with MRI or endoanal ultrasonography in the first time due to the complexity of the disease. Factors associated with operation failure were collection, fistula tract size more than 5 millimeters, and the failure of ligating the tract in one attempt.

Conclusion: LIFT procedure is one of the several sphincter saving procedures to treat FIA. Recurrence is related with the complexity of the disease. Most of the recurrence is diseases that are easier to treat, such as performing a re-operation or fistulotomy.

Keywords: Fistula in ano, LIFT, recurrence, risk factor

INTRODUCTION

Fistula in ano (FIA) is common in surgical practices. The generally accepted pathogenesis is chronic infection of the anal gland developing between the anal mucosa and skin. However, the treatment for FIA is difficult due to the risk of incontinence. Treatments for FIA are sphincter sacrifice procedure and sphincter saving procedure. Examples of sphincter sacrifice are fistulotomy, fistulectomy, and seton with staged fistulotomy (1). Examples of sphincter saving are core-out fistulectomy, advancement flap, anal fistula plug, fibrin sealing, ligation of intersphincteric tract (LIFT), and video-assisted anal fistula treatment (VAAFT). Ligation intersphincteric fistula tract (LIFT) is one of the sphincter saving procedures with promising results in success rate and postoperative continence (1-3). This study aimed to examine the recurrence group after LIFT to identify risk factors and patterns of recurrence.

MATERIAL and METHODS

A retrospective study in medical records was conducted from Januar1, 2015 to January 30, 2020. The ethics committee of Rajavithi Hospital had reviewed and approved this study, with the study number 64020. Inclusion criteria were patients who underwent LIFT operation in Rajavithi Hospital, aged between 18-70 years, and had an imaging study of fistula in pre-operative and follow up time for at least three months. Exclusion criteria were underlying colorectal cancer or pelvic organ cancer, concomitant with inflammatory bowel disease (IBD), and previous pelvic radiation. Definitions of suspect recurrence in this study are non-healing external opening after 12 weeks and the occurrence of new external opening caused by the original internal opening. The fistula in ano classification in this study is based

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on Park's anal fistula classification regarding high and low transsphincteric types, in which low transsphincteric is classified by how the tract involves one-third or less of the sphincter complex.

All data were collected and analyzed with SPSS (version 20.0). Mann-Whitney U test and Chi-square test were used to make comparisons between the groups. Univariate relationships between each independent variable and fistula formation were tested using binary logistic regression. Odds ratio (OR) with 95% confidence intervals (CI) of each variable was determined, and significant variables in the univariate analysis were included in a multivariate model of logistic regression. p-value of less than 0.05 was considered statistically significant.

RESULTS

There were 250 cases of fistula in ano operations in total. The cases were divided into 148 LIFT patients, 51 fistulotomy patients, 10 advancement flap patients, 15 seton and stage fistulotomy patients, 14 core-out fistulectomy patients, and 12 examinations under anesthesia patients.

The recurrence percentage after LIFT procedure was 22.97% (34 patients). Seventy patients who underwent LIFT operation had a preoperative imaging study with MRI or endoanal ultrasonography. The average time for diagnosing recurrence was 99.12 ± 30.08 days (mean ± SD) (ranged between 60-200 days) and the average time to conduct operation after the recurrence diagnosis was 64.68 ± 25.76 days (mean ± SD) (ranged from 30-120 days.) Comparative demographic data between failure and success of LIFT procedure is shown in Table 1. Comparative operative data is shown in Table 2. In summary, univariable analysis factors associated with recurrence after LIFT are the type of FIA, presence of collection, tract diameter that is greater than five millimeters, and more than one attempt to ligate the tract. Subgroup analysis of collection shows the presence of collection in both ischiorectal and deep post anal space, which have a high risk of recurrence. Multivariable analysis of factors associated with recurrence is shown in Table 3.

Recurrence patterns after LIFT are shown in Table 4. The most common pattern of recurrence was type 2: The remaining internal opening with a new external opening at the intersphincteric wound, which is shown in Figure 1. In this pattern, there were two cases occurred in "complex" due to multiple external openings at the first time of diagnosis. The operations for correction were as follows: Type 1 cases underwent LIFT 4 (36.4%), advancement flap 3 (27.3%), drainage seton with subsequent fistulotomy seton 1 (9.1%), and LIFT with placed drain 3 (27.3%). Type 2 cases underwent fistulotomy 15 (88.2%), LIFT 1 (5.9%), and drainage seton with subsequent fistulotomy 1 (5.9%). Type 3 cases underwent LIFT 1 (50%) and fistulectomy 1 (50%) and type IV cases underwent curettage sinus tract 1 (25%) and observation 3 (75%). Mean follow-up period in all patients was 115.42 ± 115.96 days. Recurrence after the second operation occurred in four cases, two cases after LIFT, 1 after anal advancement flap, and 1 after LIFT with placed drain. All four cases also underwent drainage seton.

DISCUSSION

LIFT is one of the sphincter saving operative procedures for treating fistula in ano. An average success rate is 60-94% (4,5), with up to eight weeks of wound-healing time. Recurrence after LIFT procedure does not have a specific definition; however, the most used definition is non-healing of external wound or an external opening after eight weeks.

Risks of recurrence can be divided into three factors: patients, diseases, and surgeons' experience. First, as for surgeons, this study does not show different results among the group of colorectal surgeons. The learning curve of surgeons in each procedure is the most important factor for an entrusted achievement of the result. However, the learning curve in LIFT does not define it. Nonetheless, Rojanasakul's study reported the high success rate of LIFT (2). Thus, LIFT procedure has been adopted in training and practice of general surgery in Thailand, as well as in this study. A surgeon who has more than 20 years of experience and has self-studied LIFT can perform the operation without any difference in result when compared to other surgeons who have learned the procedure under proctorship. Therefore, it can be assumed that the LIFT procedure is not a difficult procedure, nor does it require a steep learning curve for colorectal surgeons. Regarding the difference from laparoscopic colorectal procedure (6,7), studies show a discrimination of results in rectal cancer in comparison between general surgeons and colorectal surgeons (8). Studies also show the significance of training and the result of surgery by specialists (9,10).

The factor regarding patients, as the previous studies' report has stated, are immunocompromised host (11), Crohn's disease (12), smoking (13), diabetic mellitus (14), obesity (1), and concurrent with rectal cancer (15). These all indicate risks of failure after LIFT procedure. In the postoperative period, the study has reported that regular examination, careful attention, and wound cleansing are helpful for an early diagnosis of recurrence and complications (16).

The disease factor, based on Park's classification (17), indicates that the supra-sphincteric and extra-sphincteric fistulae were at risk of recurrence (4,5,18,19). This study shows that the most common (recurrence) is the transsphincteric type. Possible explanations are an incidence that occurs more than other types, and transsphincteric which includes semi horseshoe and horseshoe. Horseshoe is a factor related to LIFT failure (18); however. the multivariable analysis did not show any significance. The presence of collection in one or both sides of ischiorectal or deep post anal space indicates failure of clearance infection in concordance to previous study result (20), which

Table 1. Demographic data between recurrence and success after LIFT procedure

Demographic data	Recurrence (n= 34)	Success (n=114)	p
Sex (%)			0.953
Male	27 (23.1)	90 (76.9)	
Female	7 (22.6)	24 (77.4)	
Age (Mean ± SD)	38.53 ± 10.86	40.08 ± 10.48	0.454
BMI (Mean ± SD)	27.76 ± 9.49	26.03 ± 5.16	0.173
Smoking (%)			1.000
Yes	4 (11.8)	14 (12.3)	
No	30 (88.2)	100 (87.8)	
Co-morbidity (%)			0.800
Yes	27 (79.4)	97 (82.5)	
No	7 (20.6)	20 (17.5)	
Time to surgery after first visit (Mean ± SD) (days)	100.68 ± 95.13	108.28 ± 119.18	0.732
Referred from other hospital (%)			0.435
No	15 (44.1)	61 (53.5)	
Yes	19 (55.9)	53 (46.5)	
Previous surgery			0.359
No	28 (82.4)	101 (88.6)	
Fistulotomy	2 (5.9)	3 (2.6)	
LIFT	4 (11.8)	6 (5.3)	
Fistulectomy	0 (0)	3 (2.6)	
Endoanal advancement flap	0 (0)	1 (0.9)	
Fistula type (%)			**0.001**
Intersphincteric	0 (0)	3 (2.6)	
Transsphincteric: Low level	1 (2.9)	18 (15.8)	
Transsphincteric: High level	28 (82.4)	92 (80.7)	
Suprasphincteric	5 (14.7)	1 (0.9)	
Presence multiple external opening (%)	19 (55.9)	50 (43.9)	0.217
Type of imaging study (%)			**0.038***
MRI	10 (33.3)	20 (66.7)	
EAUS	4 (10.0)	36 (90.0)	
Presence of collection from imaging study (%)			<0.001*
Yes	30 (43.5)	39 (56.5)	
No	4 (5.1)	75 (94.9)	
Detail of collection from imaging study (%)			**<0.001***
One side ischiorectal	12 (31.6)	26 (68.4)	
Both ischiorectal	10 (66.7)	5 (33.3)	
Deep postanal with ischiorectal	8 (100)	0 (0)	
Perianal	0 (0)	8 (100)	

shows that horseshoe fistula has risks of recurrence and needs multiple surgeries to correct. A previous study shows types of clearance infection, such as curettage from original LIFT (2) or LIFT's modification to remove tract, which do not imply an improvement of the cure rate (1). Nevertheless, drainage placement is not strong evidence to show an improved cure rate.

Table 2. Operative data between recurrence and success after LIFT procedure

Operative data	Recurrence (n= 34)	Success (n= 114)	p
Colorectal surgeon experience (%)			0.479
5-10 years	13 (26.0)	37 (74.0)	
11-20 years	11 (18.0)	50 (82.0)	
>21 years	10 (27.0)	27 (73.0)	
Operative time (minutes) (mean ± SD)	48.97 ± 21.45	48.95 ± 22.05	0.996
Operative difficulty			
Tract diameter> 5 mm (%)			**<0.001***
Yes	26 (74.3)	9 (25.7)	
No	8 (7.1)	105 (92.9)	
Attempt ligate tract> 1 time (%)			**<0.001***
Yes	11 (57.9)	8 (42.1)	
No	23 (17.8)	106 (82.2)	

Table 3. Cox regression analysis factor associated with recurrence after LIFT procedure

Factors	Crude odd ratio	95% CI		p	Adjusted odd ratio	95% CI		p
		Lower border	Upper border			Lower border	Upper border	
Tract diameter> 5 mm	7.105	3.431	14.711	<0.001	6.113	2.902	12.876	<0.001
Attempt ligate tract> 1 time	2.453	1.195	5.038	0.015	1.898	0.920	3.912	0.083
Presence of collection	1.957	1.326	2.889	<0.001	1.272	0.855	1.894	0.236

Table 4. Patterns of fistula recurrence after LIFT procedure

Patterns	Description	n (%)
1: Original fistula	Remain same internal opening and external opening	11 (32.4)
2: Step down fistula	Remain same internal opening with new external opening at intersphincteric wound	17 (50.0)
3: New fistula	Remain same internal opening with new external opening, anywhere outside intersphincteric wound	2 (5.9)
4: Sinus	Remain in external tract	4 (11.8)

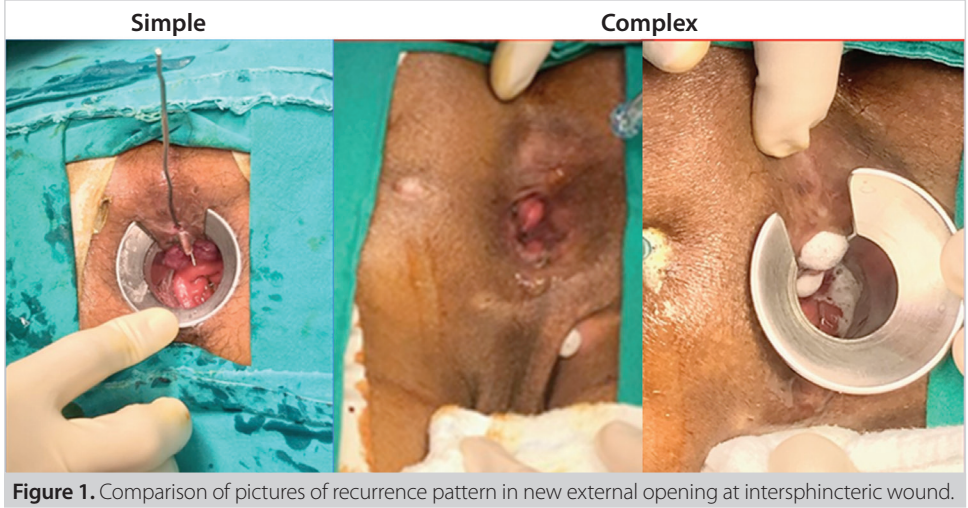

Figure 1. Comparison of pictures of recurrence pattern in new external opening at intersphincteric wound.

Early closure of external wound or an opening is one of the factors leading to failure since it has not achieved adequate sources to control in concordance with the previous study, which demonstrates the result of simple fistula surgery (21). This study shows the significance of presence of collection in univariable analysis; however, it does not show statistical significance regarding the type of collection in multivariable analysis. The other risk factor in this study was more than one intraoperative attempt to ligate the tract. The possible explanations may be a difficulty of identifying the tract in narrow intersphincteric space, high tract level, or occurrence of iatrogenic in transection tract, which leads to a poor or improper closure of the internal opening. A previous study has shown the importance of imaging study, which is the success rates of internal opening identifications and preoperative imaging studies. The success rates of rectal endoscopic anal ultrasonography (EAUS) and pelvic MRI in locating internal openings are 70-95% and 90-96%, respectively (22-24). The failure of locating internal opening is the report of the risks of operative failure, which is 20 times relative to the risk score (25). In this study, it showed similar correlation with univariable analysis. This study also showed that an intraoperative fistula tract with a diameter of more than five millimeters is a risk factor of recurrence. Technically, the closure of fistula tract via ligation or suture ligation are at risk of knot sliding, leading to an unaccomplished optimal tension of closure of fistula tract opening. Indirect comparative studies are those regarding fistula laser closure (FiLaC) and laser ablation of fistula tract (LAFT) in fistula tract size that is greater than five millimeters. Results indicate that the shrinkage of the tract is poor (26). Thus, the author suggests that suture buttress at internal sphincter on anal site and buttress on external sphincter on external site may be helpful to improve closure. However, further studies are still in need.

There are three reported patterns of recurrence (27): complete failure, partial failure, and localized failure. Later reports in patterns of recurrence regarding new occurrence of fistula character are intersphincteric fistula, remaining or original fistula, and remaining external tract (28). This study shows two points of concern. First, in comparison with previous studies, the complexity of intersphincteric or partial failure is related to multiple external openings or the presence of collection in the first diagnosis. As a result, the fistulomy in the previous recommendation may not be sufficient for correction. Therefore, the author suggests adding C in order to define the complexity of recurrence pattern. The second concern is the new pattern of recurrence, in which a new external opening occurs at the other site, out of intersphincteric wound, making it different from previous studies. The cause may be failure to close the internal opening, which leads to a new onset of infection of the new tract. However, this cannot lead to a conclusion that it is a new type of recurrence pattern since this study was conducted in a small sample group. Thus, further studies are still needed.

The limitation of this study was the variable in imaging study due to surgeon's preference and the feasibility of imaging during the study period. In addition, the operation to correct re-recurrence depended on the anatomy of the fistula as well.

CONCLUSION

Fistula in ano is a disease with a lot of myths in curative outcomes depending on diseases, patients, and surgeons. LIFT is one of the operations that has an advantage in sphincter saving, with an ability to perform a reoperation when a recurrence occurs, down stage of fistula in ano. The pattern of recurrence is still undergoing examination and studies; thus, it needs a larger database to demonstrate the number of patterns. Furthermore, there is still a chance to improve the procedure of current techniques. In the future, LIFT may potentially play a fundamental role in fistula surgery.

Ethics Committee Approval: The ethics committee, Rajavithi hospital had reviewed and approved this study, with the study number 64020.

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Author Contributions: Concept - SS; Design - SS; Data Collection and/ or Processing - SS; Analysis and/or Interpretation - SS; Literature Search - SS; Writing Manuscript - SS; Critical Reviews - SS.

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ORİJİNAL ÇALIŞMA-ÖZET
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Anal fistül tedavisinde LIFT prosedürünün başarısızlığı ve nüks için risk faktörleri

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ÖZET

Giriş ve Amaç: Anal fistül (FIA) yaygın bir anorektal problemdir. Tedavi için kullanılan çeşitli teknikler vardır ancak hepsi nüks ve idrar kaçırma risklerini taşır. Ligasyon intersfinkterik fistül traktı (LIFT), anal sfinkter fonksiyonunu koruma konusunda umut verici sonuç veren bir tedavi türüdür. Bu çalışma, LIFT başarısızlığının sonucunu ve risk faktörünü değerlendirmeyi ve nüks paternini göstermeyi amaçladı. Araştırma fonu Rajavithi Hastanesi tarafından desteklenmiştir.

Gereç ve Yöntem: Ocak 2015'ten Ocak 2020'ye kadar anal operasyonlarda 250 fistül vakası vardı. Toplam 148 hastaya LIFT operasyonu uygulandı. Hastaların ortalama yaşı 39,72 ± 10,55, ortalama takip süresi 111,86 ± 79,73 gündü. Nüksü teşhis etmek için ortalama süre 99,12 ± 30,08 gündü. Ayrıca tanı sonrası ortalama ameliyat süresi 64,67 ± 25,76 gündü. Çalışmanın analizlerinde yaş, cinsiyet, fistül tipi, operatif müdahale, iyileşme süresi, yeniden müdahaleler ve nüks ile ilgili veriler kullanıldı.

Bulgular: Yüz kırk sekiz LIFT hastasında %22,97 oranında nüks vardı. Ameliyat olan hastaların yarısında, hastalığın karmaşıklığı nedeniyle ilk kez MR veya endoanal ultrasonografi ile ameliyat öncesi görüntüleme çalışması yapıldı. Ameliyat başarısızlığı ile ilişkili faktörler, birikim, fistül yolu boyutunun 5 milimetreden fazla olması ve ilk denemede ligasyon yapılamaması olarak sunulmuştur.

Sonuç: LIFT prosedürü, FIA'yı tedavi etmek için kullanılan çeşitli sfinkter koruma prosedürlerinden biridir. Nüks, hastalığın karmaşıklığı ile ilişkilidir. Nükslerin çoğu, yeniden ameliyat veya fistülotomi yaparak tedavi etmesi daha kolay olan hastalıklardır.

Anahtar Kelimeler: Anal fistül, LIFT, nüks, risk faktörü

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ORIGINAL ARTICLE
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How much is the long-term quality of life impaired in cholecystectomy-related biliary tract injury?

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ABSTRACT

Objective: Iatrogenic bile duct injury (IBDI) is a serious complication of cholecystectomy that may crucially affect long-term quality of life and have major morbidities. Furthermore, even after reconstructive surgical treatment, such injuries still reduce the long-term quality of life. Therefore, there remains a need to investigate long-term quality of life of the patients since it is considered that there is a long-term decrease in both physical and mental quality of life. Accordingly, this study aimed to investigate the clinical evaluations and long-term quality of life of the patients who had undergone reconstructive surgery for iatrogenic bile duct injury.

Material and Methods: This clinical study included 49 patients (38 females/11 males) with cholecystectomy-associated bile duct injury and who underwent reconstruction surgery. Several parameters, including the type of bile duct injury, reconstructive surgical procedures, length of hospital stay, and complications were evaluated. Moreover, the effects of reconstructive surgical timing (perioperative, early postoperative, late postoperative) on quality of life were assessed. Long term quality of life (LTQL) levels were evaluated using the SF-36 questionnaire in patients whose follow-ups ranged from two to nine years. The SF-36 questionnaire scores were compared to the average SF-36 norm values of the healthy Turkish population.

Results: Our results showed that 73.5% of biliary tract injuries occurred after a laparoscopic surgery while 26.5% after open cholecystectomy. Of the injuries, 32.7% developed in patients with acute cholecystitis. Thirty of the patients were treated with hepaticojejunostomy. When SF-36 questionnaire scores of the study were compared to those of the healthy Turkish population, energy-vitality was found to be lower significantly in male patients (p= 0.041). However, there was no significant deterioration in female patients. Although general health perception was better in hepaticojejunostomy according to the type of reconstructive surgery performed, no significant difference was observed in the quality of life. Mental health, energy-vitality (p= 0.019), and general health perception (p= 0.026) were found to be lower in women who had E^1-E^2 injuries. Only seven of the injuries were detected perioperatively. Physical function (p= 0.033) and general health perception (p= 0.035) were found to be lower in the early postoperative treatment group in male patients in terms of the time of reconstructive surgery.

Conclusion: IBDIs cause serious morbidity. Furthermore, even after reconstructive surgical treatment, such injuries still reduce LTQL. Our results suggest that LTQL is lower, especially in male patients undergoing postoperative early biliary repair for Strasberg E^3-E^4 type injuries.

Keywords: Bile duct injury, cholecystectomy, complication, hepaticojejunostomy, quality of life, SF-36

INTRODUCTION

Cholecystectomy, which is one of the most common surgical operations in the field of general surgery, is frequently performed laparoscopically. The risk of iatrogenic bile duct injury (IBDI) is around 0.4% worldwide (1). Along with other complications and risks, IBDI also requires some invasive procedures. For example, even minor injuries may result in serious morbidity and mortality due to bile leakage and sepsis (2). Although reconstructive surgical procedures are mostly successful, lifelong problems may still occur, including serious complications such as biliary stricture, portal hypertension, cirrhosis, and liver failure. Therefore, there remains a need to investigate long-term quality of life (LTQL) of the patients since it is considered that there is a long-term decrease in both physical and mental quality of life. Accordingly, this study aimed to investigate the clinical evaluations and LTQL of patients who had undergone reconstructive surgery for IBDI. Quality of life shows differences between different groups with various education or socioeconomic status and different geographical regions. Although studies on quality of life after IBDI have been published previously, the presented study is the first one studied in the Turkish population.

MATERIAL and METHODS

The study was conducted in accordance with the Declaration of Helsinki, and the study protocol was approved by Gaziantep University Clinical Research Ethics Committee (Ethical approved number: 2018/340 on 13.03.2019).

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Starting from October 2009, patients who had undergone reconstructive surgery with a diagnosis of IBDI were scanned from the electronic archive of the hospital. Among potential participants, patients who died or could not be contacted, and those who were treated within the last two years were excluded from the study. Following an approval of participation from the patients, clinical and demographic characteristics were recorded. The following information were evaluated: primary disease, surgical method performed, type of bile duct injury according to Strasberg classification, time between the primary surgery and reconstructive surgery, reconstructive surgical procedures performed, length of hospital stay, and complications.

SF-36 questionnaire was used to evaluate LTQL (3). It was ensured that all patients answered the questions on the questionnaire with the help of a healthcare staff. At the same time, blood samples were taken from the patients to evaluate their current biochemical parameters. In this way, LTQL and current physiological parameters of the patients with IBDI after cholecystectomy were examined.

Although the same SF-36 questionnaire was applied to both sexes, the results were evaluated separately for male and female patients because Turkish norm values of the SF-36 questionnaire (4) showed differences for both sexes. Thereby, an opportunity was ensured for analyzing the data more specifically. Physical function, physical role difficulties, emotional role difficulties, energy-vitality, mental health, social functionality, pain, and general health perception were evaluated in this questionnaire. Each question in the SF-36 questionnaire was scored according to the replacement instruction in the original literature (3). SF-36 scores were then calculated by taking the arithmetic mean of the scores collected within each main parameter. The scores of all patients under eight main headings in the SF-36 questionnaire form were compared with the current SF-36 norm values of the Turkish population. Instead of uncomplicated cholecystectomy patients, Turkish norm values of SF-36 questionnaire have been used as a control group. The reason was that both Turkish norm values had been obtained considering many people, and also the norm value of uncomplicated cholecystectomy patients were similar with these results.

Patients aged 18-78 whose ASA classifications were between ASA 1 and ASA 3 and who did not have serious cardiopulmonary morbidity in their medical history were not separated into subgroups within this topic.

Since all patients did not experience the same anatomical level and the same severity of bile duct injuries, SF-36 scores of the different reconstructive surgical procedures performed to the patients were also compared. In terms of quality of life of the patients, end-to-side standard roux-en-Y hepaticojejunostomy (HJ) and other reconstructive surgical procedures (choledocoduodenostomy, common bile duct primary repair, common bile duct t-tube drainage, cystic duct ligation, Luschka ligation) were compared.

The present study was carried out in an experienced hepatopancreatobiliary center. All reconstructive surgical procedures were performed by the same team consisting of three surgeons.

Hepaticojejunostomies were classified as Strasberg E^1-E^2 and E^3-E^4, and then evaluated separately (5).

The timing of the reconstructive surgery was further evaluated with the questionnaire scores.

Moreover, the patients were divided into three groups according to the time between biliary injuries and reconstructive surgery; perioperative, early postoperative and late postoperative periods. Perioperative period was defined as the interval in which reconstructive surgery was performed intraoperatively or within the first three days according to the injury time. Early postoperative period was defined as the period between the postoperative 4^{th} day and the postoperative 30^{th} day, and late postoperative period was defined as the period after postoperative 31^{st} day.

