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AIMS AND SCOPE

Turkish Journal of Colorectal Disease is an open access, scientific and peer-reviewed journal in accordance with independent, unbiased, and double-blinded peer-review principles of the Turkish Society of Colon and Rectal Surgery.

The journal is published quarterly in March, June, September, and December in print and electronically. The publication language of the journal is English.

This journal aims to contribute to science by publishing high-quality, peer-reviewed publications of scientific and clinical importance that address current issues at both national and international levels.

Furthermore, review articles, case reports, technical notes, letters to the editor, editorial comments, educational contributions, and congress/meeting announcements are released.

The journal scopes epidemiologic, pathologic, diagnostic, and therapeutic studies relevant to managing small intestine, colon, rectum, anus, and pelvic floor diseases.

The target audience of the Turkish Journal of Colorectal Disease includes surgeons, pathologists, oncologists, gastroenterologists, and health professionals caring for patients with a disease of the colon and rectum.

Turkish Journal of Colorectal Disease is currently indexed in **TÜBİTAK/ULAKBİM, British Library, ProQuest, CINAHL, IdealOnline, EBSCO, Embase, Gale/Cengage Learning, Index Copernicus, Turkish Citation Index, Hinari, GOALI, ARDI, OARE, AGORA J-GATE** and **TürkMedline**.

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.

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Turkish Journal of Colorectal Disease is an international, open access, scientific, peer-reviewed journal in accordance with independent, unbiased, and double-blinded peer-review principles of Turkish Society of Colon and Rectal Surgery. The journal is published quarterly in in March, June, September and December in print and electronically. The publication language of the journal is English.

This journal aims to contribute to science by publishing high quality, peer-reviewed publications of scientific and clinical importance address current issues at both national and international levels. Furthermore, review articles, case reports, technical notes, letters to the editor, editorial comments, educational contributions and congress/meeting announcements are released.

The journal scopes epidemiologic, pathologic, diagnostic and therapeutic studies relevant to the management of small intestine, colon, rectum, anus and pelvic floor diseases.

Reviewed and accepted manuscripts are translated from Turkish to English by the Journal through a professional translation service. Before printing, the translations are submitted to the authors for approval or correction requests, to be returned within 7 days. The editorial board checks and approves the translation if any response is received from the corresponding author within this period.

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As a peer-reviewed journal that is independent, impartial and in compliance with the principles of double-blinded peer review, after checking the compliance of the submitted manuscript with the writing rules and plagiarism control, all articles are reviewed by the editor-in-chief, section editor, at least two reviewers, and statistic editor. All evaluation process except Editor-in-Chief is done double-blinded. After all these processes are completed, the Editor-in-Chief decides whether to publish or reject the article. In the final stage, the plagiarism review is repeated once more

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In the cover letter, the authors should state if any of the material in the manuscript is submitted or planned for publication elsewhere in any form, including electronic media. A written statement indicating whether or not "Institutional Review Board" (IRB) approval was obtained or equivalent guidelines followed in accordance with the Helsinki Declaration of 2013 update on human experimentation must be stated; if not, an explanation must be provided. The cover letter must contain the address, telephone, fax and e-mail address of the corresponding author.

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The **correspondent author's ORCID** (Open Researcher and Contributor ID) number should be provided while sending the manuscript. A free registration can create at http://orcid.org.

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Only online submissions are accepted for rapid peer-review and to prevent delays in publication. Manuscripts should be prepared as a word document (*.doc) or rich text format (*.rtf). After logging on to the web www.manuscriptmanager.net/tjcd double click the "submit an article" icon. All corresponding authors should be provided with a password and a username after providing the information needed. After logging on to the article submission system with your own password and username, please read the system's directions carefully to provide all needed information not to delay the processing of the manuscript. Attach the manuscript, all figures, tables and additional documents. Please also attach the cover letter with the "Assignment of Copyright and Financial Disclosure" forms.

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Turkish Journal of Colorectal Disease follows the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" (International Committee of Medical Journal Editors: Br Med J 1988;296:401-5).

Upon submission of the manuscript, authors are to indicate the type of trial/research and statistical applications following "Guidelines for statistical reporting in articles for medical journals: amplifications and explanations" (Bailar JC III, Mosteller F. Ann Intern Med 1988;108:266-73).

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

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

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

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

STROBE statement, a checklist of items that should be included in reports of observational studies;

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

Text Formatting

Manuscripts should be submitted in Word.

Use a standard, plain font (e.g., 10-point Times Roman) for text.

Use the automatic page numbering function to number the pages.

Do not use field functions.

Use tab stops or other commands for indents, not the space bar.

Use the table function, not spreadsheets, to make tables.

Save your file in Docx format (Word 2007 or higher) or doc format (older Word versions).

Title Page

All manuscripts, regardless of article type, should start with a title page containing:

The title of the article;

The short title of the article

The initials, names and qualifications of each author;

The main appointment of each author;

The name(s) of the institution(s) of each author;

The name and e-mail address of the corresponding author;

Full disclosures of potential conflicts of interest on the part of any named author, or a statement confirming that there are no conflicts of interest;

The word count excluding abstract, references, tables, figures and legends;

If applicable, the place and date of the scientific meeting in which the manuscript was presented and it's abstract published in the abstract book.

Article Types

Original Articles

This category includes original research, including both clinical and basic science submissions. The work must be original and neither published, accepted or submitted for publication elsewhere. Any related work, either SUBMITTED, in press, or published by any authors, should be clearly cited and referenced.

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All clinical trials must be registered in a public trials registry acceptable to the International Committee of Medical Journals Editors (ICMJE). Authors of randomized controlled trials must adhere to the CONSORT guidelines, and provide both a CONSORT checklist and flow diagram. We require that you choose the MS Word template at www.consort-statement.org for the flow chart and cite/upload it in the manuscript as a figure. In addition, submitted manuscripts must include the unique registration number in the Abstract as evidence of registration.

All authors are expected to abide by accepted ethical standards for human and animal investigation. In studies that involve human subjects or laboratory animals, authors must provide an explicit statement in Materials and Methods that the experimental protocol was approved by the appropriate institutional review committee and meets the guidelines of their responsible governmental agency. In the case of human subjects, informed consent, in addition to institutional review board approval, is required.

Original Articles should not exceed 3000 words (excluding abstract, references, tables, figures and legends) and four illustrations.

Original Articles should be organized as follows:

Abstract: The abstract must contain fewer than 250 words and should be structured as follows:

Aim: What was the purpose of the study?

Method: A brief description of the materials - patients or subjects (i.e. healthy volunteers) or materials (animals) - and methods used.

Results: What were the main findings?

Conclusion: What are the main conclusions or implications of the study?

Keywords: Below the abstract, provide up to 6 keywords or short phrases. Do not use abbreviations as keywords.

Introduction: State the purpose and rationale for the study concisely and cite only the most pertinent references as background.

Materials and Methods: Describe your selection of the observational or experimental subjects clearly (patients or experimental animals, including controls). Provide an explicit statement that the experimental protocols were approved by the appropriate institutional review committee and meet the guidelines of the responsible governmental agency. In the case of human subjects, state explicitly those subjects have provided informed consent. Identify the methods, apparatus/product** (with manufacturer's name and address in parentheses), and procedures in sufficient detail to allow other workers to reproduce the results. Give references to established methods, including statistical methods; provide references and brief descriptions of methods that have been published but are not well known, describe substantially modified methods, including statistical methods, give reasons for using them, and evaluate their limitations;

Results: Present the detailed findings supported with statistical methods. Figures and tables should supplement, not duplicate the text; presentation of data in either one or the other will suffice. Emphasize only your essential observations; do not compare your observations with those of others. Such comparisons and comments are reserved for the discussion section.

Discussion:

1. State the importance and significance of your findings but do not repeat the details given in the Results section.

2. Limit your opinions to those strictly indicated by the facts in your report.

3. Compare your finding with those of others.

No new data are to be presented in this section.

Acknowledgements: Only acknowledge persons who have made substantive contributions to the study. Authors are responsible for obtaining written permission from everyone acknowledged by name because readers may infer their endorsement of the data and conclusions. Begin your text of the acknowledgement with, "The authors thank…".

Authorship Contributions: The journal follows the recommendations of the ICMJE for manuscripts submitted to biomedical journals. According to these, authorship should be based on the following four criteria:

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

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

Final approval of the version to be published; and

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

All other contributors to the paper should be credited in the 'Acknowledgments' section.

References: The author should number the references in Arabic numerals according to the citation order in the text. Put reference numbers in the parenthesis in superscript at the end of citation content or after the cited author's name. Use the form of "Uniform Requirements for manuscript abbreviations in Turk Bilim Terimleri" (http:/www.bilimterimleri.com).

Journal titles should conform to the abbreviations used in

"Cumulated Index Medicus".

Journals; Last name(s) of the author(s) and initials, article title, publication title and its original abbreviation, publication date, volume, the inclusive page numbers.

Example: 1. Dilaveris P, Batchvarov V, Gialafos J, Malik M. Comparison of different methods for manual P wave duration measurement in 12-lead electrocardiograms. Pacing Clin Electrophysiol 1999;22:1532-1538.

Book chapter; Last name(s) of the author(s) and initials, chapter title, book editors, book title, edition, place of publication, date of publication and inclusive page numbers of the extract cited.

Example: 1. Schwartz PJ, Priori SG, Napolitano C. The Long QT Syndrome. In: Zipes DP, Jalife J, eds. Cardiac Electrophysiology. From Cell to Bedside. Philadelphia; WB Saunders Co. 2000:597-615.

Tables: All tables are to be numbered using Arabic numerals. Tables should always be cited in text in consecutive numerical order. For each table, please supply a table caption (title) explaining the components of the table. Identify any previously published material by giving the original source in the form of a reference at the end of the table caption. Footnotes to tables should be indicated by superscript lower-case letters (or asterisks for significance values and other statistical data) and included beneath the table body.

Figures: Figures should work under "Windows". Color figures or grayscale images must be at least 300 dpi. Figures using "*.tiff", "*.jpg" or "*.pdf"

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should be saved separate from the text. All figures should be prepared on separate pages. They should be numbered in Arabic numerals. Each figure must have an accompanying legend defining abbreviations or symbols found in the figure. Figures could be submitted at no additional cost to the author.

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Permissions: Authors wishing to include figures, tables, or text passages that have already been published elsewhere are required to obtain permission from the copyright owner(s) and to include evidence that such permission has been granted when submitting their papers. Any material received without such evidence will be assumed to originate from the authors.

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Abstract length: Not to exceed 250 words.

Article length: Not to exceed 4000 words.

Reference Number: Not to exceed 100 references.

Reviews should include a conclusion in which a new hypothesis or study about the subject may be posited. Do not publish methods for literature search or level of evidence. Authors who will prepare review articles should already have published research articles on the relevant subject. The study's new and important findings should be highlighted and interpreted in the Conclusion section. There should be a maximum of two authors for review articles.

Case Reports

Abstract length: Not to exceed 100 words.

Article length: Not to exceed 1000 words.

Reference Number: Not to exceed 15 references.

Case Reports should be structured as follows:

Abstract: An unstructured abstract that summarizes the case.

Introduction: A brief introduction (recommended length: 1-2 paragraphs).

Case Report: This section describes the case in detail, including the initial diagnosis and outcome.

Discussion: This section should include a brief review of the relevant literature and how the presented case furthers our understanding of the disease process.

References: See under 'References' above.

Acknowledgments.

Tables and figures.

Technical Notes

Abstract length: Not to exceed 250 words.

Article length: Not to exceed 1200 words.

Reference Number: Not to exceed 15 references.

Technical Notes include a description of a new surgical technique and its application in a small number of cases. In case of a technique representing a major breakthrough, one case will suffice. Follow-up and outcome need to be clearly stated.

Technical Notes should be organized as follows:

Abstract: Structured "as above mentioned".

Indications

Method

Comparison with other methods: advantages and disadvantages, difficulties and complications.

References, in Vancouver style (see under 'References' above).

Acknowledgments.

Tables and figures: Including legends.

Video Article

Article length: Not to exceed 500 words.

Reference Number: Not to exceed 5 references

Briefly summarize the case describing diagnosis, applied surgery technique and outcome. Represent all important aspects, i.e. novel surgery technique, with properly labelled and referred video materials. A standalone video vignette describing a surgical technique or interesting case encountered by the authors.

Requirements: The data must be uploaded during submission with other files. The video should be no longer than 10 minutes in duration with a maximum file size of 350Mb, and 'MOV, MPEG4, AVI, WMV, MPEG-PS, FLV, 3GPP, WebM' format should be used. Documents that do not exceed 100 MB can be uploaded within the system. For larger video documents, please contact info@galenos.com.tr. All videos must include narration in English. Reference must be used as it would be for a Figure or a Table. Example: ".....To accomplish this, we developed a novel surgical technique (Video 1)." All names and institutions should be removed from all video materials. Video materials of accepted manuscripts will be published online.

Letters to the Editor

Article length: Not to exceed 500 words.

Reference Number: Not to exceed 10 references

We welcome correspondence and comments on articles published in the Turkish Journal of Colorectal Disease. No abstract is required, but please include a brief title. Letters can include 1 figure or table.

Editorial Comments

Article length: Not to exceed 1000 words.

Reference Number: Not to exceed 10 references.

The Editor exclusively solicits editorials. Editorials should express opinions and/or provide comments on papers published elsewhere in the same issue. A single author is preferred. No abstract is required, but please include a brief title. Editorial submissions are subject to review/request for revision, and editors retain the right to alter text style.

Peer review of study protocols :

TJCD will consider publishing without peer review protocols with formal ethical approval and funding from a recognized, open Access, supporting research-funding boy (such as those listed by the JULIET Project). Please provide proof that these criteria are met when uploading your protocol. Any

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protocols that do not meet both these criteria will be sent for open external peer review, with reviewer comments published online upon acceptance, as with research articles. Reviewers will be instructed to review for clarity and sufficient detail. The intention of peer review is not to alter the study design. Reviewers will be required to check that the study is scientifically credible and ethically sound in its scope and methods. There is sufficient detail to instil confidence that the study will be managed and analyzed correctly.

Publishing study protocols enables researchers and funding bodies to stay up to date in their fields by providing exposure to research activity that may not otherwise be widely publicized. This can help prevent unnecessary duplication of work and will hopefully enable collaboration. Publishing protocols in full also makes available more information than is currently by trial registries and increases transparency, making it easier for others (editors, reviewers and readers) to see and understand any variations from the protocol that occur during the conduct of the study)

The SPIRIT (Standart Protocol Items for Randomized Trials) statement has now been published. It is an evidence-based tool developed through a systematic review of a wide range of resources and consensus. It closely mirrors the CONSORT statement and also reflects essential ethical considerations.

PRISMA is an evidence-based minimum set of items for reporting in systematic reviews and meta-analyses. PRISMA focuses on reporting reviews evaluating randomized trials but can also be used as a basis for writing systematic reviews of other types of research, particularly evaluations of interventions.

General TJCD policies apply to manuscript formatting, editorial guidelines, licence forms and patient consent.

- Protocol papers should report planned or ongoing studies: Manuscripts that report work already carried out will not be deemed protocols. The dates of the study must be included in the manuscript and cover letter.

Protocol for studies that will require ethical approval, such as trials, is unlikely to be considered without receiving that approval.

- **Title:** This should include the specific study type, randomized controlled trial

- **Abstract:** This should be structured with the following sections—introduction; Methods and analysis; Ethics, and dissemination. Registration details should be included as a final section, if appropriate.

- **Introduction:** describe the rationale for the research and what evidence gay it may fill.

- **Methods and analysis:**

- **Ethics and dissemination:** Ethical and safety considerations and any dissemination plan should be covered here

- Full references

- Authors contributions

- Funding Statement

- Competing Interests Statement

- **Word Count:** Not to exceed 4000 words.

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Suppose doubt exists whether the research was conducted in accordance with the 1964 Helsinki Declaration or comparable standards. In that case, the authors must explain the reasons for their approach and demonstrate that the independent ethics committee or institutional review board explicitly approved the doubtful aspects of the study.

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All individuals have individual rights that are not to be infringed. Individual participants in studies have, for example, the right to decide what happens to the (identifiable) personal data gathered, to what they have said during a study or an interview, as well as to any photograph that was taken. Hence it is essential that all participants gave their informed consent in writing before inclusion in the study. They are identifying details (names, dates of birth, identity numbers and other information) of the participants that were

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studied should not be published in written descriptions, photographs, and genetic profiles unless the information is essential for scientific purposes and the participant (or parent or guardian if the participant is incapable) gave written informed consent for publication. Complete anonymity is difficult to achieve in some cases, and informed consent should be obtained if there is any doubt. For example, masking the eye region in photographs of participants is inadequate protection of anonymity. If identifying characteristics are altered to protect anonymity, such as in genetic profiles, authors should assure that alterations do not distort scientific meaning.

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REVIEW

Mesenchymal Stem Cells for Perianal Crohn's Disease

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ABSTRACT

Unfortunately, perianal fistulizing Crohn's disease (CD) is notoriously difficult to cure. The ulceration and inflammation in CD which leads to fistulizing disease is the likely reason fistulas are notoriously difficult to treat. Most studies which evaluated the efficacy of mesenchymal stem cells (MSCs) in perianal CD had small sample sizes, which warranted wider clinical trials. Some of the available data were case reports, small case series or single arm small studies. The largest pivotal trial published to date which evaluated efficacy and safety of MSCs in perianal fistulas in CD was entitled the Adipose Derived Mesenchymal Stem Cells for Induction of Remission in Perianal Fistulizing Crohn's disease trial. MCS administration retains a high potential value in the treatment of perianal CD.

Keywords: Perianal fistula, mesenchymal stem cell, Crohn's diseas

Introduction

Crohn's disease (CD) is a chronic inflammatory disease of the gastrointestinal tract of unknown etiology, which continues to increase in incidence for unknown reasons, resulting in a significant burden to the healthcare system.[1,2] CD is characterized by persistent transmural inflammation anywhere along the gastrointestinal tract with a chronic remitting and relapsing behavior, which leaves patients on chronic immunosuppression and recurrent operations to treat the disease symptoms, but neither are curative for the disease. Perianal CD, present in over 25% of patients with CD, is notoriously difficult to treat with currently available biologics and surgical procedures. These patients experience significant morbidity due to pain, persistent drainage, recurrent perianal sepsis, and ongoing need to access medical care, resulting in increased costs[21] and impaired quality of life.[2]

Unfortunately, perianal fistulizing CD is extremely difficult to cure with 37% of patients experiencing refractory disease.[3] As a result, patients cycle through numerous immunosuppressive medications that can have significant side effects, and more than 90% undergo multiple surgical interventions[4] putting them at risk of incontinence.[5] While up to 64% can achieve fistula healing with optimized tissue flaps[5] the majority of patients cannot have a flap constructed, and 40% of patients are left with active disease, facing a lifetime of debilitating morbidity or, alternatively, a proctectomy.[6,7]

The current ineffective treatment paradigm leaves patients with incontinence, chronic narcotics, lost jobs, increased risk of opportunistic infection from biologics and increased incontinence from surgical intervention, and significantly impaired quality of life in thousands of patients. This dismal picture has spurred significant interest in investigating better treatment options that have the potential for improved efficacy without a risk of incontinence.

Mesenchymal Stem Cells for Perianal Fistulas

The ulceration and inflammation in CD that leads to fistulizing disease is the likely reason fistulas are notoriously difficult to treat.[8] The successful use of mesenchymal stem cells (MSCs) for the treatment of a refractory rectovaginal fistula in the setting of CD was first reported in 2003.[13] These promising results generated a wave of phase I,[14-19] phase II[14,20,21] and phase III[20] trials to study the safety and efficacy of using MSCs to treat perianal CD. Despite the heterogeneity in protocols using allogeneic[14,16,19,20] or autologous MSCs[13-15,17,18,21,22] derived from both bone marrow[19,22] or adipose tissue,[13,16-18,20] administered at various doses, delivered as a singular or repeated injection, and delivered with[16,17,20] or without scaffolding,[19,23] the results of all completed trials have been encouraging with regard to both safety and efficacy (Table 1).

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Table 1. Summary of prior studies of mesenchymal stem cells for perianal Crohn's disease

Name of study	Type of study	Location	Patients with CD#	Intervention
García-Olmo et al.[13]	Case report	Spain	1	Local injection of stem cells
García-Olmo et al.[17]	Phase I, open label, single arm	Spain	4	Local injection of $3x10^6$ million MSC
García-Olmo et al.[18]	Phase IIb, open label, double arm, randomized	Spain	14	Local injection of $2x10^6$ MSC plus fibrin glue as compared to fibrin glue alone; second dose of $4x10^6$ MSC if fistula healing was not seen at 8 weeks
Cho et al.[15]	Phase I, open label, single arm	Korea	10	$1x10^7$,$2x10^7$,$4x10^7$, cells/mL based on the size of the fistula (total of 3-40$x10^7$ cells)
Lee et al.[14]	Phase II, open label, single arm	Korea	33	$3x10^7$ or $6x10^7$ cells per 1 cm of fistula length; average number of $15.8x10^7$ cells), followed by a second injection of 1.5 times more cells (average number of $19.1x10^7$ cells) if fistula closure was not complete at 8 weeks
Cho et al.[21]	Phase II extension of Lee phase II	Korea	24	9-42$x10^7$ cells based on length of fistula tract
Ciccocioppo et al.[22]	Open label, single arm	Italy	10	1.5 to $3x10^7$ MSC every 4 weeks until an improvement was obtained or when autologous MSCs were no longer available (2-5 injections)
de la Portilla et al.	Phase I/IIa open label, single arm	Spain	24	Local injection of $2x10^6$ MSCs; second injection of $4x10^6$ if unhealed at 14 weeks
Panes et al.[20]	Phase III, RCT	Europe/Israel	212	Local injection of stem cells
Molenkijk et al.[19]	Open label, 4 arms	Netherlands	21	n=5 in 10^7 MSC dose (G1) n=5 in $3x10^7$ MSC dose (G2) n=5 in $9x10^7$ MSC dose (G3) n=6 in placebo (G4)
Dietz et al.[16]	Phase I, open label, single arm	USA	12	20 million cells on a GORE Bio A Plug
Panes et al.[23]	Phase III, RCT	Europe/Israel	212	Local injection of stem cells
Barnhoon	Phase I	Europe	15	Local injection of stem cells

RCT: Randomized controlled trial, MSC: Mesenchymal stem cell, MRI: Magnetic resonance imaging, SAE: Serious adverse event, AE: adverse event, TEAEs: Treatment-emergent adverse event, CD: Crohn's disease

Type and source of stem cells	Outcome	Results	Use of MRI	Adverse events
Autologous, adipose tissue	Complete epithelialization of external opening	Fistula healed in 1 week, no recurrence till 3 months post treatment	No	None
Autologous, adipose tissue	Complete epithelialization of external opening	3 of 4 rectovaginal or perianal fistula (75%) at 8 weeks	No	None
Autologous, adipose tissue	Complete epithelialization of external opening	5 of 7 fistulas (71%) in MSC versus 1 of 7 fistulas (14%) healed in fibrin glue alone at 8 weeks	No	15 non-serious AE; 4 serious AE, 1 related to MSCs (perinala abscess)
Autologous, adipose tissue	Complete epithelialization of external opening	3 of 10 patients (30%) had complete healing at 8 weeks post treatment; sustained at 8 months	No	13 AE were reported in seven patients (70%); 3 SAE in 2 patients (20%, one related with seton placement
Autologous, adipose tissue	Complete epithelialization of external opening	27 of 33 patients (82%) had complete healing at 8 weeks; 88% sustained closure at one year	No	28 AE, all unrelated to MSC; 1 SAE unrelated to MSC
Autologous, adipose tissue	Complete epithelialization of external opening	20 of 24 patients (83%) had sustained closure at two years	No	53 AE, all unrelated to MSC
Autologous, adipose	No drainage on clinical exam as well as healed on MRI	6 of 9 patients (67%) with complete closure at 8 weeks; all sustained closure at one year	Yes	No adverse events
Allogeneic, adipose tissue	absence of drainage and complete epithelization, plus absence of collections measured by MRI	5 out of 18 fistulas (28%) closed at 24 weeks post treatment. 7 out of 18 patients (47%) had closure of external openings at 24 weeks post treatment.	Yes	Four SAE (three anal abscesses and one uterine leimyoma), so the group concluded the treatment had an acceptable safety profile
Allogeneic, adipose tissue	Absence of drainage and <2 cm fluid collection on MRI	50% (n=53 of 107) healed in the MSC group compared with 34% (n=36 of 105, p=0.024) at 24 weeks	Yes	Overall, 68 (66%) in treatment, 66 in placebo (65%); SAE in 18 (17%) and 14 (14%), majority anal abscess
Allogeneic, adipose	Absence of drainage and <2 cm fluid collection	12-week fistula healing: G1: 2/5 G2: 4/5 G3: 1/5 G4:2/6	Yes	50 AE, most common was common cold, 4 abscesses
Autologous adipose tissue on matrix	Absence of drainage and improvement in Van Assche score on MRI	10 of 12 patients with healing at 6 months (83%)	Yes	No adverse events
Allogeneic, adipose tissue	Absence of drainage and <2 cm fluid collection on MRI	57% (n=49 of 86) healed in the MSC group compared with 39% (n=33 of 84, p=0.021) at 52 weeks	Yes	Most common anal pain/ abscess, study withdraw <10% related to TEAEs
Allogeneic, bone marrow tissue	Absence of drainage and <2 cm fluid collection on MRI	13/15 (87%) available for 4-year f/u. healing maintained from 1-year results	Yes	No increased adverse events from 1-year results

