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

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INSTRUCTIONS TO AUTHORS

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

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- Author Contributions Form, and
- ICMJE Potential Conflict of Interest Disclosure Form (should be filled in by all contributing authors)

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Title page: A separate title page should be submitted with all submissions, which should include:

- The full title of the manuscript as well as a short title (running head) of no more than 50 characters,
- Name(s), affiliations, and highest academic degree(s) of the author(s),
- Grant information and detailed information on the other sources of support,
- Name, address, telephone (including the mobile phone number) and fax numbers, and email address of the corresponding author,
- Acknowledgment of the individuals who contributed to the preparation of the manuscript but who do not fulfill the authorship criteria.

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

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

Manuscript Types

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

Statistical analysis to support conclusions is usually necessary. Statistical analyses must be conducted in accordance with international statistical reporting standards (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983; 7: 1489-93). Information on statistical analyses should be provided with a separate subheading under the Material and Methods section and the statistical software that was used during the process must be specified.

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

Expert Opinions: Editorial comments aim to provide a brief critical commentary by reviewers with expertise or with high reputation in the topic of the research article published in the journal. Authors are selected and invited by the journal to provide such comments. Abstract, Keywords, Tables, Figures, Images, and other media are not included.

Review Articles: Reviews with high citation potential prepared by authors with extensive knowledge on a particular field and whose scientific background has already been proven by a high number of publications in the related field are welcomed. These authors may even be invited by the journal. Reviews should describe, discuss, and evaluate the current level of knowledge of a topic in clinical practice and should guide future studies. The main text should contain Introduction, Clinical and Research Consequences, and Conclusion sections. Please check Table 1 for the limitations for Review Articles.

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Surgical Methods: Images of remarkable, striking and rare cases that emphasize the basic mechanisms of diagnosis and treatment of diseases, express discrepancies and extraordinary situations and explain new treatment techniques and options are evaluated for publication. Display items are important in this type of manuscripts, and supporting the manuscript with video (in WMV, AVI or MPEG formats) images can facilitate a faster evaluation process and increase the possibility of publication.

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

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

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

Animal Research

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

Table 1. Limitations for each manuscript type

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

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

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

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

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

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

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

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

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

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

Thesis: Yılmaz B. Ankara Üniversitesindeki Öğrencilerin Beslenme Durumları, Fiziksel Aktiviteleri ve Beden Kitle İndeksleri Kan Lipidleri Arasındaki Ilişkiler. H.Ü. Sağlık Bilimleri Enstitüsü, Doktora Tezi. 2007.

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

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

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

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CASE SERIES

CASE REPORT

FROM THE EDITOR'S DESK

Dear Authors of the Turkish Journal of Surgery,

You are now reading the September 2019 issue of the Turkish Journal of Surgery. We are happy to publish distinguished studies and case reports within the pages of the issue. Although the studies are prominently on visceral surgery, there are also very remarkable papers from other disciplines of the surgery.

Trauma is a worldwide medical problematic affecting predominantly healthy and young individuals. It is especially a prominent health issue in Turkey. Güldoğan et al. are presenting in this issue their large experience on burn patients in Ankara Numune Education and Research Hospital (1). Their study focuses particularly on the factors and predictors of mortality on major burns. I hope that you will find the results of this very interesting study interesting and helpful. It is clear that we have still much to do and analyze in this particular type of trauma.

Furthermore you may read another fascinating study of Rubinz et al., which comes from Georgetown University, Washington, USA (2). Transplantation medicine is a highly dynamic subject and there are growing numbers of patients in this multidisciplinary field. Kidney transplantation is the commonest operation in transplantation surgery. The authors of this interesting study present their experience of a modified technique of transplant nephrectomy, which is a morbid operation with potential complications. Through this technique better results were reported in regards to postoperative complications. We are hoping that these suggestions will be helpful for those who deal with kidney transplantation surgery.

Let me just suggest you to enjoy reading all the studies and case reports in this issue, which are based on great efforts and expertise.

You are always more than welcome to share with our journal your experience by submitting your work.

Best regards,

Kaya SARIBEYOĞLU
Professor of Surgery
Turkish Journal of Surgery
Editor

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2. *Rubinz R, Andaçoğlu OM, Anderson E, Corder W, Michaelson E, Moore J, Cooper M, Ghasemian S. Transplant nephrectomy with peritoneal window: Georgetown University institution experience. Turk J Surg 2019; 35: 191-5.*

ORIGINAL ARTICLE
Turk J Surg 2019; 35 (3): 155-164

Analysis of factors associated with mortality in major burn patients

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* This study was presented at the 8th Congress of the International Society for Burn Injuries, 28 July-1 August 2016, Miami, USA.

ABSTRACT

Objective: Major burn injury is a type of trauma with high morbidity and mortality rates at all age groups. There is no consensus on the provided guidelines regarding the prediction of severity of the victims. Not being accessible to sophisticated clinical and blood monitoring in developing countries, it remains a challenge for them. The aim of the present study was to analyze the factors that have an effect on mortality and serve as a guide for burn treatment. Factors affecting mortality in major burn patients treated in a burn treatment center of a third step hospital with over 30% of burns of the total body surface area were evaluated, and parameters indicating severity were specifically determined.

Material and Methods: Medical records and follow-up notes of patients hospitalized in Ankara Numune Education and Research Hospital Burn Center between 2008 and 2014 were evaluated retrospectively. Data on age, gender, comorbidities, burn percentage, locality, type of burn, process of the burn (suicide or accident), presence of inhalation injury, results of blood hemogram and biochemical tests, length of hospitalization, type of surgical procedures performed, presence of multitrauma, and ventilatory support requirement were analyzed to determine the factors affecting mortality. White blood cell count, hemoglobin count, platelet count, and lactate dehydrogenase level were examined at admission, at the middle of the clinical course, and at the end of treatment (at both exitus date or discharge date).

Results: A total of 224 patients were hospitalized with burns ≥ 30% total body surface area. Of the 224 patients, 81.7% were males, and 18.4% were females. In the mortality group, 41.3% were males, and 58.5% were females. Gender (female, p< 0.041), age (p< 0.001), age group (0–14/15–59/> 60 years, p< 0.001), total body surface area (p< 0.001), type of burn (flame, p< 0.002), presence of inhalation injury (p< 0.001), process of the burn (p< 0.002), time spent between the event and admission to the hospital (p< 0.001), length of hospitalization (p< 0.001), presence of comorbidity (p< 0.038), diabetes mellitus (p< 0.05), ventilation support (p< 0.001), lactate dehydrogenase values (lactate dehydrogenaseadmission, p< 0.001; lactate dehydrogenasemiddle, p< 0.015; lactate dehydrogenaselast, p< 0.001), white blood cell count (p< 0.001), and platelet count (p< 0.043) were found to be significant for univariate analyses. These parameters were further evaluated using multivariate analyses. Lactate dehydrogenaselast level (p< 0.001), age (p< 0.001), length of hospitalization (negative odds ratio), p< 0.001), presence of inhalation injury (p< 0.029), total body surface area burned (p< 0.029), and leukocytosis (p< 0.006) were found to be significantly associated with mortality; however, leukocytosis and length of hospitalization did not pose risk for mortality with regard to odds ratios.

Conclusion: Early recognition of the factors affecting morbidity and mortality in patients and taking preventive measures, in addition to earlier detection and prevention of complications in long-time intensive care unit patients, could reduce complication and mortality rates in major burn trauma patients. Parameters for the indication of severity and mortality are important; however, lactate dehydrogenase is an easily studied parameter and is found to have a predictive value on prognosis.

Keywords: Burn, major burn, burn and mortality

Cite this article as: Güldoğan CE, Kendirci M, Gündoğdu E, Yastı AÇ. Analysis of factors associated with mortality in major burn patients. Turk J Surg 2019; 35 (3): 155-164.

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INTRODUCTION

Major burn injury is a type of trauma with high morbidity and mortality rates at all age groups. There is no consensus on the standard guidelines regarding the prediction of the severity of the victims. At times, it is not easy to have sophisticated clinical and blood monitoring in developing countries and is still a challenge for them. Although the incidence of burn injuries has decreased significantly over the recent years, approximately 1.1 million individuals receive treatment for burn injuries each year in the United States. Approximately 45.000 of these cases are hospitalized. There are 4500 deaths due to burn injury every year (1). In the USA, burns are the fourth leading cause of death due to accidents (2). Deaths occur more frequently among young children and elderly individuals (3). Burn injuries mostly occur due to lack of attention and lack of education, and burns result in physical and psychological scars.

Burn is a life-threatening injury. It is a unique type of trauma that requires rehabilitation during and after treatment. As it is preventable, it presents an extra burden on the medical staff, the patients and their relatives, the hospital, and the national economy. For that matter, prevention and development of measures should be considered in the first place. One important factor associated with mortality and morbidity in patients with major burns is fluid resuscitation. Proper and convenient fluid resuscitation has been shown to extend life span especially in major burns.

The present study evaluated the factors associated with mortality in patients with burns, whose affected total body surface area (TBSA) was 30% or higher, and who were hospitalized for treatment in Ankara Numune Education and Research Hospital Burn Treatment Center between 2008 and 2014. Our aim was to analyze injuries caused by major burns, determine mortality rates, and provide guidance in the treatment of major burns by identifying the risk factors associated with mortality.

MATERIAL and METHODS

The study was designed according to the Declaration of Helsinki, patient rights regulation, and ethical rules. The study was approved by the ethics committee of Ankara Numune Education and Research Hospital. We retrospectively reviewed clinical records and follow-up notes of patients hospitalized for treatment in the Burn Treatment Center of Ankara Numune Education and Research Hospital Hospital between 2008 and 2014.

In order to identify the prognostic risk factors associated with mortality, age, sex, comorbidity, affected TBSA, burn type, whether it was an accidental or suicidal case, presence of inhalation injury, results of hemogram and biochemical tests, length of hospitalization, presence of multitrauma, presence of ventilatory support, and cause of mortality were evaluated.

The study only included patients whose affected TBSA was 30% or higher. White blood cell (WBC) count, hemoglobin level, platelet count, and serum lactate dehydrogenase (LDH) level were examined in particular. Additionally, LDH levels were examined at admission, at the middle of the clinical course, and at the end of treatment (at both exitus date or discharge date).

Statistical analyses were performed with 95% confidence interval. A p-value < 0.05 was accepted as statistically significant. Comparisons were performed by using t-tests, and categorical data were compared using Chi-square or Fisher's exact test as appropriate. Factors associated with mortality were assessed by using Hosmer–Lemeshow test for logistic regression analysis.

RESULTS

Demographic Data

We retrospectively evaluated the demographic data of 224 patients who were hospitalized for treatment in our hospital's burn unit between January 2008 and January 2014 and whose affected TBSA was ≥ 30%.