All statistical analyzes were performed using SPSS 22.0 Windows version. Shapiro-Wilk test was used to test normal distribution of data. Based on normal distribution validation, either Student-t or Mann-Whitney U tests were used to compare two groups and whether data were normally distributed or not, respectively. The Kruskal-Wallis test and the All-Pairwise test were used to compare more than two non-normally distributed variables. $p< 0.05$ was considered as statistically significant.

RESULTS

A total of 68 patients who had been surgically treated for IBDI after cholecystectomy between October 2009 and October 2017 were initially included in this study. As of March 2019, the patients who died and those who could not be reached were excluded from the study. Therefore, the study included 49 patients who were followed up regularly for two years after reconstructive surgical treatment. Previously, the patients had been operated with the diagnosis of acute cholecystitis (32.7%) and were operated by laparoscopic method in 73.5% of all cholecystectomies. While Strasberg type B and E^5 injuries were not seen at all, the most common injury types were E^2 and E^3 injuries.

Seven of these injuries were detected intraoperatively. While four of these patients had HJ, one patient had a t-tube drainage in the common bile duct, one patient had choledoco-duodenostomy, and last one had choledocho-coledocostomy. Reconstructive surgical procedures were required for 31 patients in the early postoperative period and 11 patients in the late postoperative period. The clinical data of these patients are shown in Table 1.

Table 1. Clinical and demographic characteristics of all patients

		Patients (n= 49)	Percent (%)
Age		18-78	44.10 ± 13.88
Sex (F/M)		38/11	
Primary disease	Acute cholecystitis	16	32.7
	Chronic cholecystitis	33	67.3
Primary surgery	Open cholecystectomy	13	26.5
	Laparoscopic cholecystectomy	36	73.5
RS times after IBDIs	Peroperative period	7	14.2
	Early postoperative period	31	63.2
	Late postoperative period	11	22.4
Injury types (Strasberg classicifation)	A	7	14.3
	C	1	2
	D	7	14.3
	E^1	7	14.3
	E^2	12	24.3
	E^3	12	24.3
	E^4	3	6.1
RS tpyes	Roux N-Y hepaticojejunostomy	30	61.2
	Other RS	19	38.8
Clinical findings	Abdominal pain	21	42.8
	Jaundice	8	16.3
	Bile drainage	8	16.3
	Sepsis	4	8.16
Complications after RS	Wound infection	10	20.5
	Cholangitis	9	18.4
	Incisional hernia	7	14.3
	Postoperative stricture	5	10.2
Length of hospital stay (day)		4-58 (avg. 13.84)	

RS: Reconstructive surgery, IBDI: Iatrogenic bile duct injury.

We compared SF-36 scores of the female patients with the average scores of the healthy Turkish female population, and no statistically significant differences were observed. A significant decrease was seen in the SF-36 scores of male patients related to energy and vitality (Table 2). Although physical role difficulties were also affected in male patients who underwent reconstructive surgery after IBDI, they did not reach to the statistically significant level when compared to the normal population.

In terms of physical function, physical role difficulty, emotional role difficulties, energy-vitality, mental health, social functionality, and general health perception, we found that patients with HJ and other surgical procedures had lower scores than average. When HJ and other reconstructive surgeries were compared, we observed that only general health perception in patients with HJ had a higher score than the patients that carried out other reconstructive surgeries (Table 3).

We further found that the recent biochemical values of all patients improved when compared to the reconstructive surgery time and most importantly remained within reference ranges.

All biliary strictures were seen in Strasberg E^3 and E^4 type injured. For this reason, we compared the E^1-E^2 with E^3-E^4 type injuries. Within this classification, a statistically significant lowness was seen at energy-vitality, mental health and general health perception. Another finding of the present study was that Strasberg E^1 and E^2 injuries in female patients always had higher scores in each SF parameters compared to those of E^3 and E^4 type injuries. Moreover, mental health, energy-vitality,

Table 2. Comparison of the SF-36 scores of the patients to LTQL norms of the healthy Turkish population

	Female/Male	Patients SF scores	Healthy Turkish population average SF scores	p
Physical function	F	88.03 ± 10.43	80.6 ± 21.7	0.003*
	M	87.27 ± 09.58	80.6 ± 21.7	0.980
Physical role difficulties	F	75.00 ± 43.11	82.9 ± 28.6	0.588
	M	63.64 ± 50.45	82.9 ± 28.6	0.646
Emotional role difficulties	F	76.31 ± 40.94	89.0 ± 22.5	0.588
	M	63.64 ± 50.45	89.0 ± 22.5	0.646
Energy-Vitality	F	58.55 ± 19.72	63.4 ± 13.7	0.138
	M	51.82 ± 19.66	63.4 ± 13.7	**0.041***
Mental health	F	67.26 ± 20.79	70.1 ± 11.4	0.679
	M	63.27 ± 21.00	70.1 ± 11.4	0.250
Social functionality	F	83.22 ± 22.93	90.1 ± 12.9	0.231
	M	80.68 ± 26.44	90.1 ± 12.9	0.587
Pain	F	80.86 ± 17.60	81.0 ± 20.2	0.821
	M	75.68 ± 19.78	81.0 ± 20.2	0.145
General health perception	F	61.32 ± 24.98	69.1 ± 16.9	0.062
	M	64.09 ± 22.56	69.1 ± 16.9	0.192

*p< 0.05.

Table 3. Comparison of LTQL of the patients with hepaticojejunostomy to other reconstructive surgery procedures

	HJ (n= 30)	Other reconstructive procedures (n= 19)	p
Physical function	87.83 ± 8.78	87.89 ± 12.28	0.793
Physical role difficulties	68.33 ± 46.39	78.95 ± 41.89	0.389
Emotional role difficulties	70.00 ± 44.07	78.95 ± 41.89	0.451
Energy-vitality	58.17 ± 16.63	55.26 ± 24.18	0.650
Mental health	68.00 ± 16.84	63.79 ± 25.94	0.535
Social functionality	84.58 ± 17.58	79.61 ± 30.96	0.957
Pain	80.67 ± 13.91	78.16 ± 23.48	0.746
General health perception	65.67 ± 21.20	56.05 ± 28.02	0.179

HJ: hepaticojejunostomy, LTQL: Long term quality of life.
p< 0.05 significant analysis.

and general health perception had significantly lower scores in injuries involving the bile duct hilus. Male patients with E^3 and E^4 types of injuries had higher scores in physical function, energy-vitality, mental health, and general health perception than those who had E^1 and E^2 injuries. Furthermore, patients with E^3 and E^4 types of injuries had lower scores in terms of physical role difficulties, emotional role difficulties, and social functionality; however, these lower scores did not reach to a statistically significant level (Table 4).

There were no statistically significant differences in the quality of life in female patients according to the reconstructive surgery period. On the other hand, physical function scores in male patients treated in the early postoperative period were found to be significantly lower than in the patients diagnosed perioperatively (p= 0.033). General health perception also had a significantly lower score in those who had early postoperative surgery compared to the others (p= 0.035) (Table 5). However, it is important to note that the number of patients for comparison was quite low in the current study.

As morbidity, nine patients were re-admitted to the hospital because of recurrent episodes of cholangitis and increased liver function tests after reconstructive surgery. Stricture occurred in

Table 4. Comparison of Strasberg E type IBDIs in terms of LTQL

	Sex	Strasberg E^1-E^2 Injury (F= 15, M= 4)	Strasberg E^3-E^4 Injury (F= 10, M= 6)	p
Physical function	F	90.67 ± 10.67	82.50 ± 07.17	0.091
	M	87.50 ± 08.66	90.00 ± 8.37	0.914
Physical role difficulties	F	80.00 ± 41.40	45.00 ± 49.72	0.115
	M	75.00 ± 50.00	66.67 ± 51.64	1.000
Emotional role difficulties	F	80.00 ± 41.40	50.00 ± 45.13	0.16
	M	75.00 ± 50.00	66.67 ± 51.64	1.000
Energy-vitality	**F**	**66.00 ± 18.63**	**47.00 ± 12.06**	**0.019***
	M	46.25 ± 13.77	60.83 ± 18.28	0.257
Mental health	**F**	**73.60 ± 18.56**	**55.60 ± 14.78**	**0.019***
	M	60.00 ± 16.97	72.67 ± 14.84	0.610
Social functionality	F	84.17 ± 20.30	75.00 ± 19.54	0.196
	M	87.50 ± 25.00	85.41 ± 18.40	0.762
Pain	F	81.83 ± 16.13	72.25 ± 12.88	0.091
	M	70.63 ± 24.36	84.17 ± 11.47	0.476
General health perception	**F**	**70.67 ± 24.99**	**50.00 ± 17.16**	**0.026***
	M	65.00 ± 14.72	71.67 ± 18.35	0.762

five of these patients in the long term. Among these patients, one is still being followed up with a percutaneous catheter, and a slight increase in current biochemical values persists. One patient, in whom the left hepatic lobe was atrophic due to stricture, was clinically compensated, and biochemical blood values were normal. Re-hepaticojejunostomy was performed in another patient due to the development of stricture after HJ. The others (patients with choledocoduodenostomy and T-tube drainage) were treated with HJ. In these patients, we observed that the results of the questionnaire in each parameter were below the norm values of the other IBDIs.

DISCUSSION

In the past two decades, there has been a steady-state increase in bile duct injuries which has also been in direct proportion to the increase in laparoscopic cholecystectomies (6). This complication is critical because it occurs twice as often as the open technique, and these injuries may be located more proximally and accompanied by vascular injuries (7,8). Since patients with bile duct injury always have a risk for long-term complications, these patients must need a lifelong follow-up for biliary tract strictures and other complications even if adequate treatment has been performed.

There are only a few studies investigating an association between the quality of life and IBDI. The main purpose of evaluating this association in previous studies is to see whether bilioenteric diversion surgeries are sufficient to keep the quality of life at normal standards or not. In previously published studies, the comparisons have been made with uncomplicated cholecystectomy patients, and it has been reported that general health, physical functions, and social functions are affected (9,10). In an earlier study in which 54 IBDI patients undergoing reconstructive surgery have been examined, the authors have reported that only emotional scores were affected (11). They have further reported that physical and social quality of life in these patients were similar to the patients with normal cholecystectomy, whereas there was greater deterioration in the psychological quality of life in these patients (11). It seems that the differences in the quality of life in that earlier study from year to year are due to external factors. However, in the current study, although evaluation with the SF-36 questionnaire is a subjective and self-assessed measurement, SF-36 questionnaire was chosen when considering that it was a more comprehensive method to assess LTQL. On the other hand, LTQL was compared with healthy people instead of patients who underwent uncomplicated cholecystectomy in the present study. Thus, possible minor thermal trauma to the common bile duct in apparently uncomplicated cholecystectomies was ruled out.

In this study, the effects of HJ and other reconstructive operations on the scores of physical function, energy-vitality, mental health, and social functionality were similar. Although physical and emotional quality scores was lower in the HJ group, there was no statistical significance, which may be due to the fact that these patients were informed that they had undergone a more complicated surgical procedure. However, in terms of general health perception, those who had HJ had higher sco-

Table 5. Comparison of LTQL according to the timing of reconstructive surgery in male patients

		n= 11	SF scores	p
Physical function	A	2	97.5000 ± 3.53553	**0.043***
	B	**7**	**82.1429 ± 7.55929**	
	C	2	95.0000 ± 7.07107	
Physical role difficulties	A	2	100.0000 ± .00000	0.195
	B	7	42.8571 ± 53.45225	
	C	2	100.0000 ± .00000	
Emotional role difficulties	A	2	100.0000 ± .00000	0.195
	B	7	42.8571 ± 53.45225	
	C	2	100.0000 ± .00000	
Energy-vitality	A	2	70.0000 ± 21.21320	0.252
	B	7	43.5714 ± 15.46886	
	C	2	62.5000 ± 24.74874	
Mental health	A	2	80.0000 ± 11.31371	0.087
	B	7	53.7143 ± 19.30211	
	C	2	80.0000 ± 16.97056	
Social functionality	A	2	93.7500 ± 8.83883	0.344
	B	7	71.4286 ± 29.50484	
	C	2	100.0000 ± 00000	
Pain	A	2	85.0000 ± 7.07107	0.298
	B	7	68.9286 ± 21.45039	
	C	2	90.0000 ± 14.14214	
General health perception	A	2	85.0000 ± 7.07107	**0.035***
	B	**7**	**52.8571 ± 19.54847**	
	C	2	82.5000 ± 17.67767	

A: The patients undergoing reconstructive procedures in the perioperative period.
B: The patients undergoing reconstructive procedures in the early postoperative period.
C: The patients undergoing reconstructive procedures in the late postoperative period.
n: Number of patients.

res. A possible interpretation of this finding is that since the tissues with impaired vascularity and thermal damage were excised during injury and HJ offered tension-free anastomosis, HJ might result in higher scores. On the other hand, the quality of life of five patients who developed strictures after hepaticojejunostomy decreased. However, this did not cause a statistically significant difference.

An appropriate timing for reconstructive surgical intervention is crucial after bile duct injuries. While the chance of successful surgery is high, especially in patients who can be intervened in the first 72 hours, sepsis is a serious problem for reconstruction in cases with longer diagnosis and patient transferring time (12-14). Previously, it has been reported that a delayed admission in IBDI is associated with the frequency of postoperative complications, requires more invasive treatments, and also, the recovery time is prolonged (15). In our study, common bile duct (CBD) transection was instantly detected intraoperatively in one patient, and end-to-end repair of the CBD was performed. HJ was also performed in the same session in three patients in whom IBDI was detected intraoperatively. For these patients, survey results were similar to the norm values in terms of this physical function, energy-vitality, general health perception, and mental health. However, they had low scores in other subtitles. Performing reconstructive repair in the same session gives a much better result for the patient, and such approach is strongly recommended (16-19). On the other hand, surgical repair is not preferred in the postoperative period of 4-30 days due to long term complications. Likewise, we also observed that physical function and general health perception decreased in those who were operated during this period. However, it is again important to highlight that the number of patients compared in this study was quite low.

Previous studies have noted that there is a significant deterioration in quality of life in IBDI patients even years after cholecystectomy (20). This health problem does not only impact an individual life but also is closely related to the increasing demand for healthcare services, its cost and litigation (21,22). Therefore, an informed consent between the doctor and the patient becomes a significant legal document in this regard. For example, a previous study has shown that almost half of the surgeons in England rarely or never mention the possibility of bile duct injury in the perioperative period (23). Therefore, the frank and clear attitude of the surgeons towards the patients and the communication with the patient in case of complications would be very beneficial in terms of quality of life.

Many studies have shown a long-term decrease in both physical and mental quality of life, even after a successful surgery following a biliary tract injury (24-27). Boerma (28) has used the SF-36 questionnaire to investigate the impaired quality of life five years following a bile duct injury during laparoscopic cholecystectomy. They have reported that despite excellent endoscopic and surgical results in 106 patients, there was a significant deterioration in physical and mental functions compared to the control groups consisting of patients with uncomplicated cholecystectomy surgery and patients with Dutch population norms. They have further suggested that a poor mental function according to the timing of reconstructive surgery treatment is an independent prognostic factor. In another previous study, de Reuver et al. (10) have reported worsening outcomes in seven of the eight sub-parameters in SF-36 questionnaire for IBDI patients compared to the those of normal population. Furthermore, Landman et al. (20) have reported that mental functions are affected in LTQL based on a comprehensive literature search. They have compared various patient groups (by sex, injury type, treatment timing) comprehensively (20). Taking all into consideration, our findings on the negative effects of IBDI on quality of life reveal that LTQL is partially affected.

This study has some limitations. First, all IBDI patients were included in this study, regardless of their treatment modality. LTQL was compared across several subgroups (by sex, type of surgery, and level of injury, timing of reconstructive surgery). In this way, we tried to prevent the effects of variability and the potential effects on the results of the survey-associated with sex while evaluating LTQL. Second, the patients were selected from a wide period of time, and the biochemistry values were examined after nine years in some patients and three years after reconstructive surgery in others. Therefore, such factors may affect the outcomes of this study. Third, the number of patients in the groups were low and we did not separate all of the patients with and without complications, which are also other limitations of this study. Last, significant accompanying vascular injuries could not be detected in the hospital records. Thus, future well-standardized studies involving multi-center data with fixing the time between the treatment and the survey time, classifying the patients with postoperative complications are still needed to support the outcomes of this current study.

Our cumulative results suggest that the LTQL of male patients, who underwent a bile duct repair in the postoperative period of 4-30 days, and the LTQL of female patients with Strasberg E^3 and E^4 injuries are mostly affected. Along with previous studies, this study reveals that even if a successful surgery is performed after IBDI, there is still a decrease in both physical and mental LTQL. Therefore, we believe that training physicians in accordance with surgical techniques and skills would reduce the possibility of bile duct injury and many patients would survive this devastating complication.

Main Points:

- Patients with bile duct injury always have a risk for long-term complications.
- An appropriate timing for reconstructive surgical intervention is crucial after bile duct injuries.
- The main purpose of this study was whether reconstructive surgical intervention was sufficient to keep the quality of life at normal standards.

Ethics Committee Approval: This study was approved by Gaziantep University Clinical Research Ethics Committee (Reference no: 2018/340, Date: 13.03.2019).

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ORİJİNAL ÇALIŞMA-ÖZET
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Kolesistektomiye bağlı safra yolu yaralanmalarında uzun dönem yaşam kalitesi ne kadar etkilenir?

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ÖZET

Giriş ve Amaç: İyatrojenik safra kanalı yaralanması, kolesistektominin önemli ölçüde uzun süreli yaşam kalitesini etkileyebilecek ciddi bir komplikasyonudur ve majör morbiditelere sahip olabilir. Ayrıca, rekonstrüktif cerrahi tedaviden sonra bile, bu tür yaralanmalar uzun vadeli yaşam kalitesini düşürmektedir. Bu nedenle hastaların hem fiziksel hem de zihinsel yaşam kalitesinde uzun süreli bir düşüş olduğu düşünüldüğünden hastaların uzun süreli yaşam kalitesini araştırmaya hala ihtiyaç vardır. Buna göre, burada iyatrojenik safra kanalı yaralanması nedeniyle rekonstrüktif cerrahi uygulanan hastaların klinik değerlendirmelerini ve uzun dönem yaşam kalitesini araştırdık.

Gereç ve Yöntem: Bu klinik çalışmaya kolesistektomi ile ilişkili safra kanalı hasarı olan ve rekonstrüksiyon ameliyatı geçiren 49 hasta (38 kadın/11 erkek) dahil edildi. Safra kanalı yaralanması tipi, rekonstrüktif cerrahi girişimler, hastanede kalış süresi ve komplikasyonlar dahil olmak üzere çeşitli parametreler değerlendirildi. Ayrıca rekonstrüktif cerrahi zamanlamasının (preoperatif, erken postoperatif, geç postoperatif) yaşam kalitesi üzerine etkileri değerlendirildi. Takipleri iki ila dokuz yıl arasında değişen hastalarda uzun süreli yaşam kalitesi düzeyleri SF-36 anketi kullanılarak değerlendirildi. SF-36 anket puanları sağlıklı Türk nüfusunun ortalama SF-36 norm değerleri ile karşılaştırıldı.

Bulgular: Sonuçlarımız safra yolu yaralanmalarının %73,5'inin laparoskopik cerrahi sonrası, %26,5'inin açık kolesistektomi sonrası oluştuğunu göstermiştir. Yaralanmaların %32,7'si akut kolesistitli hastalarda gelişti. Hastaların otuzu hepatikojejunostomi ile tedavi edildi. Çalışmanın SF-36 anket skorları sağlıklı Türk popülasyonununkilerle karşılaştırıldığında, erkek hastalarda enerji-canlılığın anlamlı derecede düşük olduğu bulunmuştur (p= 0,041). Bununla birlikte, kadın hastalarda anlamlı bir bozulma yoktu. Yapılan rekonstrüktif cerrahi tipine göre hepatikojejunostomide genel sağlık algısı daha iyi olmasına rağmen yaşam kalitesinde anlamlı fark gözlenmedi. E^1-E^2 yaralanması olan kadınlarda ruh sağlığı, enerji-canlılık (p= 0,019) ve genel sağlık algısı (p= 0,026) daha düşük bulundu. Yaralanmaların sadece yedisi ameliyat sırasında tespit edildi. Erkek hastalarda postoperatif erken tedavi grubunda rekonstrüktif cerrahi süresi açısından fiziksel fonksiyon (p= 0,033) ve genel sağlık algısı (p= 0,035) daha düşük bulundu.

Sonuç: İyatrojenik safra yolu yaralanmaları ciddi morbiditeye neden olur. Ayrıca rekonstrüktif cerrahi tedaviden sonra bile, bu tür yaralanmalar uzun süreli yaşam kalitesini azaltır. Sonuçlarımız, özellikle Strasberg E^3-E^4 tipi yaralanmalarda postoperatif erken biliyer onarım uygulanan erkek hastalarda uzun süreli yaşam kalitesinin daha düşük olduğunu göstermektedir.

Anahtar Kelimeler: Safra yolu yaralanması, kolesistektomi, komplikasyon, hepatikojejunostomi, yaşam kalitesi, SF-36

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ORIGINAL ARTICLE
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Extreme cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in treatment of peritoneal metastasis

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ABSTRACT

Objective: It was aimed to define the oncologic concept of "extremeness" in cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) to determine morbidity-mortality results and final oncologic outcomes.

Material and Methods: Prospectively recorded data of 666 patients with peritoneal metastases who had undergone CRS/HIPEC between 2007 and 2020 were analyzed. Patients were divided into two groups as extreme (n= 371) and non-extreme (n= 295). Extreme CRS was defined as resection of ≥5 major organs or creation of ≥2 bowel anastomoses or peritoneal carcinomatosis index (PCI)≥ 15 or re-cytoreductive surgery.

Results: More CC-1 or CC-2 cytoreduction (p< .001), increased mortality and morbidity (p< .001), prolonged operative time (p< .001), increased intra-operative erythrocyte suspension (p< .001), albumin (p< .001), fresh frozen plasma (FFP) (p< .001), and post-operative erythrocyte suspension (p< .001) usage were found in the extreme CRS/HIPEC group. Operative time, CC-1 or CC-2 cytoreduction, presence of ostomy, development of infection, and use of intra-operative albumin and FFP were found to be independent prognostic factors in Cox regression analysis. Three and five-year survival rates were significantly lower in the extreme CRS/HIPEC group (p< .001).

Conclusion: High-volume peritoneal metastatic disease can be completely resected with extreme cytoreduction in carefully selected patients responsive to chemotherapy. Since the significant morbi-mortality related to the treatment of peritoneal metastasis is a real concern, it should be considered in experienced complex cancer centers that provides relatively better oncological outcomes compared to conventional treatments.

Keywords: Cytoreductive surgery, hyperthermic intraperitoneal chemotherapy, peritoneal metastasis

INTRODUCTION

Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) is an effective treatment modality in peritoneal metastasis of various solid organ cancers such as colon-rectum, appendix, peritoneal mesothelioma, stomach and ovaries. In selected patients, this aggressive abdomino-pelvic oncologic approach can now be undertaken with decreasing morbi-mortality results and is associated with better survival outcome (1-6). The aim of CRS is to achieve a complete cytoreduction, in which all the visible tumor foci are removed. Only then, regional chemotherapy, HIPEC, can be applied for the eradication of microscopic disease. It has been shown in many studies that a complete cytoreduction is significantly associated with prolonged disease-free and overall survival, and is considered the most important prognostic/predictive factor (2,7). However, to reach a complete cytoreduction is a highly difficult and compelling task in a high-risk cancer patient usually treated with prior surgery and/or chemo-(radio)therapy regimens. It is associated with the center's experience of patient selection, peritoneal cancer index, the extent andntype of tumor burden, and intraoperative multidisciplinary contribution. It is often achieved through complex surgical care that requires very demanded oncologic skillsets of multivisceral organ resection and reconstructive procedures for total tumor resection and gastrointestinal continuity. All of these maximum efforts can end up with increased morbidity, prolonged hospital stay and readmission(s), exhaustion of hospital resources, and the delay of postoperative adjuvant chemotherapy.

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Very recently, many authors have described a subgroup of patients who require complex multiple peritoneal and visceral resections and multiple bowel anastomoses as "extensive" or "aggressive" or "extreme" CRS/HIPEC procedures (8-11). By bringing the cytoreductive surgery concept too far than the so-called "standard" cytoreductive ones, the researchers have reported favourable oncological outcomes with comparative perioperative morbi-mortality.

The aim of this study was to define the oncological concept of "extremeness" in CRS/HIPEC and to interrelate the extreme cytoreduction with the overall complications and final oncologic outcomes.

MATERIAL and METHODS

All procedures performed in this study were in accordance with the ethics standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethics standards. The study was approved by local ethics committee. All patients gave their written consent both for surgery and participating in the study.

This was a retrospective analysis of prospectively collected data on 666 patients with peritoneal metastasis (PM) who underwent CRS and HIPEC at our Peritoneal Surface Malignancy Center from 2007 to 2020. Patients had peritoneal metastases from various types of malignant tumors. The exclusion criteria were:

1. The presence of unresectable extra-abdominal distant metastasis
2. Extensive portal peduncle or small bowel involvement
3. Retroperitoneal bulky or plaque-type tumor invasion
4. Invasion of major vessels or bilateral ureters
5. Circumscribed pelvic side wall involvement
6. Low performance status; nutritonally-frail, and medically unfit patients
7. Refusal to sign the informed consent form (non-compliant to compos mentis)

The patients were divided into two groups as extreme and non-extreme CRS. Extreme CRS was defined as resection of ≥5 major organs or creation of ≥2 bowel anastomoses or peritoneal carcinomatosis index (PCI)≥ 15 or re-CRS. Major organs were considered as any of the following: colon, rectum, small bowel, spleen, pancreas, stomach, gallbladder, diaphragma (full thickness resection), liver (paranchymal resection> one segment), uterus/ovaries, and urinary bladder/ureter/kidney. Omentum, peritoneum, and Glisson capsule resection were not included. Patients having extreme CRS/HIPEC were compared with the non-extreme group in terms of perioperative morbidity, mortality, and the final oncologic outcomes.