Mechanism of Action of Mesenchymal Stem Cells

While the exact mechanism of MSCs in treating CD remains unknown, it is well established that MSCs exist in almost all tissues[24-26] and are believed to reduce exacerbated inflammation due to their intrinsic immunomodulatory properties. Recently, success of MSCs in treating severe inflammatory disorders, such as graft-versus-host disease[27,28] systemic lupus erythematosus,[29] myocardial infarction,[30] multiple sclerosis[31] and CD,[17] has highlighted the therapeutic benefit of the immunomodulatory characteristics of MSCs.[32-34] These immunomodulatory properties are carried out through three important steps: 1) migration to sites of active inflammation or tissue injury;[35-37] 2) secretion of anti-inflammatory molecules, such as interleukin-10, hepatocyte growth factor, transforming growth factor-beta-1[38], and indoleamine 2,3-dioxygenase;[39] and 3) paracrine signaling to nearby cells to maintain the local anti-inflammatory environment (Figure 1).[40,41] By influencing cytokine secretion profiles,[42] MSCs can modulate the function of various immune cell types including lymphocytes, dendritic cells and macrophages.[43] Significant and specific for CD is the ability of MSCs to upregulate a $CD4^+$ T-cell subset of regulatory T-cells (Tregs), a cell type known to be deficient in CD.[25,44] It has been well established that the depletion of Tregs and imbalance of Tregs with T-effector cells plays a key role in the pathogenesis of CD.[45,46] Therefore, the ability of MSCs to upregulate Tregs, migrate to sites of inflammation,[47] and dampen immune responses underscores the escalating interest in using MSCs to treat CD.[48-52]

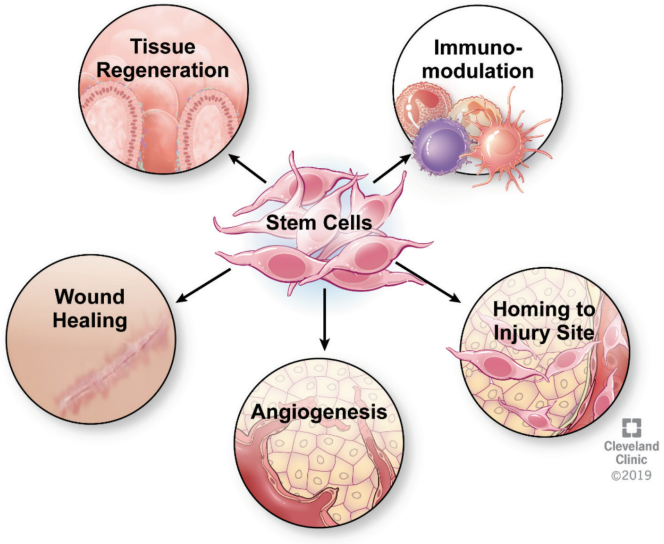

Figure 1. Mechanism of action of MCS
MSC: Mesenchymal stem cell

Application and Results of MSC in Perianal Fistulizing Crohn's Disease

Indications for the use of MSCs in perianal CD are mostly confined to fistulas. This is described in the label of the commercially approved product available in Europe (Alofiselä, Darvadstrocel, Takeda Pharma A/S, Taastrup, Denmark). According to the label, the product is indicated for treatment of complex perianal fistulas in adult patients with non-active/mildly active luminal CD, when fistulas have shown an inadequate response to at least one conventional or biologic therapy.[53,64] The product needs to be used after surgical conditioning of the fistula, with curettage of the track and closure of the internal opening with a stitch. Despite this, there is a rationale for injection of MSCs in other situations. After commercial approval, indications for the use of stem cells in perianal CD in other phenotypes will probably be explored further, for example in rectovaginal fistulas or persistent ulcers.[19]

Most studies, which have evaluated the efficacy of MSCs in perianal CD, had small sample sizes, which warranted wider clinical trials. Some of the available data were case reports, small case series or single arm small studies. The largest pivotal trial published to date which evaluated efficacy and safety of MSCs in perianal fistulas in CD was entitled the Adipose Derived Mesenchymal Stem Cells for Induction of Remission in Perianal Fistulizing Crohn's Disease (ADMIRE-CD) trial.[20] The trial was a randomized, double-blind, placebo-controlled study that tested Cx601, a 24 mL solution with 120 million expanded adipose-derived MSCs in CD fistulas. Each vial of the product had 30 million cells, and a total of four vials of the product was used in each case. The main inclusion criterion was patients with inactive or mildly active luminal CD (CDAI of 220 or less) with associated complex perianal fistulas. Patients with active proctitis, rectal stenosis, ileostomies, colostomies and rectovaginal fistulas were excluded.

All patients had a previous surgical procedure under anesthesia, with curettage of the fistula tract(s) and seton placement, if needed (two weeks before the injection of the drug). In the main surgical procedure, an unblinded surgeon injected the MSC preparation or placebo saline solution (randomized in a 1:1 ratio) in the internal opening and close to the fistula tracts, after simple closure of the internal opening with stitches. The surgeon had to be unblinded as there were evident differences between the compound and saline solution in the pre-filled syringes.

The main objective of the study was to analyze combined remission (clinical closure of all treated external openings draining initially at baseline, and the absence of collections with more than 2 cm, confirmed by [magnetic resonance

imaging (MRI)] after 24 weeks, performed by blinded gastroenterologists and radiologists.

A total of 107 patients had Darvadstrocel injections and 105 had saline injections, as a control group. After 24 weeks, more patients in the Darvadstrocel group exhibited combined remission as compared to controls [53/107 (50%) versus 36/105 (34%), respectively; with a delta of 15.2% and 97.5% confidence interval 0.2-30.3; p=0.024]. Clinical remission alone (closure of 100% of external openings) was observed in 57% of the Darvadstrocel/Cx601 patients as compared to 41% of placebo (p=0.064). Clinical response was another secondary endpoint (closure of 50% of the fistula openings) and it was observed in 71% of the Darvadstrocel group as compared to 53% of placebo patients (p=0.054). Results are illustrated in Figure 2. In terms of safety, a total of 66% (68/103) of patients in the Darvadstrocel group and 65% (66/102) in control group had post-treatment adverse events, with proctalgia, anal abscess and nasopharyngitis being the most common. Treatment-related adverse effects were found in 17% in the study group as compared to 29% in placebo, mostly anal abscesses and proctalgia. Perianal abscesses occurred in 5% of the overall patients in both groups.

The long-term results (outcomes after 52 weeks) of the same trial were published in 2018.[23] The patients from the ADMIRE-CD study were followed up to 52 weeks and an additional MRI and a clinical evaluation were performed to check the same endpoints. Combined clinical and radiological remission was observed in 58/103 (56.3%) of the Darvadstrocel/Cx601 patients, as compared to 39/101 (38.6%) in the control group, with a delta of 17.7 points, 95% confidence interval: 4.2-31.2; p=0.010). Clinical remission (100% closure of baseline fistulas) after one year was observed in 59.2% in Darvadstrocel/Cx601 and 41.6% in placebo groups, respectively (p=0.013). Clinical response was observed in 66% and 55.4% in both groups, respectively (p=0.128). These findings are illustrated in Figure 3. Importantly, from the safety perspective, anal abscesses and fistulas were observed similarly between the groups in the 1-year analysis (33% of the active group and 29.4% in the placebo group). Serious abscesses/fistulas were observed in only 6.8% and 4.9% in both groups, respectively. The rates of withdrawal from the study due to adverse events were low between the groups, 8.7% and 8.8% respectively. No new safety signal in terms of new adverse events was observed in the additional 24 weeks of this long-term study.

A similar study is currently ongoing in the United States (Adult Allogeneic Expanded Adipose-Derived Stem Cells (eASC) for the Treatment of Complex Perianal Fistula(s) in Patients with Crohn's Disease-ADMIRE-CD-II) to demonstrate efficacy for a future approval of Darvadstrocel in America by the FDA (ADMIRE-CD-II trial, details available in clinicaltrials.gov). In Europe, a post-marketing registry entitled INSPIRE (design and implementation aspects of a registry of complex perianal fistulas in CD patients treated with Darvadstrocel) aims to establish a framework to capture real-world efficacy and safety data with this commercially available MSC product.[63] The registry is beginning to capture patients from different countries, and soon a more robust picture of patients who have undergone MSC local therapy will be available.

Safety

The risk of infection and tumor is of major concern with the use of MSCs. Indeed, the safety issue has yet to be fully addressed before the treatment is officially approved for its use on CD. While toxicity remains the most important limit for hematopoietic stem cell therapy in CD patients, MSCs have shown a relatively higher safety profile.[54] Serious adverse events (SAE) requiring hospital admission are rare and are more probably related to intrinsic disease

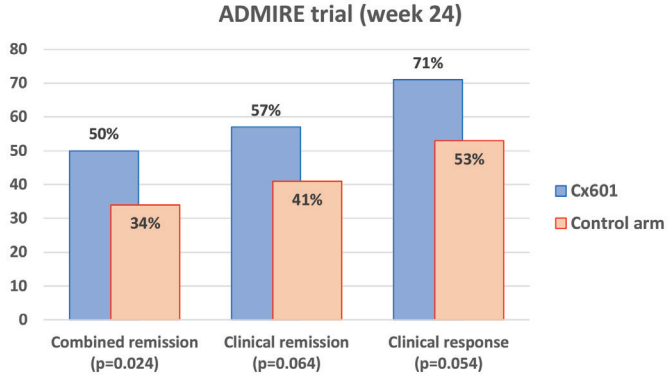

Figure 2. ADMIRE randomized trial results of efficacy at week 24

ADMIRE: Adipose Derived Mesenchymal Stem Cells for Induction of Remission in Perianal Fistulizing

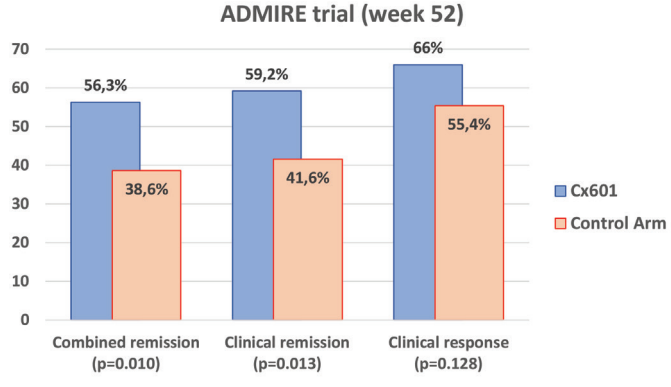

Figure 3. Long-term extension efficacy results of the ADMIRE randomized trial at week 52

ADMIRE: Adipose Derived Mesenchymal Stem Cells for Induction of Remission in Perianal Fistulizing

activity. The studies that have been published to date indicate that administration of MSCs might prompt minor adverse events, such as perianal sepsis. Indeed, a relatively high rate of perianal sepsis has been reported by phase I-II trials.[14,17,18] In the latest phase III trial published by Panés et al.[20], 68 patients (66%) in the treatment group and 66 (65%) in the control group developed AEs (adverse events), while SAEs were registered in 18 (17%) and in 14 (14%), respectively, the majority being anal abscess and proctalgia. In this study the rate of AEs and SAEs were comparable to the control groups. Arguably, the side effects have been interpreted as not directly related to MSC administration but rather to the procedure adopted for the fistula closure or preconditioning before MSC administration. Indeed a recent meta-analysis of comparative studies has shown no significant difference in AEs and SAEs when comparing MCS and non-MSC groups of patients.[55]

MSCs may show pro-tumorigenic impact in cancers, by inducing neoplastic cell proliferation and promoting angiogenesis.[56,57] To date, there are no reported cases of neoplasm developing after MCS perianal treatment. However, long-term follow up will clarify and strengthen this safety aspect.

Practical Considerations When Administering Stem Cell Therapy

Step 1 - Antibiotic Prophylaxis and Treatment

Currently, the knowledge of the potential effects of antibiotics on MSCs viability and function is scarce. However, some *in vitro* and animal studies suggest the most frequently used antibiotics (benzyl-penicillin, flucloxacillin, cefuroxime and metronidazole) have not shown any detrimental effects on the stem cells, while gentamicin and vancomycin may downregulate the proliferation and differentiation activity of MSCs.[1,2] Interestingly, bone marrow MSCs are reported to be able to take up ciprofloxacin and release it to the tissues, which could further increase the antibacterial effect of the stem cell therapy.[3,4] Until new data becomes available, we recommend standard antibiotic prophylaxis prior to surgery. In case antibacterial treatment is necessary after cells are implanted, we recommend avoiding gentamicin and vancomycin, if other alternatives are available.

Step 2 - Anesthesia

Any anesthesia protocol may be chosen, taking into consideration that the surgical insult is minimized with this technique. However, local anesthesia should be used with caution, due to the possible direct cytotoxic effect of the most frequently used anaesthetics (amide-type: ropivacaine, lidocaine, bupivacaine, and mepivacaine) to the MSCs, described after *in vitro* exposure of the cells to each of the drugs.[5] Furthermore, it was found that local anesthesia could directly and indirectly affect the anti-inflammatory capacity of MSCs, by altering the microenvironment, and modulating macrophage inflammation and MSCs secretion.[6] As local anesthesia in anal surgery is rarely applied, and in most cases, in the form of a pudendal block, the contact of the injected cells with the local anesthetics is not expected to occur and thus the surgical protocol may not be changed substantially. Nevertheless, if not strictly necessary, we recommend local anesthesia should be avoided.

STEP 3 - Surgical Preparation

Alcoholic, hydrogen peroxide and povidone-iodine solutions should be avoided in surgical preparation due to their toxicity to the cells. Polyhexamethylene biguanide, octenidine dihydrochloride and chlorhexidine (non-alcoholic) solutions seem to have the optimal profile for this purpose.[7,8] We tend to simply use normal saline with baby shampoo so that the preparation will not interfere with cell viability.

STEP 4 - Internal Fistula Orifice Location

Internal orifice location and management are the keys to successful treatment of perianal fistulas. Surgeons often inject hydrogen peroxide solution through the external opening to identify the internal opening. However, when stem cells are to be applied, in order to avoid the cytotoxic effects of the hydrogen peroxide, other methods should be employed. Probes or pure saline solution are appropriate for this purpose.

STEP 5 - De-Epithelization of the Fistula Tract

Extensive debridement of the epithelization creates an appropriate wound bed for the cells by exposing healthy tissue. We perform a deep mechanical debridement (curettage), especially of the internal orifice. Curettage is the single most effective and recognized part of fistula treatment. Bleeding from the external and internal opening should be observed to assure adequate debridement.

STEP 6 - Cleaning of the Cavities and Fistula Tracts

The tracts are cleaned with saline solution in order to remove devitalized tissue debris following curettage.

STEP 7 - Closure of the Internal Opening

We believe this surgical act should not be very aggressive. The closure should be achieved by simple 2/0 absorbable suture. The stitch must include full thickness bites, and snug pressure. Smaller and tighter bites may tear the fibrotic tissue.

STEP 8 - Stem Cell Handling and Resuspension

Stem cell handling is critical. This is a biological, living drug that comes to the operating theatre in the form of several

transparent (usually glass) vials and can be stored for a very limited time (24 hours after reception). Usually, the concentration used is 5-10 million cells/mL. Vials of cells are transported at regulated temperatures and are viable for fixed periods of time. Cells should be gently re-suspended by soft swinging movements, with care to avoid vigorous shaking. MSCs are characterized by their capacity to adhere to plastic surfaces. They should be aspirated with a large bore needle, such as a 16G.

STEP 9 - Stem Cell Injection

We recommend a slow injection process (to avoid high cell friction and cell mortality) through a fine and long needle (e.g., Abocatt 22G; Terumo). Studies have shown that up to 26G bore size needles are suitable for injecting MSCs without changing the viability and functional capacity of the cells, even after three passes through the needle.[9] We recommend injecting at least half of the total dose in the tissues around the internal orifice or orifices. The other half should be injected through the external orifice into the fistula walls in parallel to the tract.

Future perspectives of Stem Cell Therapy for Fistulas

Several unmet needs in the treatment of perianal CD with MSCs remains to be addressed. The most important issue is the presence of active proctitis during MSC administration. Perianal CD with associated variable grades of proctitis represents a relevant percentage of patients[58,59] that have been codified in the exclusion criteria of most trials. Indeed, one of the main issue in MSC administration remains to determine whether this treatment would be effective in the setting of active proctitis. Moreover, even though rarer, rectovaginal and enterocutaneous fistula patients have been excluded from the trials to date, and have limited treatment options. Thus, patients with these phenotypes may greatly benefit from MSC therapy.

The other crucial controversies regard the ideal cell dosage administration and the appropriate cellular delivery approach. In fact, no single cell dosage and administration procedure (direct injection, fibrin glue) has been consistently identified to date.[60] Once MSC administration becomes more mainstream, more widely available and, hopefully, cheaper preparation processes, and head-to-head comparison with standard therapy (including biologics and alternative surgical procedures) should be undertaken to validate the efficacy of this therapeutic approach. Furthermore, in order to overcome the issues noted and enhance the potential value of this treatment, the underlying mechanism with which MSCs promote tissue healing at the level of the fistula should be elucidated. Finally, studies addressing the impact of periodic MSCs administration are advocated to establish it as a maintenance therapy.

Conclusion

The management of perianal CD is controversial and currently used treatments have shown a relatively limited rate of success.[61] MSC administration retains a high potential value in the treatment of perianal CD. However, to date the procedure is considered as an alternative to standard medical therapy and supplementary surgical procedures.[62] Nonetheless, MSC administration is reported to be effective in inducing fistula healing but the mechanism promoting this healing is yet to be fully explored. Further studies are urgently required to determine the impact of MSC administration, and should also include complex fistulas with multiple fistula tracts, even in the presence of distal luminal disease. Of note, the lack of a widely accepted definition of fistula healing was problematic when we were comparing results of trials. Thus, a consensus definition of fistula healing should be created to further research into this promising therapeutic option for patients with perianal CD.

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RESEARCH ARTICLE

Effectiveness of Different Local Anesthesia Application Methods in Postoperative Pain Control in Laparoscopic Appendectomies: A Randomized Controlled Trial

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ABSTRACT

Aim: Postoperative pain management has long been clinically challenging. Several methods have been attempted to prevent postoperative pain. In this study, we compared the effects of local anesthetic infusion to the incision site (LAIS), transversus abdominis plane block (TAPB), and intraperitoneal local anesthetic administration (IPLA) methods on postoperative pain and patient satisfaction in acute appendicitis cases who underwent laparoscopic appendectomy.

Method: Overall, 160 patients who underwent laparoscopic appendectomy for uncomplicated acute appendicitis between December 2018 and 2019 were included. Patients were divided into four groups: Control group, LAIS group, TAPB group, and IPLA group. All patients were assessed in terms of visual analog scale (VAS) scores for pain, hemodynamic parameters, and patient satisfaction at postoperative 1, 2, 4, 6, 12, and 24 hours.

Results: VAS scores at postoperative 1, 2, 4, 6, 12, and 24 h were higher in the control group than in the LAIS, TAPB, and IPLA groups. The VAS scores of the IPLA group were significantly higher than the LAIS and TAPB groups. No significant difference was observed between the LAIS and TAPB groups. The rate of additional analgesic dose administration in the control group (97.5%) was significantly higher than in the LAIS (17.5%), TAPB (7.5%), and IPLA groups (72.5%) ($p1<0.001$; $p2<0.001$; $p3=0.005$; $p<0.05$). Further, the rate of additional analgesic dose administration in the IPLA group (72.5%) was significantly higher than in the LAIS (17.5%) and TAPB (7.5%) groups ($p<0.001$; $p<0.05$).

Conclusion: All preemptive analgesia methods were more effective in postoperative pain management compared to the control group. Furthermore, TAPB and LAIS methods were better at controlling patient-reported pain than IPLA.

Keywords: Laparoscopic appendectomy, preemptive analgesia, transversus abdominis plane block, intraperitoneal anesthesia, local anesthesia, postoperative pain management, pain relief, analgesia

Introduction

Appendectomy is the most common emergency surgical intervention in general surgery. The risk of acute appendicitis is about 7% in the life of an individual in the US.[1] The causes of postoperative pain after acute appendicitis surgery include surgical incision, peritoneal inflammation, and visceral peritoneal pain due to infection.[2] Although laparoscopic surgery is less painful than open surgery, laparoscopic interventions are not painless, especially during the early postoperative period.[3-6] Postoperative pain management has long been a clinical challenge for both surgeons and anesthesiologists.

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Preemptive analgesia is the use of drugs that regulate nociceptive activity before the emergence of stimulation that will cause pain, and it has become an important approach in reducing postoperative pain and postoperative use of opioids. The aim of preemptive analgesia is to trigger nociceptive activity with afferent stimulations that play a key role in reducing postoperative pain and preventing over-excitation of the central nervous system.[7,8] Damage to tissues and peripheral nerves cause proinflammatory cytokine release and initiates a local inflammatory process, thereby resulting in over-excitation of the peripheral and central nervous systems.[9] Some studies claim that preemptive analgesia inhibits this proinflammatory process and reduces the need for opioid use by reducing postoperative pain.[10,11] However, there are insufficient studies about the superiority of preemptive analgesic method in laparoscopic appendectomy to provide definitive evidence.

Preemptive analgesia methods include local anesthetic infusion to incision site (LAIS), transversus abdominis plane block (TAPB), and intraperitoneal local anesthetic administration (IPLA). In this study, we compared the effects of LAIS, TAPB, and IPLA methods on postoperative pain and patient satisfaction in cases of acute appendicitis that underwent laparoscopic appendectomy.

Materials and Methods

In this double-blind, randomized, controlled study, we included 160 patients aged 16-74 years who underwent laparoscopic appendectomy for acute appendicitis between December 2018 and 2019. These patients were randomized into four groups: Control group that did not undergo any additional procedure, LAIS group, TAPB group, and IPLA group. Approval for this study was obtained from the Ethics Committee Fatih Sultan Mehmet Training and Research Hospital (approval number: 56, date: 13.12.2018).

The number of patients to be included in the study was determined using 80% power and a two-tailed alpha value of 0.05. The following patients were excluded from the study: those with an American Society of Anesthesiologists (ASA) score of >4, body mass index (BMI) of >55 kg/m^2, who underwent open surgery instead of laparoscopy for any reason, those with complicated (perforated, gangrenous, or phlegmonous) appendicitis, those with >500 cc of bleeding during the operation, those with known local anesthetic allergies, those with chronic analgesic addiction, whose operative time was >120 min, and who did not agree to participate in the study. Informed consent was obtained from all patients.

The local anesthetic method to be used in each individual procedure was written in a sealed envelope and sent to the operating room. Then the solution to be applied was prepared by the surgical nurse who opened the envelope in the operating room.

All operations were performed by experienced surgeons, each having performed >500 laparoscopic appendectomies. Laparoscopic appendectomy was performed using three trocars with an intra-abdominal pressure of 14 mmHg. The placement of the trocars is shown in Figure 1. Standard anesthesia procedure was performed in all patients; anesthesia induction was performed using 2-3 mg/kg propofol, 2 µg/kg fentanyl, and 0.6 mg/kg rocuronium with Bispectral Index (BIS) of <60. After the patients were intubated, 1.5-2% sevoflurane inhalations were performed to maintain the BIS value between 40 and 60 in 40% oxygen and 60% air. In case of 20% increase in blood pressure and increase in heart rate during the operation, 0.5 mcg/kg fentanyl was administered intravenously and the administered dose of fentanyl was recorded.

In the LAIS group, after endotracheal intubation, patients were administered a total of 20 cc of 0.5% bupivacaine (vial box of 1x20 mL vial of buvasin 0.5% injection solution) solution percutaneously and subcutaneously following suitable skin staining and sterile covering (8 cc of 0.5% bupivacaine for the trocar access points of 10 mm at infraumbilical and left lower quadrant trocar entries, 6 cc of 0.5% bupivacaine for the other trocar access point of 5 mm). In the TAPB group, after endotracheal intubation, patients had a camera trocar inserted to facilitate pneumoperitoneum after appropriate skin staining and sterile covering. The patients were then injected with 20 cc of 0.5% bupivacaine (vial box of 1x20 mL vial of buvasin 0.5% injection solution) including 10 cc to the right and 10 cc to the left side using a needle inserted at the location described in Figure 2 right

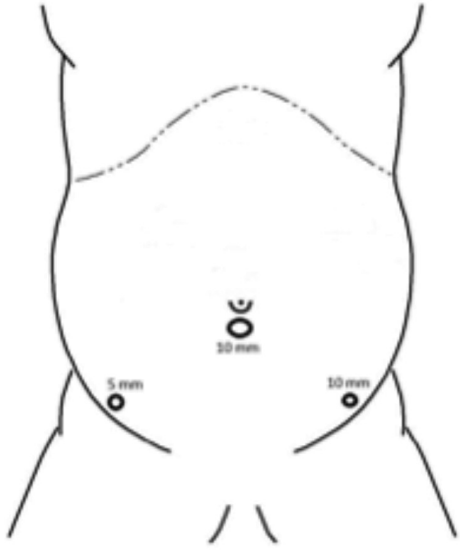

Figure 1. The placement of the trocars in laparoscopic appendectomy

between the transversus abdominis muscle and the internal oblique muscle under direct vision. In the IPLA group, after endotracheal intubation, patients were injected with a total of 20 cc of 0.5% bupivacaine solution into the appendiceal and periappendiceal areas after skin staining and sterile covering followed by pneumoperitoneum (Figure 3). The control group was not given any local anesthetic.

Approximately 30 min before the end of the operation (following removal of the appendix from the abdomen), 1 g of paracetamol and 4 mg of ondansetron were administered intravenously. At the end of the operation, the muscle relaxant effect was antagonized with 0.02 mg/kg atropine and 0.05 mg/kg neostigmine, and then the patients were extubated.