Of these 224 patients, 183 (81.7%) were males, and 41 (18.4%) were females. Median patient age was 37 years (min: 1 and max: 95). Patients were classified into three age groups: 13 (5.8%) patients in the 0–14 years age group, 184 (82.1%) patients in the 15–59 years age group, and 27 (12.1%) patients in the 60 years or older age group. Based on the type of burns, 153 (68.3%) patients were exposed to flames, 42 (18.8%) patients were exposed to electrical current, 18 (8.8%) patients were exposed to hot fluids, and 11 (4.9%) patients were exposed to chemicals or had contact burns.

Patients were evaluated according to the presence of comorbidities, and 40 (21.7%) patients had a comorbid disease. Diabetes mellitus, hypertension, and chronic obstructive pulmonary disease (COPD) were the frequently observed comorbid diseases. Burn surfaces were as follows: 53.7% (TBSA burned) for all patients, 53.6% for males, and 54% for females.

Length of hospitalization was accepted as the duration from patient's admission until problem-free discharge or death. All patients were followed up in the burn intensive care unit (ICU). Mean length of ICU stay was 26.42 ± 25.27 days. Patients were categorized based on respiratory support requirement. Non-invasive and/or invasive respiratory support was applied in 124 (55.3%) patients. Overall, 99 patients died during the hospitalization period.

In order to determine the effects of prognostic risk on mortality, age, sex, comorbidities, affected TBSA, presence of inhalation injury, length of hospitalization, time until presentation, whether it was an accidental or suicidal case, burn type, presence of multitrauma, respiratory support, and cause of mortality were evaluated statistically.

There was a statistically significant difference between the two sexes regarding mortality rate ($p< 0.041$). Mortality rate was 58.5% in females, whereas it was 41% in males. There was a statistically significant relationship between mean patient age and mortality. Mean patient age in the surviving group was 31 ± 14 years, whereas mean age in the mortality group was 43 ± 20 years. There was a statistically significant difference between the different age groups regarding mortality rate ($p< 0.001$). The highest mortality rate was observed in the 60 years or older age group. No mortality was observed in the 0-14 years age group.

Mean affected TBSA was 53.7%. Mortality rate among patients with TBSA greater than 30% was 44.2%. There was a statistically significant relationship between TBSA and mortality ($p<0.001$). There was a statistically significant difference regarding mortality rate between the different burn types ($p< 0.002$). Majority of our cases had burns after exposure to flames (68.3%), and mortality rate was higher in the group exposed to flames (53.6%), followed by electrical current, hot fluid, and others (chemical burns and contact burns).

The presence of inhalation injury had a statistically significant effect on mortality (p< 0.001). Sixty-six (67.3%) patients who developed inhalation injury lost their lives (Table 1). Time until presentation to the hospital had a statistically significant effect on mortality (Table 2).

Patients were categorized as accidental and suicidal cases based on the manner of injury. Mean TBSA was calculated in each group, and the distribution of affected TBSA was examined (Table 2). For cases that ended up with mortality, TBSA did not show any difference between these two groups. For surviving patients, affected TBSA was significantly larger among suicidal cases. This significant difference also caused TBSA to be different between the two groups in general. The relationship between the manner of injury and mortality was examined, and mortality rate showed a significant difference between accidental and suicidal cases, independent of the TBSA (Table 2). Length of hospitalization had a significant effect on mortality (Table 2).

In the present study, there were 40 patients with comorbidities. Of the 40 patients, nine had diabetes mellitus, nine had hypertension, three had concurrent hypertension and diabetes mellitus, four had COPD, three had mental retardation, three had epilepsy, five had coronary artery disease and heart failure, three had psychopathology, and one patient had volatile substance abuse. Patients were categorized in terms of the presence of comorbidity, and there was a statistically significant difference regarding mortality rate between patients with and without comorbidity (Table 2). Patients were categorized in terms of the presence of diabetes, and mortality rate was significantly higher among patients with diabetes (Table 2).

The presence of accompanying trauma did not have a significant effect on mortality (p< 0.815). In our case series, there were 20 patients with accompanying trauma. Mortality rate was 44.6% in the group with no accompanying trauma, whereas it was 40% in the group with accompanying trauma.

Respiratory support had a statistically significant effect on mortality rate (Table 2). Patients who had mortality were evaluated according to cause of death; accordingly, cause of mortality was multiple organ dysfunction syndrome (MODS) in 66 (66.7%) patients, adult respiratory distress syndrome (ARDS) in 19 (19.2%) patients, sepsis in 9 (9.1%) patients, and other causes (pulmonary embolism, cranial embolism, and acute renal failure) in 5 (5%) patients.

The relationship between laboratory parameters and mortality was analyzed. Accordingly, admission LDH levels, midhospitalization LDH levels, and end-hospitalization LDH levels and WBC and platelet counts were found to be associated with mortality. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin levels did not show a significant association with mortality (Table 3).

Logistic regression analysis was performed in order to determine the variables that will be used in the prediction of whether prognostic factors associated with mortality had any effect; further, sex, age, age group, TBSA, burn type, presence of inhalation injury, time until presentation, whether it was an accidental or suicidal case, length of hospitalization, presence of comorbid disease, presence of diabetes, LDH levels, WBC count, and platelet count yielded significant results as independent variables

Table 1. Relationships between demographical parameters and mortality

	Survivors	Exitus	p
Sex			**0.041**
Female	17 (41.5%)	24 (58.5%)	
Male	108 (59%)	75 (41%)	
Age	31.39	43.66	**0.001**
Age group			**0.001**
0-14 years	13 (100%)	0 (0%)	
15-59 years	107 (58.2%)	77 (41.8%)	
≥ 60 years	5 (18.5%)	22 (81.5%)	
TBSA	47%	63%	**0.001**
Burn type			**0.02**
Flame	71 (46.4%)	82 (53.6%)	
Electrical current	29 (69%)	13 (31%)	
Hot fluid	16 (88.9%)	2 (11.1%)	
Others	9 (81.8%)	2 (18.2%)	
Inhalation injury	32 (32.7%)	66 (67.3%)	**0.001**

TBSA: Total body surface area.

Table 2. Associations between mortality and some parameters examined

	Survivors	Exitus	p
Time until presentation			**0.011**
0-24 hours	92 (57.9%)	67 (42.1%)	
24-48 hours	15 (50%)	15 (50%)	
≥ 49 hours	18 (51%)	17 (49%)	
Manner of burn injury			**0.003**
Accident	118 (58.3%)	80 (41.7%)	
Suicide	7 (27%)	19 (73%)	
Manner of burn and TBSA relationship			**0.002**
Accident	46.32	62.65	
Suicide	51.86	62.74	
Comorbidity			**0.038**
No	113 (61.4%)	71 (38.6%)	
Yes	12 (30%)	28 (70%)	
Diabetes			**0.005**
No	123 (58%)	89 (42%)	
Yes	2 (16.7%)	10 (83.3%)	
Respiratory support			**0.001**
No	100	0	
Yes	25 (21.2%)	99 (79.8%)	
Length of hospitalization (day)	38.4	10.74	0.001

TBSA: Total body surface area.

Table 3. Distribution of laboratory parameters according to mortality state, and their effects on mortality

	Survivors		Exitus		p
	Mean	**SD**	**Mean**	**SD**	
LDH 1	468.59	470.14	664.4	495.09	**0.001**
LDH 2	323.92	149.27	605.57	816.34	**0.015**
LDH 3	254	164.05	938.84	1301.14	**0.001**
WBC	14260	9357	22362	14861	**0.001**
Platelet	279.885	145.806	235.247	173.662	**0.043**
ALT	57.23	95.77	130.01	498.38	0.121
AST	107.68	235.06	125.97	331.40	0.638
Total bilirubin	1.02	2.37	1.42	1.76	0.237

SD: Standard deviation, LDH: Lactate dehydrogenase, WBC: White blood cell.

in chi-square significance analysis, and they were included in multivariable analysis. In order to determine the dependent variable prognostic factors associated with survival, forward stepwise selection technique was used for logistic regression analysis (Table 4).

Accordingly, based on the model formed with all independent parameters, end hospitalization LDH levels, age, length of hospitalization, inhalation injury, affected TBSA, and WBC count were parameters associated with mortality.

In the table, Exp (βp) values indicate ORs. The OR represents the odds that an outcome will occur given a particular exposure, compared with the odds of the outcome occurring in the absence of that exposure. The probabilities will be interpreted in such a way that if β coefficient is positive, the parameter will

Table 4. Factors associated with mortality based on logistic regression analysis

	B	SE	Wald	df	Sig.	Exp(B)	95% CI for EXP (B)	
							Upper	Lower
LDH 3	0.005	0.002	10.891	1	**0.001**	1.005	1.002	1.008
Age	0.08	0.021	15.154	1	**0.001**	1.083	1.041	1.128
Length of hospitalization	-0.096	0.021	21.248	1	**0.001**	0.909	0.873	0.947
Inhalation injury	0.316	0.145	4.788	1	**0.029**	1.372	1.034	1.822
TBSA	0.036	0.016	4.792	1	**0.029**	1.036	1.004	1.07
WBC	0	0	7.604	1	**0.006**	1	1	1

LDH: Lactat dehidrogenase, TBSA: Total body surface area, WBC: White blood cell.

have an inverse relationship with mortality, and if it is negative, the parameter will be positively related with mortality.

According to the results, total length of hospitalization as a prognostic factor increased survival by 0.096 fold. On the other hand, mortality was increased by 0.005 fold with elevated end-hospitalization LDH levels, 0.08 fold with age, 0.316 fold with inhalation injury, and 0.036 fold with large affected TBSA.

As the classification success of our logistic regression model established to identify prognostic markers of mortality, the rate of accurate classification/accurate assignment of observations is 93.8%. In other words, the model made accurate predictions in 93.8% of the 224 patients. In this classification, six patients were misclassified in the surviving group, whereas five patients were misclassified in the mortality group. That is, 92.6% of patients who did not survive and 94.7% of the surviving patients were predicted with accuracy.

DISCUSSION

Our study included patients with 30% or higher affected TBSA. Many factors have previously been associated with mortality in the literature. When we evaluate the association between sex and mortality, we observe that there is no consensus on this subject. Some authors have found female sex as a risk factor, whereas others have not found a significant association between sex and mortality (4,5). In our study, 81.7% of patients were males, and 18.4% were females. In the group that ended up with mortality, 41.5% of patients were males, and 58.5% were females. There was a statistically significant association between sex and mortality in our study (p= 0.041). Accordingly, female sex can be interpreted as a risk factor. In their study, Kumar et al. (6) have examined causes of mortality among patients with major burns, and they have found mortality rate in female patients as 87.5%. Liodaki et al. (7) have attributed higher mortality rate among females to greater adipose tissue volume, and they have stated that the adipose tissue functions as an active immune system organ responsible for increased systemic inflammatory response in burn trauma.