Preoperative Assessment

The eligibility of the patient for CRS and HIPEC was evaluated in the multidisciplinary tumor board. The assessment for preoperative staging was initially performed with thoraco-abdominal-pelvic computed tomography and supplemented with MRI and/or positron emission tomography. Co-morbidities were assessed by Charlson co-morbidity index (12). Patients' co-morbidities, the ECOG performance and nutritional status were all managed individually and the prehabilitation program was entegrated according to the risk stratification. In patients who received neoadjuvant chemotherapy, the surgical procedure was planned to perform at least four weeks after the last dose of chemotherapy.

Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

All patients had mechanical bowel preparation and venous thromboembolism prophylaxis. Intravenous 1.5 g cefuroxime axetil and 500 mg metronidazole were administered 30 min before surgery and repeated in q8hr.

The main purpose of CRS, as Sugarbaker PH et al. have previously described, is to achieve the resection of all macroscopic visible tumor nodules in the abdomino-pelvic region (13) (Figure 1). The extent of the peritoneal cancerous involvement and the burden of the peritoneal disease were calculated by PCI (14). After the completion of the surgical procedures, completeness of the cytoreduction was measured, according to "completeness of cytoreduction" score (No residual tumor, CC-0; residual tumor ≤2.5 mm, CC-1 and residual tumor> 2.5 mm, CC-2) (15).

HIPEC perfusion was performed with closed technique and cytotoxic chemotherapy with a peritoneal dialysis solution at 42.5°C for 30 mns (Oxaliplatin) or 90 mns (Mitomycin and Cisplatin). The regimen of chemotherapeutic agent(s) to be used during HIPEC was decided by experienced medical oncologists according to the clinicopathologic and medical features of the patient and the disease. All anastomoses were performed before HIPEC.

Early Postoperative Care and Follow-Up

Common Terminology Criteria for Adverse Events was used to record postoperative morbidity and HIPEC toxicity (16). Death within 30 days after surgery and hospital mortality were recorded as mortality.

Statistical Analysis

Statistical analysis was performed using SPSS 22.0. Categorical variables were compared among the groups using Pearson $\chi 2$ test. Continuous variables were compared by independent samples t-test. Continuous variables were expressed as means and ranges, and categorical variables as frequencies and percentages.

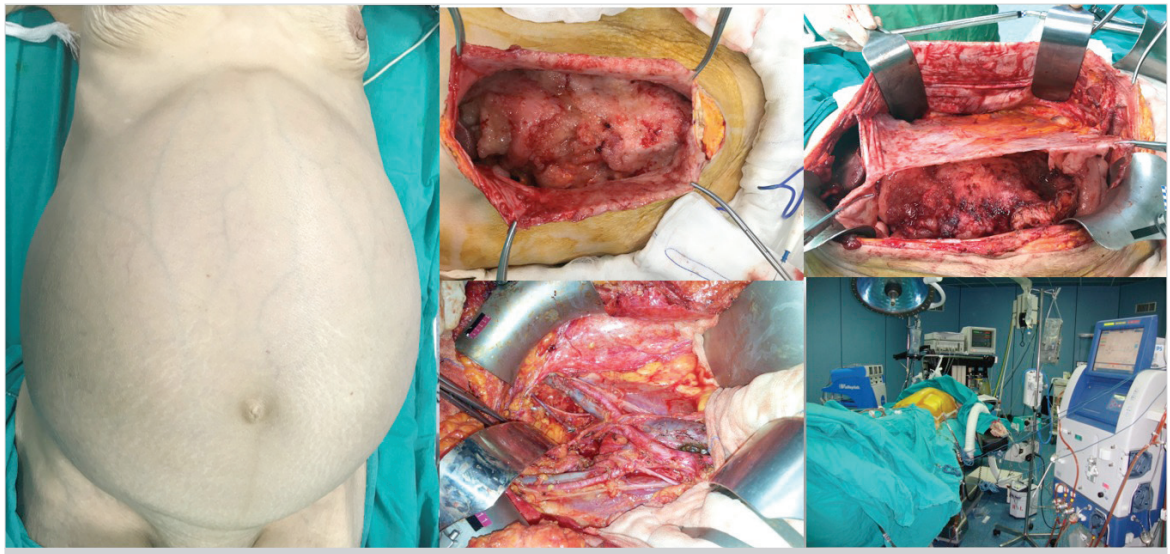


Figure 1. The technique of CRS and application of HIPEC.

Survival rates were calculated using Kaplan-Meier method and were compared with the long-rank test. Multivariate analysis to identify predictors of survival was performed by constructing stepwise Cox proportional hazard models incorporating variables selected on the basis of results of univariate analysis. p values< 0.05 were defined as statistically significant.

RESULTS

There were 666 consecutive cytoreduced and HIPEC-treated patients between 2007 and 2020. Mean age (54.2 ± 12.97 years vs 54.9 ± 21.6 years) and sex distributions (71.4% female vs 76.6% female) were similar in both groups. Median follow-up was 22 (range, 1-135) months. Overall survival in all patients was 35 months (range, 31-40 months). Primary tumors were ovarian in 280 (42.0%), colorectal in 214 (32.1%), appendix in 74 (11.1%), peritoneal mesothelioma in 37 (5.6%), gastric in 26 (3.9%) and unconventional indication in 19 (2.9%) patients. There were 371 (55.7%) patients in the extreme group and 295 (44.3%) patients in the non-extreme group. In the extreme group, PCI was ≥15 in 61.7% (n= 229), patients undergoing ≥5 major organ resections was 50.1% (186), 20.5% (n= 76) of the patients had ≥2 anastomosis, and 13.5% (n= 50) had repeated CRS procedures. In the overall group, 43.4% (n= 289) of the patients had no anastomosis, 45.2% (n= 301) had one anastomosis and 11.4% (n= 76) had ≥2 anastomosis (Table 1).

While the rate of ovarian cancer was equal in both groups, colorectal cancers were more common in the non-extreme group, in contrast to appendix, mesothelioma, and gastric cancers, which were prevelant in the extreme group (p= .007). The presence of co-morbidity was 41.0% (n= 152) in the extreme group and 44.7% (n= 132) in the non-extreme group (p= .328). The patients who received neoadjuvant chemotherapy were 62% (n= 230) in the extreme group and 64.7% (n= 191) in the non-extreme group (p= .465). Patients with metachronous disease were more in the non-extreme group (57.8%) whereas

Table 1. Clinical parameters determining the extreme CRS group

	Extreme % (n= 371)	**Non-extreme % (n= 295)**	**Overall % (n= 666)**
PCI			
≥15	61.7 (229)	0	34.4 (229)
<15	38.3 (142)	100 (295)	65.6 (437)
Number of resected organs			
≥5	50.1 (186)	0	27.9 (186)
<5	49.9 (185)	100 (295)	72.1 (480)
Number of anatomosis			
≥2	20.5 (76)	0	11.4 (76)
<2	79.5 (295)	100 (295)	89.6 (590)
Re-CRS (+)	13.5 (50)	0	7.5 (50)

those with synchronous disease were more in the extreme group (56.2%) (p= .001) (Table 2).

Operative time was longer in the extreme group [mean 369.84 min; SD (±116.04) vs 304.02 min; SD (±114.81) (p< 0.001)]. The rate of achieving CC-0 cytoreduction was higher in the non-extreme group (62.5%, 228 patients vs 90.1%, 237 patients) (p= .000). More intra-operative erythrocyte suspension (52.8% vs 27.5%) (p= .000), albumin (27.8% vs 6.2%) (p= .000), fresh frozen plasma (FFP) (41.6% vs 21.6%) (p= .000), and post-operative erythrocyte suspension (23.2% vs 11.5%) (p= .000) were used in the extreme group. Increased post-operative morbidity (p< 0.001), higher HIPEC toxicity (p= .001) and increased infection (p< 0.001) rates were detected in the extreme group (Table 3).

The associated variables such as metachronous/synchronous disease, neoadjuvant chemotherapy, completeness of cytoreduction, operative time, ostomy creation, the use of intraoperative blood products, morbidity, HIPEC toxicity, and infection were modelled into Cox proportional analysis to determine independent prognostic factors of survival. It was determined that the prolonged operative time, CC-1 or CC-2 cytoreduction status, the presence of an ostomy, the development of an infection, and the increased use of intraoperative albumin and/or FFP were independent prognostic factors. (Table 4).

Median survival was 27 months (range, 23-30) in extreme group whereas 53 months (range, 42-64) in the non-extreme group. Three and five-year K-M survival rates were significantly lower in the extreme CRS/HIPEC group (48.8% and 31.9% vs 61% and 44.5%; p< .001) (Figure 2).

There was no morbidity in 74.1% (n= 221) of the patients in the non-extreme group and in 59.8% (n= 222) of the patients in the extreme group. Overall complication rate was higher in the extreme group (124 patients; 33.4%) than in non-extreme group (70 patients; 23.7%) (p< .001). Severe complications (C-D grade III-IV) occurred in 51 (13.7%) and 38 (12.9%) patients in both arms, respectively. In our cohort, there were 89 (21.8%) patients with major complications, and 26 (29.2%) of them were re-operated for anastomotic leak (n= 13), enterocutaneous fistula (n= 2), evisceration (n= 8), mesh infection (n= 1), intra-abdominal bleeding (n= 1), and cerebro-vascular occlusion (n= 1). The complications such as intra-abdominal abscess, gastrointestinal bleeding, intra-abdominal hematoma, and pleural effusion developed in 13 patients, and these were treated with percutaneous and endoscopic interventions without any need for repeat operation. All of these patients were succesfully rescued with timely diagnosis and proper management (none 'failure-to-rescue'). Peri-operative mortality was also higher in the extreme group compared to the non-extreme group (6.7%, 25 patients vs 1.4%, four patients) (p< .001). Nine (31.3%) of 29 patients were re-explored for anastomotic leakage, but could not be rescued despite all efforts.

Table 2. Demographic and clinical characteristics of the patients

	Extreme % (n= 371)	**Non-extreme % (n= 295)**	**General % (n= 666)**	**p***
Sex				
Male	28.6 (106)	23.4 (69)	26.3 (175)	.131
Female	71.4 (265)	76.6 (226)	73.7 (491)	
Age (year, mean ± SD)	54.2 ± 12.97	54.9 ± 21.6		.620
Origin of tumors				
Ovarian	41.2 (153)	43.1 (127)	42 (280)	
Colorectal	29.1 (108)	35.9 (106)	32.1 (214)	
Appendiceal	12.7 (47)	9.2 (27)	11.1 (74)	
P. Mesothelioma	7.3 (27)	3.4 (10)	5.6 (37)	**.007**
Gastric	5.7 (21)	1.7 (5)	3.9 (26)	
Primary PM	1.9 (7)	3.1 (9)	2.4(16)	
Others	2.2 (8)	3.7 (11)	2.9 (19)	
Smoking (+)	22.4 (83)	17.2 (50)	20.2 (133)	.099
Presence of co-morbidites	41.0 (152)	44.7 (132)	42.6(284)	.328
Synchronous/metachronous				
Synchronous	56.2 (205)	42.2 (111)	50.3 (316)	**.001**
Metachronous	43.8 (160)	57.8 (152)	49.7 (312)	
Neoadjuvant chemo (+)	62.0 (230)	64.7 (191)	63.2 (421)	.465

P. Mesothelioma: Peritoneal mesothelioma.
*Pearson $\chi 2$ test and independent samples t-test.

Table 3. Surgical characteristics and outcomes

	Extreme (n= 371), n (%)	Non-extreme (n= 295), n (%)	p*
Operative time (min, mean ± SD)	369.84 SD (±116.04)	304.02 SD (±114.81)	**<0.001**
Complete cytoreduction			
CC-0	62.5 (228)	90.1 (237)	**.000**
CC-1-2	37.5 (137)	9.9 (26)	
Ostomy (+)	45.4 (167)	13.4 (39)	**.000**
Intraoperative RBCs	52.8 (195)	27.5 (80)	**.000**
Intraoperative albumin	27.8 (102)	6.2 (18)	**.000**
Intraoperative FFP	41.6 (152)	21.6 (57)	**.000**
Post-operative RBCs	23.2 (85)	11.5 (33)	**.000**
ICU (+)	62.4 (231)	37.6 (110)	**.001**
Morbidite			
Grade I-II	19.7 (73)	10.8 (32)	
Grade III-IV	13.7 (51)	12.9 (38)	**<0.001**
Grade V	6.7 (25)	1.4 (4)	
HIPEC toxicity	12.7 (47)	5.4 (16)	**.001**
Infection	28.9 (107)	12.8 (37)	**<0.001**

RBC: Red blood cell, FFP: Fresh frozen plasma, ICU: Intensive care unit.
*Pearson $\chi 2$ test and independent samples t-test.

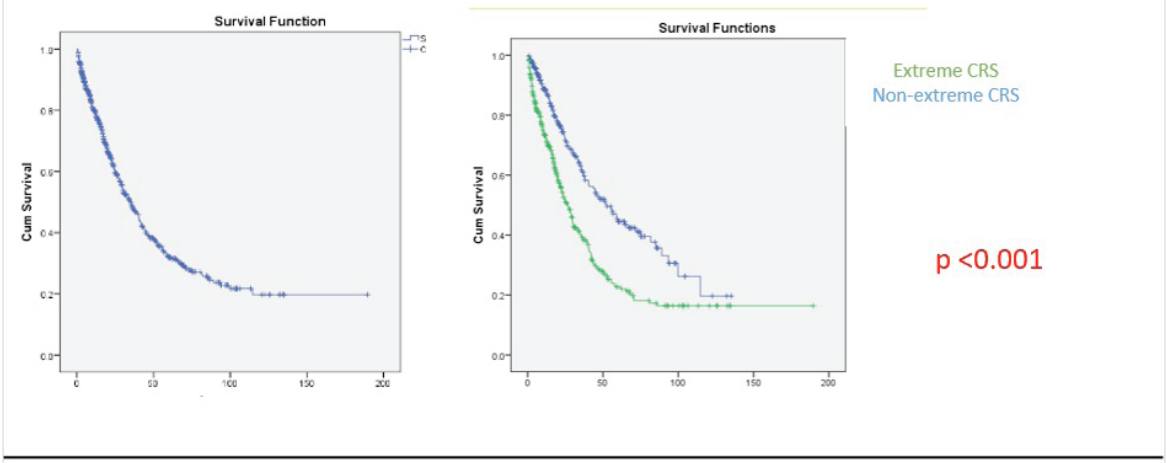
Table 4. Multivariate analysis

	HR	95% CI	p*
Synchronous/metachronous	1.492	1.028-2.166	.035
Operative time (min)	1.003	1.001-1.005	.000
CC-0/CC-1/-2	4.024	2.440-6.638	.000
Ostomy (+)	2.920	1.879-4.539	.000
Infection	1.867	1.149-3.032	.012
Intraoperative albumin	3.916	2.201-6.968	.000
Intraoperative FFP	1.725	1.138-2.614	.010

FFP: Fresh frozen plasma.
*Stepwise Cox proportional hazard models.

DISCUSSION

Although CRS/HIPEC has significant but acceptable perioperative morbidity and non-negligible mortality rates, it is the only potential oncologic management strategy with curative intent in peritoneal surface oncology centers with specific experience and expertise with multidisciplinary tumor board (1-7,17). In time, compelling evidence has emerged revealing the relatively low morbi-mortality and better oncological results with this triplet oncologic therapy. However, if we accept the establishment of complete cytoreduction as one further oncologic step over the standart conventional organ-based surgery to clear out the whole tumor burden, there even appears to be a wide spectrum of peritoneal metastatic disease that raise concerns about how far we can carry these aggressive approaches. The limit of the extensiveness/aggressiveness is still not very well-defined, and the current data is scarce. Thus, the authors aimed to evaluate the effect of extreme cytoreduction and HIPEC on post-operative morbi-mortality and final oncologic outcomes in a large group of patients at a dedicated center. Extreme CRS was defined by parameters including PCI over 15, five or more organ resections, two or more anastomoses, and repetitive cytoreductive surgeries. Procedures meeting at least one of these four parameters were determined as extreme CRS. Of 666 patients, 295 were included in the extreme CRS group. In the extreme CRS group, less CC-0 cytoreduction, more ostomy creations, and more intraoperative and postoperative blood



Overall survival	Extreme(%)	Non-extreme(%)	All pts(%)
24 mos	52.2	73.8	61.4
36 mos	39.7	61.0	48.8
60 mos	22.7	44.5	31.9

Figure 2. Overall survival in full-spectrum of the patients and in extreme and non-extreme CRS groups.

product consumption were observed. These patients experienced a higher incidence of postoperative complications, infections, HIPEC toxicity, and perioperative mortality. Additionally, the overall survival of patients with extreme CRS was inferior to that of patients with non-extreme CRS.

The limit on the extensiveness of cytoreduction to achieve the best reliable results in the management of peritoneal metastasis is still a matter of ongoing debate. Some centers determined PCI as a limiting factor and accepted PCI> 20 as not to operate (18,19). It is insistantly proven that the higher PCI score is a powerful predictor of complications and overall survival. However, high PCI score is not always possible to determine the extensiveness of the cytoreduction and the number of multivisceral organs to be removed. The difficult anatomical localization and the inherent biological aggresiveness of the tumor usually play a more important role and a small tumor with aggressive biological behavior in a low-volume disease may loco-regionally spread to multiple nearby organ(s)/structure(s). Some centers, including ours, with the guidance of John Birkmeyer's centralization effect in complex cancer care, use the experience they have developed in time to predict whether he/she can perform a complete cytoreduction or bail out surgical intervention as a threshold (20). As it is proven to be utmost important prognostic factor in the classical oncologic R0 resection, the complete cytoreduction can be the potential curative treatment only. In our opinion, this treatment modality should not be taken away from the patient even in the presence of high volume disease.

Delving into the literature, there are very few studies examining the limit on the extensiveness of CRS/HIPEC. Franko et al. have included 65 patients with CRC-PC (colorectal cancer-peritoneal carcinomatosis) who were treated with CRS/HIPEC, having the patients into two groups based on the number of multivisceral organ resections (MVR) (MVR group≥ 2 organs and non-MVR group= one or no organ resection). They have reported that MVR is unrelated to morbi-mortality, and survival. However, it has been shown that performing bowel anastomosis rather than MVR is associated with morbidity (9). Based on the center experience, taking a cut-off value of two or more organ resections for CRS/HIPEC, which often requires multivisceral organ resections, was one of the main problem of the study. In another study from the same center in which 282 patients undergoing CRS/HIPEC due to appendiceal carcinomatosis have been included, the patients have been divided into two groups as the extensive CRS group (n= 60) and the comparison group (n= 222). The extensive CRS group has been defined as patients who underwent> 3 organ resections or> 2 anastomoses. Besides, in patients with ≥5 organ resections and ≥3 anastomoses, they have defined a subgroup of patients thorough the extensive group and evaluated them separately as the extreme group (n= 10), and the term "extreme CRS" has been used for the first time in the related literature. They have elegantly repor-

ted higher median PCI, longer operative time, more blood loss, and longer hospital stay in the extensive CRS group. However, they have noted that extensive CRS, even in extreme CRS setting, is not associated with severe morbidity, 60-day mortality or inferior oncologic outcomes (11). In a retrospective study by Berger et al., 257 patients undergoing 269 procedures with a wide array of tumor origins have been included in the study. Extreme CRS group (n= 50), defined as a resection of ≥5 organs or ≥3 bowel anastomoses, has been compared with patients undergoing less extensive procedures (n= 219). They have found that there was significantly higher major 30-day morbidity and higher 90-day mortality in the extreme CRS/HIPEC group. In a subgroup analysis of colorectal cancer (CRC)-PM treated with extreme CRS/HIPEC, they have demonstrated that median disease-free survival and overall survival were worse and the extreme-CRS/HIPEC independently predicted decreased overall survival in CRC-PM patients (8).

The authors integrated the 're-cytoreduction' as a component of extremeness. After CRS/HIPEC, with the compounded effects of previous major surgery, complications, and HIPEC, reoperative abdomino-pelvic surgery potentially becomes a difficult task than a virgin abdomen is encountered. Access is limited by obliterative adhesions, often with dense scarring, the absence of planes of cleavage, and the distorted anatomical planes. The problem is increased by a history of previous pelvic sepsis or irradiation. Thus, reentry into the abdomen after previous major laparotomy should be an exceptional venture. Re-CRS often requires extensive dissection of scarred multiple adhesions, road-mapping through the ceramicized structures/tissues, and situational awareness for no-point-of return. There are limited studies showing that re-CRS/HIPEC increases long-term oncologic outcomes (three-year survival was ranging from 0% to 66% and median survival was 20 to 56 months) with acceptable morbidity and mortality rates (major morbidity and mortality were 15% to 50% and 0% to 5%, respectively) similar to initial CRS/HIPEC procedure (7,21-24). However, primary cytoreduction, which already contains marathon complex surgical procedures by its inherent nature, gains even more complexity with re-CRS. It is obvious that re-cytoreductive attempts performed in poorly selected cases at a center with a low volume and proficieny will adversely affect mortality and morbidity rates and oncological outcomes.

Morbidity following CRS/HIPEC has been very well-defined. Many high-volume centers have published 12% to 55% major morbidity rates. In most of these studies, the extent of peritoneal disease, duration of surgery, number of resected organs, and number of anastomosis have been found as predictors of morbidity (3,17,25,26). In our study, we proposed the indices of number of resected major organs, the number of anastomosis, and the repeated cytoreduction in addition to PCI for defining the extremeness of the CRS/HIPEC. The cumulative data showed that these oncologic efforts resulted with early postoperative morbidity and mortality and inferior oncologic outcomes.

Three randomized controlled trials have described the benefit of CRS/HIPEC in CRC-PM, reporting significant survival advantage as opposed to the standard therapy, and median survival in large series has ranged from 32 to 47 months with a five-year survival of 20% to 50% (7,27,28). Although this study consisted of mixed tumor origins, median survival was 27 months even in the extreme group where the tumor burden and extended radical attacks were high. In the non-extreme group, median survival was 52.6 months. There is little data on the management of patients with peritoneal metastases with traditional treatment options other than CRS/HIPEC. Verwaal et al. have discovered that median survival for CRC patients randomized to receive systemic chemotherapy (± palliative surgery) was 12.6 months (4). In a separate study, median survival for patients who underwent laparotomy and canceled CRS/HIPEC followed by palliative chemotherapy has been found as 11.2 months (19). Finally, according to a subgroup analysis of two prospective randomized studies, median survival for CRC-PM patients treated with systemic chemotherapy has been concluded as 12.7 months (29). Our study strikingly showed that in the extreme group, being the next oncological level of macroscopic tumor eradication, the final oncological results might be worse than in the non-extreme group, but it is clear that even in the extreme group, CRS/HIPEC is still a reliable curative treatment to prolong survival.

The limitations of this study include its retrospective nature with inherent bias. Many patients were regional or extra-regional referrals, who might represent the more advanced spectrum disease with different diagnostic work-ups and surgical interventions. The heterogenous nature of patient population is another drawback of this study. These patients have been treated in a real-world situation in a complex scenario, with various operative techniques differing from intraoperative findings. But this real-world basis also adds an uncontrollable variable to the data set. The data set was also collected over a long time period, which may introduce a degree of inherent bias, given the compounding effect of evolving chemotherapeutic regimens over time. Furthermore, we were unable to reflect the beneficial effects of postoperative chemotherapy that may be confounders to our current survival analysis because the patients who had a complication or had a significant co-morbidities were less likely to receive adjuvant chemotherapy, which may be one of the negative contributions for decreased survival particularly in extreme-group. Despite these limitations, this study represents one of the largest cohorts with prospectively maintained database and durable predictors of short- and long-term outcomes. The results were obtained in

carefully selected patients treated by a multidisciplinary team in a high-volume specialized cancer center. In order to minimize the effects and inaccuracies of a retrospective study, more patients were recruited, more than the number in the previous largest studies (7,11).

CONCLUSION

In conclusion, as the extent of the peritoneal metastatic disease is increased, the extremeness of the radical surgery is gradually increased to achieve complete cytoreduction in carefully selected patients. Not all high-volume peritoneal metastatic patients should be considered unresectable. Extreme cytoreduction can be a potential treatment to achieve complete resection, which the trade-off will be increased morbi-mortality.

Ethics Committee Approval: This study was approved by Dokuz Eylül University Non-Invasive Research Ethics Committee (Decision no: 2022/26-17, Date: 17.08.2022).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - SS, TB; Design - SS, TB; Supervision - SS, TB; Fundings - SS, TB; Materials - SS, TB; Data Collection and/ or Processing - SS, TB, BM; Analysis and/or Interpretation - SS, TB, HE; Literature Search - All of authors; Writing Manuscript - All of authors; Critical Reviews - All of authors.

Conflict of Interest: The authors have no conflicts of interest to declare.