For postoperative pain follow-up, the visual analog scale (VAS) was used for pain assessment. All patients were evaluated in terms of VAS scores, hemodynamic parameters, and patient satisfaction level (5: not satisfied and 1: highly satisfied) at postoperative 1, 2, 4, 6, 12, and 24 hours,

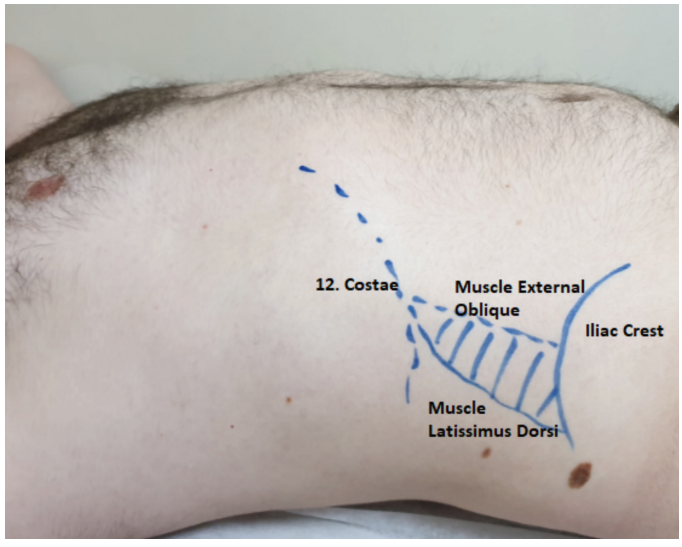

Figure 2. Transversus abdominis plane (TAP) Block application site

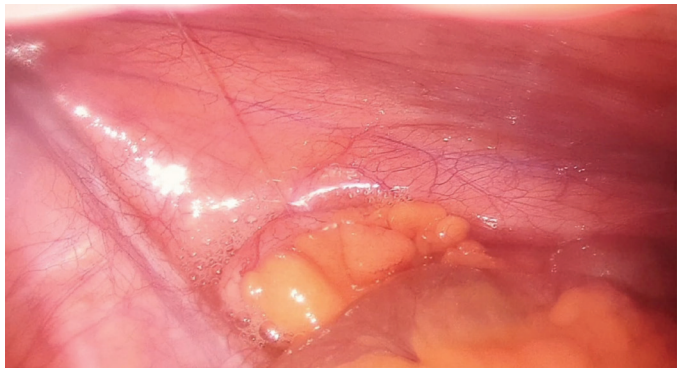

Figure 3. Intraperitoneal local anesthetic application around the appendix site

and the results were recorded. Patients with VAS score of >4 were administered 50 mg intravenous tramadol, and those with high pain levels after 30 min were administered 100 mg tramadol. Non-steroidal anti-inflammatory drug (tenoxicam 20 mg) was administered intravenously at postoperative 8 hours routinely to all patients. Thereafter, 25 mg of meperidine was administered intravenously as salvage analgesic to the patients with pain, regardless of any other existing treatment. All analgesics taken, except for routine tenoxicam treatment, were calculated and recorded as additional analgesic dose. The doses of analgesics administered during the postoperative period as well as the hours of administration were recorded.

Statistical Analysis

SPSS, version 21 was used for statistical analyses (IBM Inc., Armonk, NY, USA). To analyze the study data, the normality of distribution of the parameters was assessed using the Shapiro-Wilk test. Descriptive statistical methods (mean, standard deviation, and frequency) were used to analyze the study data, and One-Way ANOVA was used for intergroup comparisons of the normally-distributed parameters. Kruskal-Wallis test was used to make intergroup comparisons of non-normally-distributed parameters, and Mann-Whitney's U test was used to determine the group that caused the difference. Chi-square test and Fisher-Freeman-Halton test were used to compare the descriptive data. Pearson's correlation analysis was used to analyze the correlation between the normally-distributed parameters, whereas Spearman's rho correlation analysis was used to analyze the correlation between the non-normally-distributed parameters. Significance level was set at $p<0.05$.

Results

We enrolled 160 cases, including 104 (65%) males and 56 (35%) females. The age of the patients ranged from 17-69 years with a mean age of 34.74±13.81 years. The values of BMI ranged from 20-40 kg/m^2, with a mean BMI of 25.45±3.36 kg/m^2. There were four groups as follows: IBLA group, 40 patients (25%); TAPB group, 40 patients (25%); IPLA group, 40 patients (25%); and control group, 40 patients (25%).

The operative times ranged from 20-90 min, with mean and median operative times of 42.25±11.43 and 40 minutes, respectively. The length of hospitalization varied between 1 and 7 days, with mean and median lengths of hospitalizations of 1.60±0.83 and 1 day, respectively.

No significant difference was observed between the study groups in terms of age, BMI, ASA score, gender distribution ratios, previous abdominal surgery rates, incidence of

comorbid disease, operative time, and incidences of peroperative and postoperative complications (p>0.05).

The length of hospitalization in the LAIS group was significantly lower than in the IPLA and control groups [p_1=0.023 (IPLA group); p_2<0.001 (control group); p<0.05] and that in the TAPB group was significantly lower than in the control group (p=0.008) (Figure 4).

The rate of additional analgesic dose administration in the control group (97.5%) was significantly higher than in the LAIS (17.5%), TAPB (7.5%), and IPLA groups (72.5%) (p_1<0.001; p_2<0.001; p_3=0.005, respectively). Further, the rate of additional analgesic dose administration in the IPLA group (72.5%) was significantly higher than in the LAIS (17.5%) and TAPB (7.5%) groups (both p<0.001). No significant difference was observed between the LAIS and TAPB groups in terms of the additional analgesic dose administered (p>0.05; Table 1) (Figure 5).

It was found that all pre-emptive analgesic methods caused significantly less postoperative pain than the control group. VAS values of all measurement hours were significantly higher in the control group than in the LAIS, TAPB, and IPLA groups, whereas the patient's satisfaction level was lower in the control group than in the three study groups (p<0.001). VAS values of all measurement hours were significantly higher in the IPLA group than in the LAIS and TAPB groups, whereas patient satisfaction level was lower in the IPLA group than in the LAIS and TAPB groups (both p<0.001). No significant difference was observed between the LAIS and TAPB groups in terms of VAS values of all measurement hours and patient satisfaction levels (p>0.05; Table 2) (Figure 6, 7).

Postoperative complications were observed in two patients in the LAIS group, three patients in the TAPB group, and one patient in the IPLA group. Abscess occurred in the abdomen in two patients in the LAIS group and regressed with antibiotic treatment without the need for drainage. In the TAPB group, two patients developed intra-abdominal abscess and one patient developed wound infection. These complications also regressed with antibiotic treatment without any drainage. Wound infection developed in one patient in the IPLA group and regressed with antibiotic treatment. No postoperative complications were detected in the control group.

Discussion

We compared the effects of different intraoperative local anesthetic application methods on postoperative pain and patient satisfaction over the short term in patients who underwent laparoscopic appendectomy for acute appendicitis. All the local anesthesia application methods reduced postoperative pain and increased patient satisfaction. Factors such as age, gender, BMI, ASA score, and operative time did not affect postoperative pain. Thus, we believe that peroperative local anesthetic application methods reduce postoperative pain and increase patient satisfaction.

Laparoscopic appendectomy is one of the most common urgent procedures. There are many studies on the advantages of peroperative local anesthetics in eliminating pain that occurs after this operation.[4,11,12] Ekstein et al.[5] reported that the causes of early pain after laparoscopic surgeries include creating wide peritoneal irritation due to pneumoperitoneum, postoperative intra-abdominal blood accumulation, or diaphragmatic irritation.

In appendectomy, local anesthetic injection at the preincision site reduces postoperative pain scores compared to placebo.[12] Blocking the somatic nerve fibers located between the transversus abdominis muscle and the internal oblique muscle, TAP block is reported to reduce postoperative pain in laparoscopic cholecystectomy and open appendectomy.[13-16] Intraperitoneal local anesthetics before laparoscopic procedures also prevent postoperative pain, reduce stress response and the need for analgesics, and

Figure 4. Number of hospitalization days of patients according to the groups

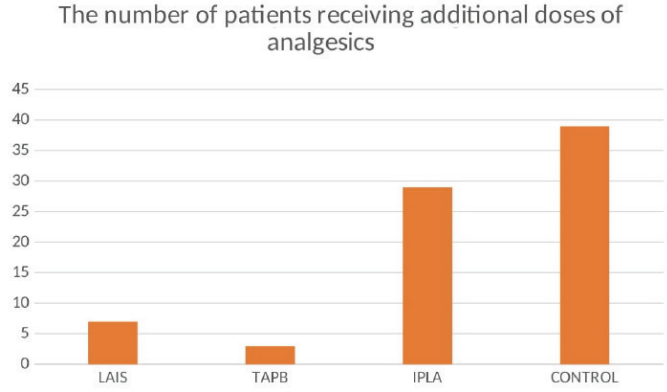

Figure 5. Number of patients who received additional analgesic doses according to the groups

extend the elapsed time until first postoperative analgesic administration.[4,11,17] However, there is no clear evidence about the superiority of these methods compared with each other. In this study, we investigated the advantages of these methods over each other. In our study, we found that these applications reduce postoperative pain and the need for additional analgesics after surgery, as well as increasing patient satisfaction. Similar to our results, Maestroni et al.[4] found that blocking pain receptors with preoperative local anesthesia reduces postoperative pain and the need for additional analgesics.

Some of the methods used to prevent pain after laparoscopic surgeries are postoperative opioid use, non-steroidal anti-inflammatory drugs, pre-incision and post-incision injections of local anesthetic drugs at the incision sites, local anesthetic spraying at the area that will cause intra-abdominal trauma or at the subdiaphragmatic region before and after the dissection, reduced pneumoperitoneum pressure, nongaseous laparoscopy, and traumatized intra-abdominal lavage with saline.[18,19] However, none of these have proven to be superior when compared to each other.

The effect of local anesthetic infiltration in the incision

Table 1. Assessment of parameters among the study groups

LAIS		Local anesthesia group			Total		p-value
		TAPB	IPLA	Control			
		Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Age		33.18±14.17	35.68±12.93	38.43±14.27	31.68±13.39	34.74±13.81	0.137[1]
BMI		25.48±3.57	25.1±3.13	26±3.34	25.23±3.45	25.45±3.36	0.644[1]
ASA (median)		1.4±0.67 (1)	1.48±0.64 (1)	1.5±0.68 (1)	1.43±0.59 (1)	1.45±0.64 (1)	0.861
Operative time (minute) (median)		41.75±14.57 (40)	42.63±9.74 (42.5)	40.13±9.09 (40)	44.5±11.54 (40)	42.25±11.43 (40)	0.372[2]
Gender n (%)	Male	26 (65%)	27 (67.5%)	27 (67.5%)	24 (60%)	104 (65%)	0.883[3]
	Female	14	13	13	16	56	-
Previous operations, n (%)	No	35 (87.5%)	28 (70%)	27 (67.5%)	31 (77.5%)	121 (75.6%)	0.154[3]
	Yes	5	12	13	9	39	-
Presence of comorbid disease, n (%)	No	36 (90%)	36 (90%)	34 (85%)	38 (%95)	144 (90%)	0.567[4]
	Yes	4	4	6	2	16	-
Comorbid diseases, n (%)	DM	2 (5%)	3 (7.5%)	3 (7.5%)	2 (5%)	10 (6.3%)	1.000[4]
	HT	3 (7.5%)	4 (10%)	5 (12.5%)	2 (5%)	14 (8.8%)	0.787[4]
	CVD	1 (2.5%)	1 (2.5%)	1 (2.5%)	1 (2.5%)	4 (2.5%)	1.000[4]
	COPD	0 (0%)	0 (0%)	2 (5%)	0 (0%)	2 (1.3%)	0.245[4]
Peroperative complications, n (%)	No	38 (95%)	40 (100%)	40 (100%)	37 (92.5%)	155 (96.9%)	0.694
	Yes	2	0	0	3	5	-
Postoperative complications, n (%)	No	38 (95%)	37 (92.5%)	39 (97.5%)	40 (100%)	154 (96.3%)	0.516[4]
	Yes	2	3	1	0	6	
Hospitalization (median)		1.3±0.46 (1)	1.45±0.64 (1)	1.68±0.83 (2)	1.98±1.12 (2)	1.6±0.83 (1)	0.0022*
Additional analgesic doses administered, n (%)	No	33 (82.5%)	37 (92.5%)	11 (27.5%)	1 (2.5%)	82 (51.2%)	<0.0013*
	Yes	7	3	29	39	78	-

[1]One-Way ANOVA, [2]Kruskal-Wallis test; [3]chi-square test; [4]Fisher-freeman-halton test; *p<0.05, SD: Standard deviation, LAIS: Local anesthetic infusion to incision site, TAPB: Transversus abdominis plane block, IPLA: Intraperitoneal local anesthetic administration, Control: Control group, BMI: Body mass index, ASA: American Society of Anesthesiologists Score, DM: Diabetes mellitus, HT: Hypertension, CVD: Cardiovascular disease, COPD: Chronic obstructive pulmoner disease

area on postoperative pain has been the subject of many studies.[12,20-26] When we examine the literature, we encounter studies that report that the LAIS method is effective in preventing postoperative pain[12,22,24] and in contrast, that LAIS has no effect.[21,23,25-27] It is not possible to reach a clear result since the application technique, application time and applied tissues of LAIS method differ between these studies. In the present study, we found that the LAIS method was effective in preventing postoperative pain.

The TAP block was first identified by McDonnell et al.[13] in 2004. There are three muscle groups in the abdominal wall: External and internal oblique muscles and transversus abdominis muscle. These muscles are innervated by somatic nerve fibers located between the transversus abdominis muscle and the internal oblique muscle.[28] Blocking these nerve fibers in the anterior abdominal wall in laparoscopic cholecystectomy and open appendectomy reduces postoperative pain.[13-16] In our study, we found that the TAPB method reduces postoperative pain and increases patient satisfaction in laparoscopic appendectomy. In the present study, the TAP Block technique was applied under direct vision after the insertion of the camera trocar. In some studies in the literature, it has been found that the application of the TAPB technique before the incision reduces postoperative pain.[12] In the study conducted by Amr et al.[29], it was found that performing TAPB application

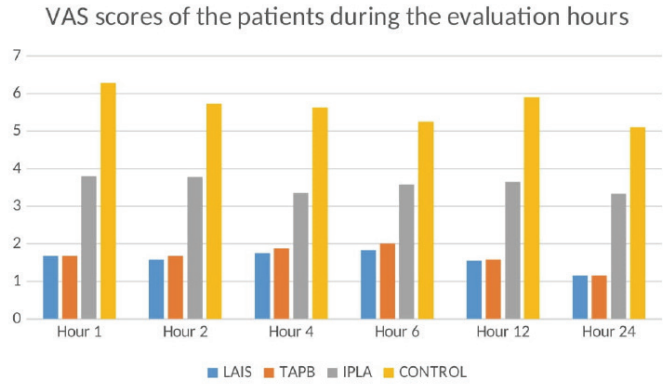

Figure 6. VAS scores of the patients during the evaluation hours
VAS: Visual analog scale

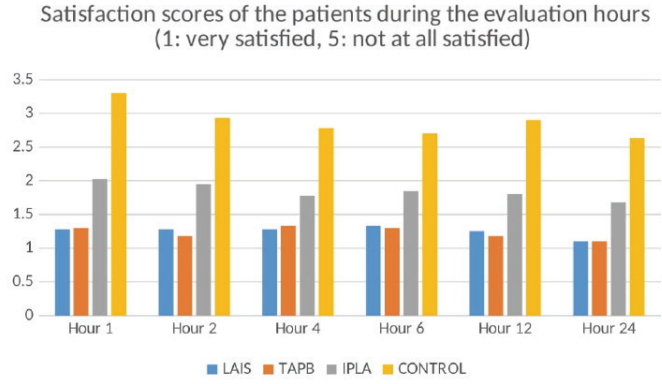

Figure 7. Satisfaction scores of the patients during the evaluation hours

Table 2. Evaluation of VAS and patient satisfaction levels among the study groups

LAIS		Local anesthesia group				p-value
		TAPB	IPLA	Control		
		Mean ± SD (median)	Mean ± SD (median)	Mean ± SD (median)	Mean ± SD (median)	
VAS	Hour 1	1.68±1.95 (1)	1.68±1.53 (2)	3.8±1.8 (3.5)	6.28±2.33 (6.5)	**<0.001***
	Hour 2	1.58±1.57 (1)	1.68±1.47 (2)	3.78±1.56 (3.5)	5.73±2.35 (6)	**<0.001***
	Hour 4	1.75±1.66 (1)	1.88±1.77 (2)	3.35±1.66 (3)	5.63±1.75 (6)	**<0.001***
	Hour 6	1.83±1.82 (1)	2±1.97 (2)	3.58±1.92 (3.5)	5.25±2.44 (5)	**<0.001***
	Hour 12	1.55±1.84 (1)	1.58±1.57 (2)	3.65±1.89 (3)	5.9±2.43 (6)	**<0.001***
	Hour 24	1.15±1.49 (1)	1.15±1.41 (1)	3.33±1.86 (3)	5.1±2.33 (5)	**<0.001***
Patient satisfaction	Hour 1	1.28±0.64 (1)	1.3±0.56 (1)	2.03±0.77 (2)	3.3±1.07 (3)	**<0.001***
	Hour 2	1.28±0.51 (1)	1.18±0.38 (1)	1.95±0.68 (2)	2.93±1 (3)	**<0.001***
	Hour 4	1.28±0.55 (1)	1.33±0.53 (1)	1.78±0.66 (2)	2.78±0.83 (3)	**<0.001***
	Hour 6	1.33±0.57 (1)	1.3±0.76 (1)	1.85±0.83 (2)	2.7±0.94 (2.5)	**<0.001***
	Hour 12	1.25±0.59 (1)	1.18±0.68 (1)	1.8±0.72 (2)	2.9±1.01 (3)	**<0.001***
	Hour 24	1.1±0.38 (1)	1.1±0.3 (1)	1.68±0.76 (2)	2.63±1.03 (3)	**<0.001***

Kruskal-Wallis test; *p<0.05, SD: Standard deviation, LAIS: Local anesthetic infusion to incision site, TAPB: Transversus abdominis plane block, IPLA: Intraperitoneal local anesthetic administration, Control: Control group, VAS: Visual analog scale

before incision reduced postoperative pain more than after incision. However, it was found that the application of TAPB method after incision decreased postoperative pain compared to not being applied.[29]

In randomized controlled trials on the use of intraperitoneal local anesthetics in laparoscopic appendectomies in adults, IPLA was found to reduce the need for postoperative analgesics; low pain scores have been detected in three studies.[30-32] Our study also found that IPLA was advantageous for postoperative pain management compared to the control group.

Opioids are effective in reducing postoperative pain, but they cannot be used safely due to their possible side effects.[33] Some of these side effects include respiratory depression, sedation, postoperative nausea and vomiting, itching, urinary retention, ileus, and constipation and, therefore, delayed discharge.[34] Due to all these side effects, anesthesiologists and surgeons currently use nonopioid analgesia. In our study, we found that preemptive analgesia reduced the need for postoperative additional analgesics and opioid. Therefore, we believe that these methods might prevent the side effects caused by the overuse of opioids.

When considering early recovery programs, postoperative pain control added to the surgical protocol is important, which results in many advantages, such as early recovery, and short hospital stay.[35,36] Local anesthetic administrations reduce surgical stress response and the need for postoperative opioid use, as well as facilitate early recovery.[36]

Study Limitations

This study has some limitations. The TAPB technique applied in this study was performed under direct vision in anesthetized patients without using sonar probe in order to prevent prolongation of the operation time. Therefore, it is impossible to assume that all blocks were working perfectly. This point may have affected the validity of the results.

Another limitation of our study was that the age range of the evaluated patients was very wide. For the purpose of this study the possibility that the degree of pain that may occur after surgery may vary depending on age was ignored.

Finally, a limitation of our study was that postoperative follow-up was terminated within 24 hours due to the discharge of the patients. Single doses of local anaesthetics provide pain relief, but the short duration of effect can be a limiting factor.

Conclusion

Using peroperative preemptive analgesia methods to prevent postoperative pain after laparoscopic appendectomy facilitates early recovery, less need for additional analgesics, and higher patient satisfaction during the postoperative period, thereby increasing the postoperative comfort of patients in the first 24 hours after surgery.

Ethics

Ethics Committee Approval: Approval for this study was obtained from the Ethics Committee Fatih Sultan Mehmet Training and Research Hospital (approval number: 56, date: 13.12.2018).

Informed Consent: Informed consent was obtained from all patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

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RESEARCH ARTICLE

The Yield of Faecal Immunochemical Test in the Detection of Colorectal Cancer within a Fast-track Pathway at York, United Kingdom

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ABSTRACT

Aim: Access to colonoscopy was limited during the Coronavirus disease-2019 (COVID-19) pandemic peak. It was, therefore, of great importance that a tool such as faecal immunochemical test (FIT) be used to identify patients with a greater likelihood of colorectal cancer (CRC).

Method: A prospective cohort of patients referred through the fast-track pathway was sent a FIT test. A cut-off of 7 µgHb/g was used as the threshold for a positive result. A receiver operating curve (ROC) was subsequently constructed to identify the ideal threshold for detecting cancer.

Results: In total, there were 1,068 patients referred to the fast-track clinic. A greater proportion of patients who were FIT positive had CRC (17.4% vs. 0.4%, p=0.001) when compared with FIT negative patients. ROC curve analysis revealed an optimum sensitivity/specificity for detecting CRC using a FIT threshold of 19 µgHb/g.

Conclusion: The yield for CRC is minimal in a FIT negative patient - such patients may be safely discharged, as long as a clinical safety net is in place. Using sensitivity and specificity analysis, patients with a FIT above 19 µgHb/g should be investigated urgently to exclude cancer.

Keywords: Faecal immunochemical test, colorectal cancer, fast track, FIT

Introduction

Colorectal cancer (CRC) is the fourth most common cancer and the second most common cause of cancer death in the UK.[1] CRC can present with one or multiple symptoms to primary care. Symptoms include a change in bowel habits in the form of diarrhoea or constipation, both in terms of frequency and stool consistency, which is the most common CRC presentation in primary care.

Colonoscopy is the gold standard investigation to detect significant bowel disease (SBP). Significant bowel pathology encompasses a spectrum of conditions, including CRC, higher risk adenoma [(HRA), defined as three or more adenomas or any adenoma >1 cm], and inflammatory bowel disease (IBD) with high sensitivity and specificity.[2] A two-week pathway was initially introduced to help patients be seen sooner. The aim was to diagnose CRC early enough to minimise CRC mortality. This pathway has led to a massive increase in the number of referrals through primary care.[3] As a consequence of the need to investigate patients quicker and better, much pressure was placed on outpatient clinics and diagnostic services, such as endoscopy units and radiology departments, to increase capacity for these patients. Traditionally, CRC yield from the two-week pathway has been low, ranging between 3-7% at best.[3] Over the last five years, fast-track referrals have increased by 90%, leaving 45% of endoscopy units failing to meet their colorectal waiting list targets.[4,5] Therefore, prompt actions were needed to deal with these problems, with the aim of reducing unnecessary colonoscopies and mitigating the associated risks and costs of inappropriate tests.

In 2017, the National Institute for Health and Care Excellence (NICE) (DG30) introduced the faecal immunochemical test (FIT) to help with the referrals of patients with low-risk symptoms that did not meet the criteria for the two-week wait (2WW) pathway.[6] Currently, a positive FIT result

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detected in a low-risk patient automatically upgrades them into a 2WW pathway. A 2WW referral is a referral from general practitioners (GPs) to provide patients with an urgent appointment when they have suspicious symptoms of cancer. However, currently, FIT has not been approved by NICE for routine use in these high-risk patients.

FIT detects the remote globin part of hemoglobin (Hb) by immunoassay in stool and can measure the faecal Hb concentration (f-Hb) to the nearest microgram of Hb per gram of faeces (µgHb/g).[7] NICE has recommended a threshold of 10 µgHb/g for a positive result. NHS England has also recently suggested that patients with a negative FIT test may be removed from the fast-track pathway and tracking list to ease pressure within the system.

A review of the published literature on FIT within a two-week pathway revealed six main projects that were done within the UK. The Nottingham series has the largest number of patients on FIT with 14,788 patients. This group published the only paper that followed the impact of FIT on yield longitudinally for two years. Access to the FIT test was via primary care. Unlike most other studies, the threshold for a positive FIT was set at >4 µgHb/g. Similarly, in Scotland, FIT was provided to primary care. The studied population was half the size of that in Nottingham, but a positive threshold was set at a higher cut-off of >10 µgHb/g. Another large national study was done recently, centered in Croydon Hospital, across 50 NHS hospitals with 9,822 patients being included with a very low threshold (>2 µgHb/g). Table 1 summarises the six main published papers.

To date, there has been little data looking at FIT in the Yorkshire region as a tool to maximise cancer detection. During the Coronavirus disease-2019 pandemic, the need for another test to aid the cancer diagnosis process has increased. As a result, York Teaching Hospital Foundation Trust adopted FIT as a diagnostic adjunct.

As seen from the published literature, there is variation in the positive FIT threshold between studies. Thresholds of 2, 4 and 10 µgHb/g have been used, and this will have an impact on reported yields within individual publications. NICE has recommended that the positive threshold for FIT be set at 10 µgHb/g. As FIT is a quantitative test, threshold values can be modified to improve the test's sensitivity or specificity. It is essential to determine the optimum cut-off value for patients with significant bowel pathology, including that of CRC, because it allows a service to define the patient group that is most at risk and prioritise them for investigations accordingly. Increasing the sensitivity of the test by reducing the threshold allows maximum detection of patients with pathology but results in a lot of negative colonoscopies and wasted capacity. Reducing the sensitivity optimises the yield for colonoscopy when it is performed but may result in some patients with significant pathology not being investigated. As there is a need to determine the optimum threshold for detection of bowel pathology in our local cohort of patients, we chose to study this in greater detail.