Although majority of the patients with major burns were young, an examination of the relationship between patient age and mortality showed that the mean age was 37 years (range: 0-95 years). Mean age of the patients in the mortality group was 43.66 years, and mean age in the surviving group was 31.39 years. Accordingly, there was a significant association between age and mortality (p= 0.001). Patients were evaluated according to age groups, and while there was no mortality in the 0-14 years age group, mortality rate was 41.8% in the 15-59 years age group and 81.5% in the 60 years or older age group (p= 0.001). Ryan et al. (8) have found age older than 60 years as a risk factor for mortality. There are also other studies that report the association between advanced age and mortality (9,10). Our results also indicate that advanced age is a significant risk factor for mortality.

In our study, the overall mean affected TBSA was 53.7%. Affected TBSA was 62.7% in the mortality group and 46.63% in the surviving group. There was a statistically significant association between affected TBSA and mortality (p= 0.001). There is a consensus in the literature that larger affected TBSA is associated with a high mortality rate (11-13). A recent study reported that affected TBSA over 40% is a risk factor for mortality. There are also other studies that found the mortality rate is 100% in the patient group with affected TBSA over 70% (14-16). In our study, mortality rate among patients with affected TBSA 30% or higher was 44.2%.

According to burn types, burn injuries most frequently occurred due to exposure to flames (68.3%); the second frequent cause was electrical current (18.8%), followed by hot fluids and others (chemical burns and contact) (4.9%). These results are consistent with previous studies from both developed and developing countries (17,18). According to mortality rates in different types of burns, 53.6% of patients with flame burns, 31% of patients with electrical burns, and 8% of patients with hot fluid burns were lost. There was a significant difference regarding mortality rates between different types of burns (p= 0.002). Previous studies have also found the relationship between mor-

tality and type of burn (19). In comparison to previous studies in the literature, our case series included a higher proportion of patients with flame burn injuries. The reason for this may be that our clinic is a reference center in Turkey, receiving more complicated patients.

According to the manner of burn injury, 198 (88.4%) patients were injured as a result of accidents, whereas 26 (11.6%) patients were injured due to suicide attempt. Of the patients, 41.7% of the accidental cases and 73% of the suicidal cases ended up with mortality. There was a significant difference regarding mortality rate between accidental and suicidal cases (p= 0.003). A review of the literature showed that mortality rate is higher among accidental cases of burn injury and is lower among suicidal cases. Mean affected TBSA in accidental cases that ended up with mortality was 62.65%, whereas it was 62.74% in accidental cases with mortality, which indicates that affected TBSA on its own is not a cause of death in patients with flame burn injuries. Probably, physiopathological changes associated with flame burn injury are the reasons for increased mortality rate. We believe that further studies are necessary to clarify this relationship. The relationship between mean TBSA and mortality was statistically significant in both the accidental and suicidal groups (p= 0.002).

According to the evaluation of the length of ICU stay and mortality, mean length of hospitalization was 10.74 days in the mortality group and 38.84 days in the surviving group. There are studies in the literature that show increased mortality rates with increased length of hospitalization (20). One shortcoming of the present study is that the study did not include patients with similar TBSA involved. Naturally, patients with higher TBSA involved may die in the early period due to burn shock, whereas causes of mortality at the long term are sepsis and multiple organ failure. Nonetheless, in order to draw a conclusion as prolonged length of hospitalization is a cause of mortality, one should conduct a prospective study including patients with similar TBSA involved. In our study, mortality rate was lower as the length of hospitalization increased, which can be explained by the fact that patients with larger affected TBSA were lost in the early period. Kala et al. (15) have reported that mean length of hospitalization is shorter when affected TBSA is above 50%. When we examine patients with prolonged length of hospitalization, we observe that the majority were treated for burn injuries affecting the extremities, and that they developed complications related with these injuries (graft and flap requirement and amputation). These patients had longer length of hospitalization because the treatment of these complications and rehabilitation procedures in the convalescence period took a long time. There is a consensus in the literature regarding the relationship between length of ICU stay and mortality. Many studies have reported increased mortality rates with prolonged length of ICU stay (21-23).

In our study, the relationship between mortality and comorbidity was statistically significant (p= 0.038). Similarly, Thombs et al. (24) have reported that mortality rate is four times higher among patients with burn injury who had three or more accompanying diseases, independent of their age. The same study has examined the association of accompanying diseases with mortality and found that hypertension and diabetes are not associated with mortality. In our study, mortality rate was 70% in the group with accompanying disease and 38.6% in the group with no comorbidity. We examined the association of diabetes with mortality. Patients were categorized based on the presence of diabetes. The frequency of wound site infection, grafting and graft complications, length of hospitalization, and risk of nosocomial infection have been shown to be increased in the presence of diabetes (25). In our series, 83.3% of patients with diabetes ended up with mortality, whereas this rate was 42% in the non-diabetic group. Diabetes had a statistically significant positive effect on mortality rate (p= 0.005). There are also other studies in the literature that have found increased mortality rate in the presence of diabetes as a comorbidity.

Major burns may be accompanied by other types of traumas, including fall from heights, extremity fractures, spinal cord injuries, intracranial bleeding, and visceral organ injuries. Fractures most often occur at the upper extremities and vertebrae (26). Accompanying traumas are more likely to occur in case of electrical burns. In our study, a total of 20 (8.9%) patients had an accompanying trauma, and 8 (40%) patients ended up with mortality (p= 0.815). Kaya et al. (27) have reported significantly increased mortality rates among patients with loss of consciousness. The same study has found a significant association between fall from heights and mortality.

Patients with burn injury are at risk due to several factors such as airway compression, requirement of endotracheal intubation, and mechanical ventilation. Inhalation of smoke causes damage to the upper respiratory tracts, and generalized massive edema in the body may cause obstruction of the respiratory tracts as well. Additionally, hypoxia that develops as a result of resuscitation during the initial treatment may lead to requirement for endotracheal intubation or mechanical ventilation. Furthermore, ARDS or acute lung injury in patients with burn may require ventilatory support (28). In our study, a total of 124 (55.4%) patients received respiratory support. Among these patients, 99 (79.8%) ended up with mortality. All patients who did not receive respiratory support survived. Mortality rate was significantly higher among patients who received respiratory support (p= 0.001). There is consensus in the literature that connection to mechanical ventilation and prolonged ventilation increase complications related to mechanical ventilation and, therefore, are associated with increased mortality (29-31). Nonetheless, it should be emphasized here that respiratory sup-

port is an obligatory part of the treatment algorithm in patients with major burns. Before announcement of death, all patients are intubated and connected to the mechanical ventilator as a standard of care. Hence, it would be wrong if we interpret it in the way that mechanical ventilation increases mortality in such patients. In fact, patients requiring mechanical ventilation have organ failures already at a level that they cannot sustain their physiological respiratory functions, and their death has nothing to do with mechanical ventilation, but it is rather related to the progressing physiopathological processes that lead to mechanical ventilation requirement in the first place. As a result, we can interpret this result as that patients requiring mechanical ventilation had increased mortality rates. On the other hand, many studies have reported that prolonged mechanical ventilation increases mortality risk due to several factors associated with mechanical ventilators.

We evaluated complete blood count and blood chemistry parameters measured at the time of admission. Elevated WBC count (p= 0.001) and reduced platelet count (p= 0.043) were found to be statistically significant. Patients were classified according to ength of hospitalization. LDH levels measured at the time of admission, at the mid-term of the hospitalization period, and at the end of the hospitalization period were found to be associated with mortality (p< 0.005). Total bilirubin, ALT, and AST levels measured at the time of admission did not show any association with mortality.

It is not fully understood why patients with burn injuries have elevated WBC count. It may be due to septic complications, thermal trauma, or inflammation (32). Orban et al. (33) have reported that 75% of the patients with major burn injuries have WBC counts above 12.000/mL. Yanculovich et al. (9) have shown that WBC count at the time of admission, together with affected TBSA, is the most important prognostic factor for predicting mortality. We also observed elevated WBC count secondary to burn and trauma, consistent with that in the literature. However, this elevation does not stand out as an independent factor for mortality. In addition, the level of elevation was not found to be a significant parameter for death.

Platelets are cells free of nucleus in the circulation, and their principal function is to maintain hemostasis. They are additionally known to play roles in wound healing and cytokinemediated immune response. Platelets have been shown to be associated with sepsis and increased mortality in critically ill patients (34). Marck et al. (23) have reported that thrombocytopenia is associated with sepsis and is one of the predictive factors for mortality. Macedo et al. (35) have noted that thrombocytopenia and anemia are associated with mortality according to the results of univariate analysis, but the same association was not observed in multivariate analysis. Wolf et al. (15) have found that thrombocytopenia (< 20.000/mL) is associated with mortality in patients with severe burns. We also found a statistically significant association between thrombocytopenia and mortality (p= 0.043).

Lactate dehydrogenase is an intracellular enzyme found in many tissues, particularly abundant in the kidneys, heart, skeletal muscle, brain, and liver. Its circulating levels rise in case of cellular injury. It is the most important enzyme of the last step of anaerobic respiration. There are five LDH isoenzymes, and these isoenzymes can be used to assess the origin of LDH elevation. Increased LDH 1 and LDH 2 isoenzyme levels can be observed following acute myocardial infarction, in hemolytic anemias, sickle cell anemia, megaloblastic anemia, acute renal cortical necrosis, and particularly skeletal muscle damage. Increased LDH 2, 3, and 4 isoenzyme levels can be seen in pulmonary embolism, following massive blood transfusions, in lymphomas, and skeletal muscle injury. Increased LDH 5 isoenzyme level occurs in liver diseases and cancers. Riaz Ahmed et al. (36) have reported that LDH 4 and LDH 5 isoenzyme levels can be used in patients with major burns with affected TBSA 30% or higher as a diagnostic marker for the interpretation of the extent of injury and during follow-up of wound healing. Liu et al. (37) have studied LDH levels following burn injuries and found elevated LDH 4 and LDH 5 isoenzyme levels, and they have stated that early detection of the elevated LDH levels may be beneficial in diagnosis and treatment. Karadaş et al. (38) have found an association between mortality and persistently elevated LDH levels. In our study, serum samples for LDH measurement were obtained at three different times. Patients were categorized based on their length of hospitalization. The first sample was obtained at the time of admission. Increased LDH level at the time of admission was found to be significantly associated with mortality for patients with major burns with 30% or higher TBSA involved (p= 0.001). Second serum LDH level was measured at the mid-term of the hospitalization period, and increased LDH level at this time was also found to be significantly associated with mortality (p= 0.015). The third sample was obtained at the end of hospitalization, and increased LDH level at this time was also significantly associated with mortality (p= 0.001). Based on the literature review, it could be concluded that analysis of LDH isoenzymes is necessary, whereas in this retrospective study, persistence of elevated LDH level or an increasing trend was directly related with mortality. At this point, it is deduced that increased LDH level is associated with mortality, without a requisition for isoenzyme analysis. In addition, isoenzyme studies were inadequate in revealing the origin of the elevation, and they failed to emphasize its clinical significance and also have a downside as the requirement of extra cost and time. Yet, based on our findings, we can say that LDH level can be used to predict mortality, without the need for isoenzyme analysis.