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ORİJİNAL ÇALIŞMA-ÖZET
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Peritoneal metastaz tedavisinde ekstrem sitoredüktif cerrahi ve hipertermik intraperitoneal kemoterapi

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ÖZET

Giriş ve Amaç: Morbi-mortalite ve nihai onkolojik sonuçları belirlemek için sitoredüktif cerrahi ve hipertermik intraperitoneal kemoterapi (SRC/HİPEK) tedavisinde onkolojik "ekstrem" kavramını tanımlamayı amaçladık.

Gereç ve Yöntem: 2007 ve 2020 yılları arasında SRC/HİPEK uygulanan peritoneal metastazlı 666 hastanın prospektif olarak kaydedilmiş verileri analiz edildi. Hastalar ekstrem (n= 371) ve ekstrem olmayan (n= 295) olmak üzere iki gruba ayrıldı. Ekstrem sitoredüktif cerrahi, ≥5 majör organ rezeksiyonu veya ≥2 bağırsak anastomozu veya peritoneal karsinomatozis indeksinin (PCI)≥15 olması veya tekrarlayan sitoredüktif cerrahi işlemleri olarak tanımlandı.

Bulgular: Daha fazla CC-1 veya CC-2 sitoredüksiyon (p< ,001), artmış mortalite ve morbidite (p< ,001), uzamış ameliyat süresi (p< ,001), ameliyat sırasında artan eritrosit süspansiyonu (p< ,001), albümin (p< ,001), taze donmuş plazma (TDP) (p< ,001) ve ameliyat sonrası eritrosit süspansiyonu (p< ,001) kullanımı ekstrem SRC/HİPEK grubunda bulundu. Cox regresyon analizinde ameliyat süresi, CC-1 veya CC-2 sitoredüksiyon, ostomi varlığı, enfeksiyon gelişimi ve intraoperatif albümin ve TDP kullanımı bağımsız prognostik faktörler olarak bulundu. Üç ve beş yıllık sağkalım oranları ekstrem SRC/HİPEK grubunda anlamlı olarak daha düşüktü (p< ,001).

Sonuç: Yüksek hacimli peritoneal metastatik hastalık, kemoterapiye yanıt veren özenle seçilmiş hastalarda ekstrem sitoredüksiyon ile tamamen rezeke edilebilir. Peritoneal metastaz tedavisinde korkulan morbidite ve mortalite sonuçları göz önüne alındığında, konvansiyonel tedavilere göre nispeten daha iyi onkolojik sonuçlar sağlayan ekstrem SRC deneyimli kanser merkezlerinde yapılmalıdır.

Anahtar Kelimeler: Sitoredüktif cerrahi, hipertermik intraperitoneal kemoterapi, peritoneal metastaz

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CASE SERIES
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Laparoscopic appendectomy: Effectiveness in children with generalized and advanced generalized peritonitis cases

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ABSTRACT

Laparoscopic appendectomy is one of the most common surgical procedures in treating pediatric appendicitis. This study aimed to investigate the efficacy of laparoscopic surgery in cases complicated with advanced generalized peritonitis in the pediatric population. The study retrospectively reviewed 55 cases of children who underwent laparoscopic appendectomies. The cases were classified as uncomplicated, complicated, or advanced generalized peritonitis. Laboratory results, diagnostic algorithms, surgical techniques, and complications were investigated. Twenty-four of the cases were boys and 31 were girls. Mean age was 11.3 ± 3 years. Twenty of the cases (36%) were uncomplicated and 35 (64%) were complicated. Nine of the complicated cases presented advanced generalized peritonitis and were additionally classified as "another special group". Mean leukocyte count and C-reactive protein levels were measured respectively as 22.49 ± 12 x 10^9/L and 120.5 ± 99 mg/L in complicated cases and as 17.06 ± 10 x 10^9 and 52.37 ± 69 mg/L in uncomplicated cases. All advanced generalized peritonitis cases had presented to the hospital with intestinal obstruction and had diffuse abdominal rigidity on physical exam. None of the cases had any complications in the intraoperative or early postoperative period. Infection complications (namely, intra-abdominal abscesses and surgical site infections) were observed in four cases (7%) in the postoperative period. Mean length of hospital stay was 5.62 ± 2.6 days and 3.95 ± 1 days in complicated and uncomplicated cases, respectively. Mean length of stay in advanced generalized peritonitis cases was 8.33 ± 2 days. It was observed that laparoscopic appendectomy might be the first choice of treatment option in cases complicated with advanced generalized peritonitis.

Keywords: Appendectomy, laparoscopy, child, postoperative complications, complicated appendicitis, advanced generalized appendicitis

INTRODUCTION

Acute appendicitis is the most common abdominal surgical pathology in children (1,2). Appendectomy is the basic therapeutic approach for acute appendicitis. Appendectomy is performed by applying conventional methods like open surgery or with less invasive laparoscopic surgery. Treatment of complicated appendicitis (e.g., gangrenous, perforated, appendiceal abscesses, plastron appendicitis, and etc.) differs according to clinical experience, the severity of illness and preference of the surgeon. Laparoscopic appendectomy has important advantages, but its applicability and safety for complicated appendicitis has been questioned in pediatric cases (3-6). This study aimed to evaluate the efficacy of laparoscopic surgery in complicated appendicitis cases in children, with a particular emphasis on missed perforated appendicitis presenting with advanced generalized peritonitis.

MATERIALS and METHODS

Between April 2016 and September 2020, 55 acute appendicitis cases were treated laparoscopically at our clinic. Laparoscopic surgery was our first choice of treatment in all complicated cases, including those with advanced generalized peritonitis, and surgical procedure was performed by a single surgeon in all cases. Ethics approval for this study was obtained from the Pamukkale University Ethics Committee (E-60116787-020-14389).

Diagnosis of Acute Appendicitis

The diagnosis of acute appendicitis was based on clinical history, physical examination, laboratory results, and radiological evaluation. Cases pre-defined as appendicitis were subsequently scanned by routine radiological examinations. Abdominal

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radiography and abdominal ultrasonography (US) were the initial radiologic evaluations. In US findings, an appendix diameter of longer than six millimeters, an uncompressible appendix, and echogenicity of tissue around the appendix confirmed acute appendicitis. Computed abdominal tomography (CT) was applied to late-admitted and obese patients and to those in whom US failed to confirm appendicitis.

Surgical Procedure

Laparoscopic appendectomy was performed using a standard three-port technique. A 10-millimeter 30° port for the camera was used for abdominal exposure, placed transumbilically using the open technique. After carbon dioxide insufflation (maximum pressure: 10-12 mmHg), an additional two working ports were inserted from the suprapubic and left lower quadrants. The mesoappendix was sectioned using a surgical energy device and hook cautery. An intracorporal suturing technique with 1-0 silk or vicryl suture material secured the base of the appendix, and appendectomy was performed. Removal of appendix specimens was accomplished through the first port site without any retrieval bags. The peritoneal cavity was irrigated and aspirated with saline solution and dried.

Definition of Advanced Generalized Peritonitis Cases Due to Missed Perforated Appendicitis

The patients classified as advanced generalized peritonitis cases were admitted to our clinic in the late onset period (i.e., more than three days) of the illness, and their diagnosis was determined according to intraoperative findings. The diagnosis of some cases was not clearly obtained in the preoperative period. The intra-abdominal cavity could not be observed during the insertion of the transumbilical port due to immense amount of inflammation. In order to insert the transumbilical port, a minimal intra-abdominal space was created with an assisted gauze technique similar to retroperitoneoscopic laparoscopic surgery. Meanwhile, bolus purulent fluid drainage was observed. Vision of the surgical site was restricted by pseudomembranes and edematous bowels, and there was an insufficient cavity in the abdomen for laparoscopic exploration. Usual laparoscopic procedures could be converted to open; however, minimally invasive surgery was preferred. Dense purulent fluid and pseudomembranes in the abdomen were removed using optical blunt dissection to provide free space in the left lower quadrant for the insertion of a five-millimeter port trocar. This trocar was placed by employing open technique. Afterwards, the inside of the abdomen was irrigated with a warm saline solution and then aspirated. A free space was created in the suprapubic area for a secondary working port. Dense inflammation, purulent fluid, and pseudomembranes were observed in all quadrants of the abdomen. The appendix was visualized by blunt dissection and all of them were in a perforated fashion. These cases were determined as a distinct group: Advanced generalized peritonitis cases due to missed perforated appendicitis. (complementary video)

Statistical Analysis

Statistics were presented as weighed means with standard deviations (after the "±" symbol). Differences between dependent groups were calculated using the paired samples t-test, and p-values less than 0.05 were considered significant.

RESULTS

Twenty-four (44%) of the cases were males, and thirty-one (56%) were females. Female-to-male ratio was 1.29. Mean hospital admission time for all patients was 1.98 ± 1.4 days (range= 1-7 days). Mean admission time for 35 complicated cases was 2.37 ± 1.6 days (range= 1-7 days) and 1.30 ± 0.7 days (range= 1-3 days) for 20 uncomplicated cases. Admission time in complicated cases was significantly longer (p= 0.002). Mean leukocyte count (WBC) and C-reactive protein levels were 20.51 ± 11.17 x 10^9/L and 96.56 ± 94.8 mg/L, respectively. Mean WBC and CRP levels were 22.49 ± 12 x 10^9/L, 120.5 ± 99 mg/L in complicated cases and 17.06 ± 10 x 10^9/L and 52.37 ± 69 mg/L in uncomplicated cases, respectively. WBC and CRP levels were significantly higher in complicated cases (p< 0.05). Small bowel obstruction was observed in all advanced generalized peritonitis cases and in five complicated cases. Intestinal obstruction was not observed in uncomplicated cases (Table 1).

Table 1. General characteristics of uncomplicated and complicated cases

	Uncomplicated n= 20	Complicated n= 35	p
Symptom duration (day)	1.30 ± 0.7	2.37 ± 1.6	0.000*
WBC x10^9/L	17.06 ± 10.8	22.49 ± 12	0.085
CRP mg/L	52.3 ± 69	120.5 ± 99	0.004*
Ileus sign (x-ray) n (%)	0	14 (40)	0.001*
LOS (day)	3.9 ± 1	5.4 ± 2	0.004*
Complication n (%)	2 (8.6)	2 (5.7)	0.062

LOS: Length of hospital stay, WOS: White blood cell, CRP: C-reactive protein.
*p< 0.05 is significant.

Ultrasonography was performed in 49 of the cases, the appendix was visualized in 32 cases (65%), all of which presented acute appendicitis. Mean appendix diameter was 9.47 ± 2 mm (range= 6-15 mm). No cases presented additional abdominal pathologies (e.g., tuba-ovarian pathology). Intravenous contrast-enhanced CT imaging was applied in 42 cases. The appendix could not be identified in five cases due to the perforated structure. In 37 cases the appendix was identified, it appeared inflamed, enlarged, periappendiceal fat stranding was observed, and mean appendix diameter was 11 ± 2 mm (range= 7-20 mm). During laparoscopic exploration, 35 cases were classified as complicated-24 due to perforation, and 11 due to gangrene. Nine (37%) of the missed perforated appendicitis cases were classified as advanced generalized peritonitis cases (Table 2). All cases were treated with broad-spectrum antibiotics. With a mean admission time of 5.01 ± 2.3 days, hospitalization for these complicated cases was significantly longer ($p< 0.05$). Mean hospitalization time of advanced generalized peritonitis cases was 8.33 ± 2 days. All patients were discharged with an oral antibiotic regimen of amoxicillin with clavulanic acid and metronidazole. Mean follow-up period was 43 months (range= 10-117 months); none of the patients experienced intraoperative complications, and only four patients had minor complications in the postoperative period. Three of these cases experienced surgical site infection (transumbilical port insertion site), and the other developed intra-abdominal abscess 15 days after the operation. This case was managed conservatively by antibiotic therapy.

DISCUSSION

Complicated appendicitis cases, especially those presenting with generalized peritonitis, can be further complicated and endangered by traditional surgical methods. These complications may be minor complications such as surgical site infection, intra-abdominal abscess, and etc., but may also be serious complications such as small bowel obstruction, solid organ injury and vascular injury. Many authors do not propose laparoscopic appendectomy to mitigate risk in already complicated cases (7). Miyano et al. are the first to report that laparoscopic appendectomy could be safely performed in pediatric cases of appendicitis accompanied with generalized peritonitis (8). However, lack of research featuring cases in which inflammation is so severe to prevent a clear view of the abdominal cavity motivated us to study such advanced peritonitis cases. Up until now, there has been lack of reports of cases of advanced generalized peritonitis treated with minimally invasive surgery.

In cases of complicated appendicitis not suitable for conservative treatment, two treatment options exist: open appendec-

Table 2. Summary of diagnosis and treatment of nine advanced peritonitis cases

Age (year)	Symptom duration (day)	WBC x10^9/L	CRP mg/L	SBO	Radiologic evaluation	Antibiotic course	LOS day	Complication
4	5	13.56	185.4	+	US: Unvisualized appandix CT: Appandix diameter 11.5 mm	Cefoperazone Gentamicin metronidazole	9	⊖
4	4	7.28	265.4	+	CT: Appandix diameter 16.5 mm	Ceftriaxone Metronidazole	7	⊖
4	4	20.64	98.6	+	US-CT: Unvisualized appandix	Ampicilline/Sulbactam Gentamicin metronidazole	6	⊖
7	7	22.00	32.5	+	US: Unvisualized appandix	Cefoperazone Gentamicin metronidazole	8	⊖
10	3	18.34	133.7	+	US-CT: Unvisualized appandix	Ampicilline/Sulbactam Gentamicin metronidazole	6	⊖
11	7	15.43	315.8	+	US: Unvisualized appandix CT: Appandix diameter: 9 mm	Meropenem Ornidazole	15	⊖
12	3	27.85	96.4	+	US: Unvisualized appandix CT: Appandix diameter: 13 mm	Ampicilline/Sulbactam Gentamicin metronidazole	7	⊖
16	5	17.82	371.1	+	US: Appandix diameter:7 mm CT: Appandix diameter:9 mm	Meropenem Teikoplanin metronidazole Fluconazole	10	⊖
16	4	35.69	219.0	+	US: Appandix diameter:5.7 mm CT: Appandix diameter:13 mm	Cefoperazone Gentamicin metronidazole	7	⊖

LOS: Lenght of hospital stay, SBO: Small bowel obstruction, US: Ultrasonography, CT: Computed tomography.

tomy and laparoscopic appendectomy. The main limiting factors of laparoscopic appendectomy for complicated cases in children are severe adhesions in the abdomen and an intra-abdominal cavity that is smaller than that of the adults. Poor visibility, limited dissection field, and severe post-operative complications have led many researchers to pursue safer and more efficacious ways of treating complicated pediatric appendicitis. Some studies (9-11) suggest open appendectomy instead of laparoscopic surgery in complicated cases while others now recommend laparoscopic appendectomy (6,12-14).

It is well known that laparoscopic surgery reduces the length of hospital stays, dependence on pain medication, and many other complications. Incidence of complications has been reported to be as high as 41% in patients undergoing laparoscopic appendectomy for complicated appendicitis (15). Laparoscopic procedure was performed in all complicated appendicitis cases in this study. Only four cases (7%) developed infectious complications. Three cases experienced surgical site infections and one developed an intra-abdominal abscess. None of the cases developed serious complications. We administered some precautionary treatments to reduce possible complications in generalized perforated appendicitis cases. These included employing the open port insertion technique, meticulous dissection, complete eradication of purulent fluid, and the removal of pseudomembranes. None of the patients in this study suffered post-operative small bowel obstruction, and only in one case was there an intra-abdominal abscess. These results suggest that laparoscopic appendectomy could be applied in all patients with complicated cases concomitant advanced generalized peritonitis.

In some complicated appendicitis cases, laparoscopic surgery might be converted to open surgery during the procedure due to poor visualization, severe inflammation, edematous bowels, and inability to perform dissection. Kyung Hye et al. have reported a conversion rate of 10% due to severe inflammation and ileus (16). In our study, severe inflammation and small bowel obstruction did not affect our decision when converting to open surgery in complicated cases.

Hospitalization periods in complicated cases were longer, especially in nine advanced generalized peritonitis cases. Although laparoscopic appendectomies do tend to shorten hospital stays; extended antibiotic duration and the presence of nine advanced peritonitis cases resulted in prolonged hospital stays in this study. It is our opinion, however, that intravenous antibiotics reduce the incidence of intra-abdominal abscesses and hospital readmissions.

One of the most important advantages of laparoscopic appendectomy is that post-operative small bowel obstruction is rarely seen. In the literature, the incidence of small bowel obstruction is 8% in complicated appendicitis while meta-analysis findings are 3.5% (8,17). Although more than half (63%) of the present study's cases were complicated and nine were generalized peritonitis, post-operative small bowel obstruction was not observed during the 43-month follow-up period. These findings are encouraging when considering the applicability of laparoscopic appendectomy in complicated pediatric cases. Surgeries are performed by many different surgeons in many clinics. The limitations of the present study include its retrospectivity and the fact that the surgeries were performed by a single surgeon experienced in minimally invasive surgery.

CONCLUSION

We propose that laparoscopic appendectomy can be performed safely in children's appendicitis cases, especially in complicated and advanced generalized appendicitis cases, even where children have small intra-abdominal cavity and inflammation amount to the whole abdomen.

Ethics Committee Approval: This study was approved by Pamukkale University Non-Invasive Clinical Research Ethics Committee (No: E-60116787-020-14389, Date: 02.02.2021).

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OLGU SERİSİ-ÖZET
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Laparoskopik appendektomi: Çocuklarda yaygın peritonitli apandisit olgularında etkinliği

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ÖZET

Laparoskopik apendektomi, çocukluk çağında en yaygın uygulanan cerrahi prosedürlerden biridir. Bu çalışmanın amacı; pediyatrik olgularda ileri yaygın peritonit ile komplike olan olgularda laparoskopik cerrahinin etkinliğini araştırmaktadır. Çalışmada, laparoskopik apendektomi yapılan 55 çocuk vakası retrospektif olarak gözden geçirildi. Olgular komplike olmayan, komplike veya ileri yaygın peritonit olarak sınıflandırıldı. Laboratuvar sonuçları, tanı algoritmaları, cerrahi teknikler ve komplikasyonlar araştırıldı. Olguların 24'ü erkek, 31'i kızdı. Ortalama yaş 11,3 ± 3 yıl idi. Olguların 20'si (%36) komplike değildi ve otuz beşi (%64) komplike idi. Komplike vakaların dokuzu ileri yaygın peritonitti, bu nedenle bunlar ek olarak "başka bir özel grup" olarak sınıflandırıldı. Ortalama lökosit sayısı ve C-reaktif protein seviyeleri komplike vakalarda sırasıyla 22,49 ± 12 x 10^9/L ve 120,5 ± 99 mg/L, komplike olmayan vakalarda 17,06 ± 10 x 10^9/L ve 52,37 ± 69 mg/L idi. vakalar. İlerlemiş yaygın peritonit olgularının tamamı hastaneye bağırsak tıkanıklığı ile başvurmuştu ve bu nedenle fizik muayenede yaygın karın rijiditesi vardı. Olguların hiçbirinde intraoperatif veya erken postoperatif dönemde herhangi bir komplikasyon gelişmedi. Postoperatif dönemde dört olguda (%7) enfeksiyon komplikasyonları (karın içi apseler ve cerrahi alan enfeksiyonları) gözlendi. Ortalama hastanede kalış süresi komplike ve komplike olmayan olgularda sırasıyla 5,62 ± 2,6 gün ve 3,95 ± 1 gündü. Yaygın peritonit olgularında ortalama yatış süresi 8,33 ± 2 gündü. Yaygın peritonit ile komplike vakalarda laparoskopik apendektominin ilk tedavi seçeneği olabileceğini gözlemledik.

Anahtar Kelimeler: Appendektomi, laparoskopi, çocuk, postoperative komplikasyon, komplike apandisit, yaygın peritonit

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Changes in cerebral oxygen saturation with the Trendelenburg position and increased intraabdominal pressure in laparocopic rectal surgery

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ABSTRACT

Objective: Position changes and increased intra-abdominal pressure in laparoscopic interventions lead to some physiopathological changes. There is no definite information in the literature regarding cerebral oxygen saturation in patients undergoing colorectal surgery. Our aim was to investigate whether there is oxygen saturation change in the brain tissue in pneumoperitoneum and the Trendelenburg position during laparoscopic rectal surgery.

Material and Methods: Cerebral oxygen saturation was measured in 35 patients who underwent laparoscopic rectal surgery in the Trendelenburg position. Measurements were made under general anesthesia in the pneumoperitoneum and the Trendelenburg position.

Results: The values that are statistically affected by the position are systolic blood pressure, mean arterial blood pressure and cerebral oxygen saturation. The Trendelenburg position does not disturb the cerebral oxygen saturation and it causes an increase in saturation. After pneumoperitoneum occurred, changes in systolic blood pressure, mean arterial blood pressure and brain oxygen saturation were detected. Cerebral oxygen saturation increases with the formation of pneumoperitoneum.

Conclusion: The Trendelenburg position and increased intraabdominal pressure during laparoscopic rectal surgery do not impair brain oxygen saturation.

Keywords: Laparoscopy, Trendelenburg position, brain oxygen saturation

INTRODUCTION

Laparoscopic surgery causes less damage to functional tissues than open surgery. Increased intraabdominal pressure puts pressure on venous vessels, reducing bleeding and the need for blood transfusion. Detailed anatomical imaging provided by optical magnification allows for successful surgical dissection. In the postoperative period, patients have less pain and analgesic requirements (1,2). Despite all of its advantages, it is compared to open surgery due to its disadvantages such as long operation time, unique complications and high cost. Although the discussions on this issue have decreased, they still continue. The rate of serious complications in laparoscopic surgery is low (1). It is known that positional changes, increased intra-abdominal pressure, and carbon dioxide (CO_2) insufflation in laparoscopic interventions cause some physiopathological changes (2). The results of studies on their hemodynamic effects in laparoscopic surgery are not compatible with each other. During laparoscopy, many factors, including general anesthesia, position, increased intraabdominal pressure and the patient's cardiac state, affect hemodynamics (3).

In laparoscopic surgery, depending on the type of operation, an upside down or head-up position is given to move the organs with the effect of gravity. These positions can cause unwanted hemodynamic changes. The changes in intracranial pressure and cerebral oxygen saturation ($bSaO_2$) that occur during this time have not been discussed much in the literature (4-6). In laparoscopic colorectal surgery, intraabdominal CO_2 gas is inflated to create a visual field. Hemodynamic changes occur due to intraabdominal pressure. Laparoscopic rectal surgery is in the Trendelenburg position and takes hours depending on the size of the surgery.

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Meanwhile, intracranial venous congestion takes place. Macroscopically, swelling and discoloration occur on the patient's face, eyelid and neck. Our aim was to investigate whether there is an oxygen saturation change in the brain tissue in the pneumoperitoneum and the Trendelenburg position during laparoscopic rectal surgery.

MATERIAL and METHODS

The study was carried out prospectively in Necmettin Erbakan University Meram Medical Faculty of Medicine between January 2019 and January 2020 with the approval of the ethics committee (2018/1601). Thirty-five consecutive patients who underwent laparoscopic rectal surgery in the Trendelenburg position were included in the study. Patients who did not want to be included in the study, who were decided to have open surgery due to complications during laparoscopic rectal surgery, who had a hematocrit value below 30, who had morbid obesity, and major bleeding during surgery were excluded from the study. Surgery of all patients was performed by the same surgical team. According to the ASA score used by the American Anesthesiologists Association, ASA 2-3 patients were operated under elective conditions. All participants gave their written informed consent after the researchers explained the aim and course of the study. Verbal consent was also obtained from all participants.

The patients were taken to the operating room after a six-hour fasting period. The same general anesthesia method was applied to all patients, and operation was performed by the same surgical team. Electrocardiogram, peripheral oxygen saturation, non-invasive blood pressure measurement and muscle relaxant monitoring with neuromuscular transducer (NMT) were performed in the operating room. Crystalloid infusion at a dose of 15 mL/kg/h was initiated by providing an iv route with a 22 gauge intracet. Patients were sedated with 0.03 mg/kg midazolam (Midolam®, Mefar, İstanbul, Türkiye). For anesthesia induction, 40 mg lidocaine (Jetmonal®, Adeka, Samsun, Türkiye), 2 mg/kg propofol (Propofol 1% Fresenius®, Kabi Fresenius AB, Uppsala, Sweden), 1 µg/kg remifentanil (Rentanil®, VEM, Ankara, Türkiye) and 0.6 mg/kg rocuronium (Myocron® VEM, Ankara, Türkiye) were administered. Patients were intubated while train of four (TOF) was 0%. The anesthesia was maintained by 30-50% FiO_2, 0.5-1 MAC desflurane (Suprane®, Baxter Healthcare, Puerto Rico, USA) inhalation and remifentanil infusion, with SpO_2 being 96-98%. During surgery, analgesic requirement of the patients was monitored using the surgical plethysmographic index (SPI), and the remifentanil infusion dose was adjusted so that the SPI was below 50. For ventilation, tidal volume was 6 mL/kg, respectively, and the frequency was set as end tidal CO_2 30-35 cm H_2O.

Nasopharyngeal temperature of the patients was adjusted to be 36-36.5 C°. Nasogastric tube and urinary catheter were placed in all patients. Invasive arterial monitoring and central vascular access were established in patients when deemed necessary. The first trocar was placed under the umbilical line by direct method. After the endo-camera control, pneumoperitoneum was created and intraabdominal pressure was kept between 10-14 mmHg. Other trocars were placed visually in the endo-camera. The patients were operated in a 30-degree Trandelenburg position.