Table 1. Summary of studies which have examined the role of FIT in colorectal cancer pathways

Paper title	Location	Positive FIT threshold	Primary or secondary care	Population size	Year
Faecal immunochemical test (FIT) is superior to symptoms in predicting pathology in patients with suspected colorectal cancer symptoms referred on a 2WW pathway: A diagnostic accuracy study[7]	Croydon University Hospital	f-Hb >2 µgHb/g	Secondary care	9,822	October, 2020
Impact of introducing a FIT for haemoglobin into primary care on the outcome of patients with new bowel symptoms: A prospective cohort study[8]	Tayside Scotland	f-Hb >10 µgHb/g	Primary care	5,422	May, 2019
Early clinical outcomes of a rapid colorectal cancer diagnosis pathway using FIT in Nottingham[9]	Nottingham	f-Hb >4 µgHb/g	Primary care	1,947	December, 2019
Adoption of FIT for 2-week-wait colorectal patients during the COVID-19 pandemic: An observational cohort study reporting a new service at a regional centre[10]	Royal Surrey NHS Foundation Trust	f-Hb >10 µgHb/g	Primary care	391	October, 2020
FIT s in the COVID-19 pandemic; safety-netting of patients with symptoms and low faecal haemoglobin concentration - can a repeat test be used?[11]	Royal Surrey NHS Foundation Trust and University of Dundee	f-Hb >10 µgHb/g	Not applicable	Not applicable	October, 2020

2WW: Two-week wait, COVID-19: Coronavirus disease-2019

Materials and Methods

Patient Population, FIT and Processing of Results

A consecutive series of patients in North Yorkshire (including the towns of York, Scarborough, Whitby, Bridlington, Selby, and Malton), referred through the fast-track pathway, were sent a FIT test as part of their diagnostic work-up. Informed consent was obtained from those patients. All patients were asked to perform a FIT test before they were assessed in the clinic regardless of their symptoms. Patients received a FIT kit via the post. This kit includes a specimen collection device and instructions leaflet on collecting the sample and how to send it back to the laboratory. The department of Clinical Biochemistry at York Hospital analyses the FIT assay twice a week. Allocations of patients were made to appropriate telephone clinic slots with a FIT result at hand. Patients were assessed at the telephone clinic within the two-week timeframe, and a FIT result would be incorporated into the investigative algorithm when it subsequently became available on the Core Patient Database (CPD).

Triage of Patients

A measured FIT of >7 µgHb/g was regarded as positive, which was determined by our local laboratory. Given the published literature, which had both thresholds that were higher and lower for a similar cohort of patients, this positive threshold was deemed reasonable. Yield for CRC and significant bowel pathology was noted. The definition of a CRC is that of a lesion situated within the colon and rectum that has a confirmed biopsy of an adenocarcinoma. Although lesions of the anus that are squamous cell in origin are regarded as clinically significant they were, strictly speaking, not included as part of the definition of CRC within this study. The definition of significant bowel pathology included CRC, HRA and IBD, as reported by previous publications. HRA was defined as three or more adenomas or any adenoma >1 cm in size.

Inclusion and Exclusion Criteria

All patients referred from primary care with symptoms that met NICE referral criteria to fast-track clinics from March to October 2020 were included. Patients were excluded if they chose not to have any investigations after clinic consultation. Similarly, patients were excluded if they were deemed too frail for investigations by clinicians. A proportion of patients were also awaiting investigations at the time of collection of data.

Data Collection

All data was secured on a password-protected Excel spreadsheet within the trust. Clinic letters, investigations, results, and demographics were obtained from the interrogation of clinical information via CPD. Demographics (NHS number, age, and gender), presenting symptoms and signs, such as the presence of rectal bleeding, presence of mass/lump, and iron deficiency anaemia, were collected. Results from the test of choice (either colonoscopy, cross-sectional imaging, or both) were collected to determine the yield from these diagnostic tests. Other findings such as diverticulosis, haemorrhoids, solitary rectal ulcers, colitis, and low-grade adenomas were also recorded.

Statistical Analysis

Categorical and continuous variables were compared using the chi-square test or Mann-Whitney U test, respectively.

A receiver operating curve (ROC) was calculated to study the sensitivity and specificity of FIT thresholds for CRC and significant bowel pathology. The optimum threshold was determined by the calculation of the Youden index.

A p-value of less than 0.05 was deemed significant.

Results

Study Population

From March to October 2020, there were 1,068 patients referred to the fast-track clinic. Sixty-five patients declined investigations and 11 were pending, leaving 992 patients for analysis. There were 527 (53%) females and 465 (47%) males. The median age was 72 (interquartile range: 63-78) years. Fifty-two (5.2%) CRCs were detected in the study population of 992 patients. The proportion of CRC cases among women and men was not statistically different (28/527 vs 24/465, p-value=0.915).

FIT Test as a Diagnostic Tool

Among the 992 patients who had FIT, 282 patients were positive (>7 µgHb/g). In total, among 282 positive patients, there were fifty-two CRC cases (17.8%) and nineteen patients (6.7%) who had significant bowel pathology. Figure 1, 2 highlight this graphically.

Sensitivity, Specificity, and ROC Analysis of FIT Testing

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value of FIT using the initial threshold of 7 µgHb/g was 94.2%, 75.3%, 17.4% and 99.6%, respectively. To optimise the threshold of detection of CRC in our study population, we decided to perform a ROC analysis. The ROC analysis revealed an area under the curve of 0.89 [95% confidence interval (CI) 0.85-0.93]. This curve is illustrated and detailed further in Figure 3.

To determine the optimum sensitivity/specificity for detecting CRC, the Youden index was calculated. The Youden index was determined using the formula: sensitivity + specificity-1 for each data point on the ROC curve. The data points are highlighted in Table 2. The best Youden index was noted at FIT threshold between 10 and 19 µgHb/g.

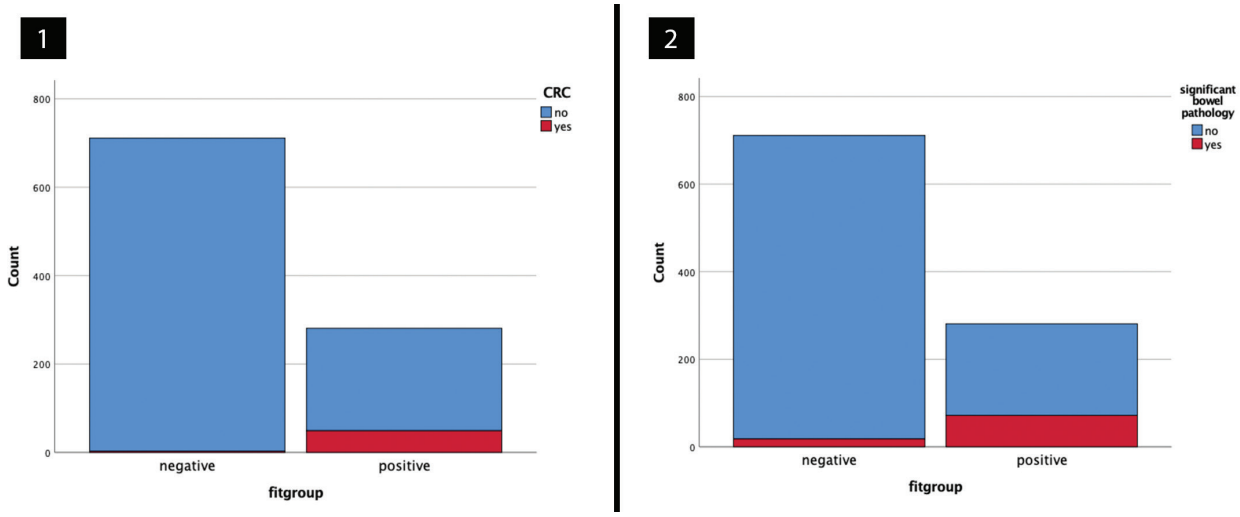

Figure 1, 2. FIT as a diagnostic tool for CRC and SBP

FIT: Faecal immunochemical test, CRC: Colorectal cancer, SBP: Significant bowel disease

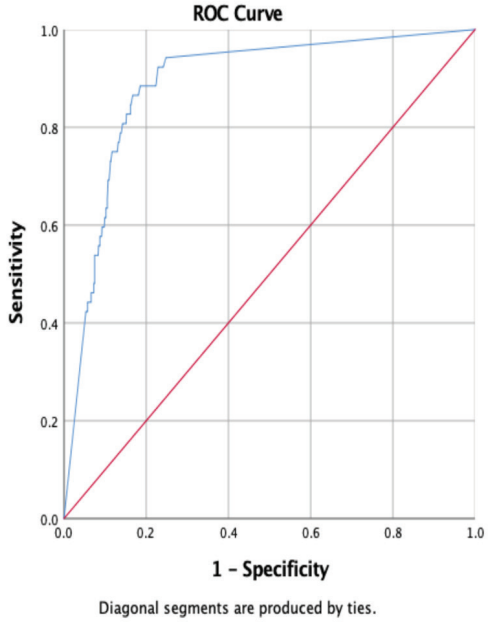

Figure 3. ROC curve

ROC: Receiver operating curve

Discussion

FIT as a Diagnostic Adjunct

The 2WW pathway has a yield of 3-4% but accounts for the detection of 30% of all CRC cases.[12-14] A longitudinal study conducted between 2009 and 2018 showed that the number of fast-track referrals for suspected CRC has doubled in the intervening period, and yet the overall yield for cancer has reduced by half because a large number of procedures need to be performed to detect occasional cancer.[14] Work from other centres also showed a similar trend - a consistent reduction in diagnostic yield with an increase in colonoscopy referrals.[15-18] The volume of endoscopy cases in the UK has nearly doubled in the last five years.[18] Each colonoscopy costs the NHS £372-£419, with an overall cost of £260 million per annum.[8,19] In contrast, NICE guidelines reported the cost of the FIT test to about £5-£6 according to the type of analyser used.[6] This would mean a saving of around £400 per patient. Therefore, better use of endoscopy and careful selection of patients who truly require the test via the 2WW pathway could potentially improve the yield for cancer and help the NHS fiscally.

It has always been a strategy to use FIT as a means to improve the 2WW pathway. This strategy aims to improve overall patient care by targeting the use of colonoscopy in the right group of patients and increasing the rates of detection of cancer and other significant bowel pathology. In our study, of the 992 patients, 282 (28%) patients were FIT positive (above 7 µgHb/g). There were 52 (5%) CRC cases. Therefore, overall cancer yield was 17%.

There were some similarities in the yield of SBP or CRC in the main projects we looked at. Some did not look at the yield of CRC separately but looked at the SBP yield as one. In Scotland, the yield for SBP in patients who had positive and negative test was 25% vs 1%, respectively, while the yield for CRC only was 8%. The projects with a FIT test threshold at 10 µgHb/g had quite a similar yield for CRC. Bailey et al.[11] in a two-year follow-up evaluation (with the largest population) had a CRC yield of 5.5%, while in Surrey, the yield was 3.7%. The previous three projects shared a positive FIT test threshold of 10 µgHb/g. In contrast, the multi-site study done in London using a threshold of 2 µgHb/g in 9,822 patients revealed a CRC yield of 17.4%,

Table 2. Sensitivity and specificity data points for each FIT threshold

Positive if greater than or equal to[a]	Sensitivity	1-specificity	Specificity	Youden index
6	1	1	0	0.00
7.5	0.942	0.248	0.752	0.69
8.5	0.923	0.241	0.759	0.68
9.5	0.923	0.237	0.763	0.69
10.5	0.923	0.229	0.771	0.69
11.5	0.885	0.223	0.777	0.66
12.5	0.885	0.218	0.782	0.67
13.5	0.885	0.206	0.794	0.68
14.5	0.885	0.205	0.795	0.68
15.5	0.885	0.202	0.798	0.68
16.5	0.885	0.195	0.805	0.69
17.5	0.885	0.191	0.809	0.69
18.5	0.885	0.189	0.811	0.70
19.5	0.885	0.185	0.815	0.70
20.5	0.865	0.181	0.819	0.68
21.5	0.865	0.178	0.822	0.69
22.5	0.865	0.174	0.826	0.69
23.5	0.865	0.173	0.827	0.69
24.5	0.865	0.172	0.828	0.69
25.5	0.865	0.169	0.831	0.70
26.5	0.865	0.167	0.833	0.70
27.5	0.846	0.163	0.837	0.68
28.5	0.846	0.162	0.838	0.68
29.5	0.827	0.162	0.838	0.67
30.5	0.827	0.16	0.84	0.67
31.5	0.827	0.156	0.844	0.67
32.5	0.827	0.154	0.846	0.67
33.5	0.827	0.152	0.848	0.68
34.5	0.808	0.151	0.849	0.66
35.5	0.808	0.149	0.851	0.66
36.5	0.808	0.145	0.855	0.66
38.5	0.808	0.143	0.857	0.67
40.5	0.788	0.139	0.861	0.65
41.5	0.788	0.137	0.863	0.65
42.5	0.769	0.134	0.866	0.64
44	0.769	0.133	0.867	0.64

Table 2. Continued

Positive if greater than or equal to[a]	Sensitivity	1-specificity	Specificity	Youden index
46	0.769	0.132	0.868	0.64
47.5	0.75	0.13	0.87	0.62
48.5	0.75	0.129	0.871	0.62
50	0.75	0.126	0.874	0.62
51.5	0.75	0.123	0.877	0.63
52.5	0.75	0.118	0.882	0.63
53.5	0.75	0.117	0.883	0.63
54.5	0.731	0.114	0.886	0.62
55.5	0.731	0.113	0.887	0.62
56.5	0.712	0.112	0.888	0.60
57.5	0.692	0.11	0.89	0.58
58.5	0.692	0.107	0.893	0.59
59.5	0.673	0.106	0.894	0.57
60.5	0.654	0.105	0.895	0.55
61.5	0.635	0.105	0.895	0.53
62.5	0.635	0.104	0.896	0.53
63.5	0.635	0.103	0.897	0.53
65	0.635	0.102	0.898	0.53
66.5	0.615	0.102	0.898	0.51
67.5	0.615	0.101	0.899	0.51
68.5	0.615	0.1	0.9	0.52
69.5	0.615	0.099	0.901	0.52
71	0.596	0.098	0.902	0.50
74	0.596	0.097	0.903	0.50
76.5	0.596	0.096	0.904	0.50
78.5	0.596	0.095	0.905	0.50
81	0.596	0.093	0.907	0.50
83	0.577	0.091	0.909	0.49
85	0.577	0.09	0.91	0.49
87	0.577	0.088	0.912	0.49
89	0.577	0.087	0.913	0.49
92.5	0.558	0.087	0.913	0.47
96.5	0.558	0.086	0.914	0.47
100	0.558	0.085	0.915	0.47
106	0.558	0.084	0.916	0.47
110.5	0.538	0.083	0.917	0.46
111.5	0.538	0.081	0.919	0.46

Table 2. Continued

Positive if greater than or equal to[a]	Sensitivity	1-specificity	Specificity	Youden index
114	0.538	0.08	0.92	0.46
116.5	0.538	0.078	0.922	0.46
118	0.538	0.077	0.923	0.46
120.5	0.538	0.076	0.924	0.46
123.5	0.538	0.074	0.926	0.46
126.5	0.519	0.074	0.926	0.45
132.5	0.5	0.074	0.926	0.43
139	0.481	0.074	0.926	0.41
150.5	0.481	0.073	0.927	0.41
162	0.481	0.072	0.928	0.41
165	0.462	0.072	0.928	0.39
167.5	0.462	0.071	0.929	0.39
195.5	0.462	0.069	0.931	0.39
222.5	0.462	0.068	0.932	0.39
227	0.462	0.067	0.933	0.40
241.5	0.462	0.066	0.934	0.40
260.5	0.442	0.066	0.934	0.38
276	0.442	0.065	0.935	0.38
285	0.442	0.064	0.936	0.38
292	0.442	0.063	0.937	0.38
297.5	0.442	0.062	0.938	0.38
303	0.442	0.061	0.939	0.38
308.5	0.442	0.059	0.941	0.38
322	0.442	0.057	0.943	0.39
348.5	0.423	0.057	0.943	0.37
373	0.423	0.056	0.944	0.37
387.5	0.423	0.055	0.945	0.37
395	0.423	0.054	0.946	0.37
399.5	0.423	0.053	0.947	0.37
401	0	0	1	0.00

which was close to our CRC yield (18.4%) using a higher threshold of 7 µgHb/g. It would seem that our CRC yield was indeed higher than those obtained from the other studies. It is difficult to explain the exact reasons for this observation when we control the variation seen in thresholds. However, it is possible that our patient population has a high incidence of cancer when compared with those from the other studies. What is clear from the data published at the time of writing is that FIT thresholds are inversely proportional to cancer yield.

In a recent two-year evaluation study performed in Nottingham, the authors retrospectively examined the stratification of FIT in conjunction with blood results to help to prioritise and detect CRC in more than 14,000 symptomatic patients. Only six CRC cases were detected in 11,194 patients who had FIT under 20 µg/g with normal blood tests and normal clinical examinations. Furthermore, it also showed that 5,588 patients (over 60 years) with FIT <4 µgHb/g were investigated by GPs after applying FIT results. With the implementation of FIT testing, the Nottingham group predicted that more than 230 additional referrals per month over two years had been avoided.[11]

In our series, there were only 52 cancers in 992 patients, which means that 95% of patients referred on a fast-track pathway did not have cancer. Three patients who were negative on FIT testing (<7 µgHb/g) had CRC. On closer examination, one patient had cancer in the rectosigmoid region, one in the distal transverse colon and one in the anal region. The presence of cancers in a FIT negative cohort is a little concerning. From a population perspective, patients who have a negative FIT result rarely have cancer, as this was only observed in 3 out of 711 (0.4%) patients. However, if one were to examine this from a cancer perspective, 3 out of 52 (6%) cancers were FIT negative. If one in every 20 cancers is not detected by a FIT test, then a serious question is raised. Although the risk of CRC is low in a FIT negative patient, is it low enough to justify the discharge of patients without any investigations at all? For this reason, guidelines in England contain a caveat. The guidelines stipulate that patients referred with NG12 symptoms who have negative FIT results (<10 µgHb/g) should be given a safety net appointment a few weeks later to ensure resolution and/or improvement of symptoms. Similar recommendations exist in Scotland. Patients who are negative on FIT testing should be re-assessed in six weeks to ensure the resolution of symptoms. If symptoms persist in these patients, then they should be re-referred to secondary care or be considered for a repeat FIT test.[20,21] Despite the above recommendation, there is insufficient evidence at this juncture to support serial FIT testing in patients with persistent symptoms who were negative at their index FIT.

The Optimum FIT Threshold

Using the initial threshold of 7 µgHb/g for FIT, we found that our sensitivity, specificity, PPV, and negative predictive value for the detection of CRC was 94.2%, 75.4%, 17.4% and 99.6%, respectively. Our results largely mirror the findings that were reported from previous publications. As mentioned, a few centres have been at the forefront

of employing FIT to assess high-risk symptoms, such as the group in Nottingham, Dundee, and London.[8,9,22] In Nottingham, Chapman et al.[22] looked at 1,106 patients with NICE NG12 symptoms. Rectal bleeding was excluded from this study. Sensitivity of FIT in CRC detection was 97.5%, 87.5% and 60% at cut-offs of 4 µgHb/g, 10 µgHb/g and 150 µgHb/g, respectively; the PPV for CRC at the same cut-offs were 12.5%, 14.6% and 35.8%, respectively. The Dundee authors studied 1,447 patients who had a FIT before colonoscopy. FIT sensitivity was 90.5%, and PPV was 11% at a cut-off of 10 µg/g. The largest multicentre London-based study conducted on 9,822 patients in 50 NHS hospitals from October 2017 to December 2019, revealed that sensitivity could be further improved to 97% if the threshold was reduced to 2 µgHb/g[23]. Last but not least, NICE as a governing body suggested that the threshold of a positive FIT be set at 10 µgHb/g for assessment of DG30 patients. This seems a reasonable compromise, but it does reduce the sensitivity slightly to 94%.

FIT has a high sensitivity of 94% but a lower specificity of 75% at a cut-off of 7 µgHb/g. A reduction of the threshold below 7 µgHb/g will increase the sensitivity marginally, but this translates to a larger number of unnecessary colonoscopies, the majority of which will be falsely positive. As the 3 FIT negative CRCs were not detected below the cut-off of 7 µgHb/g, it is intuitive to increase the threshold further in our study population to increase the specificity of the test and reduce the need for unnecessary colonoscopy.

As such, a ROC curve was performed in our study cohort to determine the ideal threshold of FIT so that both sensitivity and specificity could be maximised. Our ROC curve had an area under the curve of 0.89 (95% CI: 0.85-0.93) and confirmed that an increase of the FIT threshold to 19 µgHb/g optimised the utility of FIT in our study population to detect cancer. Our findings are mirrored by the Nottingham study, which showed that at a threshold of 20 µgHb/g, only one CRC case would have been missed in patients with normal blood results and rectal examination.[11] Therefore, we believe that patients with a FIT threshold of less than 19 µgHb/g should be safely reassured that their symptoms are unlikely to be due to CRC and their symptoms are most likely due to other pathology. At this cut-off, sensitivity was 89%, specificity was 81%, and the negative predictive value remained very high. In other words, patients referred through NICE guidelines and who have a FIT under 19 µgHb/g have a risk of less than 1% of CRC. Persistent symptoms may reflect other non-malignant pathology, which requires investigation, but this could be done via routine referrals rather than current fast-track pathways, which we know are increasingly overwhelmed. Although we have a decent sample size, we would have preferred to study a greater number of patients. This would have allowed us to identify more cancer patients who were FIT negative and determine the factors that may have led to this observation. We recognise that our study does not contain an original hypothesis or design but repeats studies in the published literature using a different cohort of patients. Moreover, the findings from this study cannot be generalized globally and is valid only within the UK. Patients that are eligible for the two-week pathway may create a selection bias and therefore thresholds values for FIT sensitivity and specificity in this study are applicable only for this particular population.

Conclusion

Patients who test positive on FIT are more likely to have CRC or other significant bowel pathology. The yield for CRC and significant pathology is minimal in a FIT negative patient - such patients may be safely discharged with appropriate safety-netting in place, either at the primary or secondary care level. A FIT threshold of 19 µgHb/g had the optimum sensitivity and specificity using ROC analysis in the tested population. Those patients with a FIT above 19 µgHb/g should be investigated urgently to exclude cancer. There remains an absence of national guidance on FIT stratification within the two-week pathway for patients with CRC. However, many trusts have begun incorporating FIT into their local pathway to circumvent the problems associated with capacity and access to colonoscopy. Further studies with large patient numbers are needed to address some of the unanswered questions regarding FIT.

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Ethics

Ethics Committee Approval: Retrospective study.

Informed Consent: Informed consent was obtained from those patients.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Supervision: J.R., M.L., Data Collection or Processing: A.E., M.S., P.B., Analysis or Interpretation: A.E., Writing: A.E.

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

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RESEARCH ARTICLE

How can I Start an Multidisciplinary Team for Management of Rectal Cancer Patients? Analysis of the Feasibility of Using American National Accreditation Program for Rectal Cancer Patients Standards in a Low-Income Country Hospital

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ABSTRACT

Aim: The advent of the multidisciplinary approach to rectal cancer patients has resulted in a paradigm shift when treating these patients. Few programs exist that lay the basis for establishing basic principles for creating such committees.

Method: During the year 2021, a multidisciplinary team was created in a university hospital in Buenos Aires for the management of patients with rectal cancer, following the guidelines proposed by the "National Accreditation Program for Rectal Cancer Patients (NAPRC)". After the first four months of using this system, a summary of the program was made. The feasibility of applying these guidelines in our hospital was evaluated, and the first patients presented in committee were considered.

Results: During the study period, four committee meetings were held and 17 patients with a mean age of 69 years (29-86) were presented, following the standards proposed by the NAPRC. Of these patients, 64.70% (11/17) had lower rectal tumors, 94.11% (16/17) were adenocarcinomas, and locally advanced stage was found in 68.75% (11/16). In 75% (12/16), neoadjuvant therapy was recommended, and one patient had a complete clinical response after neoadjuvant treatment. Following NAPRC recommendations, all patients fulfilled the requirements for the MDT team approach.

Conclusion: NAPRC guidelines could be of use in establishing a multidisciplinary committee to approach patients with rectal cancer in hospitals of low-income countries. Further experience needs to be presented to evaluate if the use of this guidelines is associated with improved clinical results.

Keywords: Rectal, cancer, MDT, radiotherapy, neoadjuvant

Introduction

Worldwide, colorectal cancer is the third most common cancer, and represents the second largest cause of cancer-related deaths.[1] Moreover, the incidence of this type of tumors has been increasing in a younger population, who seem to have worse prognosis.[2] However, the prognosis and functional results in rectal cancer patients has improved due to advances in its treatment and centralization of care in specialized centers.[3]

For these reasons, the American College of Surgeons launched the National Accreditation Program for Rectal Cancer (NAPRC) in 2007, intending to set the basis of multidisciplinary management of rectal cancer patients, and therefore, improve results of treatment.

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The purpose of this article is to present the program and evaluate the feasibility and applicability of NAPRC standards in a university hospital in a low-income country.

Materials and Methods

This manuscript was performed following international guidelines for data protection, and all patients involved signed an informed consent to share their anonymized information for investigation purposes.

During the period between June and September 2021, a multidisciplinary care program for patients with rectal cancer was created, following the standards proposed by the NAPRC.

Basis of the NAPRC

The main objective of the NAPRC was to ensure that patients with rectal cancer receive adequate care, based on a multidisciplinary model of care.

The program is based on four fundamental principles:

- Establish a multidisciplinary team committed to the objective of the program with specialists in the area.
- Improvement of the patient care processes.
- Improvements in the results obtained by auditing the care processes.
- Adoption of adequately validated performance measures.

The multidisciplinary committee must have specialists in pathology, imaging diagnosis, colorectal surgery, clinical oncology and radiotherapy (RT).

In turn, a program director in charge of chairing the committee and reporting its performance, and a program coordinator responsible for registering and monitoring patients during their treatment must be appointed. Figure 1 shows the structure of the rectal cancer MDT in our hospital.

The statute of the program recommends a periodicity of at least two meetings every month. However, due to the clinical reality and the volume of patients in our environment, it was carried out on a monthly basis. Likewise, a minimum percentage of "presenteeism" for each member of the committee has been established, which varies according to specialty (for surgeons, it is 50%). "Presentism" is controlled by the program coordinator.