CONCLUSION

Major burns are a type of trauma with high morbidity and mortality, and all age groups are at risk. The clinical picture in major burns involves various systems. Our study included a total of 224 patients with major burns who had 30% or larger TBSA involved, and the overall mortality rate was 44.2%.

We evaluated parameters that could be associated with mortality. Female sex, age, age group, affected TBSA, type of burn, presence of inhalation injury, time until presentation to our hospital, whether it was an accidental or suicidal case, length of ICU stay, presence of comorbid disease, presence of diabetes, and presence of accompanying trauma were found to increase mortality in patients with 30% or larger TBSA involved in univariate analysis. Among the laboratory tests that were requested at the time of admission and during treatment, increased WBC count, elevated LDH level, and reduced platelet count were found to increase mortality. We observed that prolonged length of hospitalization had a favorable effect on survival in multivariate analysis.

In our study, the most frequent causes of mortality following burn injury were MODS, ARDS, sepsis, and others (pulmonary embolism, cranial embolism, and acute renal failure, among others). Although these clinical identities were mostly interrelated, they may also be encountered on an individual basis. Additionally, an extremely high WBC count at the time of presentation should be considered as a warning sign for possible serious inflammatory response or sepsis. Elevated LDH levels should prompt reconsideration of diagnostic and therapeutic protocols. Thrombocytopenia and disturbances of blood glucose regulation may be signs of sepsis development. It should be kept in mind that patients connected to the mechanical ventilator may develop secondary infections, and since these infections reduce survival, these patients should be disconnected from the mechanical ventilator.

Early recognition of factors leading to morbidity and mortality and taking necessary measures and, additionally, early detection of complications that may develop after long-term follow-up in the ICU, and proper actions would reduce both complication rates and mortality rates in patients with major burns.

From another perspective, the best way to reduce mortality associated with major burns is to prevent burn injuries.

Moderate and serious injuries should be treated in specialized centers for better outcomes. Owing to the advances in burn care, even patients with very large affected areas may survive with proper care. Future efforts should focus on the reduction of scar formation and the expedition of the healing process and will aim to improve functional and cosmetic outcomes.

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ORİJİNAL ÇALIŞMA-ÖZET
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Majör yanıklı hastalarda mortalite ile ilişkili faktörlerin analizi

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ÖZET

Giriş ve Amaç: Majör yanıklar yüksek morbidite ve mortalite ile seyreden, tüm yaş gruplarının risk altında olduğu bir travma türüdür. Bu çalışmadaki amacımız yanıklara bağlı gelişen yaralanmaları analiz etmek, mortalite oranlarını belirlemek, mortaliteyi etkileyen risk faktörlerini belirlemek ve yanık tedavisinde yol göstermektir. Bu tez çalışmasında, üçüncü basamak bir sağlık kurumunun, yanık tedavi merkezinde, yanık yüzey alanı %30 ve üzeri olan majör yanıklı hastalarda, mortaliteye etki eden faktörlerin araştırılması amaçlanmıştır.

Gereç ve Yöntem: 2008-2014 yılları arasında Ankara Numune Eğitim ve Araştırma Hastanesi yanık kliniğine başvuran ve yatırılarak takip edilen hastaların klinik kayıtları ve takip notları geriye dönük olarak incelenmiştir. Hastalarda mortaliteye etki eden prognostik faktörleri tespit amacıyla yaş, cinsiyet, ek hastalık varlığı, yanık yüzdesi, hastanın geldiği yer, yanık türü, yanığın meydana geliş şekli, inhalasyon yaralanması varlığı, kan hemogram testleri ve biyokimyasal değerleri, yatış süresi, operasyon tipi, multitravma varlığı, solunum desteği ve mortalite nedenleri incelecek parametreler olarak belirlenmiştir. Çalışmada hastaların başvuru anındaki beyaz küre düzeyi, hemoglobin düzeyi, trombosit düzeyi, laktat dehidrogenaz düzeyleri özellikle irdenlenmiştir. Bununla beraber hastaların hastanede yattığı süre zarfında, hastaneye başvuru anında bakılan laktat dehidrogenaz (LDH) geliş değeri; yatış süresinin ortasında bakılan LDH orta değeri; ve yattığı sürenin sonunda bakılan LDH son değerleri de esas alınmıştır.

Bulgular: 2008-2014 yılları arasında, Ankara Numune Eğitim ve Araştırma Hastanesi yanık ünitesinde yatırılarak tedavi edilen hastalardan toplam vücut yanık alanı (TVYA) ≥ %30 olan 224 hastanın demografik özellikleri, geriye dönük olarak incelendi. Çalışmamızda hastaların %81,7'si erkek, %18,4'ü kadın olarak izlendi. Ölüm görülen grupta ise %41,5 erkek, %58,5 kadın mevcuttu. Univariyant analizde anlamlı çıkan veriler (cinsiyet, yaş, yaş grubu, yanık yüzey alanı, yanık türü, inhalasyon yaralanması varlığı, yanığın meydana geliş şekli, hastaneye başvuru süresi, yatış süresi, ek hastalık varlığı, diyabet, solunum desteği, LDH değerleri, lökosit değeri, trombosit değeri) multivaryant analiz ile değerlendirildiğinde; LDH çıkış değeri, yaş, yatış süresi, inahlasyon yaralanması varlığı, yanık yüzey alanı ve lökositoz istatistiksel olarak artmış mortalite riski ile ilişkili bulunmuştur.

Sonuç: Hastalarda morbidite ve mortaliteye etki eden faktörlerin erken dönemde fark edilmesi ve önlemlerin alınması ayrıca yoğun bakımda takip edilen hastaların uzun dönem takipleri sonrasında oluşabilecek komplikasyonların erken tanınıp tedbir alınması majör yanıklı hastalarda hem komplikasyon oranlarını hem de mortalite oranlarını azaltacaktır. Diğer bir bakış açısıyla majör yanıklara bağlı mortaliteyi azaltmanın en iyi yolu yanıklardan korunmaktır. Orta ve büyük şiddette yaralanmalar daha iyi sonuçlar alabilmek için bu konuda özelleşmiş merkezlerde tedavi edilmelidirler.

Anahtar Kelimeler: Yanık, majör yanık, yanık ve mortalite

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Relationship between functional constipation and anal-retentive behavior features

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ABSTRACT

Objective: Constipation is the most commonly seen defecation problem related to several environmental factors. Defecation is learned in the childhood anal period in which anal characteristic features appear. Problems in the childhood anal period may affect not only characters but also defecation function. This study aimed to evaluate the relationship between constipation and anal characteristic features of participants with functional constipation.

Material and Methods: Patients with functional constipation were included into the study according to the ROME III criteria. Patients with irritable bowel disease, slow transit constipation, outlet obstruction constipation, malignancy, and psychiatric diseases were excluded from the study. Patients filled out Personality Belief Questionnaire, Hospital Anxiety and Depression Scale, and Obsessive Belief Questionnaire. The results were compared with healthy individuals.

Results: A total of 47 patients with functional constipation were included in the study. Avoidant, obsessive-compulsive, antisocial, narcissistic, and paranoid personality traits were found to be higher in patients with constipation than in the control group. Perfectionism/certainty, importance and control, and hospital anxiety scores were found to be higher in patients with constipation than in the control group.

Conclusion: Constipation may be related to several factors, such as socioeconomic environment, emotional stress, age, and diet, among others. Here, it was found that anal-retentive behavior features are prominent in functional constipation. Biofeedback, which can be regarded as psychotherapy of defecation control, can be used for treatment.

Keywords: Anal-retentive, biofeedback, constipation, childhood, personality disorders

INTRODUCTION

Defecation is a complex mechanism composed of sympathetic and parasympathetic systems, sacral spinal cord reflexes, normal anorectal sensation, and voluntary control of the external sphincters (1). Impairments of this process are called defecation disorders and generally associated with constipation. The term "Functional Defecation Disorders (FDDs)" has been preferred to describe constipation associated with anorectal dysfunction, according to recent consensus (ROME III) (2). Constipation is the etiology of most benign anorectal diseases, such as hemorrhoid and chronic anal fissure. Although anatomical and functional factors related with senility and sex have been addressed for etiology, constipation is also a common problem in children (3-5).

In addition to anatomical factors, psychological factors also play a role (6,7). Anal stage is defined as the period of controlling defecation in children. In this period, children learn how to hold their stool and defecate. Children understand the important part of defecation (i.e., voluntary control of the sphincter) during this period. Defecation control is the interaction, communication, and exertion of power by children against their environment. Children experience several conflicts in this period. These conflicts may lead to anal-retentive personality, which includes willfulness, stinginess, excessive thoroughness, and excessive tidiness (7,8). Early toilet training, excessive parent-child conflict, irrational fears, and anxieties around toileting can also lead to constipation in children (9).

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This study sought to evaluate the possible existence of anal-retentive personality features in patients with FDD.

MATERIAL and METHODS

This retrospective descriptive study was performed at the Department of General Surgery, Kocaeli University. The local ethics committee of Kocaeli University (KOÜKAEK 2015/49) approved the study. Inclusion criteria to the study was being diagnosed with FDD according to the ROME III criteria at the Department of Gastroenterology and referred to the general surgery outpatient clinic between February 2015 and March 2016 (2,10). Gastroenterology reports were reviewed to ascertain whether or not patients had been evaluated by anal manometry and colon transit time measurement in order to rule out slow transit constipation and outlet dysfunction. Patients who had previously known psychiatric, oncologic, inflammatory, and neurological diseases were excluded from the study. Patients admitted to the general surgery outpatient department were examined for hemorrhoid or anal fissure related with constipation. Chronic anal fissure is diagnosed as fissure in the anal canal present for ≥ 3 months and is indurated, fibrotic, has anal skin tags, and is located in the midline. Patients who had previously undergone surgical treatment for hemorrhoids or anal fissure were not included in the study. Patients with constipation were divided into two groups: those with (i.e., constipation with disease) and those without benign anorectal disease (i.e., constipation without disease). The control group was composed of healthy individuals with no previous gastrointestinal or psychiatric diseases. Demographic data included age, sex, body weight, and height. Informed consent was obtained from all of the participants of the study.