Brain oxygen saturation was measured with a near infrared spectroscopy device (INVOS™ 5100C Cerebral/Somatic Oximeter, Medtronic, Minneapolis, USA). Cerebral SaO_2 saturation was measured from the right and left cerebral hemispheres with a catheter placed in the patient's frontal region (noninvasive). Measurements were performed consecutively under general anesthesia before the pneumoperitoneum, after the pneumoperitoneum was formed and after the pneumoperitoneum was terminated. Before, during and after the Trendelenburg position, serial measurements were made, and the results were recorded. The position and pneumoperitoneum values were compared independently in the study. Following the creation of the pneumoperitoneum, it was measured after waiting 10 minutes, then position measurement values were taken after positioning. In surgeries lasting one hour or longer, measurements were repeated every hour.

Parameters examined were age, sex, tumor location, surgery performed, intraabdominal pressure, operation time, pneumoperitoneum duration, ASA score, pulse, systolic arterial pressure (SAP), mean arterial pressure (MAP), peripheral oxygen saturation (SaO_2), right cerebral oxygen saturation ($bSaO_2$), left cerebral $bSaO_2$ and fraction of inspired oxygen (FiO_2).

Statistical Analysis

Kolmogorov-Smirnov and Shapiro-Wilk tests were used to control the distribution of the parameters. Whether there was a statistically significant difference between recurrent systolic blood pressure, mean arterial pressure, heart rate, FiO_2, SO_2, right and left brain oxygen saturation measurements in the patients was determined by repeated measured variance analysis. If this result was found to be significant, the measurement times that caused a significant difference were determined with the Bonferroni corrected multiple comparison test. In cases where the result of Friedman test statistics was significant, measurement times that caused the difference were determined using the Bonferroni corrected Wilcoxon sign test. In the interpretation of statistical hypothesis tests, type 1 error was accepted as 0.05. The collected data were analyzed by SPSS program.

RESULTS

Thirty-five patients, seven females and 28 males, with a mean age of 63.71 years (50-84), were included in the study. All of the patients had been operated for rectal cancer. Six patients underwent anterior resection and 29 patients underwent low anterior

Table 1. Demographic and operative information

		n= (35)
Sex (n)	Female	7 (20%)
	Male	28 (80%)
ASA score (n)	ASA 2	26 (74.3%)
	ASA3	9 (25.7%)
		Mean ± SD
Age		63.71 ± 8.79
Intraabdominal pressure		12.64 ± 0.8
Operation duration (minutes)		153.71 ± 33.57
Pneumoperitoneum time (minutes)		102.09 ± 24.31
Major intraoperetive complication		0

ASA: American Society of Anesthesiologists.

resection. According to the evaluation of anesthesia, the ASA score was three in nine of the cases and two in 26 cases. No major complications developed in any of the patients during the operation. Intraabdominal pressure was on average 12.64 (12-14) mmHg. The operation time was 153.71 minutes (90-220) and pneumoperitoneum time was 102.09 minutes (70-150) (Table 1).

Change in parameters according to the Trendelenburg position (Table 2)

The values that are statistically affected by the position are systolic blood pressure, mean arterial blood pressure and brain oxygen saturation. SAP and MAP increase with the Trendelenburg position. However, this increase was not statistically significant. After correction of the position, there is a serious decrease in SAP and MAP pressure ($p< 0.001$). Blood pressure cannot reach the baseline value after correcting the Trendelenburg position ($p< 0.001$). It can reach normal values in the postoperative recovery room. Increased cerebral oxygen saturation was found with the Trendelenburg position ($p< 0.001$). The Trendelenburg position does not disturb the brain oxygen saturation and causes an increase in saturation. Pulse peripheral SaO_2 and FiO_2 change were not affected by the position. We found a minimal decrease in heart rate due to the position, but this was not statistically significant.

Change in parameters according to pneumoperitoneum status (Table 3)

It was seen that some increase in the heart rate occurs after pneumoperitoneum. However, we detected some decrease in

Table 2. Change in parameters according to surgical position change

	Before position	During position	After position	p*
Pulse	69.9 ± 10.4	66.3 ± 10.8	65.2 ± 9.1	0.3
SAP	122.5 ± 24.4[a]	127.3 ± 18.3[b]	107.1 ± 14[c]	<0.001 (a-c), (b-c)
MAP	91.7 ± 19.1[a]	94 ± 10.9[b]	76.3 ± 10[c]	<0.001 (a-c), (b-c)
SaO_2	97.9 ± 1.5	97.5 ± 1.7	98.5 ± 1.2	0.17
Right $bSaO_2$	64.6 ± 7.2[a]	67.4 ± 8[b]	69.5 ± 7.8[c]	<0.001 (a-b), (a-c)
Left $bSaO_2$	65.7 ± 8.4[a]	67.5 ± 8.5[b]	68.2 ± 9.8[c]	<0.001 (a-b), (a-c)
FiO_2	82.5 ± 14.2	46.7 ± 6.8	56.2 ± 19.2	0.17

SAP: Systolic arterial pressure, MAP: Mean arterial pressure, SaO_2: Oxygen saturation, $bSaO_2$: Cerebral oxygen saturation, FiO_2: Fraction of inspired oxygen.
Pulse, SaO_2 and FiO_2 values of the patient are given in the table. Values resulting in $p< 0.05$ are presented.
*The columns between the calculated p values are shown with upper symbols.

Table 3. Change in parameters according to the pneumoperitoneum status

	Before pneumoperitoneum	During pneumoperitoneum	After pneumoperitoneum	p*
Pulse	66.2 ± 11.9	67.1 ± 11.5	65 ± 8.2	0.24
SAP	102.7 ± 25.1[a]	122.3 ± 27.8[b]	110.3 ± 19.1[c]	<0.001 (a-b), (b-c)
MAP	70.2 ± 10.7[a]	87.9 ± 17.3[b]	78.6 ± 10.6[c]	<0.001 (a-b), (a-c), (b-c)
SaO_2	98.4 ± 1.7	98.6 ± 0.9	98.5 ± 1.1	0.53
Right Brain SaO_2	61.5 ± 8.6[a]	64.1 ± 8[b]	70.2 ± 6.7[c]	<0.001 (a-b), (a-c), (b-c)
Left Brain SaO_2	64.3 ± 8.8[a]	65 ± 8.4[b]	69.4 ± 8.1[c]	<0.001 (a-c), (b-c)
FiO_2	46.6 ± 8.3	44.9 ± 6.6	49.4 ± 14.3	0.13

SAP: Systolic arterial pressure, MAP: Mean arterial pressure, SaO_2: Oxygen saturation, $bSaO_2$: Cerebral oxygen saturation, FiO_2: Fraction of inspired oxygen.
Pulse, SaO_2 and FiO_2 values of the patient are given in the table. Values resulting in $p< 0.05$ are presented.
*The columns between the calculated p values are shown with upper symbols.

the end of the pneumoperitoneum (p> 0.24). As with the change of position, the parameters most affected by the pneumoperitoneum were systolic blood pressure, mean arterial blood pressure and brain oxygen saturation. SAP and MAP increase with pneumoperitoneum and decrease after the pneumoperitoneum, but remain higher than the baseline value (p< 0.001). It can reach normal values in the postoperative recovery room. Increased cerebral oxygen saturation was detected with the formation of the pneumoperitoneum (p< 0.001). Pneumoperitoneum did not impair cerebral oxygen saturation. However, there are differences in the right and left hemispheres of the brain. Brain oxygenation in the right half of the brain is better at the end of the pneumoperitoneum. However, left brain oxygenation baseline value was found to be better than the right. The change in pulse SaO_2 and FiO_2 was not affected by position.

DISCUSSION

A pneumoperitoneum is created for laparoscopic surgery. Pneumoperitoneum is done by CO_2 insufflation. Studies have been conducted to reveal the effects of increased intraabdominal pressure. Cardiopulmonary and renal effects have been examined in most of these studies (2). When intraabdominal pressure increases during laparoscopic surgery, there is a decrease in cardiac performance. Hypercapnia in the pneumoperitoneum increases the incidence of cardiac arrhythmias. However, information about its effect in the intracranial area is limited. This limited information has generally been obtained from the colorectal non- surgical field. In our study, it was found that SAP and MAP increase with pneumoperitoneum and decrease after the pneumoperitoneum, but higher than the basal value (p< 0.001). We found that cerebral oxygen saturation increased with the formation of pneumoperitoneum (p< 0.001).

There are few studies on the effects and complications of laparoscopic surgery position. In these publications, findings about the prolonged Trendelenburg position are presented. However, almost all of these works have been obtained from gynecological and urological surgeries (2). Data on colorectal laparoscopic surgery are limited. The effect of the prolonged Trendelenburg position on the brain has not been fully studied. In particular, there is no definitive data on the change in cerebral oxygen saturation. This issue has been tried to be enlightened in our study. Cardiovascular and pulmonary effects occur rapidly with the Trendelenburg position. However, its effects on the brain appear more slowly (2). An increase in venous return to the heart is observed with the Trendelenburg position. The most important effect of this increase is gravity. With the effect of increased venous transformation, an increase in arterial pressure and central venous pressure is observed (7,8). An increase of 53-125% in central venous pressure, 15% and 35% in mean arterial pressure is observed. In our study, MAP increased by 25.2%. Most of the studies have problems regarding sex distribution. Studies consist of either the female gender sex to gynecological surgery work or the male sex due to prostatectomy surgery. Therefore, the studies do not provide a complete sex sample. The advantage of our study is that it includes the male and female sexes. Mean arterial pressure and systolic arterial pressure increases with position. However, when the position is corrected after surgery, it falls more than the pre-position value and the patients are hypotensive, and this was found to be statistically significant in our study. Adaptation time does not improve rapidly with the correction of the position. It is low for a while. These values improve in the recovery room. There is not enough data in the literature on this subject.

We do not have complete information about intracranial changes during and after laparoscopic surgery performed in the Trendelenburg position. The information obtained on this subject is in the form of case reports. A case with hemiparesis after urological surgery has been reported (9). After the surgery performed in the Trendelenburg position, it has been found that the brain had cognitive impairment. A change in the mini mental state test has been found in the study (10). However, no change has been detected in other neuroconscious tests. Temporary blindness is observed after laparoscopic surgery (11). Optic nerve damage has been considered as causes of blindness. Neuroconscious values of the patients were not examined in our study. Neurological deterioration was not detected in any of our patients. Neurological defect did not occur. None of our patients had vision problems. Inconsistent results have been found in studies on cerebral oxygen saturation during surgery performed in the Trendelenburg position (5,6,12,13). In the study of Lee JR et al., they have found that the brain oxygen value decreased in the gynecological operation performed in the laparoscopic Trendelenburg position (14). Other studies show that there is no increase or change in cerebral oxygen saturation (12,13). In the study conducted by Park EY et al., it has been found that cerebral oxygen saturation increased with the position during robotic prostatectomy (15). However, there is no study conducted during laparoscopic colorectal surgery. In our study, we detected a significant increase in brain oxygen saturation with the Trendelenburg position. After bringing the position to normal, we saw that this increase continued. The position did not cause deterioration in brain oxygen saturation.

Pneumoperitoneum and Trendelenburg position are performed sequentially during surgery. We think that both Trendelenburg position and pneumoperitoneum affect brain oxygen saturation. However, we think that the Trendelenburg position affects more.

CONCLUSION

The Trendelenburg position and increased intraabdominal pressure during laparoscopic rectal surgery do not impair brain oxygen saturation. On the contrary, it causes an increase in this value.

Ethics Committee Approval: This study was approved by Necmettin Erbakan University Meram Faculty of Medicine Pharmaceutical and Non-Medical Device Ethics Committee (Decision no: 2018/1601, Date: 07.12.2018).

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ORİJİNAL ÇALIŞMA-ÖZET
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Laparoskopik rektum cerrahisinde Trendelenburg pozisyonu ile serebral oksijen satürasyonundaki değişiklikler ve artan intraabdominal basınç

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ÖZET

Giriş ve Amaç: Laparoskopik girişimlerde pozisyon değişiklikleri ve intraabdominal basınç artışı bir takım fizyopatolojik değişikliklere yol açmaktadır. Laparoskopik cerrahiye bağlı oluşan hemodinamik etkiler ile ilgili çalışmaların sonuçları birbirleriyle uyumlu değildir. Kolorektal cerrahi uygulanan hastalarda beyin oksijen satürasyonu ile ilgili literatürde kesin bilgi yoktur. Amacımız laparoskopik rektal cerrahi esnasında pnömoperitoneum ve Trendelenburg pozisyonunda beyin dokusunda oksijen satürasyon değişimi olup olmadığı araştırmaktır.

Gereç ve Yöntem: Çalışma etik kurul onayı alınarak prospektif olarak gerçekleştirildi. Trendelenburg pozisyonunda laparoskopik rektum cerrahisi yapılan 35 hastanın beyin oksijen satürasyonu ölçüldü. Ölçümler genel anestezi altında pnömoperitoneum ve Trendelenburg pozisyonunda yapıldı.

Bulgular: Çalışma laparoskopik rektum cerrahisi uygulanan yedisi kadın, 28'i erkek 35 hasta üzerinden yapıldı. Pozisyondan istatistiksel olarak etkilenen değerler sistolik kan basıncı, ortalama arteriyel kan basıncı ve beyin oksijen satürasyonudur. Trendelenburg pozisyonu beyin oksijen satürasyonunu bozmamakta hatta satürasyonda artmaya neden olmaktadır. Pnömoperitoneum gerçekleştikten sonra sistolik kan basıncı, ortalama arteriyel kan basıncı ve beyin oksijen satürasyonunda değişme tespit edildi. Pnömoperitoneum oluşumu ile beyin oksijen satürasyonu artmaktadır.

Sonuç: Laparoskopik rektal cerrahi esnasında yapılan Trendelenburg pozisyonu ve intraabdominal basınç artışı beyin oksijen satürasyonunu bozmamaktadır.

Anahtar Kelimeler: Laparoskopi, Trendelenburg pozisyonu, beyin oksijen satürasyonu

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Impact of bariatric and metabolic surgery education program on the knowledge and attitude of medical students

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ABSTRACT

Objective: Bariatric and metabolic surgery (BMS) is the most effective treatment method of morbid obesity. Optimum education of medical students regarding BMS is important for proper assessment of morbidly obese patients in the future.

Material and Methods: Medical students from five and six years were determined as the targeted study population. A survey including 17 questions was applied through a web-based survey platform. Students who replied the survey were classified into two groups: distinct bariatric and metabolic surgery education program (BMSEP) (+) and (-). The answers of two groups were compared using Chi-square test.

Results: In total, 845 students replied the survey. Surgery referral rates were higher (33.4% vs. 26.5%, $p< 0.05$), referring to alternative treatment methods were low (4.9% vs. 11.9%, $p< 0.05$), the answer rate of "absolutely agree" was higher and "have no idea" was lower in questions regarding the indications of BMS for the sample patient with body mass index (BMI)> 40 kg/m^2 and the sample patient with BMI between 35-40 kg/m^2 in the BMSEP (+) group ($p< 0.05$). However, the two groups were comparable for the answers given for the sample patient of BMI 30-35 kg/m^2 with uncontrolled diabetes. The rate of first-degree relative referral to BMS when indicated was higher in the BMSEP (+) group. Effectiveness of surgery, cost and risk perception were comparable between the two groups.

Conclusion: This study showed that medical students who have a distinct BMSEP in their medical school have better level of knowledge and comparable risk perception regarding BMS. Structured education programs in BMS may directly improve knowledge, perception, and attitude of medical students and indirectly increase the role of primary care physicians in patient referral to BMS and long-term follow-up.

Keywords: Medical education, morbid obesity, bariatric surgery, medical student

INTRODUCTION

Multidisciplinary and staged approach is necessary in the treatment of morbid obesity. Bariatric surgery is the most effective treatment modality for morbidly obese patients, and it has been widely utilized. Bariatric procedures are successful in treating metabolic problems secondary to obesity, and lately the reported mortality rate is 0.18% (1,2). Nevertheless, medical society is biased despite of the advantages of bariatric surgery. Thus, bariatric surgery may not be offered as an option to the patients who may potentially benefit (3). Primary care physician (PCP) referral increases the bariatric surgery acceptance rate in morbidly obese patients (4). In a previously published study from our center, it has been shown that the referral rate of morbidly obese patients to bariatric surgery is higher among primary care physicians (PCPs) who are in the early period of their career (5).

Optimum education for medical students regarding the treatment of obesity and bariatric surgery is an important factor affecting their future perspective. Various studies have reported that the curriculum for obesity and its treatment in several medical schools is inadequate (6). A survey study investigating medical education regarding obesity and its treatment in the United States has concluded that only 10% of the program directors reported their curriculum as sufficient (7). According to the same study, one third of medical schools do not have obesity medicine in their current curriculum and do not have a plan on adding it. Another survey study evaluating the evolution of medical knowledge in medical students from the first year to the fourth year has shown that despite the significant improvement in

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knowledge, 60% of the medical students do not identify obesity as a disease (8). Interestingly, there are limited studies evaluating the curriculum for bariatric surgery and perspective of medical students regarding bariatric procedures (9).

In our country, education in obesity medicine should fill the following criteria according to the National Medical Education Core Program (UTCEP): A PCP should have adequate knowledge in diagnosis and treatment options, refer to a specialist after performing preliminary physical examination and tests, perform long term follow up, and employ disease prevention and control measures. Most of the medical schools configure their curriculum based on these criteria. However, there is no recommendation for implementing bariatric and metabolic surgery (BMS) as a distinct education program in UTCEP, it is left to the self-initiative of the medical schools (10).

There is no published study investigating the level of knowledge regarding obesity and BMS among the medical doctors who graduated from medical schools where BMS is a distinct education program in the curriculum. In this survey study including medical students from years five and six, it was aimed to compare the knowledge levels and perspectives of medical students in BMS and whether or not they had BMS as distinct education program in the medical school.

MATERIAL and METHODS

Survey Design

The target population of this study were medical students from years five and six in Türkiye since they were supposed to complete their basic training in obesity medicine. The survey was generated by an experienced bariatric surgeon (HO) after cautious review of the previously published similar articles and international guidelines. Then input of the executive council members of Turkish Society for Bariatric and Metabolic Surgery was obtained. After having tested the survey in a population consisting of 10 students, it was finalized comprising 17 questions that may be answered in three or four minutes. Survey questions consisted of informed consent (one question), presence of BMS education program (BMSEP) (one question), demographics (two questions), success of medical treatment (two questions), basic knowledge on surgery, indications, follow up, referral and education (11 questions). Demographics, practical approach, and requirement questions were multi choice and single answer while others were created in five points Likert's scale (absolutely disagree, disagree, have no idea, agree, absolutely agree). Survey questions are presented in appendix one. This study was approved by the institutional review board (2019-10/4).

Data Collection and Statistical Analysis

Based on the data obtained from the Turkish Council of Higher Education (YOK), there were 24.500 medical students from years five and six in 2019. We aimed to query 800 students within a 95% confidence interval and a sampling error of 3%. The survey was performed via Survey Monkey Inc (San Mateo, California, USA). The web link of the survey was shared in social media, and answers were obtained from 845 students. The students were classified into two groups based on the presence of BMSEP in their medical school curriculum [BMSEP (+) and BMSEP (-)]. The distinction between these two groups was made according to the answer given to the question of whether there was BMSEP in addition to the obesity education program, independent of the content of the curriculum.

Two groups were compared with univariate analysis, chi-square and Fisher's exact tests were utilized. A p value lower than 0.05 was accepted statistically significant. Statistical analysis was performed using the software Survey Monkey Inc (San Mateo, California, USA).

RESULTS

In total, 845 students replied the survey. There were 85 medical schools in Türkiye during the study period. No students replied to the survey from 34 medical schools while there were 15 medical schools with more than 20 responders (Question 2). Of the medical students, 47% were year five and 53% were year six (Question 3). Obesity medicine and its treatment were included in the curriculum of all medical schools while BMSEP was present in only 36. Among the responders, 484 (57%) students had BMSEP in their curriculum (Question 4).

Majority of the students in both groups reflected diet, exercise and behavioral changes will not be adequate in the treatment of obesity, and the groups were comparable (p= 0.45). The rate of referral to surgery for the patients who failed to lose weight with diet, exercise and behavioral changes was higher among the students who had BMSEP (33.4% vs 26.5%) and referral rate to alternative methods was lower in this group (4.9% vs 11%, p= 0.002).

Answer "absolutely agree" was more frequent (27.5% vs 16.3%, p= 0.0001) and "have no idea" was rare (10.9% vs 19.6%, p= 0.0003) to the question regarding the sample patient with a body mass index (BMI) of >40 in the BMSEP (+) group. The answer for the question regarding the sample patient with comorbidity and BMI between 35 and 40 was similar to the previous question: BMSEP (+) group stated "absolutely agree" (25.4%) and "have no idea" (12.6%) while the BMSEP (-) group stated "absolutely agree" (17%) and "have no idea" (21%) (p values are 0.004 and 0.0006, respectively). However, the groups were comparable for the answer to the question uncontrolled diabetes mellitus (DM) with BMI between 30 and 35.

There were more students in the BMSEP (+) group who stated that surgical treatment was more efficient and would refer their first-degree relatives to surgery when indicated. Groups were comparable in terms of the "have no idea" answers regarding

surgical mortality rate. Additionally, the answers regarding "postoperative long-term follow-up of the patients may be done by the PCP" question were comparable. There was no difference between the groups among the subjects desired to be concentrated on during BMS training (Question 16). Students thinking that their education of BMS was adequate were more frequently found in the BMSEP (+) group. The answer "have no idea" was rare and the answer "since they do not accept" was more frequent to the question "for what reason you may not recommend BMS to your relatives" in BMSEP (+) group. Two groups were comparable in terms of answers "not efficient", "high cost" and "high risk". However, risk perspective was high in two groups. Answers to the multi-choice questions are present in Figures 1, 2, 3 and to the Likert scale questions in Figure 4.

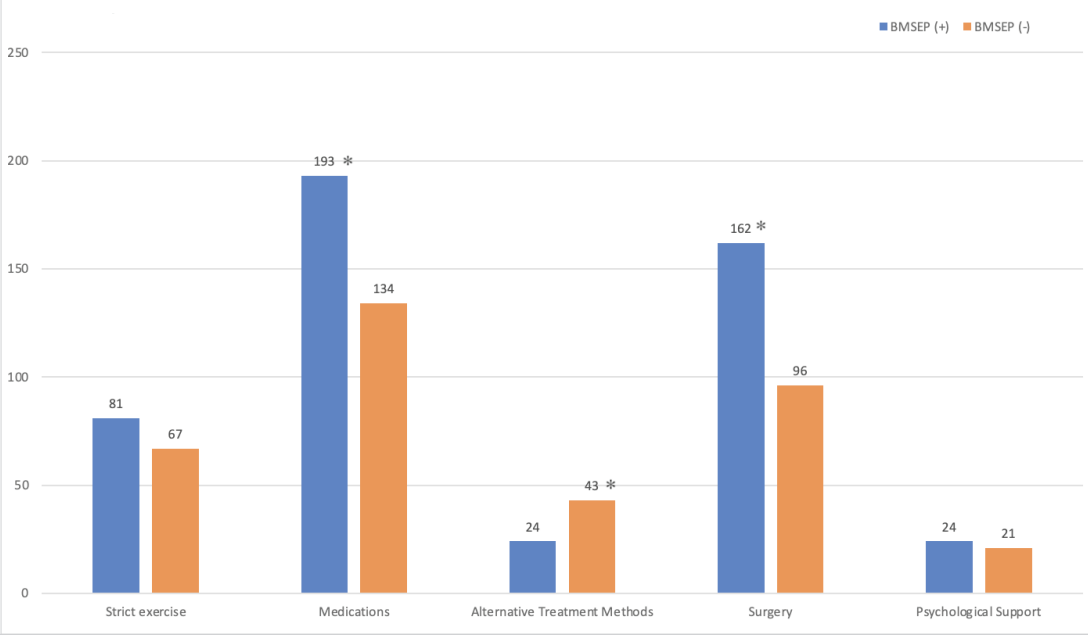

Figure 1. Answers to the question for the choice of treatment in patients who failed to lose weight with diet and exercise (Question 6). Surgery referral answer was more common while medical treatment and alternative treatment methods answers were rare among the students in BMEPS (+) group ($p< 0.001$).