Regarding the data storage of each program, at our hospital we adapted a model used at the Cleveland Clinic, Florida, United States. A copy of this file can be seen in Figure 2.

Accreditation to the program requires that a minimum of 50% of rectal cancer patients treated at the institution have a clinical record. Once the treatment has been decided, the patient must start the treatment received within 60 days of the decision.

The requirements of each area will be developed below.

Pathology

The program requires that at least 90% of surgical specimens are evaluated by a professional who is part of the team.

The anatomo-pathological report protocol is carried out following the bases proposed by the "College of American

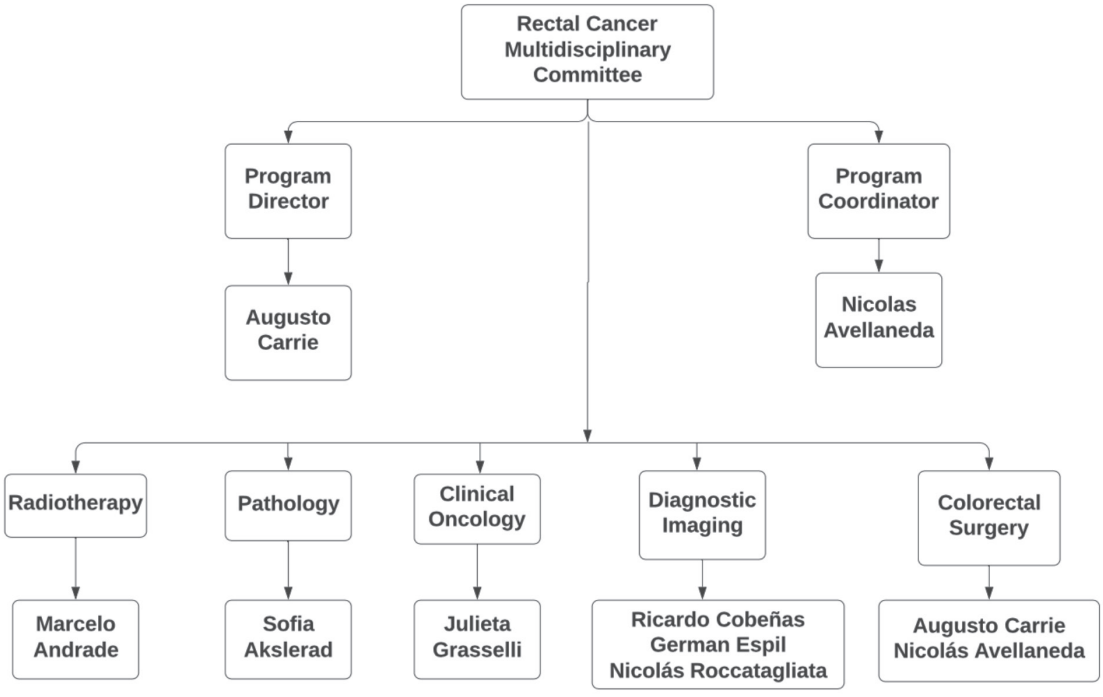

Figure 1. Structure of the rectal cancer committee

Pathologists (CAP)",[4] and photographs of the surgical specimens must be recorded.

Summarizing the CAP standards, a correct evaluation should include the anatomical location of the specimen, evaluation of the mesorectum, depth of invasion and margins. At the microscopic level, it is essential to establish the histological type, the grade and the presence of lymphatic embolism or tumor implants in the specimen. Lymph nodes affected must also be assessed.

Regarding the evaluation of the mesorectum after a total or partial excision, the classification proposed by Nagtegaal et al.[5] is used, which establishes three categories according to the quality of the mesorectum: incomplete; partially complete; or complete.

The circumferential margin of resection is measured from the maximum depth of the tumor to the margin of resection.[6]

To stratify the histological grade of the tumor, the CAP establishes four histological grades, from 1 to 4 (1 well differentiated and 4 undifferentiated).

Finally, in patients who have previously undergone neoadjuvant treatment for rectal cancer, the modified Ryan score[7] is the parameter used to confirm the degree of response to therapy, and establishes four levels or grades, which must be measured according to the tumor (and not in the lymph nodes).

Tumors should be staged according to the classification of the "American Joint Committee on Cancer".[8]

Clinical Oncology

Rectal cancer treatment has been revolutionized after the advent of neoadjuvant therapy for patients with locally advanced rectal tumors and those with lower rectal tumors, allowing strategies aimed to organ preservation in the latter group.[9-11]

The guidelines of the "National Comprehensive Cancer Network (NCCN)"[12] are used to choose the appropriate treatment for each patient presented to the committee. It should be noted that this program, having been founded in the United States, the NCCN guidelines are used to accredit it as a specialized rectal cancer center.

The regimen used for neoadjuvant therapy combines RT (to be discussed in the corresponding section) with oral capecitabine (825 mg/m^2 twice daily during RT days) or 5-fluoracil (225 mg/m^2 per day) in patients who cannot receive capecitabine.

MDT RECTAL CANCER

Date: Name: Age: Operation:
Phone: Date:
H.C: Surgeon: Oncologist: Type of surgery:
Familial history of cancer: Approach:
Location: Recurrence (Yes/No): Stoma:
Diagnosis date: Post-Operative complications:
Colonoscopy date and report: Staging (TNM):
Pathology report (outside/CEMIC): Specimen photo (Yes/No):
CEA and CA 19-9 pre tx:
MRI Staging (first): Recommendation:
Sphincter involved (first): Neoadyuvance:
CRM Involved (first): Adjuvance:
Distance from anal verge (first): Palliative treatment:
CT for systemic staging (first):
MRI for liver (first):
PET Scan (First):
Previous treatment:

Neoadyuvant Treatment (Yes/No):
Chemotherapy:
Radiotherapy:
End date:
Adverse events:

Re staging date and time after finishing neo-adyuvant therapy:
CEA and CA 19-9 pre tx:
MRI Staging:
Sphincter involved:
CRM Involved:
Distance from anal verge:
CT for systemic staging:
MRI for liver:
PET Scan:
Type of cancer (histology):

Figure 2. Patient clinical file presented to a multidisciplinary committee (adaptation of the file used by the Cleveland Clinic, Florida, United States)

At present, a neoadjuvant treatment scheme different from the conventional one has been proposed, called "Total Neoadjuvant Therapy",[13,14] which aims to carry out the complete chemotherapy treatment scheme prior to surgery, and within the committee we are carrying out currently the first experiences with this new line of treatment.

Finally, postoperative chemotherapy is indicated for patients who have undergone surgery for advanced tumors and have not received previous treatment, and for those categorized after the postoperative study of the specimen as high-risk stage II or III, according to the classification of the patient by AJCC. These patients receive a regimen based on fluopyrimidines, with or without oxaliplatin.

Diagnostic Imaging

Imaging studies play a fundamental role, since they will directly affect the staging of the tumor and, therefore, the choice of the corresponding treatment.

For all this, the program requires that at least 90% of diagnostic studies be reported by a specialist who is accredited as part of the multidisciplinary team.

Both the imaging protocol and standardized report templates are based on the Society for Abdominal Radiology guidelines[15-17].

Staging

The guidelines established by the AJCC classification[8] are followed for staging patients.

The location and relationship (distance) with the external anal margin, the sphincter/anorectal junction complex, and the anterior peritoneal reflex are evaluated. Morphology, dimensions in the three planes and characteristics of the signal (mucinous component) are also detailed.

Regarding the T- variable, the T2-weighted images are evaluated, determining the involvement of the different layers of the rectal wall (mucosa, submucosa and muscularis propria) and its extramural extension measured in millimeters, as well as its relationship with neighboring organs and structures (sphincter complex in the case of tumors of the lower rectum).

For extramural vascular invasion, the classification established by Gina Brown[18] is taken into consideration.

In relation to variable N, the size and location of the lymph nodes are determined, as well as the characteristics of their margins, signal and morphology. The presence of mesorectal tumor deposits is also taken into account.

Finally, the mesorectal fascia is considered free when a distance greater than or equal to 1 mm is seen from the tumor, lymph nodes, or satellite deposits.

Re-staging

When analyzing the images of patients who have already received treatment, a comparative evaluation of the characteristics of the primary tumor is made in relation to its behavior in diffusion sequence and the signal changes it presents in TSE T2 sequences linked to a fibrous and/or mucinous component, establishing the degree of tumor regression.

Lymphatic structures are examined, evaluating changes in the characteristics described in the baseline examination and determining the presence of new adenopathies. Finally, the Mandard score[19,20] is used to report the degree of response to neoadjuvant treatment.

Figure 3 shows a rectal adenocarcinoma magnetic resonance image (MRI) before and after finishing neoadyuvant treatment.

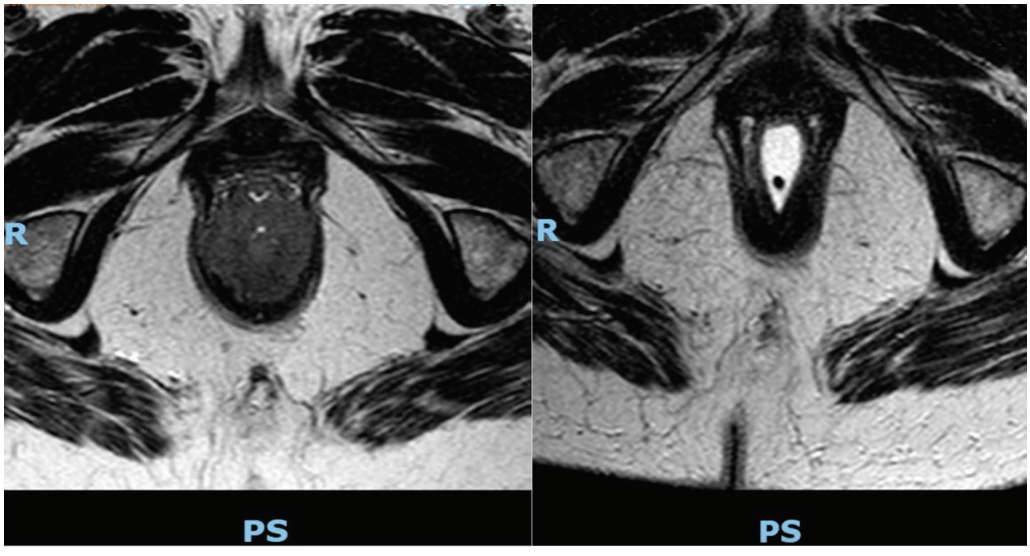

Figure 3. MRI staging of rectal adenocarcinoma pre-neoadjuvant therapy (left) and post-neoadjuvant therapy (right)
MRI: Magnetic resonance image

Colorectal Surgery

The specialization and centralization of rectal cancer surgery is directly associated with the morbidity and mortality of the procedures, and with the patients' prognosis.[21-24]

For this reason, in the department of surgery, these type of procedures are performed exclusively by a senior colorectal surgeon assisted by a junior colorectal surgeon. This represents a requirement to accredit the program: 80% of all procedures in patients with rectal cancer must be performed by a specialized surgeon who is also part of the committee.

The surgical protocol is carried out following the guidelines of the "Standardized Synoptic Operational Report Committee (OSTRiCh)[25,26]. This synoptic summary includes data such as type of anastomosis, level of mesenteric vessel ligation, pneumatic test (whether performed or not, type) and 95% of the protocols for patients operated on at the institution must have been written following this protocol.

The result of the surgery should be discussed in committee, comparing the intraoperative findings with the result of the pathology protocol.

Oncology Radiotherapy

RT has become one of the fundamental pillars of rectal cancer treatment. An adequate selection of patients associated with a correct implementation and execution of this therapy is essential for the approach to these patients.

RT, in its different techniques, fractionations and modalities, is intended to treat rectal cancer, due to its action in the microenvironment of the neoplastic cell, affecting its replication and survival due to different intra- and extra-cellular effects. Due to the duration of the therapy, treatments may be long-term (25-28 days) or short-term (5 days).

Different publications support the usefulness of RT in mid- and low-rectal cancer patients and its indications in different clinical scenarios.

To perform these treatments at our institution we have high-tech equipment and appliances that allow us to perform different techniques:

- Three-Dimensional Conformal Radiotherapy;
- Intensity Modulated Radiation Therapy;
- Volumetric intensity modulated radiation therapy by VMAT arches;
- Image Guided Radiation Therapy;
- Body Stereotactic Radiosurgery.

The effectiveness of these treatments and the minimization of side effects are closely linked to the technology used, which is why we use a linear accelerator that allows complex treatments to be carried out with the highest radiation dose adjustment and maximum protection of the organs that adjoin the areas to be treated. This unit is a Varian Trilogy model that was the first linear accelerator to offer synchronized images. Its On-Board Imager® (OBI) kV imaging system provides various imaging modalities, including kV, MV, CBCT, and fluoroscopy. Clinicians obtain high-quality images of soft tissue, bone anatomy, or other markers for optimal patient positioning. In addition, OBI allows you to use radiographic, fluoroscopic, and CBCT modes to control the size, shape, and location of the target.

As a planning system, and using the systems and techniques described above, we can quickly and accurately plan the treatments, by reconstructing the patient in 3D using the planning computed tomography image and merge it with other imaging modalities such as positron emission tomography and MRI, managing to expand information for a better quality of treatment.

Statistical Analysis

The software Stata (Statistical data analysis), version 11.1, was used for the analyses (Statacorp, College Station, Texas, USA). Categorical variables are described as percentages whereas numerical variables are described as median and range.

Results

In a period of four months from the beginning of program activities, 15 patients were presented at a monthly multidisciplinary committee meeting with 87.5% of the program members present.

The main characteristics of the patients are summarized in Table 1.

Eleven patients with locally advanced rectal adenocarcinoma were presented in committee:

- Five patients with lower rectal tumors underwent surgery after finishing neoadjuvant treatment without a complete clinical response.
- One patient received conventional Miles surgery for a locally advanced rectal tumor at another hospital, and it was decided to undergo adjuvant chemo-radiotherapy.
- Two female patients presented after completing neoadjuvant treatment for tumors of the middle and lower rectum. Of these, one presented with a complete clinical response (with subsequent follow-up), while the other presented with progression at the systemic level (with subsequent systemic treatment).
- One patient was re-staged after neoadjuvant treatment, Miles laparoscopic surgery for adenocarcinoma with invasion of the anal sphincter complex and adjuvant treatment (with subsequent follow-up).

Table 1. Patient characteristics

Variable	Percentage
Median (range) age (years)	69 (44-86)
Female sex	47.06 (8/17)
Location	
Upper rectum	17.65 (3/17)
Medium rectum	17.64 (3/17)
Lower rectum	64.70 (11/17)
Histology	
Adenocarcinoma	94.11 (16/17)
Neuroendocrine tumor	5.89 (1/17)
Adenocarcinoma - stage	
Early tumor	18.75 (3/16)
Locally advanced tumor	68.75 (11/16)
Metastatic tumor	12.50 (2/16)
Neoadjuvant therapy	75 (12/16)
Complete clinical response	8.33 (1/12)
Surgical Treatment	76.47 (13/17)

- One patient was diagnosed with a locally advanced low rectal tumor with invasion of the sphincter complex (neoadjuvant).

- Eight weeks after ending neoadjuvant treatment, one female patient presented with a tumor of the lower rectum with an almost complete response (and the plan was to repeat the studies at 12 weeks).

Two female patients presented with metastatic disease at diagnosis:

- One patient underwent neoadjuvant therapy and subsequently underwent low anterior resection + single liver metastasectomy.

- One patient had multiple liver metastases at the time of presentation to the committee (and underwent subsequent chemotherapy).

Two patients with adenocarcinoma of the upper rectum and one patient with a neuroendocrine tumor were presented in committee without evidence of locally advanced disease or distant metastases and were planned for surgery.

All patients were duly registered, and the specimen photographs of those operated on were attached to the corresponding clinical record.

Discussion

The aim of this article is to present an initial experience of a newly formed multidisciplinary group treating patients with rectal cancer in a lower income country, following the guidelines of a North American program. However, it must be mentioned that the way patients are managed in low-income countries might be different from that of countries such as United States, and this aspect should be taken into consideration while assessing the feasibility of using NAPRC's standards.

To begin with, given that centralization of care is an issue in underdeveloped countries, the volume of patients who are treated in a center seeking for accreditation might be lower. Then, periodicity of meetings required within the standards should be modified according to this reality. Another problem that arises is the fact that the same patient can be operated in one institution while receiving neoadjuvant or adjuvant treatment in another institution. Even when a hospital has facilities to offer chemotherapy treatment, it may not have the equipment to perform radiotherapy. This is not the case in our institution, but it is a reality evident in any low-income country, and a possible modification of the program suggesting ways to perform multidisciplinary treatment of patients, including professionals from different institutions should be considered.

Lastly, lack of access to high-quality technology, especially when it comes to MRI and radiotherapy equipment, might be a concern.

However, we believe that the adoption of this program with the purpose of standardizing and favoring the multidisciplinary approach of patients with rectal cancer is feasible but would probably require adaptations in low-income countries. Nevertheless, this approach appears to be useful and may have a direct impact on improving the quality of the care, with consequent improvement in the results of the treatment and in the experience of the patient, during their treatment.

Conclusion

Current evidence demonstrates the importance of multidisciplinary management of patients with rectal neoplasms. Therefore we believe that the basic precepts of the NAPRC can be used in hospitals in developing countries to standardize and improve the care of these patients. Although formal accreditation is not available outside the United States, we do not rule out that in the future, and adapting the requirements to the reality of foreign hospitals, a similar program could be proposed to lay the foundations for multidisciplinary management programs of rectal tumors in hospitals in low-income countries.

Lastly and importantly, the impact of using these guidelines in terms of clinical and oncological results of patients with rectal cancer is yet to be evaluated and will require larger and longer-term studies.

Ethics

Ethics Committee Approval: This manuscript was performed following international guidelines for data protection, and all patients involved signed an informed consent to share their anonymized information for investigation purposes.

Informed Consent: All patients involved signed an informed consent to share their anonymized information for investigation purposes.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: N.L.A., S.A., J.G., M.A.I., R.C., G.E., N.R., A.C., Concept: N.L.A., S.A., D.F., R.C., N.R., A.C., Design: N.L.A., J.G., M.A.I., G.E., Data Collection or Processing: N.L.A., S.A., D.F., A.C., Analysis or Interpretation: N.L.A., J.G., M.A.I., D.F., R.C., G.E., N.R., A.C., Literature Search: N.L.A., S.A., D.F., R.C., N.R., A.C., Writing: N.L.A., S.A., J.G., M.A.I., R.C., G.E., A.C.

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RESEARCH ARTICLE

Laparoscopic Versus Open Complete Mesocolic Excision with Central Vascular Ligation for Right-sided Colon Cancer: Early Postoperative Outcomes

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ABSTRACT

Aim: To evaluate postoperative histopathological findings and short-term clinical outcomes of laparoscopic complete mesocolic excision (L-CME) versus open-complete mesocolic excision (O-CME) for right-sided colon cancers.

Method: A total of 36 eligible patients were included. Patients were divided into two main groups as L-CME (n=21) and O-CME (n=15). Demographic parameters, intraoperative findings, early postoperative outcomes and histopathological findings were compared between the groups.

Results: Age, sex, body mass index, American Society of Anesthesiology scores, comorbid diseases, neoadjuvant treatment, carcinoembryonic antigen level, and tumor locations were similar in L-CME and O-CME groups. tumor, node, and metastasis stage, mean proximal and distal surgical margin distances, and mean total retrieved lymph nodes (L-CME: 27.9 vs O-CME: 28.4; p=0.368) were similar between the groups. Duration of operation (L-CME: 171.9 vs O-CME: 164.7 minutes; p=0.287), estimated blood loss (L-CME: 130 vs O-CME: 143.3 mL; p=0.508), length of hospital stay (L-CME: 8.6 vs O-CME: 11.5 days; p=0.936), intraoperative complication rates, postoperative non-surgical complication rates (L-CME: 4.8% vs O-CME: 20.0%; p=0.214), postoperative mortality rates (L-CME: 0.0% vs O-CME: 13.3%; p=0.085), and re-operation rates (L-CME: 4.8% vs O-CME: 6.7%; p=0.806) were also similar between the groups. First flatus time was shorter (L-CME: 2.5 vs O-CME: 2.9 days; p=0.038), postoperative surgical complication rate was less (L-CME: 14.3% vs O-CME: 53.7%; p=0.008), overall postoperative 30-day complication rates were less (L-CME: 14.3% vs O-CME: 60.0%; p=0.004), and the severity of complications were less (p=0.016) in L-CME group.

Conclusion: L-CME is technically feasible and safe for right colon cancers. It appears to be non-inferior to O-CME in terms of harvested lymph nodes and it provides faster postoperative recovery.

Keywords: Laparoscopic right hemicolectomy, complete mesocolic excision, central vascular ligation, D3 lymph node dissection, right colon cancer

Introduction

Colorectal cancer (CRC) is the third most common cancer and the second leading cause of cancer death worldwide, according to the 2020 data of the World Health Organization.[1] Surgical approaches still represent the mainstay of potentially curative treatments for CRC. Complete mesocolic excision (CME) with central vascular ligation (CVL) was first proposed as open surgery by Hohenberger et al.[2] The key feature of this approach is the mobilization of the colon within the avascular embryological planes between the retroperitoneal and mesocolic fascia and the ligation of the supplying arteries at their origin. In this way, the collection of lymph nodes along the entire length of the main vessels is ensured. As a result, en-bloc and complete resection of the mesocolon and draining lymph nodes is achieved.[2] Surgery performed according to the principles of surgical oncology affects long-term outcomes, while minimal invasive approaches is key for better postoperative short-term outcomes.[3] Thanks to recent technological developments and increasing experience with minimally invasive colorectal surgery, laparoscopic CME with CVL can be performed safely today.

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Laparoscopic approaches are associated with improved postoperative recovery and decreased morbidity compared with open approaches for CRCs. Although the duration of operation is longer, laparoscopic colorectal resections provide reduced postoperative complications, decreased intraoperative blood loss and length of hospital stay. Furthermore, a laparoscopic approach has similar rates of dissected total lymph nodes, disease free survival, overall survival and recurrence as open colorectal resections. As a result, laparoscopy is considered the gold standard surgical approach, having better short-term and comparable long-term outcomes compared to open surgery in CRCs.[4-7] However, considering the vascular anatomical variety, laparoscopic right hemicolectomy with CME is considered more challenging in relation to the higher technical complexity than conventional open surgery.[5,8,9] Therefore, the expected advantages of minimally invasive surgery in right hemicolectomies may not be achieved in inexperienced hands.

According to the results of published studies, focusing on the short-term clinical outcomes and the survival benefits of CME for right-sided colon cancers, this technique provides a significant decrease in local recurrence and improvements in cancer related 5-year survival. However, it seems to expose patients to a higher risk of surgical complications.[2,10] As a result, the indication for this procedure is still controversial. Based on these considerations, we present our early-period clinical outcomes and histopathological results of laparoscopic right hemicolectomy with CME in comparison with open surgery to evaluate the feasibility and the safety of the laparoscopic procedures for right-sided colon cancers.

Materials and Methods

Patient Selection and Study Overview

This is a single-center, prospectively collected, and retrospectively analyzed study from Fırat University Medical Faculty Hospital, Surgical Oncology Unit, enrolling all consecutive patients who underwent laparoscopic and open colon resections for right-sided colon cancer between April 2019 and April 2021. All the patients were histologically confirmed adenocarcinoma by preoperative colonoscopy with biopsies. To evaluate the extent of the disease, oral and intravenous, contrast-enhanced, thoraco-abdomino-pelvic computed tomography were examined for all patients. Positron emission tomography examinations were also used, if required. After clinical staging, all the patients were treated according to the National Comprehensive Cancer Network guidelines.

Right-sided colon carcinoma was defined as adenocarcinoma of any of the cecum, the ascending colon, the hepatic flexure, and the first-third of the transverse colon. In our department, CME with CVL has been implemented as the standard surgical approach for colon cancers since early 2018. Inclusion criteria were: aged 18 years and older; Eastern Cooperative Oncology Group (ECOG) score of 0 (asymptomatic) or 1 (symptomatic but completely ambulatory); and American Society of Anesthesiology (ASA) score 1-3. Exclusion criteria were: history of previous colectomy; history of other malignant diseases; emergency surgery due to complications caused by colon cancer such as bleeding, obstruction or perforation; and ECOG score of 2 or more; presence of metastasis to one or more distant sites or organs or peritoneal metastasis (M1+); and cases with simultaneous cholecystectomy or partial/total organ resections for invasion or metastasis. Out of 65 patients, 36 patients fulfilled the study criteria and were included for further analysis. The patients were categorized into two main groups according to the surgical procedure performed as open-complete mesocolic excision (O-CME) and laparoscopic-complete mesocolic excision (L-CME). In addition, patients were divided into subgroups according to the surgery performed for different tumor locations as right hemicolectomy or extended right hemicolectomy. The flow chart of patient enrollment is shown in Figure 1.

Data Collection Process

Demographic parameters, preoperative laboratory tests, intra-operative findings, post-operative short-term clinical outcomes and histopathological data were recorded. Gender, age, comorbid diseases, body mass index (BMI) (kg/m^2), ASA scores, and history of neoadjuvant chemotherapy or radiotherapy were recorded. Surgical procedures (laparoscopic/open surgery and right hemicolectomy/extended right hemicolectomy), duration of operation (minutes), estimated intraoperative blood loss (mL), length of hospital stay (days), first flatus time (days), intraoperative complications, postoperative 30-day complications and mortality rates, repeat surgery, tumor location and histological type (classic/mucinous), morphological differentiation grade (well, moderate or poor), tumor size (cm), proximal and distal surgical margin (cm), number of dissected lymph nodes, number of metastatic lymph nodes and the pathologic stage were also recorded.