Personality Belief Questionnaire-Short Form

Personality Belief Questionnaire-Short Form (PBQ-SF; Turkish version) is composed of questions that query an individual's basic beliefs about himself, other people, and the world (10). In its initial configuration, PBQ has several questions assessing each personality disorder found in the Diagnostic and Statistical Manual of Mental Disorders (DSM) (i.e., avoidant, dependent, passive-aggressive, obsessive-compulsive, antisocial, narcissistic, histrionic, paranoid, schizoid/schizotypal, and borderline). In each question, participants scored the statement from 0 to 4 according to their beliefs. Validity and reliability of the Turkish version of the questionnaire were performed by Taymur et al. (11).

Hospital Anxiety and Depression Scale

Hospital Anxiety and Depression (HAD) is composed of 14 questions that evaluate depression and anxiety of the participant. The aim of the scale is not to diagnose but instead to define the risk groups for anxiety and depression. HAD was developed by Zigmoid et al., and the validity and reliability were evaluated (12). Validity and reliability of the Turkish version of the questionnaire were performed by Aydemir (13).

Obsessive Beliefs Questionnaire

Obsessive Beliefs Questionnaire (OBQ) was developed by the Obsessive-Compulsive Cognitions Working Group and is composed of 44 questions scored on a 7-point Likert scale (14). The subgroups of OBQ include Responsibility/Threat Estimation, Perfectionism/Certainty, and Importance and Control Thoughts. Validity and reliability of the Turkish version of the questionnaire were performed by Boysan et al. (15).

Statistical Analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences version 17.0 (SPSS; IBM Corp., CA, USA). A p-value < 0.05 was accepted as statistically significant. Data were expressed as mean ± SD. Distribution of parametric data was evaluated by Kolmogorov-Smirnov test. Statistical data of the three groups with normal distribution were compared with the ANOVA post hoc Tukey test. Kruskal-Wallis test was used for the comparison of data with non-normal distribution. Categorical comparison was performed by Chi-square test. Subgroup comparisons of OBQ were performed by Mann-Whitney U test.

RESULTS

During a 12-month period, a total of 47 patients with FDD were included into the study. A total of 23 individuals were included into the study as the control group. Table 1 shows the demographic results. There is no statistical difference between the groups by age, sex, weight, and height.

Table 2 shows OBQ and HAD scale results. There is no statistical difference between the groups for the HAD depression scale and

Table 1. Demographics of the patients

	Constipation with disease (n= 31)	Constipation without disease (n= 16)	Control (n= 16)	p
Sex (male/female)	12/19	11/5	10/13	0.135
Age (years)	39.3 ± 13.8	37.4 ± 13.2	44.3 ± 10.3	0.197
Height (cm)	164.1 ± 17.8	169.5 ± 8.2	167.8 ± 10.5	0.396
Weight (kg)	72.6 ± 16.2	72.0 ± 14.3	80.7 ± 19.7	0.169

* ANOVA is used for comparison of the mean age, height and weight of the groups. Kruskal-Wallis is used to compare the ratio of sexes between groups.

Table 2. Comparison of obsessive beliefs, anxiety and depression among the study groups

	Constipation with disease (n= 31)	Constipation without disease (n= 16)	Control (n= 23)	p
OBQ (responsibility/threat estimation)	58.6 ± 14.4	65.2 ± 17.9	54.0 ± 18.6	0.131
OBQ (perfectionism/certainty)	62.7 ± 16.7$^{\alpha}$	65.0 ± 20.4$^{\beta}$	51.0 ± 20.5	**0.02** $^{\alpha}$p= 0.037, $^{\beta}$p= 0.009
OBQ (importance and control thoughts)	39.6 ± 12.7$^{\alpha}$	38.5 ± 11.2$^{\beta}$	31.4 ± 11.8	**0.036** (0.018-0.04-0.893) $^{\alpha}$p= 0.004, $^{\beta}$p= 0.018
HAD depression scale	7.0 ± 3.5	7.4 ± 4.9	5.0 ± 3.7	0.108
HAD anxiety scale	8.6 ± 4.9$^{\alpha}$	7.3 ± 5.1$^{\beta}$	5.4 ± 2.7	**0.016** (0.014-0.677-0.217) $^{\alpha}$p= 0.014, $^{\beta}$p= 0.67

* Kruskal Wallis test is used for comparision of groups. Mann-Whitney U test is used to compare two groups.
α: Comparison between patients with constipation with disease and control group.
β: Comparison between patients with constipation without disease and control group.

the OBQ Responsibility/Threat estimation subgroups (p= 0.108 and p= 0.131, respectively). The Perfectionism/Certainty score of the patients with constipation with disease and without disease was significantly higher than that of the control group (p= 0.037 and p= 0.009, respectively). There were no significant differences between the patients with constipation with and without disease (p= 0.479). The Importance and Control Thoughts score of the patients with constipation with and without disease was significantly higher than that of the control group (p= 0.018 and p= 0.04, respectively). There were no significant differences between the patients with constipation with and without disease (p= 0.893). HAD score was significantly higher in patients with constipation with disease than in the control group (p= 0.014). However, the difference in anxiety scores between the patients with constipation without disease and the control group was not significant (p= 0.217).

Table 3 shows PBQ-SF subgroup comparisons between the groups. The obsessive-compulsive type beliefs were more common in patients with constipation with and without disease than in the control group (p= 0.028). Avoidant and narcissistic beliefs were more common in patients with constipation with disease than in the control group. Antisocial and paranoid beliefs were more common in patients with constipation with disease than in the control group.

Table 3. Comparison of personality beliefs among the study groups

Personality belief questionnaire (PBQ), subgroups	Constipation with disease (n= 31)	Constipation without disease (n= 16)	Control (n= 23)	p
Avoidant*	13.8 ± 5.7$^{\alpha}$	12.1 ± 3.8	10.0 ± 5.0	**0.029** ($^{\alpha}$p= 0.022)
Dependent*	8.8 ± 5.7	9.1 ± 5.4	6.4 ± 4.0	0.176
Passive-aggressive*	12.6 ± 4.7	12.1 ± 3.8	11.4 ± 6.1	0.720
Obsessive-compulsive*	15.4 ± 4.5$^{\alpha}$	15.6 ± 5.4$^{\beta}$	8.0 ± 4.4	**< 0.001** ($^{\alpha}$p< 0.001, $^{\beta}$p< 0.001)
Antisocial**	10.9 ± 6.0$^{\alpha}$	9.0 ± 4.3	6.4 ± 4.9	**0.019** ($^{\alpha}$p= 0.008)
Narcissistic*	10.1 ± 5.6$^{\alpha}$	9.6 ± 4.3	6.7 ± 3.5	**0.03** ($^{\alpha}$p= 0.028)
Histrionic*	8.1 ± 6.1	7.8 ± 3.8	5.3 ± 3.8	0.112
Schiizoid/schizotypal*	12.7 ± 6.3	11.3 ± 5.4	9.4 ± 6.7	0.178
Paranoid**	12.3 ± 6.1$^{\alpha}$	7.8 ± 3.3	8.0 ± 5.8	**0.011** ($^{\alpha}$p= 0.011)
Borderline*	9.5 ± 6.3	8.9 ± 3.8	6.5 ± 3.9	0.099

*ANOVA posthoc Tukey is used for comparison.
** Kruskal-Wallis test is used for comparison.
α: Comparison between patients with constipation with disease and control group.
β: Comparison between patients with constipation without disease and control group.

DISCUSSION

Our study showed that anal-retentive characteristic features related to the period of defecation control are significantly higher in patients with constipation than in healthy people. Constipation is one of the most common gastrointestinal disorders seen by gastroenterologists and primary care physicians. The prevalence of the disease in adults older than 60 years of age is 33%, whereas the overall prevalence among adults of all ages is approximately 16% (16). Constipation reduces quality of life and poses a large economic burden, with more than $820 million spent on laxatives per year (17). Chronic constipation is defined as infrequent bowel movements and myriad symptoms (hard stool, straining, feeling of incomplete evacuation, sensation of fecal obstruction, and digitation for defecation) with less than three bowel movements per week for at least 3 of the prior 12 months. FDD includes primary constipation and has different features than slow transit constipation and obstructed constipation. In our study, FDD-related constipation is diagnosed using the ROME III criteria and excludes outlet dysfunction and slow transit constipation (10).

Our study showed that patients with constipation have much more anal-retentive behavior features than healthy subjects. Anal-retentive behavior features are developed during the anal stage of children between the ages of 1 and 3 years (18). Anal-retentive personality has an excessive amount of libido fixated on the pleasures discovered during the period of toilet training. Control of defecation is a kind of libido that leads to anal-retentive personality during the time when superego is formed (18). Freud suggested that children in the anal stage of development regard the release of their feces as a gift to the parent-a gift that can be given or withheld. Toilet withholding is the most common response seen in that period. Anal-retentive children hold their feces in a miserly fashion, releasing waste only when strongly encouraged or rewarded (19). These characteristics are supposedly present in anally fixated adults who demand that others offer them devotion and sacrifice. Anal-retentive adults hoard love and affection while commonly withholding their own affection from others. Another type of an anal-retentive person is an individual who seeks to obsessively control his or her environment and the people in his or her life, often by being stingy or miserly (19). Fixation at this stage can lead to a highly moralistic and overly controlled personality style.

It has been reported that voluntary holding in healthy people can remarkably delay defecation and, at the same time, slow transit through the ascending colon and rectosigmoid tract (20). This type of mechanism often produces constipation in children and can continue into adulthood as an acquired illness behavior (21). One-third of patients with functional constipation had reported constipation since childhood, whereas others developed constipation during adulthood (22). The onset of symptoms during childhood suggests that at least one-third of patients with functional constipation may have never learned the art of proper defecation or acquired faulty habits during toilet training (23). Early toilet training, excessive parent-child conflict, and irrational fears during the anal stage may result in functional constipation (9). In addition to these withholding features, psychosocial experiences, physiological functioning, or susceptibility to developing a functional gastrointestinal disorder, including functional constipation, is seen (24). It has been shown that physiological stress, anxiety, socioenvironmental factors, and genetic predisposition may also contribute to the development of constipation (24,25). Psychological distress is associated with pelvic floor tension and increased extrinsic nerve supply and rectal mucosal blood flow to the gut (26). The mechanism in emotional stress and constipation result in the alteration of bowel habits via the brain-gut axis.