(* shows the statistically significant differences between the groups)

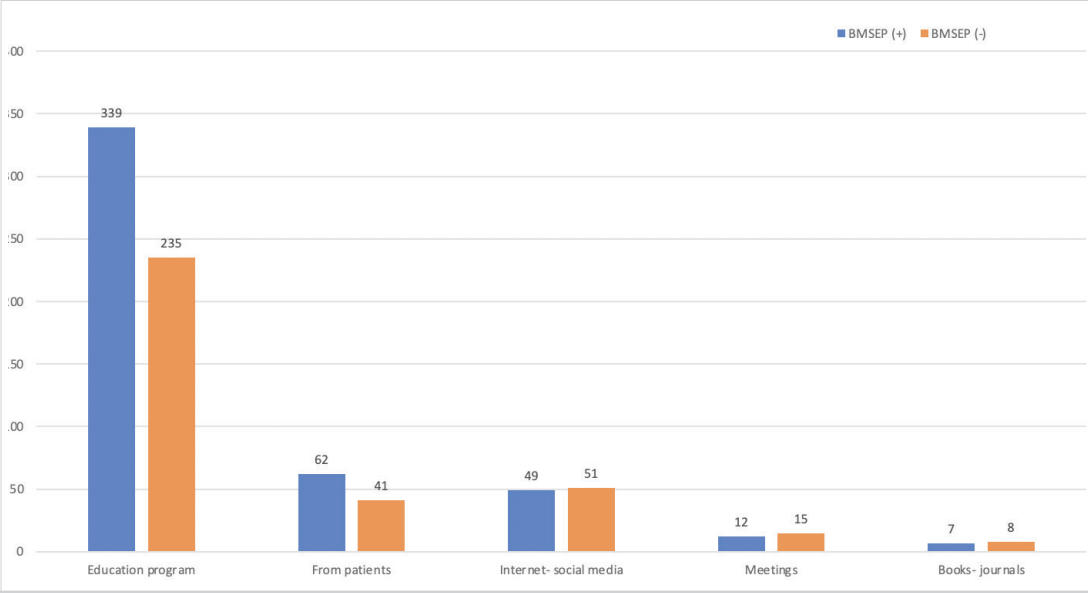

Figure 2. Responses to the question "How did you receive information on bariatric and metabolic surgery?" (Question 7). There were no significant differences between two groups ($p> 0.05$).

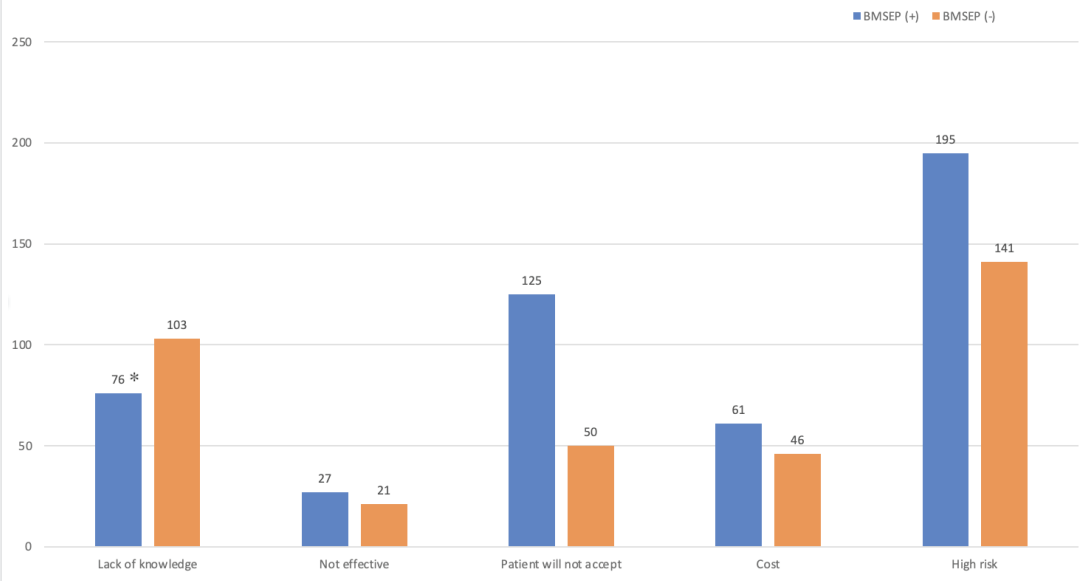

Figure 3. Responses to the question "When it is indicated, for what reason you may not recommend bariatric and metabolic surgery to your first-degree relatives? (Question 14). "Lack of knowledge" response rate was lower while "Patient will not accept" response rate was higher in BMSEP (+) group ($p< 0.001$). Risk perception was comparable between the groups.

(* shows the statistically significant differences between the groups).

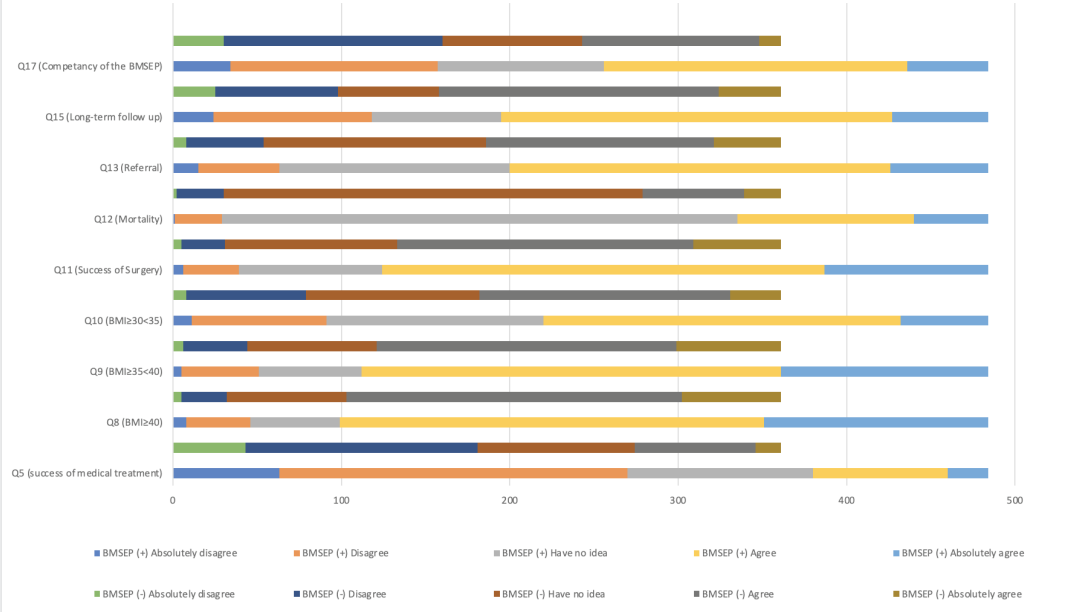

Figure 4. Answers of the students who took the survey to the questions in Likert scale. Students in the BMSEP (+) group replied the questions more accurately in terms of surgical indications, patient referral to surgery and competency of the BMSEP.

Likert's scale (absolutely disagree, disagree, have no idea, agree, absolutely agree).

DISCUSSION

This study aimed to evaluate the knowledge of medical students about BMS and was conducted with 845 medical students in Türkiye. Students in the BMSEP (+) group answered the questions regarding surgical indications, patient referral to BMS, efficacy of BMS, referral of relatives and adequacy of BMS education more accurately. However, mortality and risk perspectives of the students were comparable in both groups.

Sufficient education and active participation in the processes of medical students in terms of obesity and its treatment is very important (11). The number of studies evaluating the competence of education for the management and treatment of

morbidly obese patients are limited. A previously published systematic review reported that most of the medical students are negatively biased about obese patients and most of the medical schools do not have an integrated obesity medicine education (12). In the study of Jay et al., it has been reported that physicians who have had additional education in obesity medicine feel more comfortable while treating obese patients (13). Similarly, young physicians who have worked on obesity and its management during their medical education are diligent in presenting treatment options to obese patients and answer questions about BMS more accurately (14). Our previously conducted study including PCPs showed that young physicians were better equipped in BMS indications and referral of patients to BMS (5). These results may be interpreted as improvement of obesity medicine education in recent years despite the major gaps in medical education process.

In most medical schools in our country and in the world, BMS education is given under obesity medicine education, not as a separate program. Since BMS is widely being performed and has become an important subspecialty in surgery, it has become a distinct education program during surgery rotation of medical students. In the present study, there were 36 medical schools having BMSEP (+). The number of studies investigating the knowledge and perceptions of medical students regarding BMS are limited. Banasiak et al. have first emphasized problems and deficiency of BMS education in medical schools. Students who were educated in BMS responded to the questions regarding bariatric surgery more accurately. This study suggests adding BMS education in the curriculum (15). In a study including 298 medical students from the same medical school, it has been reported that the knowledge of medical students was insufficient while they were willing to improve it. The rate for accurate identification of surgical indications was 36.6%, students who believed surgery was a safe alternative in the treatment of obesity was 46%, and students who said they would refer patients to BMS when indicated was 74%. Majority of the students find themselves inadequate in the management of obesity (16). Another study including 468 medical students from year six has reported that students have limited knowledge of BMS but are willing to improve. Majority of the students (77%) have reported that they have not received sufficient education in BMS. It has been concluded that BMS is not a distinct education program in the curriculum among almost all the medical schools (17). Roberts et al. have evaluated the attitude of 13 medical students from year three before and after having received education about BMS. After the education, students' knowledge about obesity, patient education and referral to BMS have been improved significantly. Although conducted with a very limited number of students, this study is important for demonstrating that education improves the perspective of medical students about BMS (18). In our study, the perception of success with diet and exercise was too low, and the groups were comparable. Referral of obese patients to surgery rate was higher than it was reported in the literature, and this difference was higher in the BMSEP (+) group.

Knowledge level on the indications of BMS was evaluated via three different cases. Two cases were presented in compliance with the National Health Institute consensus criteria while one case was presented as a patient with 30-35 kg/m^2 body mass index, uncontrolled diabetes mellitus that could not be controlled with medications, which is a relatively new indication (19,20). Referral to surgery rate was twofold high in the BMSEP (+) group in the first two questions. However, groups were comparable for the question regarding metabolic surgery indication. This may be associated with a need for update in the curriculum of BMS education program since the indication is new. Comparison of published articles in this topic may not be feasible since content of the questionaries and question technics are different. Characteristics of the questions in Matlok et al.'s study are like formal examination questions evaluating the knowledge level of participants. The question technic is totally different in our study, mostly Likert scale questions were preferred. This method is useful especially in terms of evaluating the attitude of participants and comparing groups. When the results of our study were scrutinized, presence of BMSEP had positive impact on evaluating surgical indications and patient referral to BMS. However, risk perception was still high for BMS referral, participants did not think the quality of BMS education was adequate, particularly in terms of surgical indications and risk of surgical mortality. Further studies investigating the content of curriculum may be necessary for making a precise decision.

This study has several limitations. While the number of participants is adequate, there were no students who answered the questionaries from some of the medical schools. Although the study is quantically satisfactory, it may not reflect the national data precisely. Another issue is inquiring only the presence of BMSEP, not its content. The students were simply asked if there was a separate BMS course, and the results were evaluated according to this answer. However, this is the first study from our country investigating the impact of BMSEP on the knowledge of medical students. This study showed that the existence of the BMS course alone has a positive contribution to the perception and knowledge of the students. The next process will be to investigate the structure of the program and the impact of its operation.

CONCLUSION

As a conclusion, this study showed that the level of knowledge among the medical students who studied BMS as a separate program was higher. However, attitudes were comparable due to risk perception and cost. We did not inquire the content of

BMSEP, but even the presence of BMSEP may improve the knowledge level and attitude of medical students. Structured education programs in BMS may positively influence knowledge, perception, and attitude of medical students. This approach may increase the role of PCP's in-patient referral to BMS and long-term follow-up.

Ethics Committee Approval: This study was approved by Uludağ University Faculty of Medicine Clinical Research Ethics Committee (Decision no: 2021-6/30, Date: 26.05.2021).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - HÖ; Design - HÖ, MN; Supervision - HÖ; Fundings - HÖ; Materials - HÖ, ÖI; Data Collection and/ or Processing - HÖ, MN, ÖI; Analysis and/or Interpretation - HÖ, MN, ÖI; Literature Search - HÖ, ÖI; Writing Manuscript - HÖ, ÖI; Critical Reviews - HÖ, MN.

Conflict of Interest: The authors have no conflicts of interest to declare.

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ORİJİNAL ÇALIŞMA-ÖZET
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Bariyatrik ve metabolik cerrahi dersinin tıp öğrencilerinin bilgi ve tutum düzeylerine etkisi: Türkiye anket çalışması

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ÖZET

Giriş ve Amaç: Bariyatrik ve metabolik cerrahi (BMC), morbid obezitenin en etkili tedavi yöntemidir. Tıp öğrencilerinin BMC konusunda optimum eğitimi, gelecekte morbid obez hastaların doğru değerlendirilmesi için önemlidir.

Gereç ve Yöntem: Beşinci ve altıncı yıllarındaki tıp öğrencileri hedef kitle olarak belirlendi. Web tabanlı bir anket platformu aracılığıyla 17 sorudan oluşan bir anket uygulandı. Anketi yanıtlayan öğrenciler iki gruba ayrıldı: farklı bariyatrik ve metabolik cerrahi eğitim programı (BMCEP) (+) ve (-). İki grubun cevapları ki-kare testi kullanılarak karşılaştırıldı.

Bulgular: Toplamda 845 öğrenci anketi yanıtladı. BMCEP (+) grubunda ($p< 0,05$) cerrahi sevk oranları daha yüksek (%33,4'e karşı %26,5, $p< 0,05$), alternatif tedavi yöntemlerine başvurma oranı düşük (%4,9'a karşı %11,9, $p< 0,05$), vücut kütle indeksi (VKİ)> 40 kg/m^2 olan örnek hasta ile VKİ 35-40 kg/m^2 arasında olan örnek hasta için BMC endikasyonlarına ilişkin sorularda "kesinlikle katılıyorum" yanıt oranı daha yüksek ve "fikrim yok" daha düşüktü. Ancak, VKİ 30-35 kg/m^2 ve kontrolsüz diyabetli örnek hasta için verilen cevaplar açısından iki grup benzerdi. Birinci derece akraba endike olduğunda BMC'ye sevk oranı BMCEP (+) grubunda daha yüksekti. Ameliyatın etkinliği, maliyet ve risk algısı iki grup arasında benzerdi.

Sonuç: Bu çalışma, tıp fakültelerinde belirgin bir BMCEP'e sahip olan tıp öğrencilerinin BMC ile ilgili daha iyi bilgi düzeyine ve karşılaştırılabilir risk algısına sahip olduğunu göstermiştir. BMC'de yapılandırılmış eğitim programları, tıp öğrencilerinin bilgi, algı ve tutumlarını doğrudan geliştirebilir; dolaylı olarak birinci basamak hekimlerinin BMC'ye hasta sevki ve uzun süreli izlemdeki rolünü artırabilir.

Anahtar Kelimeler: Tıp eğitimi, morbid obezite, bariyatrik cerrahi, tıp öğrencisi

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ORIGINAL ARTICLE
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The effect of different therapeutic treatments on the frequency of postoperative hypocalcemia in patients with thyroidectomy

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ABSTRACT

Objective: Thyroid gland surgery and its surgical complications are situations that a surgeon frequently encounters in his daily practice. In our study, it was aimed to examine the effect of different treatment methods given to patients who underwent thyroidectomy on hypocalcemia.

Material and Methods: Three hundred and seventy-one patients who underwent thyroidectomy at Ondokuz Mayıs University Medical Faculty General Surgery clinic between December 2016 and January 2021 were retrospectively included in the study. Parameters such as surgery indications, fine needle aspiration biopsy results, preoperative serum calcium values, type of surgery, serum calcium values at postoperative 1st day and 1st month, postoperative hospital stay, drugs prescribed at discharge, histopathological diagnosis of the patient, and whether there was incidental parathyroidectomy or not were included.

Results: Mean age of 371 patients who underwent thyroidectomy was 49 (19-82) years. Total thyroidectomy was the most common type of thyroidectomy with 61% (n= 225) of the patients. There was a significant decrease in pre-op and post-op calcium values in all three types of surgery performed on the patients, and there was no significant difference between the different types of surgery. Post-operative day one and month one serum calcium values were significantly increased in all groups (p= .000). The increase in post-op serum calcium level was most common in the group using calcium carbonate + cholecalciferol + calcitriol.

Conclusion: The use of post-op calcitriol in patients undergoing thyroidectomy seems to be quite effective in preventing the development of hypocalcemia.

Keywords: Thyroidectomy, hypocalcemia, calcitriol, thyroid diseases

INTRODUCTION

Thyroid gland diseases are conditions affecting approximately 5% of the population and are frequently encountered by a surgeon in his/her daily practice (1). Although thyroid surgery is considered a low-risk and safe approach today, the patient should be followed closely for postoperative complications (2).

The first successful thyroid surgery in humans was performed and documented by Ebu'l Kasım El Zehravi (963-1013) (3). It is also called Albucasis or Elzahawi in European sources. These methods were published by Roger Frugardi in 1170 (4). Thyroid surgery, which had a mortality rate of approximately 40% until the 1850s, became much less mortal and effective especially after the 1850s (5).

However, another problem is hypothyroidism, which develops in patients who survive thyroidectomy. This condition was first treated with subcutaneous injection of the thyroid extract in 1891, and after the effectiveness of the treatment was proven, it was discovered that oral therapy had similar efficacy, and oral replacement therapy was started (6).

Today, oral replacement therapy is not only for hypothyroidism, but also for calcium deficiencies (7,8). Postoperative hypocalcaemia can be affected by many conditions such as the surgeon, the center, and the risk factors of the patient, and it can be seen in the literature at rates up to 50% (2,8,9). Postoperative hypocalcaemia may be asymptomatic or may be of varying severity ranging from tetany,

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laryngospasm, cardiac arrhythmias and death (10). Therefore, surgeons should diagnose and treat postoperative hypocalcaemia in a timely manner. On the other hand, preoperative and postoperative calcium and vitamin D preparations are recommended in the American Thyroid Association guidelines although there is no consensus on a standard prevention treatment (10). In our study, it was aimed to examine the effect of prophylactic hormone therapy given to patients who underwent thyroidectomy on hypocalcaemia.

MATERIAL and METHODS

The study retrospectively included 371 patients who underwent bilateral total thyroidectomy, completion thyroidectomy, and intrathoracic substernal thyroidectomy by the same surgeon in the General Surgery clinic of Ondokuz Mayıs University Faculty of Medicine between December 2016 and January 2021.

Parameters such as patients' indications for surgery, fine needle aspiration biopsy results, preoperative serum calcium values, type of surgery, serum calcium (n= 8.5-10.3 mg/dL) values at postoperative 1st day and 1st month, postoperative hospital stay, drugs prescribed at discharge, histopathological diagnosis, and whether there was an incidental parathyroidectomy or not were included in the study.

Patients who had deficiencies in these parameters, did not come to their follow-ups, cases with accompanying parathyroid surgery or those who did not use the prescribed drugs were excluded from the study.

The patients were divided into three groups according to the treatments they received (or did not receive). No drugs, calcium carbonate + cholecalciferol or calcium carbonate + cholecalciferol + calcitriol. Only calcium carbonate + cholecalciferol was started in patients with symptomatic hypocalcaemia. If the patient had symptomatic hypocalcaemia at discharge and parathormone levels were below the normal range, calcitriol was added. The treatment was terminated if parathormone values were found to be normal in the postoperative one-month follow-up.

Since the center where the study was conducted is an education clinic dealing with oncological cases, central lymph node dissection with nerve monitoring is routinely performed in all cases.

IBM SPSS (Statistical Package for the Social Sciences) 20.0 package program was used for data analysis. Descriptive statistics were summarized as frequency and percentage. Chi-square test was used for comparison of qualitative variables, Student-t test, Mann-Whitney U and ANOVA tests were used for comparisons of independent groups. Wilcoxon test was used for dependent group comparisons. However, corrections were not made for multiple comparisons.

Approval for this study was obtained from the Clinical Research Ethics Committee of Ondokuz Mayıs University with the application dated 16.04.2020 and application number 2020000416-5.

Statistical significance level was taken as $p< .05$.

RESULTS

Mean age of 371 patients who underwent thyroidectomy was 49 (19-82) years. Total thyroidectomy was the most common type of total thyroidectomy with 61% (n= 225) of the patients (Table 1).

Incidental parathyroidectomy was seen in 20.1% of the patients (n= 72), and no significant correlation was found between the types of surgery and the incidence of incidental parathyroidectomy (p= .453). Hypocalcaemia was observed in 69.4% (n= 50) of 72 patients with incidental parathyroidectomy and 47.4% (n= 136) of 287 patients without incidental parathyroidectomy. Mean serum calcium level of the patients with incidental parathyroidectomy was 8.2 (min= 6.1, max= 9.9) while the mean of patients without incidental parathyroidectomy was 8.5 (min= 5.8, max= 11.5). Presence of incidental parathyroidectomy has a statistically significant effect on hypocalcaemia (p= 0.001).

Serum PTH levels were measured on post-op day one from 346 patients. Median value was found to be 24.66 pg/mL (min= 1.2, max= 168.6) (normal value= 15-65 pg/mL). There was a statistically significant difference between the groups with and without incidental parathyroidectomy (p< 0.001).

In 71% (n= 262) of the patients, the biopsy result was malignancy or suspected malignancy, and no suspicion of malignancy was found in 29% (n= 109). Of the patients, 88% (n= 325) were hospitalized for less than one postoperative day. Calcium levels observed in the postoperative 1st day and 1st month controls of the patients are given in Table 2.

Mean post-op calcium values of 325 patients who were discharged one day after the operation were 8.45 ± 0.613, and the average of 46 patients who were discharged more than two days later was 7.793 ± 0.796, and the difference between them was statistically significant (p< 0.001) (Table 3).

There was a significant decrease in preoperative and postoperative calcium values in all three types of surgery, and no significant difference was observed between the different types of surgery (Table 4).

Table 1. Distribution of thyroidectomy types applied to patients

Type of surgery	n	%
Total thyroidectomy	225	61
For completion + recurrence	51	13
Intrathoracic-substernal	95	26
Total	371	100

Table 2. Hypocalcaemia development rates of the patients on the postoperative 1st day (Post-op-1) and postoperative 1st month (Post-op-control)

Followed patient group	n	%
Post-op-1 hypocalcaemia, post-op-control hypocalcaemia	24	6.4
Post-op-1 hypocalcaemia, post-op-control normocalcemia	171	46.1
Post-op-1 normocalcemia, post-op-control hypocalcaemia	4	1.2
Post-op-1 normocalcemia, post-op-control normocalcemia	172	46.3

Table 3. Hypocalcaemia development status according to discharge days

	Discharge day				
	Day 1		Day 2 and later		
Development of hypocalcaemia	n	%	n	%	p
No	172	95	9	5	**<0.001**
Yes	153	80.5	37	19.5	
Total	325	87.6	46	12.4	

Table 4. Calcium values before and after the operation according to the types of surgery (mg/dL)

Type of surgery	Pre-op/Post-op	Median	Min	Max	p
Total thyroidectomy	Pre-op	9.5	7.8	11.6	**<0.001**
	Post-op	8.4	5.8	10.2	
Completion thyroidectomy	Pre-op	9.4	7.5	12	**<0.001**
	Post-op	8.6	6.4	9.5	
Intrathoracic	Pre-op	9.6	8.1	12.9	**<0.001**
	Post-op	8.4	6.1	11.5	

In 98% (n= 364) of the patients, levothyroxine 100 microgram was started on the 1st postoperative day. Likewise, 2500 mg calcium carbonate + 9.68 mg cholecalciferol was started in 90% (n= 334) of the patients, and calcitriol 0.25 microgram was started in 23% (n= 86) of the patients.

Regardless of the drug effect, there is a time-dependent increase in serum calcium values even if the patients do not use any drugs. The change in serum calcium values over time according to the drug groups used is given in Table 5, and post-op 1st day and 1st month serum calcium values increased significantly in all groups (p< 0.001).

Post hoc multiple comparison test was performed to determine the difference between the groups. Accordingly, the difference in post-op 1st day and post-op 1st month serum calcium levels was significantly higher in the group using calcium carbonate + cholecalciferol + calcitriol compared to the other two groups (p= .004, p= .041, respectively) (Table 6).

Table 5. Post-op 1st day and post-op 1st month serum calcium values according to the drug groups used (mg/dL)

Group	n	Post-op 1st day average	Post-op 1st month average	Difference (mean ± Std. deviation)	p
No drugs	25	9	9.6	0.652 ± 0.142	**<0.001**
Calcium carbonate + cholecalciferol	212	8.5	9.5	0.956 ± 0.42	**<0.001**
Calcium carbonate + cholecalciferol + calcitriol	78	7.8	9.05	1.275 ± 0.12	**<0.001**

*Patients with missing data were not included.

Table 6. Multiple comparison results of post-op 1st day and post-op 1st month serum calcium levels difference according to the drug use groups (mg/dL)

Drug		Mean difference	Standard error	p
No drugs	Calcium carbonate + cholecalciferol	-0.30	.15	.141
	Calcium carbonate + cholecalciferol +calcitriol	-0.62	.19	**.004**
Calcium carbonate + cholecalciferol	No drugs	0.30	.15	.141
	Calcium carbonate + cholecalciferol + calcitriol	-0.32	.13	**.041**
Calcium carbonate + cholecalciferol + calcitriol	No drugs	0.62	.19	**.004**
	Calcium carbonate + cholecalciferol	0.32	.13	**.041**

DISCUSSION

Thyroid pathologies are one of the most common endocrine pathologies after diabetes mellitus, and therefore, thyroid operations are very vital in the general surgical practice (11). Postoperative hypocalcemia after thyroidectomy is one of the most common complications, and it has been reported in the literature that temporary hypocalcemia can occur at a rate of 6-50% and permanent hypocalcemia at a rate of 1-2% (2,9,12,13). In our study, it was aimed to evaluate the efficacy of drug treatments for hypocalcemia in 371 patients operated in our center.

In patients with positive malignancy, the rate of bilateral total thyroidectomy and complementary thyroidectomy surgery increases, on the contrary, the rate of intrathoracic-substernal thyroidectomy decreases (14,15). In our study, 71% (n= 262) of the patients had biopsy results as malignancy or suspected malignancy, therefore, the rates of total thyroidectomy were higher than intrathoracic-substernal thyroidectomy.