The greatest tumor dimension was recorded for tumor size. Surgical margin status was grouped as R0 (no cancer cells seen microscopically), R1 (cancer cells present microscopically) and R2 (presence of macroscopic residual tumor), according to the American Joint Committee on Cancer's (AJCC) 8th edition guidelines.[11] Tumor staging was also categorized according to AJCC 8th edition. Estimated blood loss was measured by suction volumes and number

of gauzes used during surgery. Intraoperative complications were classified as vascular or organ injuries. Postoperative 30-day complications were classified as surgical and systemic (non-surgical) complications and were graded according to the modified Clavien-Dindo Classification (CDC) system (Table 1)[12]. Minor complications were defined as CDC grades 1 and 2, and major complications were defined as CDC grades 3-5.

Preparation for Surgery and Surgical Procedures

The patients received antibiotic prophylaxis orally with ciprofloxacin and metronidazole and low-weight-molecular-heparin was administered the day before surgery. Intravenous cephalosporin was given 30 minutes prior to skin incision. No mechanical bowel preparation was used routinely.

All the patients with right-sided colon cancers included in the study were operated by the same specialized surgical team. Right hemicolectomy was performed for tumors located at the cecum and the ascending colon, and extended right hemicolectomy was performed for tumors of the hepatic flexure and transverse colon. The planning of open or laparoscopic surgery preference was made randomly for all patients considering with the availability of technical materials. Laparoscopic procedures were performed using four working ports including an infraumbilical optic port in both right and extended right hemicolectomies. In O-CME cases, the intra-abdominal space was entered with a partial upper and lower midline incision. An electronic scalpel was used for mobilization and dissection in laparoscopic and open procedures. In L-CME cases medial-to-lateral approach and in O-CME cases lateral-to-medial approach was preferred for the mesocolon dissection along the mesenteric axis. The ileocolic vessels were transected at their origin. After exposing the mesocolic interface, a wide separation was achieved between the right colon and retroperitoneal

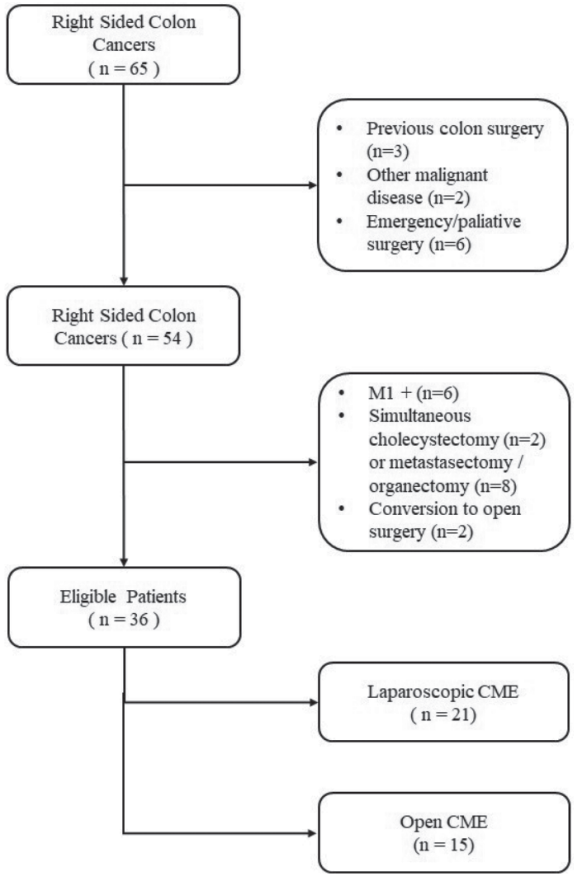

Figure 1. Flow chart illustrating patient enrolment
CME: Complete mesocolic excision

Table 1. Comparison of patient characteristics

	O-CME, (n=15)	L-CME, (n=21)	p
Age (years)	68.9±13.9	61.5±11.0	0.138
Gender			
Female	6 (40.0)	15 (71.4)	0.059
Male	9 (60.0)	6 (28.6)	
BMI (kg/m^2)	28.3±3.4	27.3±3.9	0.268
ASA score			
II	5 (33.3)	12 (57.1)	0.158
III	10 (66.7)	9 (42.9)	
Presence of comorbidities			
None	3 (20.0)	10 (47.6)	0.194
1	5 (33.3)	6 (28.6)	
≥2	7 (46.7)	5 (23.8)	
Previous abdominal surgery	1 (6.7)	8 (38.1)	**0.032**
Neoadjuvant treatment	1 (6.7)	1 (4.8)	0.806
Preoperative CEA level	14.2±21.0	5.8±11.9	0.119
Tumor location			
Cecum	6 (40.0)	7 (33.3)	0.353
Ascending colon	6 (40.0)	5 (23.8)	
Hepatic flexure	3 (20.0)	6 (28.6)	
Transverse colon	0 (0.0)	3 (14.3)	
Extent of resection			
Right colectomy	12 (80.0)	12 (57.1)	0.151
Extended right colectomy	3 (20.0)	9 (42.9)	

Data presented as mean ± standard deviation, minimum-maximum range or number (%). Bold values indicate statistical significance p<0.05. BMI: Body mass index, ASA: American Society of Anesthesiologists, O-CME: Open-complete mesocolic excision, L-CME: Laparoscopic-complete mesocolic excision, CEA: Carcinoembryonic antigen

structures in the inferior part, and the pancreatic head and the transverse colon in the superior part. Then, dissection proceeded along the superior mesenteric vein, exposing the gastro-pancreato-colic (GPC) trunk of Henle. The middle colic artery was then identified at its origin at the superior mesenteric artery and was transected at the root of its right colic branch in case of right hemicolectomy, or at the origin of middle colic artery in case of extended right hemicolectomy. Lymph nodes located along the right gastroepiploic arch were also included in the lymphatic dissection field in extended right hemicolectomy cases. The omentum, transverse mesocolon and transverse colon were divided, taking into account that at least macroscopically 10 cm distal surgical margin especially in hepatic flexure or transvers colon located cancers. Then, the terminal ileum was divided at approximately 15-20 cm from the ileocecal junction, considering the area feeding by the ileocolic vessels and to achieve negative surgical margin in cecal-located cancers.

A Pfannenstiel incision was made for specimen retraction in L-CME cases. Intracorporeal anastomosis was performed with endo-stapler as isoperistaltic side-to-side and staple openings were closed in double layers with 3/0 PDS sutures. For O-CME cases, end-to-side ileo-transversostomy was the preferred technique with double layers suturing with 3/0 PDS sutures. A drainage catheter was placed in the operation field routinely. The oncological principles and surgical technique of CME with CVL are shown in Figure 2.

Postoperative Patient Care and Clinical Outcomes

Nasogastric tube was removed at the end of the surgery. The postoperative vital signs of the patients and the characteristics and amounts of the contents of the drainage catheter were recorded daily. Low-molecular-weight-heparin was administered postoperatively at 8 hours after surgery. A fluid content diet was started routinely on the third postoperative day and a solid diet was started on the fourth day for all patients. Patients were discharged when adequate oral food intake and regular defecation habit was established, and if there was no need for fluid infusion, dependence for mobilization, and analgesic medication. After discharge, all patients underwent weekly outpatient follow-up and clinical findings were recorded for the first month post-operatively.

Statistical Analysis

All analyses were performed using IBM SPSS Statistics, version 22.0 (IBM Inc., Armonk, NY, USA) and RStudio. Categorical variables are expressed as numbers and percentages, whereas continuous variables are summarized as median and minimum-maximum. According to the distribution of variables, χ^2 or Fisher's exact tests were used to compare differences in discrete or categorical variables.

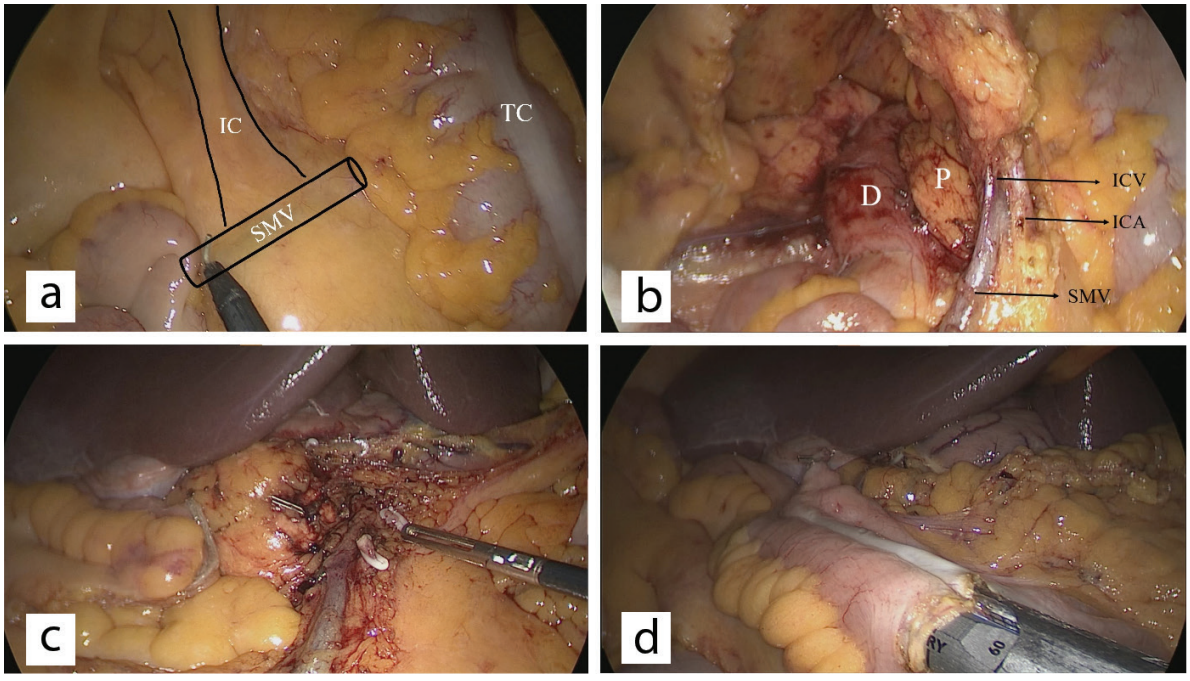

Figure 2. Lymphatic and vascular disection during laparoscopic extended right hemicolectomy with complete mesocolic excision. a) Illustration of superior mesenteric vein and ileocolic vessel bundle. b) Ileocolic artery and ileocolic vein at their origin from the SMV and SMA. c) Final vascular ligatures d) Intracorporeal isoperistaltic side-to-side ileo-transverse anastomosis

TC: Transverse colon, IC: Ileocolic vessels, SMV: Superior mesenteric vein, D: Duodenum, P: Pancreas, ICV: Ileocolic vein, ICA: Ileocolic artery, SMA: Superior mesenteric artery

The Mann-Whitney U test was used for comparison of continuous variables between the groups. The statistical significance level for all tests was considered to be $p<0.05$.

Results

The mean age of the patients was 64.6 years. Of the patients 21 (58.3%) were female and 15 (41.7%) were male. Mean BMI of the patients was 27.7 kg/m^2. Tumor locations were 13 (36.1%) in the cecum, 11 (30.6%) in the ascending colon, 9 (25.0%) in the hepatic flexure and 3 (8.3%) in the first third of the transverse colon. Right hemicolectomy was performed in 24 (66.7%) cases and extended right hemicolectomy was performed in 12 (33.3%) cases. O-CME was performed in 15 (41.7%) while L-CME was performed in 21 (58.3%) of the patients included in the study.

There was no intraoperative transfusion requirement in any of the patients. One case was converted to open surgery due to technical problems. Duodenum injury occurred in one case, liver injury in one case, and GPC trunk injury in two cases in whom the laparoscopic procedure was performed. Organ and vascular injuries in these cases were managed with laparoscopic approaches without conversion to open surgery. In open procedures, there were two cases of vascular injury, one was to the right colic vein and the other was to GPC trunk. There was one case that required re-operation due to anastomotic leakage after a laparoscopic procedure. Another case was re-operated due to evisceration after open procedure. Two of the patients who underwent open surgery died postoperatively due to non-surgical complications. One was due to pneumonic septicemia and the other was due to cardiac complications. The surgical margin assessments were R0 in all cases.

Comparison of demographic parameters, clinical findings and surgical procedures of the groups are shown in Table 1. There was no difference between the groups in terms of mean age, gender distribution, mean BMI, ASA score, comorbid diseases, neoadjuvant therapy history, preoperative carcinoembryonic antigen levels, and tumor locations. However, previous abdominal surgery history was higher in the L-CME group (38.1% vs 6.7; p=0.032). Although the number of patients who underwent extended right hemicolectomy procedure was higher in the L-CME group, the difference was not significant (42.9% vs 20.0%; p=0.151).

When the post-surgical histopathological findings were compared between the groups, there were no significant differences between the histological type, tumor diameter, depth of tumor invasion (pT), lymph node involvement (pN), distant organ metastasis status, pathologic tumor, node, and metastasis stage, tumoral morphological differentiation grade, total number of retrieved lymph nodes (O-CME: 28.4±9.1 vs L-CME: 27.9±15.5; p=0.368), number of metastatic retrieved lymph nodes, and proximal and distal margin distance (Table 2).

Duration of operation, estimated blood loss, and length of stay were similar between the groups. There were no differences in intraoperative or postoperative non-surgical complication rates between the groups. Additionally, mortality and re-operation rates were similar. However, mean first flatus time was earlier (L-CME: 2.5±0.7 days vs O-CME: 2.9±0.8 days; p=0.038), postoperative surgery related complications (L-CME: 14.3% vs O-CME: 60%; p=0.008), overall postoperative 30 days complications (L-CME: 14.3% vs O-CME: 53.7%; p=0.004) and minor complication rate (L-CME: 9.5% vs O-CME: 33.3%) and major complication rate (L-CME: 4.8% vs O-CME: 26.1%) were significantly (p=0.016) lower in the L-CME group (Table 3).

Discussion

Our results showed that duration of operation, estimated blood loss, intraoperative complications, postoperative surgical and non-surgical complication rates, mortality and re-operation rates were similar between L-CME and O-CME procedures for right sided colon cancers. Moreover, the mean number of retrieved lymph node counts and surgical margin distances were also similar. However, the onset of intestinal motility time was shorter, overall postoperative short-term complication rates and the severity of complications was lower in the L-CME group. The length of hospital stay was relatively shorter in the L-CME group but the difference was not significant.

CME is the dissection in the embryological plane to create an intact envelope of the mesocolic fascia, which results in the removal of a specimen that contains the draining lymphatics and the lymph nodes which may have potential metastasis by central ligation of the supplying vessels. This procedure provides improved specimen quality and better oncological results.[4-7] However, it has not gained widespread preference for right-sided colon cancers due to both technical and oncological concerns. In systemic reviews, L-CME for right colon cancers is associated with higher intraoperative complications and postoperative morbidity, particularly due to the complex and highly heterogeneous vascular anatomy of the right colon as compared with the left colon and rectum. It was shown that, the surgical challenges involve potential vascular injuries to the GPC colic trunk, middle colic vein, and superior mesenteric vein, due to the necessity of the ligation of the vessels at their roots and excessive traction. Moreover, the survival benefits of L-CME are still controversial for right colon cancers.[13]

Table 2. Comparison of histopathological findings

	O-CME, (n=15)	L-CME, (n=21)	p
Histological type			
Adenocarcinoma	14 (93.3)	14 (66.7)	0.058
Mucinous adenocarcinoma	1 (6.7)	7 (33.3)	
Tumor size (cm)	6.3±3.3	5.8±2.1	0.949
Depth of tumor invasion			
pTis	0 (0.0)	1 (4.8)	0.396
pT1	1 (6.7)	0 (0.0)	
pT2	0 (0.0)	1 (4.8)	
pT3	11 (73.3)	18 (85.7)	
pT4a	2 (13.3)	1 (4.8)	
pT4b	1 (6.7)	0 (0.0)	
Lymph node involvement			
pN0	3 (20.0)	11 (52.4)	0.198
pN1a	4 (26.7)	6 (28.6)	
pN1b	4 (26.7)	3 (14.3)	
pN1c	2 (13.3)	0 (0.0)	
pN2a	1 (6.7)	1 (4.8)	
pN2b	1 (6.7)	0 (0.0)	
Metastasis			
M0	12 (80.0)	19 (90.5)	0.370
M1a	3 (20.0)	2 (9.5)	
pTNM stage*			
0	0 (0.0)	1 (4.8)	0.538
I	1 (6.7)	1 (4.8)	
II	2 (13.3)	7 (33.3)	
III	9 (60.0)	10 (47.6)	
IV	3 (20.0)	2 (9.5)	
Morphological differentiation			
Well	2 (13.3)	2 (9.5)	0.773
Moderate	9 (60.0)	15 (71.4)	
Poor	4 (26.7)	4 (19.0)	
Total retrieved lymph nodes	28.4±9.1 (11-44)	27.9±15.5 (10-64)	0.368
Metastatic retrieved lymph nodes	1.7±2.1	0.9±1.2	0.185
Proximal margin distance (cm)	13.2±6.2	15.1±8.9	0.653
Distal margin distance (cm)	13.5±6.0	14.9±7.9	0.898

Data presented as mean ± standard deviation, minimum-maximum range or number (%). *For pTNM stage the 8th edition of AJCC TNM staging system was used. O-CME: Open-complete mesocolic excision, L-CME: Laparoscopic-complete mesocolic excision, AJCC: American Joint Committee on Cancer, pTNM: Pathologic tumor, node, and metastasis

Table 3. Comparison of intraoperative findings and early-period clinical outcomes

	O-CME, (n=15)	L-CME, (n=21)	p
Duration of operation (minutes)	164.7±33.9	171.9±22.4	0.287
Estimated blood loss (mL)	143.3±84.0	130±93.5	0.508
First flatus (days)	2.9±0.8	2.5±0.7	**0.038**
Length of stay (days)	11.5±9.8	8.6±3.2	0.936
Intraoperative complications			
Vascular injury	2 (13.3)	2 (9.5)	0.454
Organ injury	0 (0.0)	2 (9.5)	
Total	2 (13.3)	4 (19)	
Postoperative Surgical complications			
None	7 (46.7)	18 (85.7)	**0.008**
Anastomotic leakage	0 (0.0)	1 (4.8)	
Prolonged ileus	1 (6.7)	1 (4.8)	
Bleeding	0 (0.0)	0 (0.0)	
Abscess	2 (13.3)	0 (0.0)	
Wound infection	2 (13.3)	1 (4.8)	
Evisceration	1 (6.7)	0 (0.0)	
Total	8 (53.7)	3 (14.3)	
Postoperative non-surgical complications			
None	12 (80.0)	20 (95.2)	0.214
Respiratory	1 (6.7)	1 (4.8)	
Cardiovascular	2 (13.3)	0 (0.0)	
Total	3 (20.0)	1 (4.8)	
Overall postoperative complications (30 days)	9 (60.0)	4 (14.3)	**0.004**
Clavien-Dindo score			
Minor (I-II)	5 (33.3)	2 (9.5)	**0.016**
Major (III-V)	4 (26.1)	1 (4.8)	
Mortality	2 (13.3)	0 (0.0)	0.085
Re-operation	1 (6.7)	1 (4.8)	0.806

Data presented as mean ± standard deviation, minimum-maximum range or number (%). Bold values indicate statistical significance p<0.05. O-CME: Open-complete mesocolic excision, L-CME: Laparoscopic-complete mesocolic excision

The mainstay of potential curative treatment of right colon cancers is still surgery and it also plays a critical role in staging. A minimum 12 lymph nodes should be evaluated for an accurate staging, according to guidelines.[14] Also, the increased number of harvested lymph nodes is associated with improved local control and overall survival.[15,16] L-CME may have the potential to harvest more lymph nodes than in O-CME. However, it was shown in recent systematic reviews that the difference in number of harvested lymph nodes is not significant between laparoscopic and open CME procedures, as in the results of the present study. Nevertheless, L-CME appears superior to O-CME in terms of overall 3- and 5-year recurrence rates. These results were underlined in the same review as the only measurable parameter of oncological adequacy of L-CME and it was recommended that there is a need for further confirmation of the results by enlarging the cohort of studies.[17]

Minimal invasive approaches should offer better short-term outcomes but they require advanced experience in laparoscopic techniques because this type of procedure is harder to perform and requires a longer learning curve. In recent studies, it was shown that laparoscopic approaches provide lower overall complications, lower estimated blood loss, lower wound infection rates, and shorter hospital stay, especially in high volume centers.[17,18] In this study, in line with the published data, postoperative overall complication rates and the severity of the complications were lower in laparoscopic procedures. In contrast, there were no differences in duration of operation and estimated blood loss between laparoscopic and open surgeries. Notably, length of hospital stay and postoperative mortality rates were lower in L-CME, but these were not significantly so when compared to open procedures at our center. Another issue to consider is earlier intestinal motility after postoperative surgery, which is associated with faster postoperative recovery. In systemic reviews, it was demonstrated that postoperative first flatus time was similar in open and laparoscopic procedures.[18] In contrast, our results demonstrated that first flatus time was significantly shorter in the L-CME group, which should be considered as an additional benefit of the laparoscopic approach.

Laparoscopy may fail and require conversion to open surgery due to uncontrollable vascular injury, organ injury or adhesions related to previous surgery. There are some consequences for the patients that should be considered in case of conversion to open surgery, such as longer duration of operation, complicated and longer hospital stay or postoperative intensive care unit requirement.[19] In our laparoscopic case series, two patients were converted to open surgery because of unexpected widespread adhesions, although neither patient developed any negative consequences of conversion.

Study Limitations

The current study has several limitations. The potency of this study is limited due to its retrospective nature and limited number of patients. Furthermore, overall survival and local recurrence rates could not be evaluated due to the short follow-up period of the patients. Further high volume, prospective, randomized, controlled studies are needed to increase the quantity of the data and quality of the evidence.

Conclusion

This study demonstrated that L-CME is not inferior to O-CME for right-sided colon cancers in terms of feasibility of the surgical principles and lymphatic dissection width. Moreover, earlier onset of intestinal motility, lower surgery related postoperative complications and overall postoperative short-term complication rates, and lower severity of complications make laparoscopic procedures safe and favorable for right colon cancers.

Ethics

Ethics Committee Approval: This study was approved by the Fırat University Faculty of Medicine Ethics Committee (approval number: 86033, date: 09.11.2021) and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice.

Informed Consent: Informed consent from each patient was waived due to the retrospective nature of the study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.L., E.A., M.Y., Y.S.İ., Concept: A.L., E.A., Y.S.İ., Design: A.L., E.A., V.K., İ.K., Data Collection or Processing: V.K., İ.K., E.K., A.A., Analysis or Interpretation: V.K., İ.K., E.K., A.A., Literature Search: A.L., A.A., M.Y., Writing: A.L., M.Y., Y.S.İ., E.K.

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

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CASE REPORT

Fistula-in-ano Extending to the Thigh

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ABSTRACT

Fistula-in-ano tracts are usually short and open around the perianal region but it is uncommon to have tracts opening beyond this region. Hence, complex fistulas remain a therapeutic challenge and are often linked to recurrence. We describe herein an unusual fistula-in-ano extending to the mid-thigh posteriorly which was managed successfully by fistulectomy and secondary healing.

Keywords: Complex fistula, fistula-in-ano, fistulectomy, thigh

Introduction

A fistula is an abnormal communication between two epithelialized surfaces.[1]

A typical fistula-in-ano usually consists of a tract with an internal opening in the anus or rectum and external opening(s) on the perianal skin.[2] It is quite uncommon for the fistula to extend beyond the perineal region.[3] The majority of anorectal fistulas are cryptoglandular in origin. Other causes include trauma, Crohn's disease, malignancy, radiation, or unusual infections (tuberculosis, actinomycosis, and chlamydia).[2]

Diagnosing a fistula-in-ano can be complicated in the presence of unusual clinical symptoms.[4] This happens because the fistula can traverse unusual courses (complicated tracts, curved tracts, multiple openings or those which take a circuitous path to the anal canal) causing diagnostic dilemma.[2,4] The need for treatment is because of persistence as spontaneous healing rarely occurs. This may be due to epithelialization of the fistula tract, which prevents the fistula from closing.[2]

Due to different etiologies and risk factors, the approach to management varies.[1] It is necessary to have a patient-oriented approach depending on the complexity. This report highlights a rare presentation of a common condition - fistula-in-ano and its management.

Case Report

A 42-year-old man from Dar-es-Salaam presented to us with three weeks history of pus discharge from the right thigh, which was gradual in onset. The pus was foul smelling, blood stained and approximately 10 cc per day. It was associated with swelling of the thigh and sharp pain around the anal orifice, which was severe on defecation. The pain was relieved by use of over-the-counter analgesics. The condition was also associated with intermittent low-grade fever. The patient reported the condition to have persisted for more than eight years during which he has undergone multiple surgeries on the same limb at various centers but without success.

In 2012, the patient underwent incision and drainage at a regional level hospital during which 1500 milliliters of pus were drained. Thereafter, the patient attended and was scheduled for surgery on multiple occasions at a tertiary level hospital; however, the surgery never took place.

There was no history of abdominal pain, distention, constipation or diarrhea. There was no history of inflammatory bowel diseases or diabetes. He was hypertensive on regular

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oral therapy. The patient did not consume alcohol or use tobacco. He was not addicted to any prescription or recreational drug. There was no significant personal or family history of chronic diseases. The patient denied being on any medication.

On general examination, the patient was overweight. Examination of abdominal systems was unremarkable, apart from digital rectal exam which was tender and hence not completed. Local examination revealed a scar from previous incision and drainage in the posterior proximal half of the right thigh, which was oozing seropurulent effluent. There was another scar in the distal third of the thigh posteromedially. No overt sinus or fistula was noted around the perianal region (Figure 1).

The patient underwent colonoscopy, which was unremarkable, and magnetic resonance fistulogram which revealed a long track arising from the posterior external anal sphincter at six o'clock tracking into the right gluteus muscle and inferiorly to the posterior fascia between the semitendinosus and biceps femoris muscles. The track exited through the subcutaneous tissue of the right proximal posterior thigh. The fistula track measured approximately twenty-two centimeters in length. Features suggested fistula-in-ano with the external opening at the right proximal posterior thigh (Figure 2).