The prevalence of obsessive beliefs, such as Perfectionism/Certainty and Importance and Control Thoughts, in patients with constipation is significantly higher than that in healthy controls. Anxiety about making a mistake, precise and excessive desire to finish a task, strict and inflexible attitudes toward beliefs, and uncomfortable feelings about uncertain events are higher in patients with constipation. Higher rates of obsessive beliefs in patients with constipation demonstrate that these patients attach importance to compulsive thoughts, and that they need much more control for these thoughts (11). The desire to maintain control is a coping mechanism for individuals, and uncontrolled life events are predictive of psychological stress (24). Previous studies have shown a high prevalence of emotional distress including anxiety, depression, and social dysfunction in patients with functional constipation (24). In the present study, we did not only show high anxiety and social dysfunction rates but also found that other personality disorders are associated with anal characteristic features. It has been shown that stress may act via the enteric nervous system to inhibit colonic motility and thus prolong colonic transit (24). However, in our study, we included patients with normal transit time.

The Personality Belief Scale was prepared according to personality disorders in DSM IV (18). Avoidant, obsessive-compulsive, paranoid, antisocial, and narcissistic beliefs are more common in patients with constipation than in healthy subjects. The most significant difference between the constipated and control groups was obsessive beliefs. Obsessive personality features overlap with anal characteristic features. Individuals with anal characteristic features are rigorous, prim, perfectionist, extremely niggling, and dislike uncertainty. There is limited information about obsessive-compulsive disorder and obsessive-compulsive personality disorder among patients with constipation. Thus, we thought that the subject was worth investigating. The present study also found that paranoid personality including skeptical and insecure features and thoughts about the control of other people and the desire to find secret meanings in events was much more com-

mon in patients with constipation with diseases. Furthermore, antisocial personality (including difficulty coping with societal rules and undeveloped superego) and narcissistic personality (including exaggerated appraisal of one's personal features) were much more common in patients with constipation with diseases. However, only obsessive-compulsive personality beliefs were significantly higher in both patients with constipation with and without disease. This shows that obsessive-compulsive features are important parts of anal-retentive behavior features. On the other hand, some features are more prominent in patients with constipation and disease than in patients with constipation only, which may be due to the severity of anal-retentive behavior features. Unfortunately, the limitation of the present study was that it was unable to describe the relationship between the severity of the disease and the anal-retentive behavior features. Anal characteristic features are not the disease to be treated, but when personality disorders are observed, first line of therapy may be psychotherapy.

Biofeedback is a learning strategy derived from psychological learning theory (27). The basis of the use of this treatment is feedback signals from various autonomic systems that shape the behavior of the organ in a desired direction. Biofeedback is used for several gastrointestinal diseases including constipation, incontinence, and gastric motility, among others. Biofeedback treatment in constipation is much more effective for improving muscle coordination control than for treating slow transit time constipation (27). Taken together, biofeedback can be regarded as a kind of psychotherapy for defecation control. Patients with functional constipation and anal characteristic features may benefit from both biofeedback and psychotherapy.

CONCLUSION

Anal-retentive behavior features are more prominent in patients with constipation. Anal-retentive behavior features are developed during the anal period in which defecation is learned, and there might be a relationship between these two entities. Biofeedback treatment is one of the modalities for both anal-retentive behavior features and functional constipation.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Kocaeli University School of Medicine.

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ORİJİNAL ÇALIŞMA-ÖZET
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Fonksiyonel kabızlık ve tutucu-anal kişilik özellikleri arasındaki ilişki

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ÖZET

Giriş ve Amaç: Kabızlık çok sık görülen bir defekasyon problemi olup çeşitli çevresel faktörlerle ilişkilidir. Defekasyon, anal dönem kişilik bulgularının oluştuğu çocukluk anal dönemde görülür. Çocukluk anal dönemdeki problemler sadece kişilik özelliklerini değil defekasyon fonksiyonlarını da etkileyebilir. Bu çalışmada fonksiyonel kabızlığı olan hastalarda kabızlık ve anal kişilik bozukluğu arasındaki ilişki incelenmesi amaçlanmıştır.

Gereç ve Yöntem: Çalışmaya ROME III kriterlerine göre fonksiyonel kabızlığı olan hastalar dahil edildi. İrritabl bağırsak hastalığı, yavaş geçişli konstipasyonu, çıkış obstrüksiyonu olan, malignitesi olan, psikiyatrik hastalığı olan hastalar çalışma dışı bırakıldı. Hastalar kişilik inanç, hastane anksiyete, depresyon ve obsesif inanç anketi doldurdu. Konstipe hastalar benign anorektal hastalığı olan ve olmayan olarak iki gruba ayrıldı. Elde edilen bulgular sağlıklı gönüllülerle karşılaştırıldı.

Bulgular: Fonksiyonel kabızlığı olan 47 hasta çalışmaya dahil edilmiştir. Çekingen, obsesif kompulsif, antisosyal, narsist, paranoid kişilik inançları kabız ve hastalıklı hastalarda kontrol grubuna göre daha fazla bulunmuştur. Mükemmelliyetçilik, önem, kontrol ve hastane anksiyetesi kabız ve hastalıklı grupta kontrol grubuna göre daha fazla bulunmuştur.

Sonuç: Kabızlık sosyoekonomik, duygusal stres, yaş ve diyet gibi çeşitli faktörlerden etkilenir. Bu çalışmada fonksiyonel kabızlığı olan hastalarda tutucu anal kişilik özelliklerinin daha belirgin olduğunu bulduk. Biofeedback bir çeşit defekasyon kontrol psikoterapisi olduğundan tedavide kullanılabilir.

Anahtar Kelimeler: Kabızlık, anal, çocukluk, kişilik bozukluğu, biofeedback

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ORIGINAL ARTICLE
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Secondary encapsulating peritonitis: a study of cases over five years

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ABSTRACT

Objective: Cocoon abdomen or sclerosing encapsulating peritonitis is a rare condition characterized by bowel entrapment in a cocoon-like membrane. Primary and secondary types have been described. Most patients present acutely with intestinal obstruction or peritonitis but history of long standing chronic symptoms may be present. The condition is usually not detected on imaging, and diagnosis at laparotomy is common. Surgical treatment includes excision of the membrane with adhesiolysis.

Material and Methods: A 5-year study of the patients operated for cocoon abdomen in our hospital was conducted. Analysis of patient symptoms, imaging findings, intra-operative findings and histopathology was carried out.

Results: Five males and three females were included into the study. Mean age was 29.6 years. Five patients presented with acute intestinal obstruction and three patients with perforation peritonitis. Laparotomy was performed in all cases. Successful excision of the membrane was done in all patients of obstruction while membrane excision could only be done in one patient of peritonitis. Histopathology revealed tuberculosis in six patients, one patient was already on anti-tubercular treatment and one patient had carcinoma. There was one mortality.

Conclusion: Cocoon abdomen is a rare condition. Tuberculosis should always be considered as a cause in endemic areas. Surgery is the preferred treatment and involves excision of the membrane but can be difficult in patients with superadded peritonitis or malignancy.

Keywords: Cocoon abdomen, perforation peritonitis, sclerosing encapsulating peritonitis, tuberculosis, cocoon carcinomata

INTRODUCTION

The term cocoon abdomen was first used by Foo et al. in 1978 when they described plastic adhesions with a fibrotic membrane occurring in young adolescent females in a virgin abdomen (1). Peritonitis chronica fibrosa incapsulata and sclerosing encapsulating peritonitis (SEP) are the other terms used in the literature for the same condition (2). The condition is characterized by partial or complete encapsulation of the bowel resulting in bowel obstruction of varying degrees associated with an inflammatory process of the peritoneum. A separate distinct condition is primary peritoneal encapsulation which is essentially a congenital duplication of the peritoneum in the absence of any inflammatory or sclerotic process (3). A preoperative diagnosis is seldom made and most of the cases are detected at laparotomy performed for small bowel obstruction. Histopathological analysis of the membrane provides a definitive method of ascertaining the underlying etiology.

MATERIAL and METHODS

We analysed the patients with an intraoperative finding of cocoon abdomen operated in our hospital over the past five years from 2013 to 2017, and eight such cases were identified. The study included five patients who presented prospectively and three cases which were identified retrospectively. Only patients with a virgin abdomen were included into the study and patients with any history of abdominal surgery were excluded. Study of patient characteristics including symptoms, abdominal signs, imaging findings, intra-operative findings and histopathological analysis were implemented (Table 1). Informed consent was taken from all the patients before surgery. Ethics committee approval was not needed as all patients presented with acute abdomen and needed surgical intervention.

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Table 1. Important patient parameters with management and outcome

Age/Sex	Clinical presentation	Imaging	Intraoperative findings	Procedure	Postoperative	HPE
28/M	**AIO** Per abdomen-lump in left iliac fossa right side of abdomen empty	**USG-** a large fluid filled bowel segment 12.2 x 7.1 x 10.6 cm with sluggish peristalsis **X-ray-** multiple air fluid levels	Full encapsulation of bowel Bowel localized over left iliac fossa Multiple tubercles over stomach Meckel's diverticulum Ascites	Adhesiolysis with removal of membrane	Prolonged ileus	Caseating granuloma
16/M	**AIO** Case of pulmonary TB on ATT since 5 1/2 months Rec SAIO	**CECT-** dilated jejunal and ileal loops with massive ascites **USG-** dilated bowel loops with ascites **X ray-** multiple air fluid levels	Full encapsulation of bowel Tubercles over serosal surface	Adhesiolysis with removal of membrane	Prolonged ileus	Chronic nonspecific inflammation
21/F	**PP** Per abdomen: hard stony feel to abdomen	**USG-** Pyoperitoneum- aspiration yielded pus	Thick fibrotic plastered membrane covering the bowel with ileal perforation Pyoperitoneum 1 litre	Limited adhesiolysis Ileostomy with mucous fistula	Necrosis of stoma Burst abdomen Re-explored on 7th POD revision of stoma and tension sutures	Caseating granulomas
60/M	**PP** A hard stony feel to abdomen more towards left side of abdomen	**USG-** Ascites with diffuse thickening of bowel loops (5 mm) Cholilithiasis	Thick fibrotic plastered membrane covering the bowel with perforation Pyoperitoneum 300 mL	Limited adhesiolysis with ileostomy	Postop sepsis and MODS Hypercalcemia not responding to standard treatment Prolonged ileus	Carcinoma with immunohistochemistry suggestive of GI or peritoneal origin
35/M	**AIO** Recurrent SAIO	**X-ray-** multiple air fluid levels **USG-** dilated bowel loops with sluggish peristalsis	Full encapsulation of bowel Localized ascites in pelvis= 100 mL	Adhesiolysis with removal of membrane	Postop uneventful	Caseous necrosis
12/F	**PP**	**X-ray-** free air under diaphragm **USG-** free fluid	700 mL of pus A localized membrane covering jejunum 2 large 2 cm perforations in jejunum Tubercles studded over whole bowel	Resection of bowel with ileostomy done	SSI Rest uneventful	Caseous necrosis
30/M	**AIO** Recurrent SAIO	**X-ray-** multiple air fluid levels **USG-** dilated and thickened bowel loops	Partial encapsulation of the ileum in membrane with an ileal stricture	Adhesiolysis with removal of membrane	SSI Prolonged ileus	Caseating granuloma
35/F	**AIO** Central distension, flanks comparatively empty	**CECT-** dilated ileal and jejunal loops with transition point at mid-ileal level **X ray-** multiple air fluid levels **USG-** dilated bowel loops	Encapsulation of whole of whole of small bowel in a thick whitish membrane	Adhesiolysis with removal of membrane	Postop uneventful	Caseating granulomas

AIO: Acute intestinal obstruction, USG: Ultrasonography, TB: Tuberculosis, ATT: Anti-tubercular treatment, SAIO: Sub-acute intestinal obstruction, CECT: Contrast enhanced computed tomography, PP: Perforation peritonitis, POD: Postoperative day, MODS: Multiple organ dysfunction syndrome, GI: Gastrointestinal, SSI: Surgical site infection.