Due to its anatomical variations, even with careful dissection and sufficient anatomical information, it is very difficult to recognize and preserve the parathyroid tissue during the operation. In the literature, it has been reported that incidental parathyroidectomy occurs in 6-28% of thyroidectomy operations (16). Similarly, incidental parathyroidectomy was found in 20.1% of the patients in our study. In addition, it was observed that the surgical method applied did not make a statistically significant difference in the incidence of incidental parathyroidectomy in the pathology specimen.

Various strategies have been used to diagnose and manage hypocalcaemia after thyroidectomy. The traditional approach to inpatient clinical assessment and monitoring of serum calcium levels is still used by many institutions around the world (17). When the literature is reviewed, many studies have shown that the measurement of serum PTH levels after surgery can be used as a predictor of the development of hypocalcaemia after thyroidectomy (17-19). Although there are studies suggesting PTH measurement routinely post-op, this approach is not cost-effective. However, since our clinic is an education clinic, serum PTH levels were measured in 93.2% (n= 346) of the patients, and most of them were found to be within the normal range (median= 24.66 pg/mL) (min= 1.2, max= 168.6).

Mean serum calcium (mean= 7.793 ± 0.796) in patients with a hospital stay of two days or longer was found to be lower than the mean calcium (mean= 8.45 ± 0.613) of patients discharged on the 1st postoperative day. In this respect, it has been observed that low calcium levels on the first postoperative day are a significant indicator for prolonged hospitalization. However, considering the final serum calcium values, hypocalcemia was observed in only 1.2% (n= 4) of the patients in the post-op 1st month controls.

A significant decrease was observed in the mean of pre-op and post-op serum calcium values after thyroidectomy in all age groups, regardless of the type of surgery. The main factor affecting serum calcium values in post-op 1st month controls was the type of drug used.

When the postoperative 1st month control calcium values were examined, an increase in serum calcium levels was observed even if the patients did not use any medication. Although the lowest increase was observed in this group, the difference in calcium levels between the post-op 1st day and 1st month was still statistically significant. The highest increase was in the group using calcium carbonate + cholecalciferol + calcitriol.

On the other hand, the difference in calcium levels between the 1st day and 1st month was not statistically significant between the group that did not use drugs and the group that used only calcium carbonate + cholecalciferol. In a meta-analysis involving 2.285 patients in 2013, it was stated that the use of post-op vitamin D preparations had an effective role in preventing post-op hypocalcemia and its use was recommended (20). In another

study involving 200 patients, the use of vitamin D has been found to be effective in preventing post-op hypocalcemia (21). Similarly, in our study, the increase in serum calcium levels in the group receiving calcitriol + calcium carbonate + cholecalciferol was significantly higher than in both groups.

Our study has some strengths and weaknesses. First, since the patient group followed up with calcitriol in isolation in our clinic is not crowded, the therapeutic and efficacy of calcitriol was demonstrated by comparing three patient groups who did not receive replacement, only calcium carbonate + cholecalciferol, and took both drugs. On the other hand, although Graves' disease is a risk factor for postoperative hypocalcemia, there is no relevant data in our study and we do not have preoperative vitamin D levels of patients for whom we planned total thyroidectomy. In addition, it may be more appropriate to include not only the 1st month but also the future follow-ups of the patients. However, after this period, patients either do not come for follow-ups or continue their follow-ups in internal clinics. On the other hand, the selection of patients operated by the same surgeon is one of the strengths of our study in order to include and standardize all patients within a period of more than four years. In addition, the large number of patients included is also statistically significant. However, there is a need for further studies that include patients followed up with calcitriol in isolation and include long-term follow-up results.

CONCLUSİON

In our study, we found that incidental parathyroidectomy was independent of the type of surgery. In the early postoperative period, serum PTH levels of most patients were found to be within the normal range. However, the use of calcitriol appears to be quite effective in patients with decreased PTH levels. On the other hand, even if no post-operative medication was given to the patients, it was observed that the serum calcium levels of the patients increased, which was statistically similar to the group using calcium carbonate + cholecalciferol. The highest increase was in the group using carbonate + cholecalciferol + calcitriol, which was found to be significantly higher than the other groups. The use of post-op calcitriol in patients undergoing thyroidectomy seems to be quite effective in preventing the development of hypocalcemia.

Ethics Committee Approval: This study was approved by Ondokuz Mayıs University Clinical Research Ethics Committee (Decision no: OMÜ KAEK 2020/416, Date: 27.08.2020).

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ORİJİNAL ÇALIŞMA-ÖZET
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Tiroidektomi olan hastalarda farklı terapötik tedavilerin postoperatif hipokalsemi sıklığına etkisi

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ÖZET

Giriş ve Amaç: Tiroid bezi cerrahisi ve cerrahi komplikasyonları cerrahın günlük pratiğinde sıklıkla karşılaştığı durumlardır. Çalışmamızda tiroidektomi yapılan hastalara verilen farklı tedavi yöntemlerinin hipokalsemiye etkisinin incelenmesi amaçlanmıştır.

Gereç ve Yöntem: Çalışmaya Aralık 2016- Ocak 2021 yılları arasında Ondokuz Mayıs Üniversitesi Tıp Fakültesi Genel Cerrahi kliniğinde tiroidektomi uygulanan 371 hasta retrospektif olarak dahil edildi. Hastaların ameliyat endikasyonları, ince iğne aspirasyon biyopsisi sonuçları, preoperatif serum kalsiyum değerleri, ameliyat tipi, postoperatif birinci gün ve birinci aydaki serum kalsiyum değerleri, postoperatif yatış süresi, taburculukta reçete edilen ilaçlar, hastanın histopatolojik tanısı, insidental paratioridektomi olup olmadığı gibi parametreler çalışmaya dahil edildi.

Bulgular: Tiroidektomi yapılan 371 hastanın ortalama yaşı 49 (19-82) yıl idi. Hastalara %61 (n= 225) ile en çok total tiroidektomi uygulanmıştı. Hastalara uygulanan üç ameliyat tipinde de pre-op ve post-op kalsiyum değerlerinde anlamlı düşüş mevcut olup farklı ameliyat tipleri arasında belirgin fark görülmemiştir. Tüm gruplarda post-op birinci gün ve birinci ay serum kalsiyum değerleri anlamlı derecede yükselmiştir (p= ,000). Post-op serum kalsiyum düzeyi artışı en çok kalsiyum karbonat + kolekalsiferol + kalsitriol kullanan grupta olmuştur.

Sonuç: Tiroidektomi uygulanan hastalarda post-op kalsitriol kullanımı hipokalsemi gelişimini önlemede oldukça etkili görünmektedir.

Anahtar Kelimeler: Tiroidektomi, hipokalsemi, kalsitriol, tiroid hastalıkları

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ORIGINAL ARTICLE
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Etiology and severity features of acute pancreatitis in HIV-positive patients with different immune status

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ABSTRACT

Objective: Acute pancreatitis is common in HIV-infected patients; however, the causes and severity of pancreatitis in HIV-positive patients have a number of significant features that affect both the severity of destruction of the pancreas and the methods of diagnosis and treatment.

Material and Methods: Anamnestic data, results of diagnosis and treatment of two groups of patients with acute pancreatitis were analyzed. The first group included 79 patients with acute pancreatitis combined with HIV infection who were admitted to the clinic for the period from 2017 to 2021. In people living with HIV, drugs and infectious agents caused acute pancreatitis in 11.4% and 24.1% of the cases, respectively. As our study showed, in patients with normal immune status, the drug etiology of pancreatitis prevailed in the structure of the causes of AP, in patients with immunodeficiency, infectious causes of pancreatitis were dominant.

Results: According to the results of data analysis, it is clear that HIV infection is a factor that makes the course of pancreatitis about two times worse regardless of the presence of immunosuppression. The etiological structure of HIV-associated acute pancreatitis directly depends on the patient's immune status and differs in many ways from that of HIV-negative patients or patients receiving ART.

Conclusion: The severity of the disease and the risk of death remain high in acute pancreatitis caused by infectious agents against the background of immunosuppression.

Keywords: Acute pancreatitis, HIV-infection, antiretroviral therapy, immune status, SAPS II

INTRODUCTION

The HIV pandemic has been a global threat to human health for the past 30 years. As of 2021, there are up to 38.4 million people living with HIV worldwide (1,2), and among them 1.562.570 patients live in the Russian Federation (3). People living with HIV suffer from a large number of various diseases which are not so different from the main population in their nosological composition (but not in occurrence rate). Various forms of acute pancreatitis (AP) are no exception, the incidence of which in Russia in 2021 was 37.8 per 100.000 population. At the same time, attention has been drawn to the extremely high mortality rate in certain clinical forms of acute pancreatitis (18-25%) (4).

The number of researchers claim that the main mechanisms of the pancreas damage in HIV-induced disease include the direct impact of the virus on organ tissues, inflammatory and destructive changes on the background of opportunistic infections and/or the toxic effect of ART drugs leading to the death of gland cells (5-9). The risk of acute pancreatitis has until recently been associated with the use of nucleoside reverse transcriptase inhibitors such as zidovudine, didanosine and stavudine (8). Modern ART drugs rarely lead to the development of acute pancreatitis but can cause transitory hyperamylasemia (9). As for opportunistic infections that affect the pancreatic tissue with a low immune status, the most common references in the literature are cytomegalovirus infection (CMV), tuberculosis (TB) and non-tuberculosis mycobacteria (NTMB), toxoplasma and pneumocyst (9-11).

The incidence and prevalence of AP vary depending on the characteristics of the studied population and the method of data collection, but the risk clearly increas-

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es with the progression of the disease and the stage of HIV infection. Therefore, given the high frequency of HIV infection in the population and taking into account the increased risk of acute pancreatitis in people living with HIV the problem of HIV/pancreatitis comorbidity is topical for clinical practice (12-14).

MATERIAL and METHODS

This is a retrospective study based on a retrospectively collected database from two centers, Moscow Research and Clinical Center for TB Control & Rozanov Moscow Regional Hospital.

Approval for the study was obtained from the ethics committee of Moscow Research and Clinical Center for TB Control (Protocol No: 325, Date: 13.05.2022). Informed written consent was obtained from all patients included in the study.

In order to achieve this goal, the diagnosis and treatment results of two groups of patients with acute pancreatitis were analyzed. The first group included 79 patients with an established diagnosis of AP in combination with HIV infection who were admitted to the clinic in the period from 2017 to 2021. The second group consisted of 558 patients with an established diagnosis of acute pancreatitis without HIV infection who were on inpatient treatment for the same period of time. In the first group of patients, males dominated (59; 74.7%) and aged from 24 to 63 years, the age of women (20; 25.3%) ranged from 34 to 57 years. The cohort of HIV-negative patients was also predominantly male (376; 67.4%) aged 19 to 69 years. The diagnosis of acute pancreatitis was established on the basis of clinical, laboratory, and instrumental criteria (15).

Additionally, the following laboratory tests were used in the group of patients with HIV infection: detection of the causative agent of tuberculosis and NTMB in sputum and other biological fluids by polymerase chain reaction (PCR) and using cultural and bacterioscopic techniques, quantitative determination of cytomegalovirus DNA (CMV DNA) in the blood, as well as determination of genetic material of toxoplasma and pneumocyst in biological material using PCR diagnostics. In cases of fatal outcomes, histological studies obtained during autopsy were used to confirm the diagnosis.

In the group of HIV-positive patients, the immunogram of each patient was studied which reflected the state of the immune system at that time. If the number of helper T-lymphocytes in 1 mL of blood (CD^{4+}) was more than 200, it was considered an acceptable immune indicator, in which the risk of developing opportunistic infections is minimal, on the contrary, when the number of CD^{4+} cells was less than 200 in mL, it was defined as immunosuppression with a high risk of secondary diseases (16).

The severity of patient's condition with acute pancreatitis was assessed on the SAPS II score (Original Simplified Acute Physiology Score). This is an original simplified scale for assessing physiological disorders which uses 15 readily determined biological and clinical indicators (17), the resulting sum of points allowed predicting mortality in each specific case of acute pancreatitis. Patients' treatment was carried out according to the protocols proposed in the clinical guidelines for acute pancreatitis and, in some cases, was supplemented by draining endoscopic interventions aimed at decompression of the Wirsung's duct and bile ducts as well as punctures of acute fluid accumulations (if necessary).

Descriptive statistics of the research results are presented in the tables. In the course of statistical data processing, extensive indicators were calculated and their 95% confidence intervals (95% CI) by the Wilson method determined the probability of a statistical error of the first kind (p). When analyzing cross-tabulation tables with a dimension of more than 2 x 2 Fisher's exact test was used. To test the hypothesis about the effect of HIV status on the severity of patients' condition on the SAPS II scale, we compared groups of HIV-negative and HIV-positive patients with different immunogram characteristics (CD^{4+}< 200 and CD^{4+}> 200 cells in MCL). Since using point indicators needs operating with nonparametric data, we applied quartile test to compare them and the Mann-Whitney U test to calculate the statistical significance of the differences.

RESULTS

The sex and age composition of the studied groups is presented in Table 1. As can be seen from Table 1, sex differences in the study groups were statistically insignificant (p= 0.2). Age differences were also statistically insignificant (p= 0.4). Thus, the main and control groups were balanced by sex and age.

All patients included in the study had acute pancreatitis, the interstitial form of the disease being established in 62 HIV-positive patients (78.5%; 95% CI 68.2-86.1), and necrotizing pancreatitis,

Table 1. Sex and age composition of the study groups

Group	Sex	Total	Up to 20 years old	Up to 21-30 years old	31-40 years old	41-50 years old	Over 50 years old
HIV+	m	59	0	8	26	16	9
79	w	20	0	0	9	9	2
HIV-	m	376	2	69	165	102	38
558	w	182	1	13	49	57	62

respectively, was detected in 17 cases (21.5%; 95% CI 13.9-31.8). In HIV-negative patients, interstitial pancreatitis was diagnosed in 429 cases (76.9%; 95% CI 73.2-80.2), and necrotizing one-in 129 patients (23.1%; 95% CI 19.8-26.8). Differences in the frequency of necrotizing pancreatitis in the main and control groups were statistically insignificant (p= 0.7). Mortality was seen in six patients in the group with HIV infection (7.6%; 95% CI 3.5-15.6), and in 18 cases (3.2%; 95% CI 2.1-5.0) in the group with HIV-negative patients (p= 0.1). In the group with HIV-negative patients, the main factor of the occurrence of the pathological process in the pancreas could be considered the use of alcohol and fatty foods (291; 52.2%); however, it should be noted that when using radiological diagnostic methods in this group of patients, there was no indication of the presence of concretions in the gallbladder and ducts as well as no mention of the use of medicines and prior infectious diseases. The presence of gallstones and the dilatation of Wirsung's duct (more than 2 mm), common bile duct (more than 8 mm) and intrahepatic bile ducts (more than 2 mm) were considered by us as the second main cause of AP in this group of patients (201; 36.0%).

When collecting anamnesis in three cases, it was found out that one patient developed AP against the background of epidemic parotitis and two more patients with the manifestation of adenovirus infection (without mentioning the alimentary factor and in the absence of concretions and biliary hypertension). Thus, these facts allowed us to believe that the cause of AP in these observations was a viral infection (0.5%) (18). Other six (1.1%) cases of AP we regarded as a lesion of the pancreatic parenchyma due to the use of medications: in four patients, there was a link between the initiation of treatment of hypertension with angiotensin converting enzyme inhibitors (lisinopril), and in two more cases-with the use of atorvastatin (19,20). In 57 (10.2%) patients, it was not possible to establish the etiology of acute pancreatitis.

The severity of acute pancreatitis on the SAPS II scale in the group of HIV-negative patients was determined by the number of points: up to 14 points in 225 patients (40.3%), from 15 to 34 points in 288 cases (51.6%), which means that the overwhelming number of patients (91.9%) had pancreatitis in mild and moderate form in which the risk of death does not exceed 15.3%. Only in 45 cases (8.1%) AP was severe with the sum of points from 38 to 70 according SAPS II and the risk of death was determined in the range from 21.3% to 83.8%. It should be noted that all 18 fatal cases were related to this group of patients.

Analyzing the causes of acute pancreatitis in HIV-positive patients revealed that alimentary factors caused pancreatitis in 25 patients (31.7%), biliary concretions and hypertension in 13 patients (16.5%), but we were unable to establish initiating factors of the disease in 13 cases (16.5%). People living with HIV had acute pancreatitis due to drugs and infectious agents in 11.4% (9) and 24.1% of cases, respectively (19). Establishing causal relationships, we proceeded from the following considerations: the onset of acute pancreatitis was associated with the ART administration in five patients (lopinavir + ritonavir, darunavir, kemeruvir), at this there were no mention of errors in diet and alcohol consumption, biliary concretions and signs of ductal hypertension were not visualized by ultrasound, and the phenomena of AP were stopped with the withdrawal of medicines (7,9). In four more patients, acute pancreatitis was probably associated with the use of the combined drug trimethoprim + sulfamethoxazole. The symptoms of acute interstitial pancreatitis also regressed after the end of the course of treatment (21).

The most interesting group was a cohort of 19 HIV-positive patients in whom we considered a viral or bacterial infection to be the cause of acute pancreatitis. In 13 patients, acute pancreatitis was associated with cytomegalovirus infection (CMV), and in two cases, the process was destructive and resulted in the death of patients. In all patients, PCR diagnostics showed CMV DNA in blood leukocytes exceeded 2-3.5 Lg per 100 thousand cells (22). Indirect signs of cytomegalovirus as an etiological factor of AP were: CT-symptoms of viral pneumonia in nine patients and CMV-retinitis in five cases as well as positive clinical course in response to ganciclovir therapy in 10 cases (Figures 1 and 2). As noted above, we were able to verify the diagnosis in two patients using autopsy examination of pancreatic tissues (Figure 3).

In one HIV-positive patient with generalized tuberculosis, damaged lungs and mesenteric lymph nodes, it was possible to identify the tuberculosis etiology of necrotizing pancreatitis according to postmortem examination: the presence of caseous necrosis in the gland tissue and a positive PCR test for DNA of tuberculous mycobacteria (Figure 4).

In the other five observations, we linked the etiology of AP directly to the human immunodeficiency virus. A prerequisite for

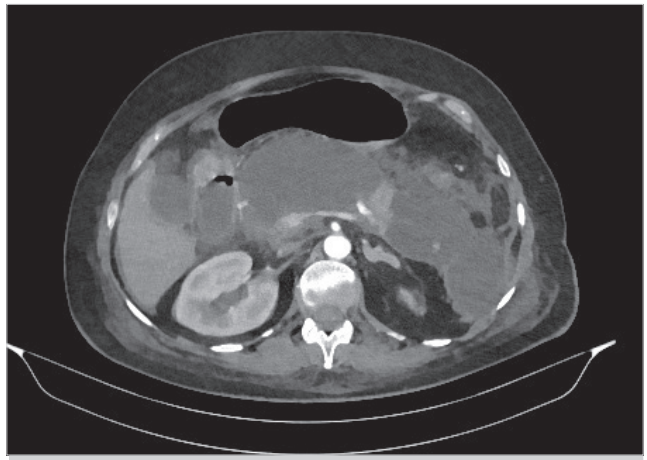

Figure 1. CT scan. Acute necrotizing pancreatitis associated with CMV.

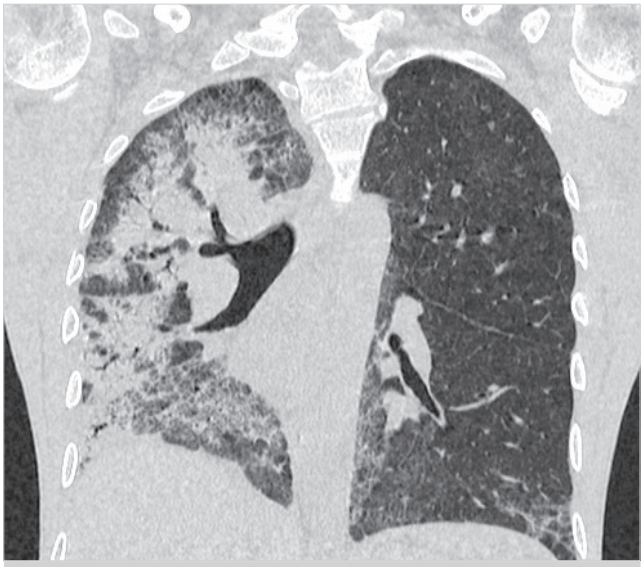

Figure 2. CT scan. Right-sided viral pneumonia associated with CMV.

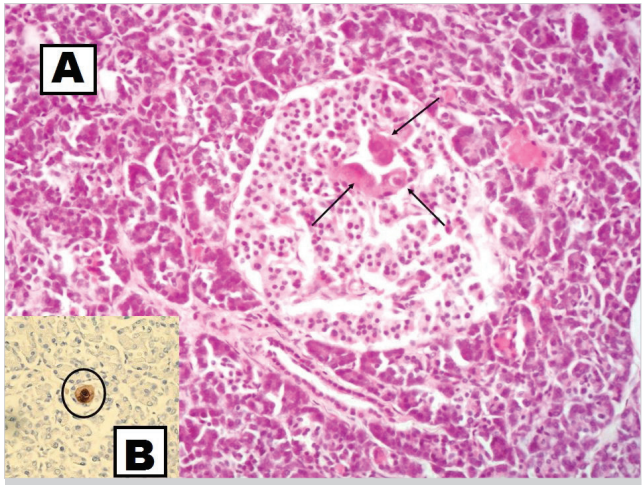

Figure 3. A. Cytomegalovirus pancreatitis. Cytomegalic transformation of Langerhans islet cells (indicated by arrows). Stained with hematoxylin and eosin. X400. **B.** "Owl's eye cell" in the pancreas during immunohistochemical examination with antibodies to cytomegalovirus. X400.

this conclusion was the Marques LM et al. study (2015) in which there was a direct correlation between sudden hyperglycemia and hypotrophic changes in the pancreas against the background of HIV infection. According to a number of researchers, the virus causes apoptosis of acinar and islet cells which leads to exocrine and endocrine organ failure (23,24). The combination of newly diagnosed hyperglycemia, signs of pancreatic hypotrophy (reduction in size with CT and ultrasound), the presence of HIV infection as well as hyperamylasemia and a typical clinical picture of the disease, we interpreted as pancreatitis directly associated with the human immunodeficiency virus. In our observations it was not possible to prove the link of non-tuberculosis

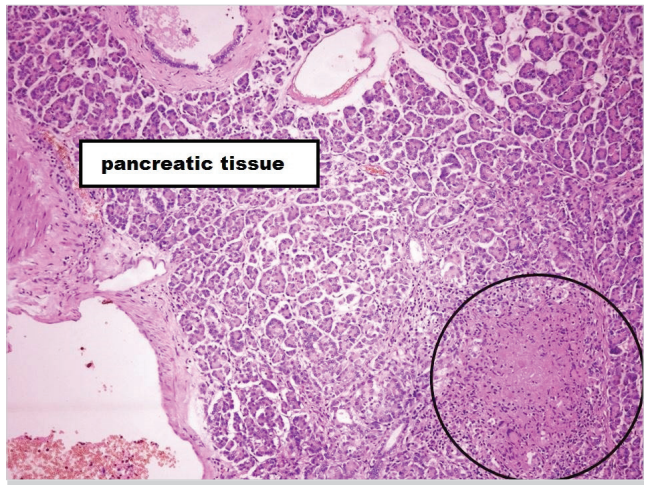

Figure 4. Tuberculosis of the pancreas. There is a miliary lesion in the pancreas with a necrosis site in the center. Stained with hematoxylin and eosin. X200.

mycobacteria, toxoplasmas and pneumocysts with the development of acute pancreatitis in people with HIV infection.

When analyzing the physiological state within the HIV-positive group according to the SAPS II scale, the severity of the disease was slightly different in patients with low immune status (CD^{4+} cells less than 200) and with CD^{4+} lymphocytes more than 200 in 1 mL. Thus, we observed the sum of points from 0 to 14 only in six patients without immunodeficiency (7.6%), from 15 to 34 points in 32 cases (40.5%) with normal immunogram and in six cases with immunosuppression (7.6%), that is, more than half of the patients (55.7%) had pancreatitis in mild and moderate-severe form in which the risk of death did not exceed 15.3%. Only in four patients with more than 200 CD^{4+} cells and in five patients with immunodeficiency (11.4%), AP was severe, along with this total score on the SAPS II score ranging from 38 to 70, the risk of death was determined in the range from 21.3% to 83.8%. At the same time, 26 patients with a CD^{4+} cell less than 200 whose the total score was 38 (21.3% risk of death) demonstrated a moderate-severe course of AP-no deaths were recorded among them.

DISCUSSION

In the last decade, due to the introduction of new drugs for the treatment of HIV that are less toxic to the pancreas, a wider coverage of ART has also changed the structure of etiological factors for the occurrence of acute pancreatitis in HIV-positive patients (7,9). In the conducted study, we made an attempt to compare the severity of the course and the totality of the causes of AP in HIV-infected and HIV-negative patients (Figure 5).