Hematological and biochemical parameters of the patient were within normal range. Serology for hepatitis A, B and C, and human immunodeficiency virus were negative.

The patient was scheduled for surgery and the following were encountered intra-operatively: methylene blue dye injected at the discharging site in the posterior mid-thigh was noted to come from the anal os about 20 mm from the anal verge. A 5 Fr ureteric catheter was inserted but was unsuccessful beyond three centimeters. A hemostat forceps was inserted and a longitudinal incision made from the caudal to the cranial end where the fistula formed a T-shaped tract; one leading towards the anal canal at two centimeters from the anal verge and another laterally about three centimeters (Figure 3).

The fistula was determined to be a Park's type 1 inter-sphincteric fistula. The fistula tract was opened and subsequently excised, measuring thirty-two centimeters. The wound was laid open, washed thoroughly, and packed with paraffin dressing (Figure 4).

The excised tract was sent for histology and revealed fragments of fibrous wall infiltrated by mononuclear inflammatory cells and foreign body giant cells, suggestive of chronic granulomatous inflammation (Figure 5).

Post-operatively, the patient improved significantly with the wound healing rapidly by secondary intention (Figure 6). He underwent daily dressings, followed by sitz-bath and was kept on oral flucloxacillin 500 milligram per oral three times a day for fourteen days, and thereafter dressing only was performed.

Discussion

Fistula-in-ano is one of the oldest pathologies in mankind and was first analyzed by Hippocrates.[5] The incidence rates for men and women are 12.3 and 5.6 in 100,000 population respectively, though it's difficult to make accurate estimations due to the embarrassing symptoms.[6,7] Fistula-in-ano is a chronic manifestation of an acute perirectal abscess that when ruptured or drained, forms an epithelialized tract connecting the abscess in the anus or rectum to the perineal skin. It is estimated that 40% of peri-anal abscesses will be accompanied or preceded by fistula.[2,7] These patients often present with recurrent malodorous perianal discharge, pruritus, recurrent abscesses and perianal pain.[2] From the

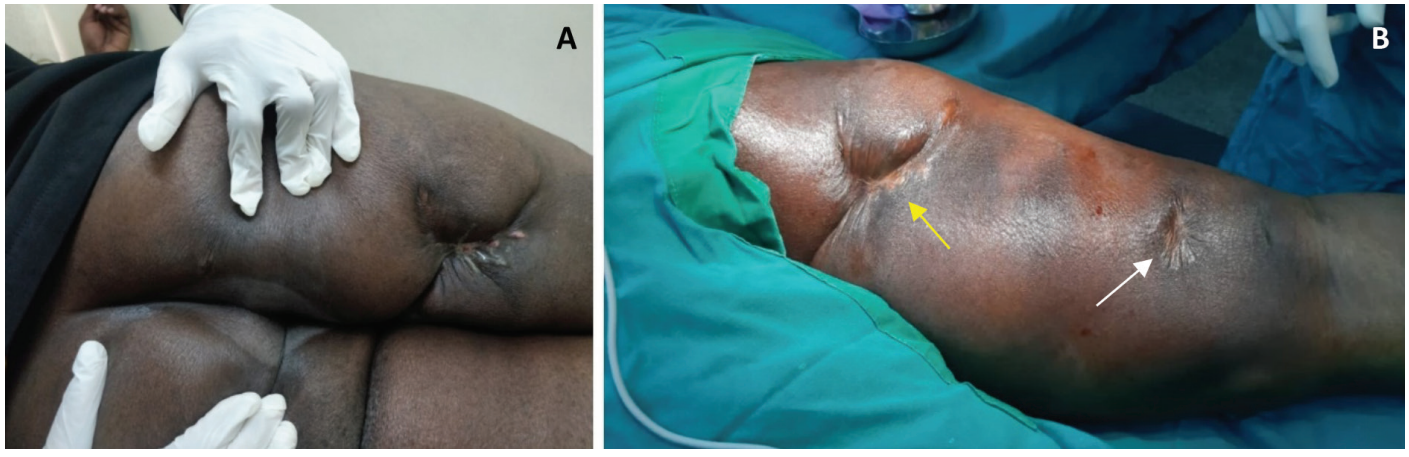

Figure 1. Pre-operative images showing scars from previous incision and drainage (A). Site of active pus discharge where the contrast was injected (yellow arrow), a healed scar with a tract underneath that was not stained by contrast and as such, did not appear on the magnetic resonance imaging (white arrow) (B)

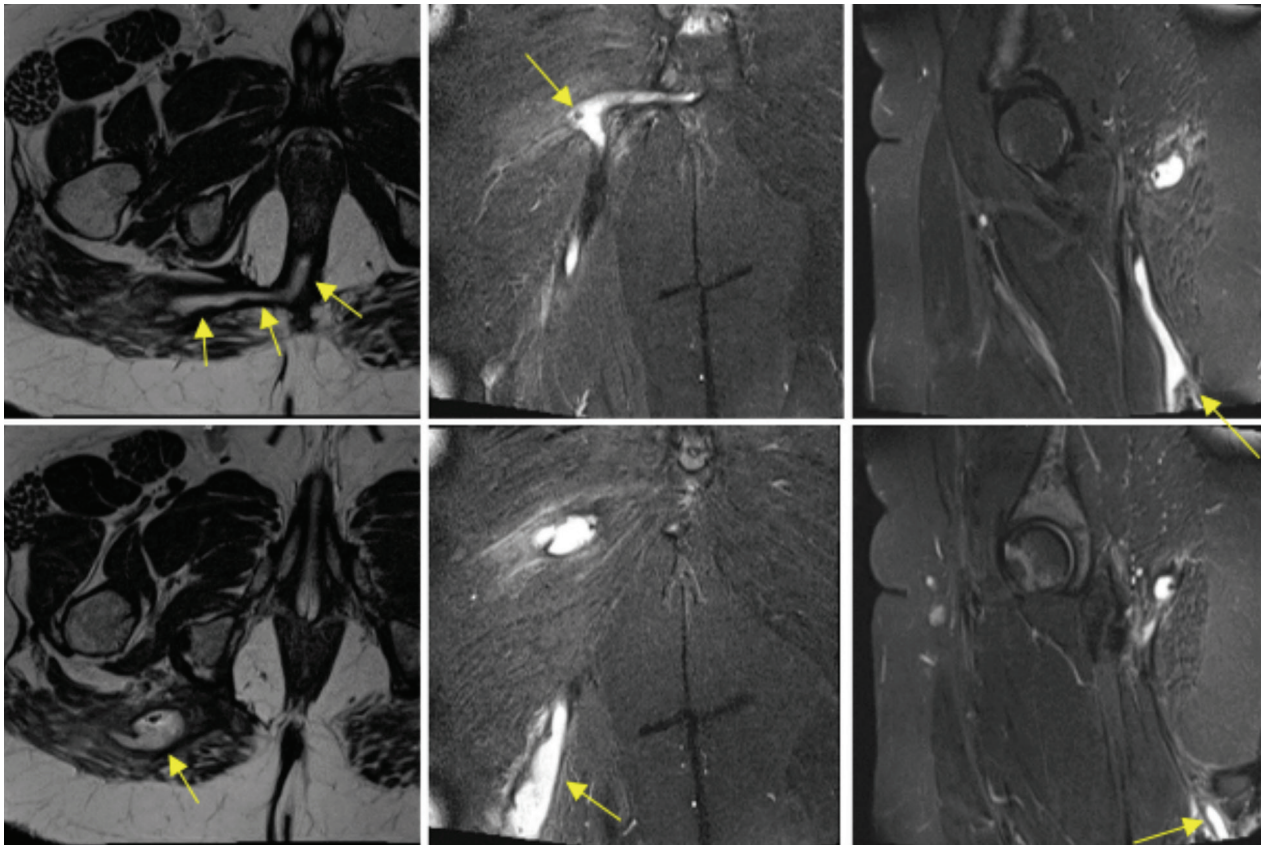

Figure 2. Magnetic resonance fistulogram (T2 axial, T2 fat sat coronal and sagittal images) shows a long sinus track arising from the posterior external anal sphincter at 6 o'clock, tracking into the right gluteus muscle and inferiorly to the posterior thigh muscle fascia (between the semitendinosus and biceps femoris muscles). The sinus track exits through the subcutaneous tissue of the right proximal posterior thigh. The tract measured approximately 22 centimeters in length

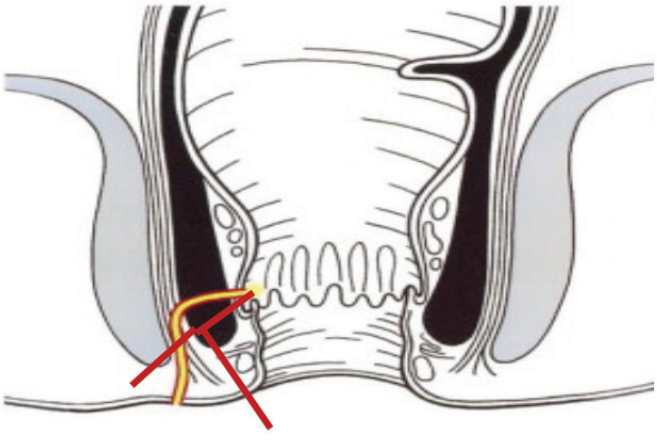

Figure 3. T-shaped tract (red); one leading towards the anal canal and the other ending as a blind sinus laterally (image courtesy: science direct)

index case, it is evident that the patient also presented with continuous recurrent discharge from the external site (thigh), and had a history of low-grade fevers, intermittent perianal pain and underwent several incisions and drainage of the abscess.

A typical fistula tract has an internal (primary) opening in the rectum or anus and an external (secondary) opening on the perirectal skin.[2] In contrast, our patient presented with an unusually long tract with the secondary opening on the thigh, causing a diagnostic dilemma similar to that reported by Ertekin et al.[2] in their case report. The most common taxonomy used to classify fistula-in-ano is the Park's classification; inter-sphincteric (70%), trans-sphincteric, supra-sphincteric, and extra-sphincteric (1%). This is described by the course of the fistula tract in relation to the anal sphincters. The commonest type also has the best prognosis as also revealed by rapid recovery of our patient.

The majority of fistulas are cryptoglandular in origin, as in the index case. Other causes can be trauma, Crohn's disease, malignancy, radiation, infections such as tuberculosis or chlamydia, but all of these risk factors were ruled out in our case.[6,8]

Management of fistula-in-ano varies according to its complexity. For complex fistula, a Seton suture is advocated to allow drainage of sepsis and a mature tract of fibrous tissue to develop. After this, definitive fistula treatment is considered from the various options described

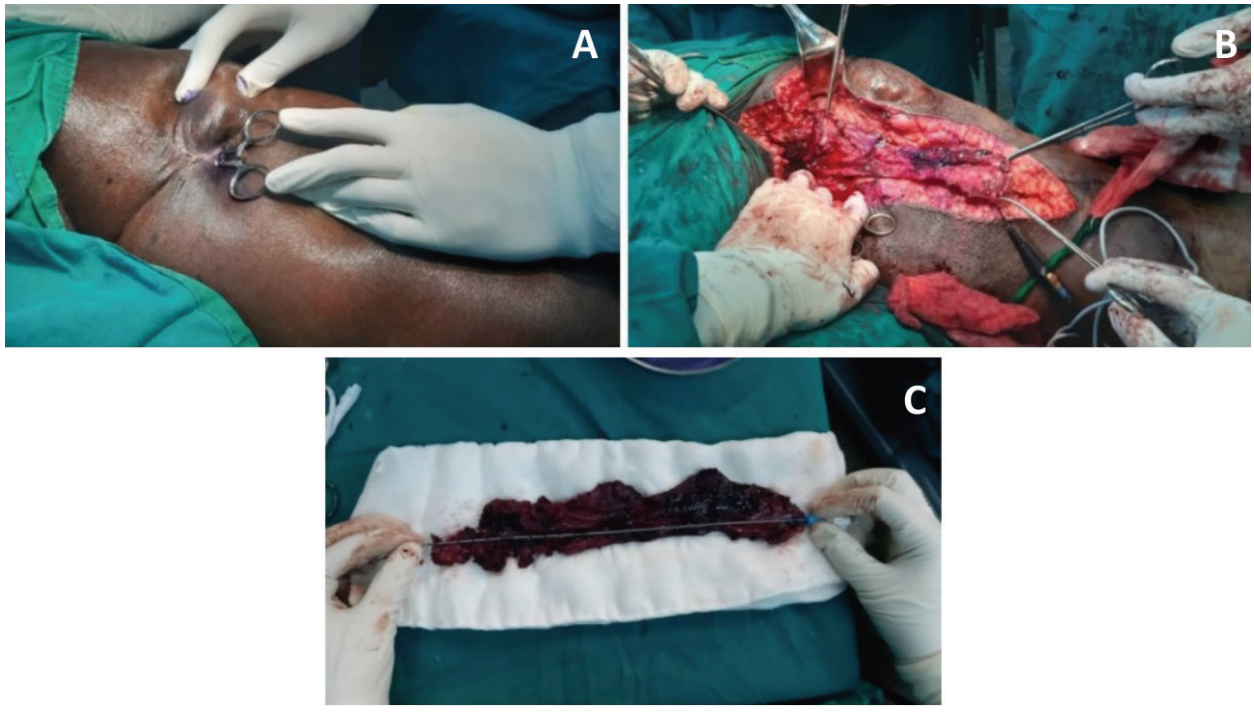

Figure 4. Intraoperative images showing a straight hemostat inserted in the distal os of the fistula (A), the entire length of the tract laid open (B), and the length of the excised tract tissue (C)

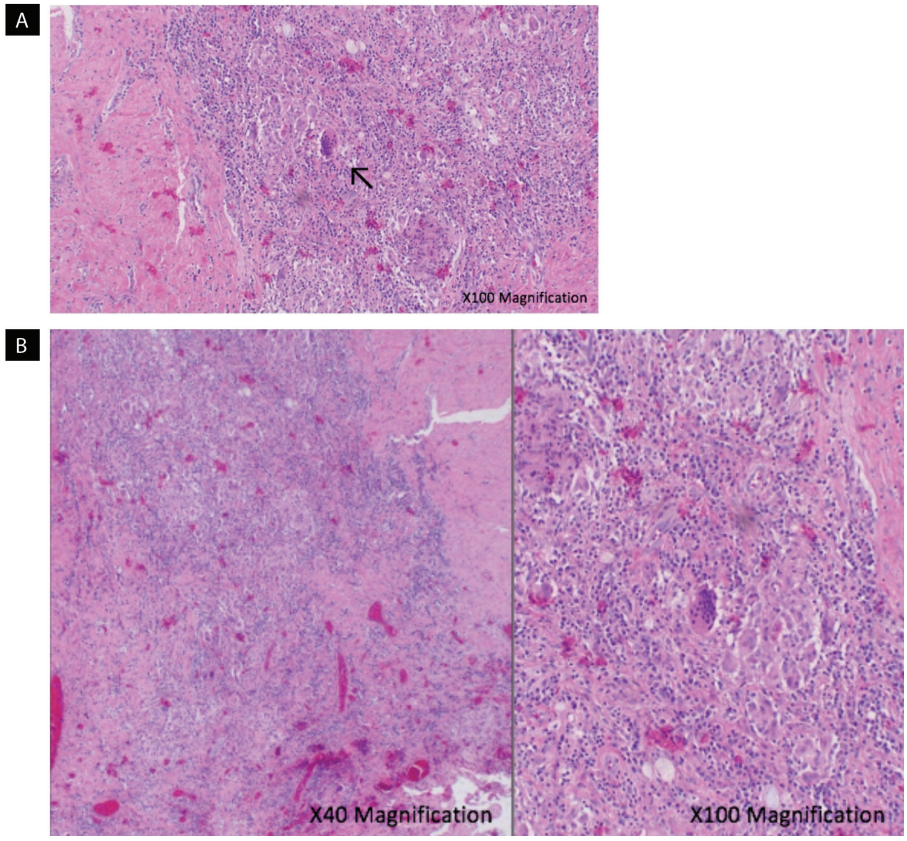

Figure 5. (A) hematoxylin and eosin-stained sections showing focus of dense chronic inflammation consisting of foreign body giant cell indicated by an arrow (↖) raising concern about granulomatous inflammation. (B) A and B sections from the wall of the cystic lesion of the fistula, exhibiting extensive mononuclear inflammatory cells with some giant cells, again raising concern about granulomatous inflammatory process (conventional hematoxylin and eosin staining)

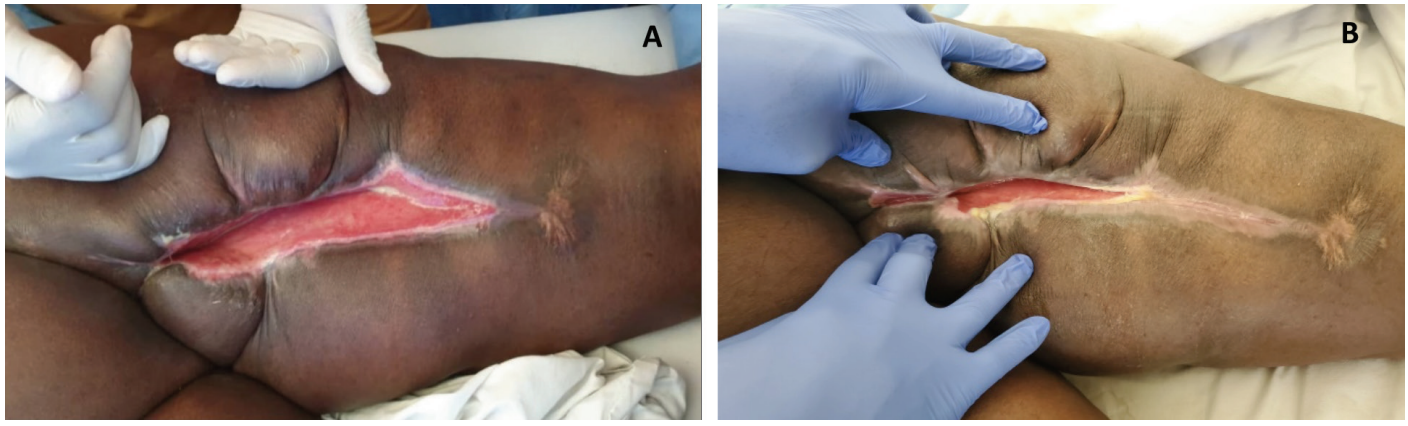

Figure 6. Healing by secondary intention six weeks (A) and eighteen weeks (B) post operation

in the literature.[7] Keogh and Smart[7] proposed the use of radiofrequency ablation after the use of Seton suture to minimize tissue destruction, as seen in fistulectomy and fistulotomy, and this would be less painful. Due to high recurrence rates and complications from various surgical techniques, other authors are still attempting to identify optimal methods, such as the use of Ayurvedic *Kshara Sutra* with a reported success rate of 96.6%.[9] Fistulotomy has been described to be superior to fistulectomy. However, we opted for the latter since the fistula tract had significant fibrosis, which would hinder healing by granulation and could potentially be a source of retained infection due to accumulation of debris. We wanted to leave fresh tissues free from chronic inflammation to promote healing. Moreover, the history of recurrence favored fistulectomy over fistulotomy. The risk of incontinence from fistulectomy was assessed to be negligible as more than two thirds of the fibers were spared. Other surgical modalities include advancement flaps with or without fibrin sealant.[2] Ertekin et al.[2] opted for a more conservative approach using 1% silver nitrate solution to irrigate the fistula but with a long healing period.

Conclusion

Fistula-in-ano is not a completely innocuous disease and patients should be counseled to seek prompt and adequate treatment. Although various treatment modalities have been described, no treatment is considered optimal.

Acknowledgements: We are grateful to the patient for letting us use his case to report this rare condition.

Ethics

Informed Consent: Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.T., A.D.M., K.C., Concept: M.T., J.L., K.C., Design: M.T., J.L., Data Collection or Processing: M.T., A.M., A.D.M., Analysis or Interpretation: M.T., P.A., A.S., Literature Search: M.T., J.L., A.M., Writing: M.T., J.L., A.M.

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

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CASE REPORT

A Rare Cause of Massive Lower Gastrointestinal Hemorrhage in a Young Patient: Colonic Angiodysplasia

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ABSTRACT

Angiodysplasia (AD), also called colonic arteriovenous malformation or colonic angioma, is the most common vascular anomaly of the gastrointestinal tract. It is the second most common cause of lower gastrointestinal (GI) bleeding after diverticulosis in the elderly population (usually over 60 years). In this study, we present a young patient with colonic AD, which caused massive lower GI bleeding. A 46-year-old male patient was referred to our hospital, which was a full-fledged hospital, due to lower GI bleeding. There was no abnormality on physical examination or blood tests, with the exception of hemoglobin, which was only 8 mg/dL. The patient underwent selective visceral angiography due to sub-optimal colonoscopic examination because of bleeding within the lumen. In super-selective ileo-colic arteriogram, bleeding was detected in the ileocecal artery tract and an "arterial embolization + microcoil" procedure was performed. However, the patient underwent emergency operation due to continuing hemorrhage and deterioration of his general medical condition. "Laparoscopic right hemicolectomy + end-to-side ileotransversostomy" was performed in the operation. Histopathological examination of the excised specimen revealed colonic AD. Selective angiography is a very important diagnostic method to identify the location of the lesion, especially in massive GI bleeding in young patients, and it should not be forgotten that AD maybe the etiology. Superselective angiography and embolization are feasible methods for treatment, but it should be kept in mind that surgery may also be necessary in cases of repeated or unstoppable bleeding.

Keywords: Angiodysplasia, colon, massive bleeding, lower gastrointestinal tract

Introduction

Angiodysplasia (AD), also called colonic arteriovenous malformation or colonic angioma, is the most common vascular anomaly of the gastrointestinal tract (GIT).[1,2] The term "angiodysplasia" was first used by Galdabini in 1974. It is the second most common cause of lower gastrointestinal (GI) bleeding in the elderly (usually over 60 years of age) after diverticulosis. It is rare in young people.[2,3] Small bowel ADs constitute 30-40% of GI bleeds of unknown origin. ADs in the large intestine are most commonly located in the cecum and right colon.[3] Bleeding due to AD can lead to massive lower GI bleeding at a rate of 15%. The diagnosis of AD can be made by colonoscopy, capsule endoscopy, angiography, computed tomography and endoscopic biopsy[4-6]. Angiography plays an important role in both the diagnosis and treatment of GI bleeding. Enlarged, distorted and thin-walled vessels are characteristic histopathological findings.[5] Conservative follow-up is the first choice treatment for AD. If bleeding continues, endoscopic methods, such as sclerotherapy, thermal coagulation and band ligation, can be used. Surgical treatment may be used in patients who do not respond to medical and endoscopic treatment.[3-5]

In this study, we present a young 46-year-old patient with colonic AD causing massive lower GI bleeding.

Case Report

A 46-year-old male patient was referred to our hospital due to lower GI bleeding. The patient stated that he had seen

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blood in his stool intermittently (1-2 times/month) for the previous six months and that he had been treated for hemorrhoids and anemia in the health institutions he had gone to. There was no change in the patient's bowel habit. He had no complaints, such as nausea, vomiting or fever. There was no history of bleeding disorder or malignancy in the patient's history and family history. The patient's physical examination was unremarkable.

There was copious amount of fresh blood mixed with stool on rectal examination. Colonoscopy could not be evaluated optimally because there was bleeding in the lumen, but pathologies including mass, hemorrhoids or fissures were not evident in the anal canal. At the time of admission, the patient's hemoglobin level was 8 mg/dL and upper GI endoscopy was normal. While the patient was being examined, massive lower GI bleeding developed. The patient's hemoglobin level was 4 mg/dL and a total of 15 units of fresh whole blood was given. The interventional radiology team in our hospital was alerted and emergency selective visceral angiography was planned for the patient. In the super-selective ileo-colic arteriogram, "bleeding was detected in the ileocecal artery trace (Figure 1)" and "arterial embolization + microcoil" procedure was performed (Figure 2). Selective vasopressin infusion was used for embolization. However, as the bleeding did not stop and the general condition of the patient deteriorated, the patient was taken to emergency surgery. The patient underwent a laparoscopic right hemicolectomy and end-to-side ileotrasversostomy. On histopathological examination of the excised specimen, enlarged vein clusters and proliferating venous vessels in the mucosa and submucosa, of approximately 2.5 cm, were seen in the ascending colon, and the patient was diagnosed as having "AD in the ascending colon" (Figure 3). The patient did not develop any complications in the postoperative period and was discharged on the eighth day. There was no evidence of bleeding in the patient who was followed up for about eight months after the procedure. The patient underwent screening colonoscopy at six months post-procedure, and the entire colon was evaluated as normal. Informed consent was obtained.