RESULTS

Mean age of the patients was 29.6 years (ranging from 12 years to 60 years). There were five males and three females. Five patients presented to us with features of acute intestinal obstruction (AIO) and three patients presented with features of perforation peritonitis (PP).

Patients presenting with AIO had features of small bowel obstruction like acute abdominal pain, vomiting, abdominal distension and obstipation. Three patients had history of recurrent episodes of subacute intestinal obstruction (SAIO), others presented more acutely with only 4-5 days history. Of the three patients with AIO, two had disproportionate distension of the abdomen confined to one half of the abdomen. In one patient, the distension was mainly confined to the left side of the abdomen, initially giving a suspicion of sigmoid volvulus while the right side of the abdomen felt empty on palpation. The 2nd patient had central abdominal distension with comparatively empty bilateral flank region. One of the patients was a known case of pulmonary tuberculosis taking anti tubercular treatment (ATT) for the last five and a half months.

In patients with perforation peritonitis, one had typical guarding and rigidity associated with PP. In the other two patients, a more stony hard feeling on palpation was present, which was different from the normally seen rigidity and guarding in PP patients.

Abdominal X-ray was done in all cases. All AIO patients showed multiple air fluid levels on radiograph. Only one patient with PP showed free gas under the diaphragm. Ultrasonography (USG) was done in all patients which showed features consistent with AIO and PP in the respective group of patients but no features suggestive of any cocoon were present. Computed tomography (CT) abdomen conducted in two cases showed thickening of the bowel loops in one patient with a suspicious membranous layer engulfing the bowel and dilated bowels loops with a transition point in the other patient.

Intraoperatively, in patients with AIO, four of the 5 patients had a thick whitish membrane engulfing whole of the small bowel (Figure 1), and in one patient the membrane was only partially engulfing the bowel with a part of the bowel free. Adhesiolysis was done in all cases and the whole of the membrane was excised out.

In two patients of PP, in contrast, the membrane was not delineable and instead a plastered cemented layer (Figure 2) was covering the whole of the bowel. In one patient, iatrogenic injury occurred while dissecting and with much difficulty the site of injury was brought out as a double barrel stoma. Another peculiar thing in this patient was that the mesentery was virtually non-existent and only small sub-millimetric vessels arising from within the cocoon supplied the bowel with the mesenteric fat totally resorbed into the inflammatory process. Another patient in this group presented with the same abdominal finding of plastered cocoon, an ileostomy was done in this patient and few bits of tissue from the adhesions were sent for biopsy which revealed carcinoma (Figures 3 and 4), immunohistochemistry (IHC) of which was suggestive of possible origin from gastro-intestinal (GI) tract or peritoneum. In the 3rd patient, after sepa-

Figure 1. Encapsulating membrane opened (arrows) with underlying bowel.

Figure 2. Plastered cocoon in a patient with peritonitis (arrow).

Figure 3. Cocoon with a fibrotic membrane of cancer.

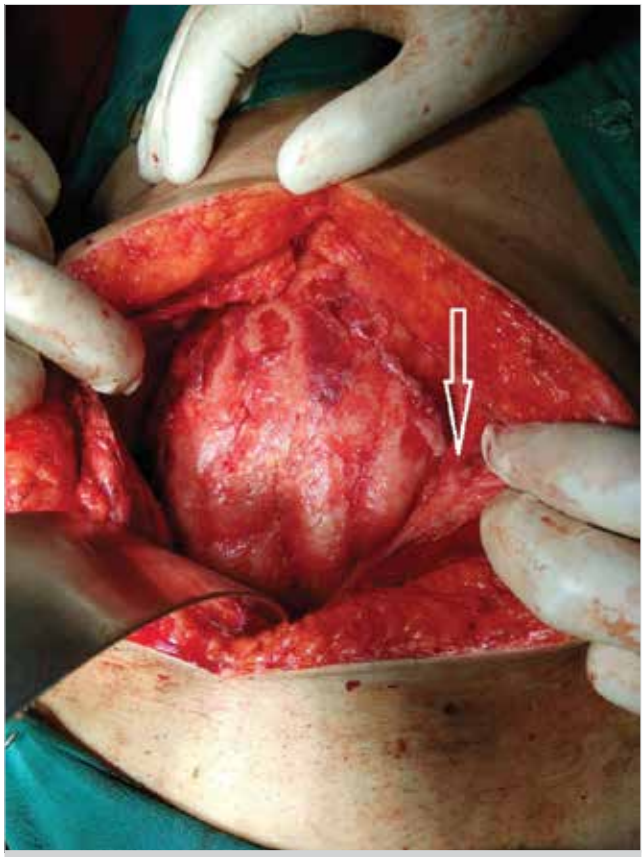

Figure 4. Matted bowel loops with overlying thick peritoneum (arrow).

rating the cocoon membrane, two perforations (= 3 cm) were found in the jejunum and whole of the serosal surface of the bowel was studded with tubercles (Figure 5). Resection of the perforated segment with ileostomy was done.

In the post-operative period, among patients with AIO, two patients developed surgical site infection (SSI) managed with

Figure 5. After opening the membrane, underlying bowel shows perforation with studding of bowel by tubercles.

wound care and dressings. In four patients, there was prolonged ileus following surgery and was managed conservatively with nasogastric aspiration and intravenous fluids, which resolved only after 6-8 days after which the patients were gradually started on oral diet.

In the peritonitis group, one patient developed burst abdomen with necrosis of the ileostomy post-operatively. This patient was re-explored on the 7th postoperative day and refashioning of the stoma was done with closure of the abdominal wall with tension sutures. Another patient with PP developed postoperative hypercalcemia (serum calcium= 13 mmol/L with normal parathormone levels) which was unresponsive to standard treatment. This patient ultimately developed sepsis with multiple organ dysfunction (MODS) and lost on 11th postoperative day (POD), which was the only mortality in our study. Histopathological examination (HPE) of the adhesion band in this

patient later revealed carcinoma. HPE of all other patients was suggestive of tuberculosis, except in one patient who was already on ATT, it showed only chronic inflammation. All patients documented with tuberculosis were started on ATT.

DISCUSSION

Abdominal cocoon or sclerosing encapsulating peritonitis is an uncommon condition. Two varieties of this condition have been described: Primary and Secondary. Primary or idiopathic form is most commonly seen in adolescent girls and retrograde menstruation with viral infection has been postulated as a cause although it has not been validated as yet since the condition is also found in men (4).

The secondary form where there is a definite cause has been associated with the use of practolol, abdominal tuberculosis, chronic ambulatory peritoneal dialysis, sarcoidosis, systemic lupus erythematosus, cirrhosis and ventriculoperitoneal and peritoneovenous shunts (5). In our part of the world, tuberculosis is an important cause of the condition. Singh et al. (6) and Wani et al. (7), in their studies, have reported abdominal tuberculosis as causing cocoon abdomen in nine (out of 18) and eleven (out of 11) patients, respectively. In our study, we also found tuberculosis in six of the patients while one patient was already taking ATT for pulmonary tuberculosis.

In our study, one case was diagnosed as adenocarcinoma with IHC suggestive of origin from the gastrointestinal tract or peritoneum. Although rarely reported in the literature, a few studies have described malignancy as a causative factor of SEP. Jimil et al. (8) have described metastatic mucinous adenocarcinoma in their patient causing cocoon carcinomatosa. Katz et al. (9), in their patient, have indicated moderately differentiated adenocarcinoma as the cause of SEP with immunohistochemistry suggestive of origin from peritoneum or ovary. Similarly, Wang et al. (10) have described cocoon-like formations in patients with stage IV gastroentero-pancreatic NETs and postulated that SEP may be a terminal culmination point in the disease progression of this condition.

The clinical presentation of SEP is usually non-specific and includes colicky abdominal pain, vomiting, nausea, or constipation. Rarely, SEP may present with perforation peritonitis. Patients usually report to the emergency departments with signs and symptoms of intestinal obstruction or perforation and usually undergo operations on an urgent basis (11).

Conventional radiographs may show air fluid levels in patients who present with intestinal obstruction or free gas under the diaphragm in patients with peritonitis.

USG findings, though not confirmatory, include dilated bowel segments encased by a dense fibrous membrane or free abdominal fluid and a thickened peritoneal layer (12). However, these findings are non-specific and can be found in many other inflammatory processes of the peritoneum.

Contrast-enhanced computed tomography (CECT) is the most helpful radiological tool for confirming the diagnosis, planning therapy, and avoiding unnecessary resection in patients with SEP (11). Characteristic CT finding helpful in clinching the diagnosis is conglomeration of contrast dense small bowel loops in the centre encased by contrast free capsule in the periphery (3).

Appropriate treatment of this condition is controversial. In patients with mild symptoms, conservative treatment with total parenteral nutrition, nasogastric decompression and peritoneal rest is usually attempted as a first measure as in most cases of intestinal obstruction. In this subset of patients, various drugs have been found to be helpful in ameliorating the fibrotic process include colchicine, steroids, and immunosuppressive agents like azathioprine and mycophenolate mofetil (13).

Surgery, however, remains the mainstay of treatment in most cases. The basis of any surgery is the removal of the membrane and division of any adhesions. Various procedures described in the literature include resection of the peritoneum and fibrous tissue and separation of adhesions to release the bowel, partial membrane excision with adhesiolysis, resection and anastomosis, resection and anastomosis with protective stoma, depending on patient-related factors (3,14). However, Wang et al. (10) have found surgery not very helpful in patients with cocoon secondary to carcinoma in their study.