The differences in the structure of the etiological causes of pancreatitis between the groups were statistically significant ($p< 0.001$). This made it possible to reject the null hypothesis

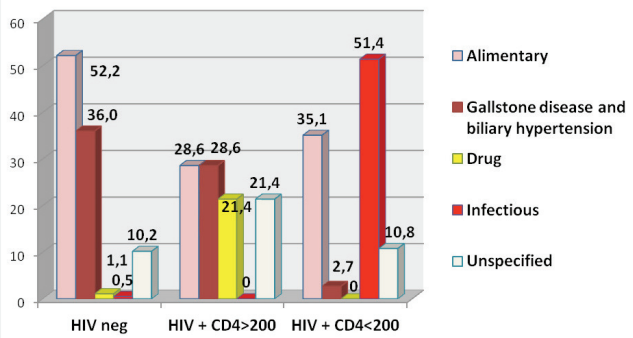

Figure 5. Structure of causes of acute pancreatitis in HIV-negative patients and HIV-positive patients with different immune status.

and confirm the previously described in the literature provisions about the possible predominance of the medicinal etiology of pancreatitis as a consequence of taking medicals, including antiretroviral, in a group of HIV-infected patients and infectious etiology in the same group due to immunodeficiency (5,8,11,22).

The comparison of the results of our study and the data published by Anderson et al. (2017), based on the analysis of the causes of AP in 2001-2010, clearly demonstrates the changes in the etiological structure of AP (25). Thus, according to the authors, gallstones and biliary hypertension have caused acute pancreatitis in 23.6% of HIV-negative patients and 17.9% of HIV-infected (1: 1.3) which is fundamentally different from the data we obtained where this ratio was 36.0% and 16.5%, respectively (2.2; 1). Probably, this can be explained by hereditary factors that in most cases determine the formation frequency of gallstones in different ethnic groups and residents of different continents as well as the nature of nutrition and lifestyle. In our study, the vast majority of the individuals were Europeans, while in the analysis conducted by Anderson et al. (25), they were immigrants from the African continent. Alcohol and fatty food, as causes of AP, still occupy the leading positions in both groups of patients. Thus, more than 10 years ago, alimentary factors triggered pancreatitis in 24.5% of HIV-positive patients and 68.3% of HIV-negative patients (1; 2.8). According to the results of our research this ratio is approximately 52.2% and 31.7% (1; 1.6).

Over the past decade, in the group of patients living with HIV, a significant decrease in cases of acute pancreatitis associated with ART could be noted, so in the past, medications caused 35.8% of the cases of AP, but according to the data we received, their share may be about 11.4%. This can probably be explained by the widespread introduction into clinical practice of less toxic to the pancreas integrase inhibitors and non-nucleoside reverse transcriptase inhibitors. Infectious agents are still factors in the development of acute pancreatitis in HIV-infected patients in about one in five cases, 18.9% according to Anderson et al. (25) and 24.1% according to the results of their own research (p= 0.3).

The high frequency of infectious and drug etiology of pancreatitis in the group of HIV-positive patients should logically correlate with the immune status of the patient. As our study showed, in patients with normal immune status who are highly likely to regularly take ART the drug etiology of pancreatitis prevailed in the structure of the causes of AP and in patients with immunodeficiency infectious causes of pancreatitis prevailed respectively. The results of testing this hypothesis are presented in Table 2.

Differences in the frequency of the causes of AP in the groups are statistically significant (p< 0.001). This allows to reject the null hypothesis and accept an alternative hypothesis about the role of the immune status in the genesis of pancreatitis in HIV-infected patients. Although the group of patients with HIV-positive status and the number of CD^{4+} cells over 200 in MCL differs in structure from patients without HIV infection but is closer to it compared to patients with low immune status (Figure 5).

When comparing the score assessment of the severity of the patients' condition using the SAPS II scale, the differences between the groups were statistically significant (p< 0.001). According to the results of data analysis, it is clearly visible that HIV infection is a factor that, regardless of the presence of immunosuppression, aggravates the course of pancreatitis by about two times (Table 3).

Nevertheless, if we compare the severity of pancreatitis in groups with normal immune status and with immunosuppression it turns out that in patients with CD^{4+} lymphocytes more than 200 AP is more severe and the number of points on the SAPS II scale is on average 38, versus 24. In our opinion, this is

Table 2. Causes of pancreatitis in HIV-positive patients with different immune status

	Etiology of pancreatitis									
	Alimentary		**Gallstone disease and biliary hypertension**		**Drug**		**Infectious**		**Unspecified**	
Number of CD^{4+} cells in MCL.	**abs.**	**%**	**abs.**	**%**	**abs.**	**%**	**abs.**	**%**	**abs.**	**%**
>200	12	**28.6**	12	**28.6**	9	**21.4**	0	**0.0**	9	**21.4**
<200	13	**35.1**	1	**2.7**	0	**0.0**	19	**51.3**	4	**10.8**

Table 3. Comparison of indicators of the severity of the condition of patients with HIV-negative and HIV- positive status, according to the SAPS II scale

	Quartils			
Group	0%	25%	50%	75%
HIV-	9	14	17	24
CD^4> 200	14	17	24	34
CD^4< 200	24	38	38	38
CD^4< 200-17	7	21	21	21
HIV+	14	24	34	38
HIV+ (CD4< 200-17)	7	17	21	29

due to incorrect scoring in the group of HIV-positive patients with normal immune status (17). As practice shows, 17 points are automatically mistakenly added to the total score of these patients indicating that the patient has AIDS. If we consider the severity of the condition of this subgroup of patients with HIV infection and take into account the adjustment of the sum of points by 17, it turns out that the severity of the course of pancreatitis in them differs little from the severity of the course of AP in the group of HIV-negative patients (21 and 17 respectively). Pancreatitis is most severe in people with low immune status, which is probably due to frequent infectious causes: pneumonia, meningoencephalitis and generalized infections complicating the course of the disease.

CONCLUSION

Currently, there is a clear tendency to change the environmental background in acute pancreatitis in HIV-infected patients. Modern medicals used for ART are much less likely to cause acute pancreatitis and the causes of pancreatic damage in this group do not differ much from the triggers of acute pancreatitis in HIV-negative patients. The same trend concerns the severity of the course of the disease and the risk of death in patients receiving modern antiretroviral therapy, with a CD^{4+} lymphocyte count of more than 200 cells per μL. On the contrary, the severity of the disease and the risk of death remain high in acute pancreatitis caused by infectious agents against the background of immunosuppression. Timely determination of the etiological factor of acute pancreatitis in HIV-infected patients is a key moment for adequate etiotropic therapy and reducing the risk of death.

Ethics Committee Approval: This study was approved by the Ethics Committee of Moscow Research and Clinical Center for TB Control (Protocol No: 325, Date: 13.05.2022).

Peer-review: Externally peer-reviewed.

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Conflict of Interest: The authors have no conflicts of interest to declare.

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ORİJİNAL ÇALIŞMA-ÖZET
Turk J Surg 2023; 39 (1): 76-82

Farklı bağışıklık durumlarına sahip HIV pozitif hastalarda akut pankreatitin etiyolojisi ve şiddet özellikleri

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ÖZET

Giriş ve Amaç: Akut pankreatit, HIV ile enfekte hastalarda sık görülür, ancak HIV pozitif hastalarda pankreatit nedenleri ve şiddeti, hem pankreasın yıkımının şiddetini hem de tanı ve tedavi yöntemlerini etkileyen bir takım önemli özelliklere sahiptir.

Gereç ve Yöntem: İki grup akut pankreatitli hastanın anamnestik verileri, tanı ve tedavi sonuçları incelendi. Birinci grup, 2017-2021 yılları arasında kliniğe başvuran HIV enfeksiyonu ile kombine akut pankreatitli 79 hastayı içermektedir. HIV ile yaşayan insanlarda ilaçlar ve enfeksiyöz ajanlar sırasıyla olguların %11,4'ü ve %24,1'inde akut pankreatite neden olmuştur. Çalışmamızın da gösterdiği gibi, AP'nin nedenlerinin yapısında immün durumu normal olan hastalarda pankreatitin ilaç etiyolojisi, immün yetersizliği olan hastalarda pankreatitin enfeksiyöz nedenleri baskındı.

Bulgular: Veri analizi sonuçlarına göre, HIV enfeksiyonunun, immünsupresyon varlığından bağımsız olarak, pankreatit seyrini yaklaşık iki kat kötüleştiren bir faktör olduğu açıktır. HIV ile ilişkili akut pankreatitin etiyolojik yapısı doğrudan hastanın bağışıklık durumuna bağlıdır ve birçok yönden HIV negatif hastalardan veya ART alan hastalardan farklıdır.

Sonuç: İmmünsupresyon zemininde enfeksiyöz ajanların neden olduğu akut pankreatitte hastalığın şiddeti ve ölüm riski yüksektir.

Anahtar Kelimeler: Akut pankreatit, HIV enfeksiyonu, antiretroviral tedavi, bağışıklık durumu, SAPS II

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CASE REPORT
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A rare location of papillary carcinoma: Thyroglossal duct cyst

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ABSTRACT

The inadequate closure of the thyroglossal tract paves the way for a thyroglossal cyst. Thyroglossal duct cyst (TDC) malignancy is quite rare. A thirty-nine-year-old female patient was admitted to the polyclinic with a complaint of palpable mass in the neck. Findings compatible with TDC were determined in the patient's neck screening and it was considered to be malignant due to irregular margins, apparent vascularization and punctual calcifications. Fine needle aspiration biopsy was unremarkable. TDC was excised by Sistrunk procedure and frozen examination was performed. Total thyroidectomy was performed additionally since the result of the frozen examination was found to be compatible with the primary papillary carcinoma of TDC. If preoperative biopsy does not provide a diagnosis, frozen section study will be beneficial in terms of both providing the early diagnosis and directing the operation strategy during the surgery in clinically or radiologically suspected patients.

Keywords: Frozen section, papillary carcinoma, sistrunk procedure, thyroglossal duct, thyroidectomy

INTRODUCTION

While the thyroid gland progresses from foramen caecum to the region in front of the thyroid cartilage during the embryologic period, it leaves an epithelial trace called the thyroglossal tract in the region it has passed. The inadequate closure of this thyroglossal tract paves the way for a thyroglossal cyst (1). Thyroglossal duct cyst (TDC) is the most common congenital abnormality in the neck region (2). It usually presents with midline neck mass during the early childhood, while it is rarely observed during adulthood. It is often benign, but malignant tumor may develop by 1% (3).

Here, we aimed to present a patient who was diagnosed with primary papillary carcinoma of the TDC, with the intraoperative frozen section.

CASE REPORT

A thirty-nine-year-old female patient was admitted to the general surgery polyclinic with a complaint of palpable mass in the neck. The patient had no history of smoking, alcohol consumption, radiotherapy and familial history of thyroid cancer. During the physical examination, we palpated a mass approximately 1.5 cm in diameter between the submental region and thyroid cartilage, which was mobile by swallowing. There was no cervical lymphadenopathy. The thyroid function tests of the patient were normal. Neck ultrasonography (USG) revealed multinodular goiter containing nodules the largest of which was 6 mm in size, and TDC that was 12 mm in size in the midline between the hyoid bone and thyroid cartilage. TDC was considered to be malignant due to irregular margins, apparent vascularization and punctual calcification. Findings compatible with TDC were determined in the patient's neck magnetic resonance imaging (MRI) (Figure 1). The result of the fine-needle aspiration biopsy (FNAB) was atypia of undetermined significance. The Sistrunk procedure (SP) was planned in the preoperative period. In operation, TDC was resected and frozen examination was performed. Since the result of the frozen examination was found to be compatible with the papillary carcinoma of TDC, total thyroidectomy (TT) was performed additionally. Postoperative period was un-

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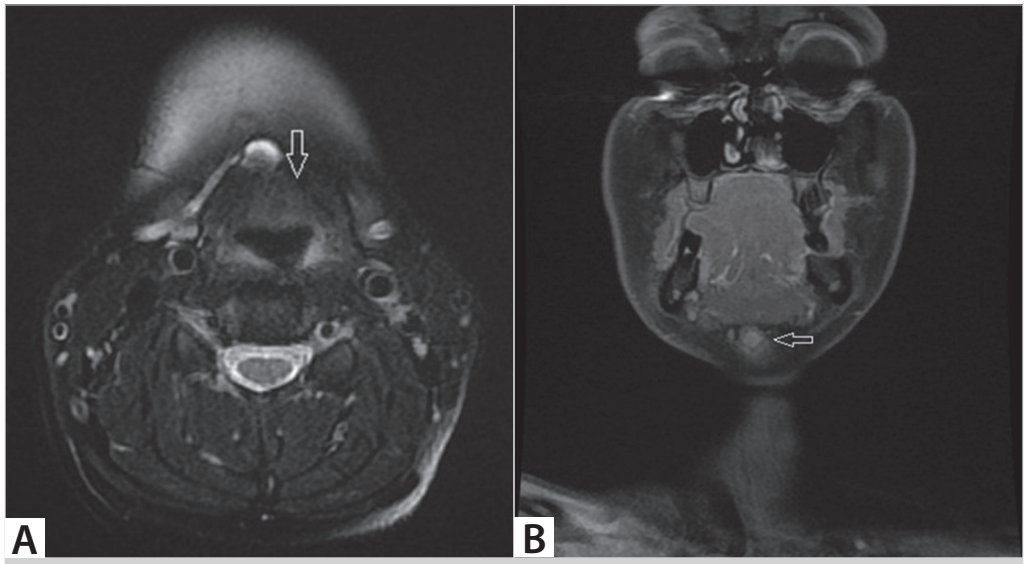

Figure 1. A. Thyroglossal duct cyst (arrow) in fat-supressed T2-weighted axial sections. **B.** Thyroglossal duct cyst (arrow) in contrast enhanced fat-supressed T1-weighted coronal sections in Magnetic Resonance Imaging.

eventful and the patient was discharged on the postoperative day two without any complications.

In the histopathological examination of the tumor, it was reported that the size of the localized papillary tumor in TDC was 8 mm and that the surgical margins were intact. No malignancy was observed in the thyroidectomy material. The metastasis scans of the patient were negative, and thyroid suppression treatment was initiated. The patient had remained well for two years with no evidence of recurrence or distant metastasis.

Written informed consent was obtained from the patient for this study.

DISCUSSION

TDC malignancy is quite rare. Just like in thyroid cancers, papillary cancer is observed in more than 80% of patients. Mixed papillary-follicular (8%) and squamous cell carcinoma (6%) are the most common types after papillary cancer (4). TDC malignancy may be seen in an isolated embryological thyroglossal duct remnant or develop secondary to metastasis of thyroid carcinoma (1). According to a review study published in 2016 (5), the mean age is 39 at the time of diagnosis, and it emerges more frequently in females (68.3%) compared to males. The most common cause of admission is the asymptomatic neck mass (95.1%), while less than 5% of patients are symptomatic. The patient reported here was a female at the age of 39 and was admitted to the hospital due to an asymptomatic neck mass. No malignancy was detected in the thyroidectomy material, and there was a primary tumor that originated from TDC.

USG, computed tomography (CT) and MRI can be used for the diagnosis. The presence and size of the cyst, the presence of a solid or cystic component, accompanying thyroid or lymph node pathologies can be detected by means of USG. The presence of a solid component, wall thickening and especially calcification means suspected malignancy (6). CT can demonstrate the cyst in which the fluid level is observed, increasing intensity in the cyst wall, and calcification foci. MRI can demonstrate the cyst wall with the increased signal intensity compared to surrounding tissues both in T1 and T2 sections (7). FNAB is recommended if there is doubt in the imaging. In a review study, Rayess et al. (5) reported that FNAB was performed in 78.6% of patients and malignancy could be demonstrated in only one-fourth of these patients as a result of biopsy. In the same study, it was stated that frozen examination provided a diagnosis in only 6% of patients. In our patient, FNAB was performed due to the suspicious malignant findings detected in imaging, but it did not provide diagnosis. On the other hand, intraoperative frozen section provided a final diagnosis and changed surgical strategy.

SP is applied in the treatment of TDC. However, a consensus has not been achieved regarding the need for thyroidectomy, central or lateral lymph node dissection and radioactive iodine treatment in the presence of TDC malignancy. Many authors recommend performing TT in addition to SP by considering the applicability of radioactive iodine treatment after TT and the presence of accompanying thyroid malignancy in one-third of patients (5, 8). In the patient reported, early diagnosis was obtained with the intraoperative frozen section study, and TT was performed in the same session since it was not possible to make a discrimination between primary or secondary TDC malignancy by considering multiple nodules located in the thyroid tissue.

CONCLUSION

TDC malignancy is a pathology that is rarely observed and is difficult to diagnose before surgery. If FNAB does not provide a diagnosis, we believe that a frozen section study will be beneficial in terms of both providing the early diagnosis and directing the operation strategy during the surgery in clinically or radiologically suspected patients.

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OLGU SUNUMU-ÖZET
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Papiller karsinomun nadir yerleşimi: tiroglossal kanal kisti

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ÖZET

Tiroglossal kanal trasesinin yetersiz kapanması, tiroglossal kist oluşumuna yol açar. Tiroglossal kanal kisti (TDC) malignitesi oldukça nadirdir. Otuz dokuz yaşında kadın hasta boyunda palpabl kütle şikayeti ile polikliniğe başvurdu. Hastanın radyolojik taramasında TDC ile uyumlu bulgular belirlendi. Düzensiz kenarlar, belirgin vaskülarizasyon ve noktasal kalsifikasyonlar nedeniyle lezyon malign kabul edildi. İnce iğne aspirasyon biyopsisi tanısal değildi. TDC Sistrunk prosedürü ile eksize edildi ve frozen inceleme yapıldı. Frozen incelemenin sonucu TDC'nin primer papiller karsinomu ile uyumlu bulunması üzerine total tiroidektomi ameliyata eklendi. Ameliyat öncesi biyopsi tanısal olmazsa, hem klinik hem de radyolojik olarak şüpheli hastalarda ameliyat sırasında erken tanı ve operasyon stratejisinin yönlendirilmesi açısından frozen kesit çalışmanın yararlı olacağı kanaatindeyiz.

Anahtar Kelimeler: Frozen inceleme, papiller kanser, Sistrunk prosedürü, tiroglossal kanal, tiroidektomi

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CASE REPORT
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Experience of kidney transplantation to a patient with Bernard Soulier syndrome: A case report

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ABSTRACT

Renal transplantation could be a challenging operation in patients with haemorrhagic diathesis, with predictable difficulties or even with unpredictable hurdles. Bernard Soulier Syndrome (BSS) is one of the ethiologies of the thrombocytopenia and it is a rare hereditary disease associated with defects of the platelet glycoprotein complex glycoprotein Ib/V/IX and characterized by large platelets, thrombocytopenia, and severe bleeding symptoms. Here, we present a challenging renal transplantation in BSS.

Keywords: Bernard Soulier syndrome, kidney transplantation, thrombocytopenia

INTRODUCTION

It is important to know coagulation parameters of a surgical patient, for avoiding uncontrollable bleeding. Platelet count is one of these parameters. Thrombocytopenia is defined as a platelet count below the lower limit of normal (<150.000/µL). Degrees of thrombocytopenia can be further subdivided into mild (100.000 to 150.000/µL), moderate (50.000 to 99.000/µL), and severe (<50.000/µL) (1). Severe thrombocytopenia may lead to a greater risk of bleeding. Low platelet levels and its clinical results are shown in Table 1. BSS is a disease characterized by prolonged bleeding time, thrombocytopenia, and extremely large platelets and has a prevalence of less than 1 in 1.000.000. We here in report the first case of a BSS patient undergoing a successful surgical procedure for kidney transplantation under the guidance of thromboelastography (TEG).

CASE REPORT

A 17-year-old, 172 cm, 55 kg-male patient, who had end stage renal disease due to vesicoureteral reflux, was admitted for preemptive living-related kidney transplantation. The patient was refused from many other transplantation centers, because of BSS. After routine evaluation of the patient, we planned to perform kidney transplantation with plateletpheresis transfusions by follow-up of thromboelastogram (Table 2). His preoperative platelet count was 26000/µL. The evening before surgery, two units of plateletpheresis transfusions were given in 15 minutes. The patient's platelet count was increased to 225000/µL, following plateletpheresis transfusions (Our aim was: preoperative platelet count >50000/µL). In the morning of surgery, five units of plateletpheresis were transfused in 30 minutes. In the operation period, nine units of plateletpheresis transfusions were given again in 60 minutes. Additionally, we also gave fresh frozen plasma (three units) to the patient to prevent uremic hemorrhagic diathesis. There was no bleeding complications in the peroperative period. In the postoperative period, two units of plateletpheresis transfusions were given prophylactically in 15 minutes for the first day, and one unit was given in 10 minutes for the second and third day. The patient's platelet count was between 125000 and 227000/µL, thromboelastogram values were in normal ranges, and there was no bleeding complication in the postoperative period. The patient was discharged on the fifth postoperative day with a creatinine level of 1.37

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Table 1. Thrombocytopenia classification and clinical presentation

Platelet count	Clinical results
>100.000/μL	No bleeding from thrombocytopenia
50-100.000/μL	May bleed longer than usual in response to surgery/trauma
20-50.000/μL	Bleeding from minor trauma
5-20.000/μL	May have spontaneous bleeding
<5.000/μL	Risk of life-threatening spontaneous bleeding

mg/dL. Renal function tests were normal and there were no BSS related other symptoms during the four years.

DISCUSSION

BSS is one of the ethiologies of the thrombocytopenia and it is a rare autosomal recessive coagulopathy. The syndrome was named by Dr. Jean Bernard and Dr. Jean Pierre Soulier (2). It is characterized by prolonged bleeding time, thrombocytopenia, increased megakaryocytes, and enlarged platelets. Thrombocytopenia is likely due to decreased platelet survival. This syndrome is associated with quantitative or qualitative defects of the platelet glycoprotein complex GPIb/V/IX (3). The incidence of BSS is estimated to be less than one case per million people, based on cases reported from Europe, North America, and Japan (4).

There are as yet no defined protocols for the perioperative management, which can be very complex and challenging in patients with coagulopathies, in particular BSS. When performing a literature search, our case was the first case of a Bernard-Soulier syndrome patient undergoing kidney transplantation. In a study about bleeding risk of surgery and its prevention in patients with inherited platelet disorders, Orsini S. et al recommended that prophylactic treatment is associated with a significant reduction of the bleeding frequency (5).

Following a routine evaluation of the patient, we planned to perform kidney transplantation with prophylactic treatment via plateletpheresis transfusions under the guidance of TEG. TEG is used for the diagnosis of bleeding-coagulation disorders and in determining efficacy of treatment by providing evaluation of coagulation parameters in many aspects in a short time. Table 3 summarizes the characteristics of plateletpheresis administrations in the preoperative, peroperative and postoperative period. Prior to surgery, platelet count should have a threshold of 50.000/μL. The patient's platelet count was between 125.000 and 227.000/μL, and thromboelastogram values were in nor-

Table 2. Patient's hemoglobin, platelet, creatinin, and thromboelastogram values

	Pre-op (POD -1)	Per-op (POD 0)	Post-op (POD 1)	Post-op (POD 2)	Post-op (POD 3)	Post-op (POD 4)	Post-op (POD 5)
Hemoglobin (g/dL)	10	7.2	10	9.2	9.1	9.1	9.1
Platelet (μL)	26000	225000	203000	227000	188000	156000	125000
Creatinine (mg/dL)	6.4	4.6	2	1.3	1.38	1.36	1.37
Thromboelastogram							
Platelet agregation (51-69 mm)		43.7	43.8	53.5	47.5	49	42.1
Activity of fibrinogen (55-78 degree)		52.5	58.9	43.5	52.4	54.9	44

POD: Postoperative day.

Table 3. Our plateletpheresis transfusion protocol

	Plateletpheresis transfusion protocol		
	Timing	**Units**	**Duration**
Preoperative	-The evening before surgery, -In the morning of surgery (Control platelet count: 225000/μL)	-2 units -5 units	-in 15 minutes -in 30 minutes
Peroperative	In the operation	9 units	in 60 minutes
Postoperative	-POD 1 -POD 2 -POD 3	-2 units -1 unit -1 unit	-in 15 minutes -in 10 minutes -in 10 minutes

POD: Postoperative day.

mal ranges during in the hospital stay. There was no intra- or postoperative bleeding complications. Following an uneventful postoperative recovery, the patient was discharged on the fifth postoperative day with a creatinine level of 1.37 mg/dL, and a platelet count of 125.000/µL.

CONCLUSION

Surgical bleeding risk in inherited platelet disorders is substantial, especially in inherited platelet function disorders, like BSS. We performed living-related kidney transplantation - a major surgical operation - to a BSS patient, by guidance of TEG and prophylactic treatment. Herein, we intend to highlight that TEG guidance and prophylactic treatment would allow effective operative management and is associated with a significant reduction of the bleeding frequency in inherited platelet disorders.

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Bernard Soulier Sendromlu hastaya böbrek nakli deneyimi: olgu sunumu

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ÖZET

Böbrek nakli ameliyatı, Bernard Soulier sendromu (BSS) gibi hemorajik diyatezi olan hastalarda oldukça zor bir ameliyattır. BSS, trombositopeninin etiyolojilerinden biridir ve trombosit glikoprotein kompleksi glikoprotein Ib / V / IX'in kusurlarıyla ilişkili ve büyük trombositler, trombositopeni ve ağır kanama semptomları ile karakterize nadir görülen kalıtsal bir hastalıktır. Bu çalışmada BSS tanılı bir böbrek nakli olgusu sunuyoruz.

Anahtar Kelimeler: Bernard Soulier sendromu, böbrek nakli, trombositopeni

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