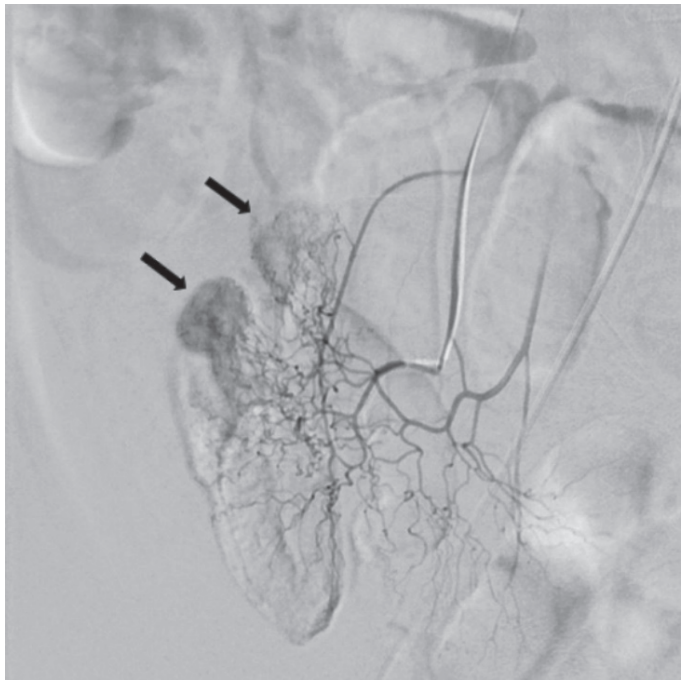

Figure 1. Active bleeding from the ileo-colic artery (superselective right ileo-colic arteriogram)

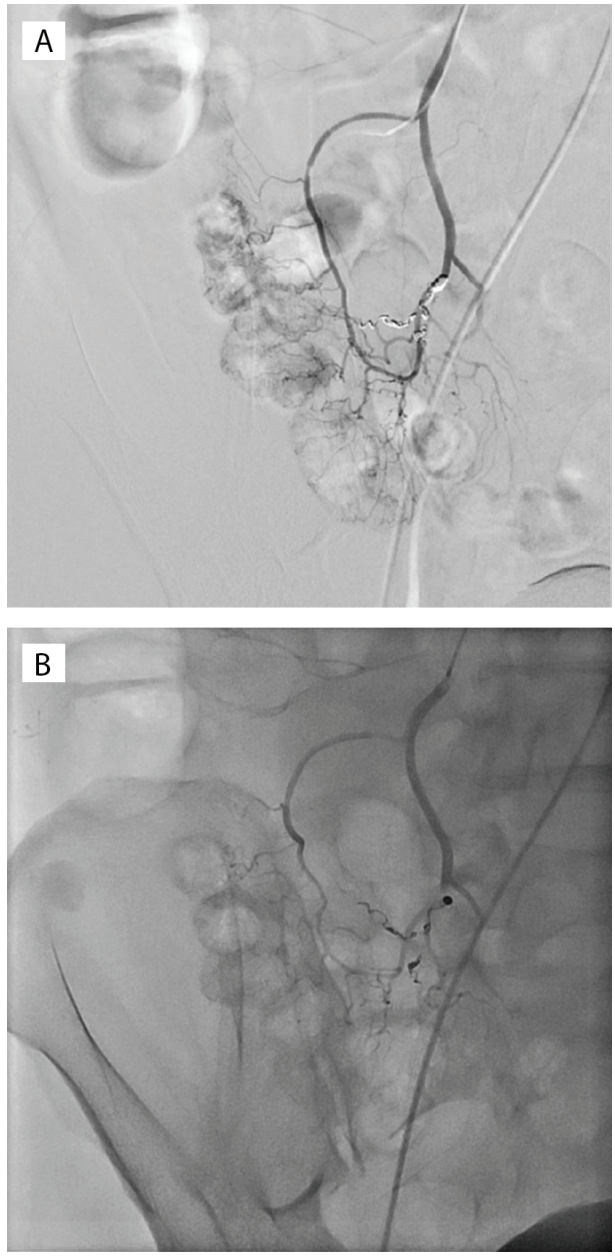

Figure 2. Embolization and microcoil occlusion of the bleeding artery in the superselective angiogram

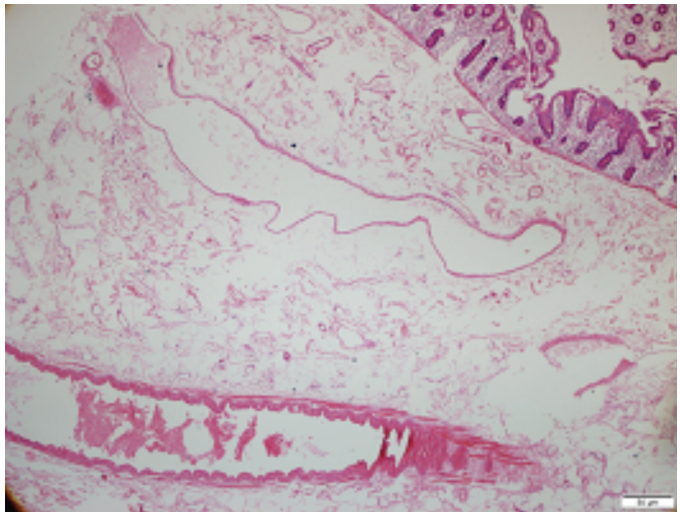

Figure 3. Angiodysplastic lesion in the submucosa of colon

Discussion

AD, which is one of the causes of lower GI bleeding, is a localized vascular anomaly in the cecum and right colon (77%),[1,2] and is especially seen in the elderly. In colonoscopic examination performed in healthy individuals over 50 years of age in the United States, the frequency of AD was found to be 0.8%.[3] In another study, AD was found incidentally at a rate of 2% with colonoscopy performed in people over the age of 65 without bleeding.[7] In the study of Tan et al.[8], AD was reported as the cause of GI bleeding in 19% of the patients. AD is most common between the ages of 60 and 80. It is seen equally in men and women[4]. Our patient was a 46-year-old male patient. Although most of the patients are asymptomatic, iron deficiency anemia may progress in the form of chronic or massive bleeding. The pathophysiology of AD is unknown.[3] Lesions are usually small (2-5 cm in diameter) and may be single or multiple. In our patient, the lesion was 2.5 cm in diameter and single. AD can be ubiquitous in the GIT, but it is most commonly located in the ascending colon and cecum (77%).[9] In our patient, AD was localized in the ascending colon.

The most important complication of AD is bleeding. Bleeding due to AD usually stops spontaneously, but the possibility of repeated bleeding is high.[9] In our patient, intermittent bleeding episodes were observed for about six months, and massive bleeding occurred during the last hospitalization.

The diagnosis of AD is made by colonoscopy. In hemorrhagic AD, bleeding can usually be controlled with sclerotherapy, electrocauterization or argon plasma coagulation during colonoscopy.[10] However, in cases where the bleeding site cannot be detected or the bleeding cannot be stopped during colonoscopy, selective angiography is a method that can be used to identify the bleeding site and to stop the bleeding. When the bleeding rate is more than 0.5 mL/min, the probability of detecting the bleeding area in angiography increases. After the location of the bleeding lesion is determined by angiography, bleeding may be stopped by embolization or microclip applications.[8,9] Tan et al.[8] reported that embolization and microclip combination was used in 9% of patients in their study. Othman et al.[9] reported that bleeding was stopped in all patients with superselective angiography and embolization. However, in our patient, although superselective angiography, embolization and microclip application were performed, the bleeding did not stop and the flow rate decreased. Due to the general condition of the patient, the procedure was not repeated.

The definitive treatment for ADs of the colon is surgical resection. Surgical intervention is accepted as the last option in the treatment of patients.[7-10] Tan et al.[8] reported that bleeding recurred after embolization in 22% of patients in their study and surgery was applied to these patients. Meyer et al.[11] reported that recurrent bleeding was not observed in 63% of the patients who underwent right hemicolectomy for AD during their mean follow-up of 3.6 years, while 37% had recurrent intestinal bleeding of varying degrees. We followed our patient for eight months and we did not detect any more signs of bleeding.

In conclusion, selective angiography is a very important diagnostic method for identifying the location of the lesion, especially in massive GI bleeding in young patients, and it should not be forgotten that AD may be the etiology. Superselective angiography and embolization are applicable methods for treatment, but it should be kept in mind that surgery may be necessary in recurrent or unstoppable bleeding.

Ethics

Informed Consent: It was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.K., V.Ç., Ö.B., Concept: E.K., Design: E.K., Data Collection or Processing: E.K., V.Ç., Analysis or Interpretation: E.K., F.C., N.E., Literature Search: E.K., F.C., S.K., Writing: E.K., N.E.

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

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

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CASE REPORT

Perianal Pilonidal Fistula

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ABSTRACT

Perianal pilonidal fistula can sometimes be mistaken as perianal fistula of cryptoglandular origin. Careful physical examination of the natal cleft and the anal canal is the mainstay of the correct diagnosis. The treatment of the disease is surgical. In this article, we report the management of a young male patient with perianal pilonidal fistula originating from the natal cleft.

Keywords: Perianal fistula, pilonidal disease, surgery

Introduction

Pilonidal disease is generally located in the natal cleft but its secondary tracts can sometimes have their opening in the perianal region. They have no connection with the anal canal. Pilonidal pits can be detected at the midline of the buttocks. Sometimes this may be confused with perianal fistula of cryptoglandular origin. Most of the time, careful physical examination under good lighting is enough for the correct differential diagnosis.

Case Report

A 22-year-old male patient was complaining about discomfort from his bottom for two years. He had also experienced purulent discharge from a hole near his anus from time to time. Physical examination in the lithotomy position revealed a fistula opening at the 7 o'clock position, 3 cm from the anus, and a midline pit orifice located in the natal cleft (Figure 1). After it was determined that there was no fistula connection with the anal canal, fistulectomy and primary suturing was performed under spinal anesthesia (Figure 2-4). He was discharged the next day and the wound healed without any complication in the subsequent three weeks. The patient provided written consent for publication.

Discussion

Pilonidal disease is a problem of the natal cleft in human beings. Secondary tracts of the disease can sometimes have their opening in the perianal area. Notaras observed that the direction of natal cleft sinus tracts usually extend in a cephalad direction (93%) while only 7% of cases progress caudally.[1] Contrary to the literature, we have experience of many cases of pilonidal disease with caudal extension around the anus (secondary perianal pilonidal disease), as in this case.

Primary perianal pilonidal disease invading the anal canal can also be encountered, but it is very rare. There are only a few cases reported in the literature.[2-4] The disease can be confused with a perianal fistula of cyrptoglandular origin. If the distinction cannot be made between pilonidal disease and a perianal fistula, magnetic resonance imaging would be helpful.[5,6] Correct diagnosis, and thus optimal management plan for the disease, must be established before surgery. Examination under anesthesia would also be useful for this purpose.

The treatment of secondary perianal pilonidal fistula with midline pits is surgical. Lay open or fistulectomy and primary suturing is the treatment of choice. Marsupialization can be performed as a less invasive technique.[7] Open

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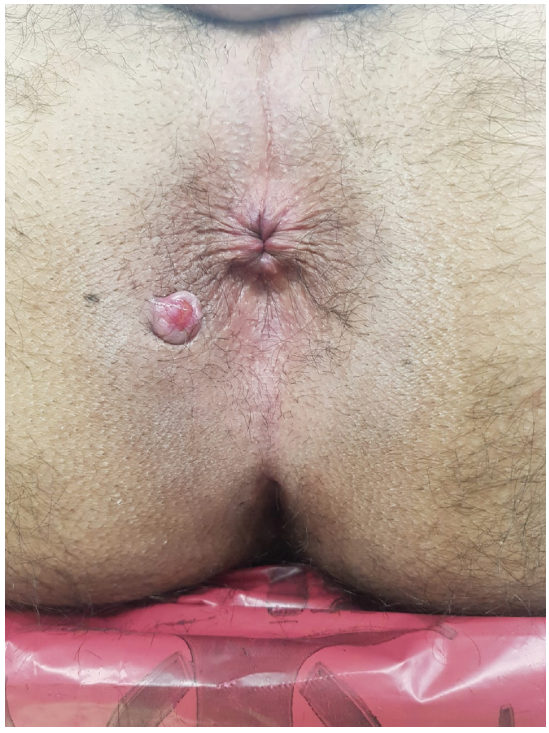

Figure 1. Perianal secondary orifice of pilonidal disease in the lithotomy position

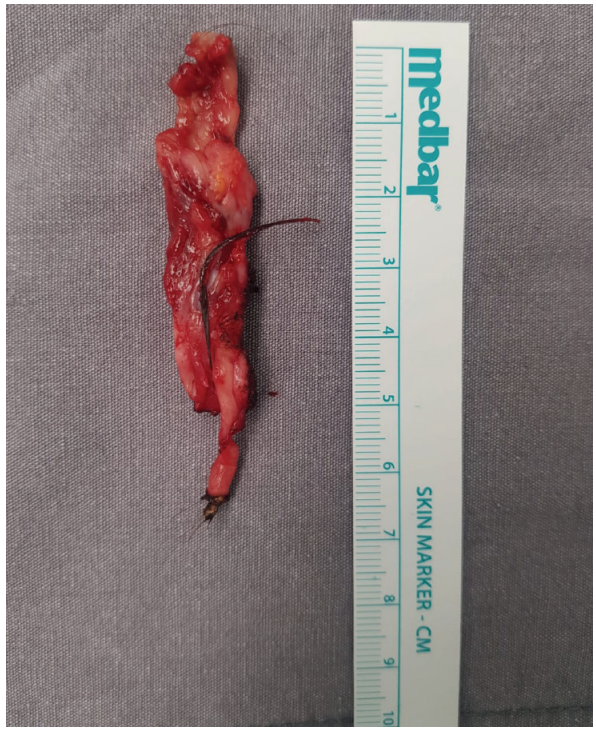

Figure 3. Fistulectomy tract with the hair bundle in it

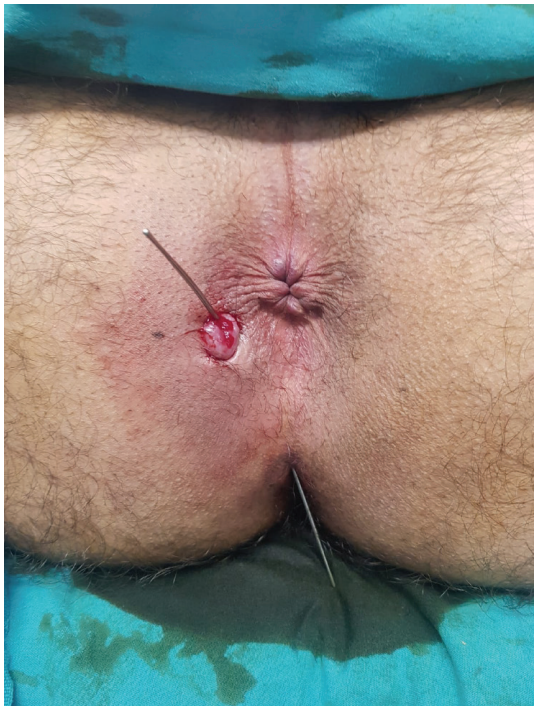

Figure 2. Fistula tract between the secondary pilonidal orifice and the midline pit is indicated with a stylet

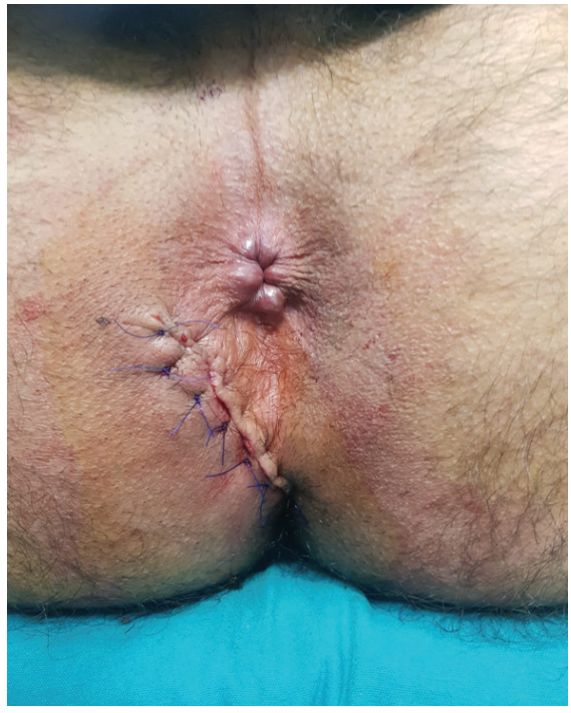

Figure 4. Primary suturing of the wound

excision or various flap techniques have also been used for treatment.[8,9] Invasive procedures are not suitable because of the proximity of the disease to the anal canal. Furthermore, wound breakdown after flap coverage of the defect can occur before complete wound healing has taken place, then subsequent wound infection and discharge may ensue. These complications may lead to high recurrence rates.[10] The authors believe that wide skin excision is not necessary since the skin is not involved with this condition. The simpler the treatment, the better the results!

Secondary perianal pilonidal disease is not a rare disease. Perianal fistula of cryptoglandular origin should be excluded in the differential diagnosis.

Ethics

Informed Consent: The patient provided written consent for publication.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: G.N., M.B., H.O.İ., Concept: G.N., M.B., Design: G.N., M.B., Data Collection or Processing: G.N., M.B., H.O.İ., Analysis or Interpretation: G.N., M.B., H.O.İ., Literature Search: G.N., M.B., H.O.İ., Writing: G.N., M.B.

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CASE REPORT

A Rare Cause of Acute Abdomen: Meckel's Diverticulitis Due to Meckel's Enteroliths

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ABSTRACT

Meckel's diverticulum is the most common congenital anomaly of the gastrointestinal tract. It is usually asymptomatic and detected incidentally. Stone formation in Meckel's diverticulum is extremely rare and less than half of them are radio-opaque. Diagnosis may be confused with acute appendicitis and gallstones. In this case, we present a rare cause of acute abdomen with Meckel's diverticulum complication. Ischemic Meckel's Diverticulitis due to Meckel Enterolitis can be considered among the differential diagnoses, especially in young patients with peritonitis.

Keywords: Diverticulitis, enterolith, meckel diverticulum

Introduction

Meckel's diverticulum is the most common congenital anomaly of the gastrointestinal system and is seen in 2-3% of the population.[1,2] It occurs as a result of incomplete obliteration of the omphalomesenteric canal. It is usually asymptomatic and is detected incidentally. Stone formation in the Meckel's diverticulum is extremely rare.[2,3] We present a patient who presented with acute abdomen due to Meckel's enterolith in our clinic.

Case Report

An 18-year-old male patient was admitted to the emergency department with complaints of widespread abdominal pain and nausea. On physical examination, there was widespread peritonitis with defense and rebound in all quadrants. In the laboratory analysis of the patient, white blood cell count was 19,900/mm^3 (lymphocyte 3.2%-neutrophil 93.1%), hemoglobin was 12.6 g/dL and C-reactive protein was 30.9 mg/dL. Since the patient had common acute abdomen findings, the emergency abdomino-pelvic computed tomography (CT) was "Abscess pouch between the small intestine segments and radiopaque fecalitis?" viewed. "Perforated appendicitis? is considered." and was reported by radiologist (Figure 1). An appearance compatible with Ischemic Meckel Diverticulitis associated with the midline small intestine was detected in the exploration performed in the patient, who was taken into emergency operation. The diverticulum was attached to the root of the small bowel mesentery and there were lymphadenopathies reaching 2 cm around it (Figure 2, 3). Considering the suspicion of a tumor in the Meckel's diverticulum, the patient underwent segmental small bowel resection including diverticulum and lymph nodes in the small bowel mesentery. In the intraoperative examination of the specimen, two enteroliths (1x1.5 cm and 1.7x1.1 cm) were found in the diverticulum (Figure 4). The patient was discharged on the sixth postoperative day without any complications. The patient's histopathology was reported as Meckel's diverticulitis and reactive lymph nodes which included perforation, abscess focus, ulcer and necrosis findings. Informed consent was obtained.

Discussion

Meckel's diverticulum is the most common congenital anomaly of the gastrointestinal system. The lifetime risk of being symptomatic was estimated to be 4-16%. Patients usually present with bleeding (especially in children), obstruction, intussusception, diverticulitis, and perforation.[2,4] In the data of the Mayo Clinic, the rate of enterolith (stone) seen in Meckel's diverticulum was reported

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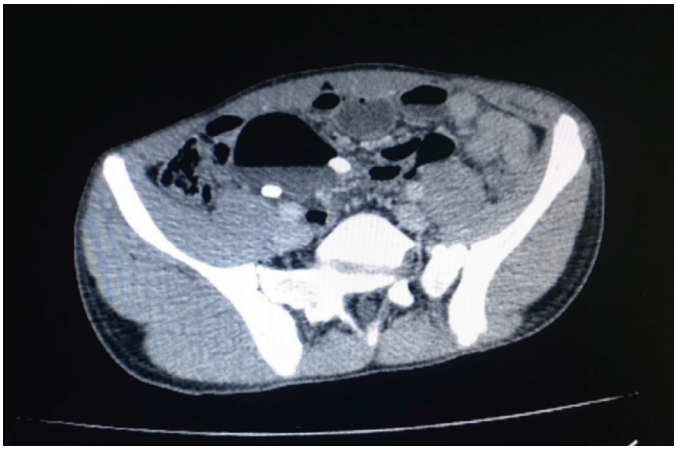

Figure 1. Computed tomograpy of patient

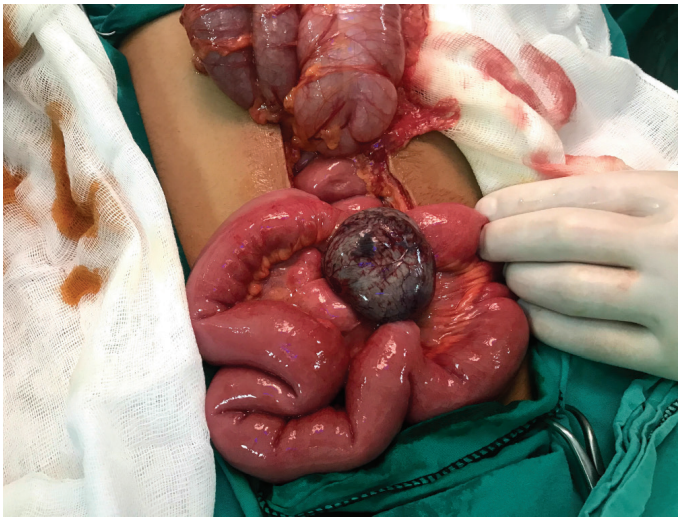

Figure 2. Ischemic diverticulitis with lymphadenopathies in the mesentery

as 6.1% in histopathological examination of the specimen in symptomatic patients.[5] Nevertheless, clinical presentations of complications caused by enteroliths are very rare and there are a limited number of case reports in the literature.

The pathogenesis of enterolith formation in Meckel's diverticulum is unknown. Decreased peristalsis and stasis in the diverticulum area are blamed. Since the neck of the Meckel diverticulum is generally wide, they are secondary enteroliths around the food residues trapped in the diverticulum. However, in our present case, primary enterolith with a narrow diverticulum neck and containing calcium phosphate was found.[6] Approximately one third of the enteroliths are radiopaque.[7] In our case, two enteroliths were seen in CT sections.

Meckel's diverticulum most commonly presents with obstruction in adult patients. The second most common presentation is diverticulitis. Diverticulitis usually develops as a result of obstruction of the narrow necked diverticulum

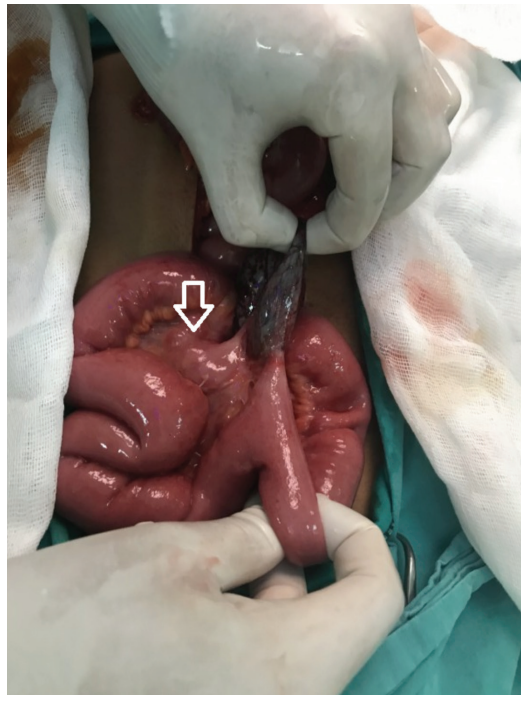

Figure 3. Lymphadenopathies in the mesentery are shown with arrow

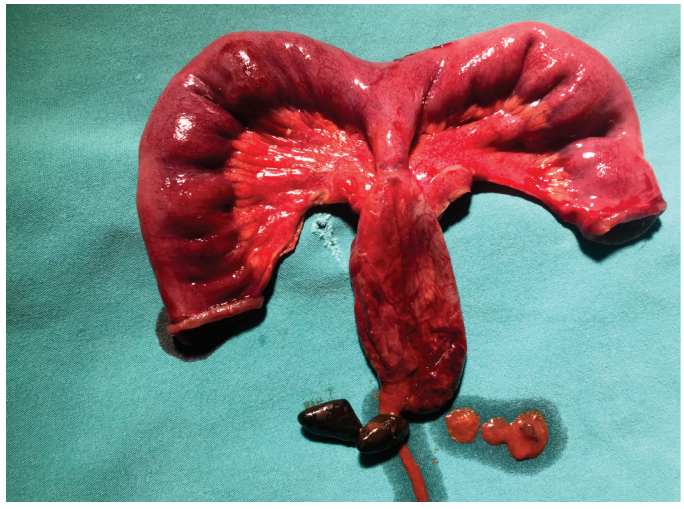

Figure 4. Excised specimen with two enteroliths

and gives the same clinical symptoms as acute appendicitis. Generally, the diagnosis is made during surgery in the patients who are being operated with a pre-diagnosis of acute appendicitis.[8] In our case, diverticulitis due to enterolith was detected in the patient who was operated with a pre-diagnosis of perforated acute appendicitis. The enteroliths found in our case caused ischemia of the diverticulum by closing the diverticulum neck, therefore inflammatory lymph nodes developed in the surrounding area.

In this case, we present a possible cause of acute abdomen with a complication of Meckel's diverticulum. Meckel's

Enterolith induced Ischemic Meckel's Diverticulitis can be counted among the differential diagnoses.

Ethics

Informed Consent: It was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.S., S.İ.B., Concept: M.S., S.İ.B., Design: M.S., S.İ.B., Data Collection or Processing: M.S., S.İ.B., Analysis or Interpretation: M.S., S.İ.B., Literature Search: M.S., S.İ.B., Writing: M.S., S.İ.B.

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