Meticulous surgical technique is essential to prevent iatrogenic bowel injuries. In our experience at two points of time, extreme care is to be exercised during surgery. First is while opening the peritoneum, which is quite thickened in these patients and densely adherent to the cocoon membrane. While opening the peritoneum, there is a danger of inadvertent entry into the bowel. Second is to find an adequate spot for entry into the cocoon. In our experience, it is easier to open the membrane near the apex of the cocoon as the bowel is not much adherent at this site. Rest of the dissection is usually straightforward as a well-defined plane is usually present between the membrane and bowel. Another thing of note is that in patients with peritonitis complicating the cocoon, the bowel and membrane form one thick adherent plastered layer in which dissection is virtually impossible. The wise thing to do in this group of patients is to perform an ileostomy and not to attempt complete removal of the membrane.

Postoperative period is usually prolonged and rough in these patients. The most common postoperative complications are early postoperative small bowel obstruction, intra-abdominal infection, entero-cutaneous fistula, short bowel syndrome, and bowel perforation (11). In our study, we observed prolonged ileus and delayed return of bowel movements in many patients

probably due to extensive dissection, which, however, resolved with conservative approach in all the patients.

CONCLUSION

In conclusion, cocoon abdomen or SEP is a rare condition. Most cases are detected at laparotomy. Surgical technique should be meticulous and consist of dissection and excision of the membrane. Tuberculosis should always be considered as a possible etiology in endemic areas. In cases of carcinoma, it usually represents a final result of the disease pathway and surgery is seldom of any benefit.

Ethics Committee Approval: Ethics committee approval was not needed as all patients presented with acute abdomen and needed surgical intervention.

Informed Consent: Informed consent was taken from all the patients before surgery.

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ORİJİNAL ÇALIŞMA-ÖZET
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İkincil enkapsüle peritonit: beş yıllık hasta serisi

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ÖZET

Giriş ve Amaç: Abdominal koza veya sklerozan enkapsüle peritonit, koza benzeri bir membran içerisinde bağırsak sıkışması ile karakterize nadir bir durumdur. Birincil ve ikincil türleri tanımlanmıştır. Çoğu hasta bağırsak tıkanıklığı veya peritonit ile akut olarak başvurmakta ama uzun süredir varolan kronik belirti öyküsü de bulunabilmektedir. Görüntüleme yöntemlerinde bu durum tespit edilemeyebilir ve tanı genellikle laparotomi sırasında konulur. Cerrahi tedavi, adezyolizis olan membranın eksizyonudur.

Gereç ve Yöntem: Hastanemizde, beş yıllık süreçte abdominal koza sebebiyle opere edilen hastaların analizi yapıldı. Analiz, hasta belirtileri, görüntüleme bulguları, intraoperatif bulgular ve histopatolojiyi içerdi.

Bulgular: Çalışmaya beş erkek, üç kadın hasta dahil edildi. Ortalama yaş 29.6 idi. Beş hasta akut bağırsak tıkanıklığı, üç hasta da perfore peritonit ile başvurdu. Tüm olgulara laparotomi uygulandı. Tıkanıklığı olan tüm hastalarda başarılı bir membran eksizyonu gerçekleştirilirken, perfore peritonit olan hastaların sadece birinde yapılabildi. Histopatolojik inceleme altı hastada tüberküloz tanısı koydu. Bir hasta zaten antitüberküloz tedavisi almaktaydı ve bir hastada karsinom saptandı. Bir hastamızda mortalite görüldü.

Sonuç: Abdominal koza nadir bir durumdur. Endemik bölgelerde tüberküloz her zaman göz önünde tutulmalıdır. Cerrahi, tercih edilen tedavi yöntemi olup membranın eksizyonunu içermektedir fakat peritonit veya maligniteli hastalarda zor olabilir.

Anahtar Kelimeler: Koza karnı, perforasyon peritonit, sklerozan enkapsüle peritonit, tüberküloz, koza karsinomu

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ORIGINAL ARTICLE
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Single-stage treatment with ERCP and laparoscopic cholecystectomy versus two-stage treatment with ERCP followed by laparoscopic cholecystectomy within six to eight weeks: a retrospective study

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ABSTRACT

Objective: Obstructive jaundice is one of the earliest symptoms of a hepatobiliary system disorder. The aim of the present study was to compare single stage endoscopic retrograde cholangiopancreatography (ERCP)/laparoscopic cholecystectomy (LC) and two-stage ERCP and LC with respect to the frequency of imaging, duration of anesthesia and the length of stay in our clinic.

Material and Methods: Of the 350 patients undergoing ERCP between 01.01.2015 and 31.12.2016, 31 patients with single-stage ERCP and LC were assigned to Group A and 25 patients with two-stage ERCP followed by LC within 6-8 weeks were assigned to Group B. Eligibility criteria included ERCP duration, difficulty of the procedure, bile duct stones as demonstrated by imaging methods, no contraindications for LC and no suspected or known malignancy. The same surgeon performed ERCP and LC in both groups.

Results: No cases of morbidity or mortality occurred in any groups. The average length of stay was 8.03 ± 4.97 days in Group A, which was significantly longer (9.92 ± 4.05 days) in Group B ($p< 0.026$). However, the length of stay (in days) was calculated as the time from presentation to hospital until discharge and not the time elapsed after the procedure. Imaging methods were used 3.9 ± 3.07 times in Group A and significantly more frequently (5.92 ± 2.55 times) in Group B ($p< 0.001$). Total duration of anesthesia was not statistically significantly different between the study groups (154.06 ± 53.76 min in Group A and 167.04 ± 75.17 min in Group B).

Conclusion: In conclusion, single-stage ERCP/LC is associated with shorter hospital stay and lower frequency of imaging and can be safely used in selected cases. No cases of pancreatitis or mortality occurred following the single-stage procedure. The single-stage procedure can be safely used in selected patients with obstructive jaundice.

Keywords: Endoscopic retrograde cholangiopancreatography, laparoscopic cholecystectomy, magnetic resonance cholangiopancreatography, ultrasonography

INTRODUCTION

Obstructive jaundice is one of the earliest symptoms of hepatobiliary dysfunction. Patients with obstructive jaundice are referred as outpatients or by ambulance to facilities providing endoscopic retrograde cholangiopancreatography (ERCP). ERCP is performed only in selected specialized centers because it is an invasive procedure that involves risks and requires teamwork, expertise and close monitoring. About 60-80% of patients with gallstones are asymptomatic. Scientific studies have shown that clinical manifestations develop in 1-2% of patients with silent gallstones each year (1). As reported in the literature, the majority of common bile duct (CBD) calculi originate from the gallbladder and migrate to the bile duct secondarily. The prevalence of choledocholithiasis varies between 10 to 18% in patients undergoing cholecystectomy for symptomatic gallstones, and in 25% of the cases, choledocholithiasis may be detected intraoperatively. The current gold standard method is laparoscopic cholecystectomy (LC) which may be performed with or without intraoperative cholangiography (IOC). While about one-third of patients with choledocholithiasis will spontaneously clear the CBD within 6 weeks, severe adverse events of untreated CBD stones such as cholangitis and pancreatitis may develop in the remaining patients. It is therefore generally recommended to detect and treat choledocholithiasis. No single method or algorithm has been shown to be superior to others when treating the obstructing complications of calculous bil-

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iary disease including choledocholithiasis, cholangitis and acute biliary pancreatitis (2).

In recent years, studies on single-stage ERCP and LC have been published in the literature. In our clinic, the single-stage approach is performed during the same surgical session for the treatment of selected patients presenting with choledocholithiasis. The ability to perform ERCP and surgical treatment in the same unit allows us to eliminate organizational problems. Generally, our approach to patients with obstructive jaundice involves single-stage ERCP and LC, ERCP followed by surgery within 4-6 weeks and in the case of difficult stones or failed ERCP, laparoscopic or conventional cholecystectomy. Surgically, these procedures are performed with the following sequence: choledochotomy, IOC, stone removal followed by T-tube placement or choledochoduodenostomy.

Our paper "Approach to patients with obstructive jaundice: Single-stage ERCP and laparoscopic cholecystectomy" was presented as an oral presentation at 14th National Hepato-gastroenterology Congress in April, 2017.

MATERIAL and METHODS

Of the 350 patients undergoing ERCP between 01.01.2015 and 31.12.2016, 31 patients were assigned to Group A to undergo single-stage ERCP and LC and 25 patients were assigned to Group B to undergo two-stage ERCP followed by LC within 6-8 weeks (Table 1). Eligibility criteria included ERCP duration, the difficulty of the procedure, bile duct stones as demonstrated by imaging methods, no contraindications for LC and no suspected malignancy. Patients assigned to the single-stage treatment first underwent ERCP procedure in the operating room. After ERCP, patient's position was changed and LC was performed under standard conditions. In the two-stage approach, LC was performed within 6-8 weeks. The aim was to compare the study groups with respect to the frequency of imaging, duration of anesthesia and length of stay. Our hospital does not have an institutional ethics committee. Thus, the current research was conducted in accordance with the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects".

Table 1. Surgical rates of open and laparoscopic cholecystectomy

		Number	%
Group	Group 1	31	55.4
	Group 2	25	44.6
Surgery	Open	7	12.5
	LC	49	87.5
Gender	Male	21	37.5
	Female	35	62.5

LC: Laparoscopic cholecystectomy.

Statistical Analyses

The normality of distribution of continuous variables was tested by Shapiro-Wilk test. Mann-Whitney U test was used for the comparison of two independent groups of variables with a non-normal distribution and Chi-square test was used to assess the relation between categorical variables. Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 24.0 and a p value less than 0.05 was considered statistically significant.

RESULTS

No cases of morbidity or mortality occurred in any groups. IOC was not needed at the time of LC in two-stage Group B patients. Two patients from Group B awaiting LC presented to the emergency room with biliary episodes within 6-8 weeks after ERCP and LC was performed following preliminary arrangements.

The frequency of imaging methods was assessed for both groups before and after ERCP (Table 2). On average, imaging methods were used 3.9 ± 3.07 times in our Group A series after single-stage procedure and significantly more frequently (5.92 ± 2.55 times) in Group B ($p< 0.001$). Thus, the frequency of imaging was lower in our Group A series. Successful cannulation was achieved in 95% of two-stage Group B patients and in 100% of one-stage Group A patients; the greater success rate in Group A was related to the fact that patients with failed cannulation were not included in this group. One case of moderate pancreatitis and one case of mild pancreatitis as diagnosed by Atlanta classification occurred in Group B patients. Patients responded well to the medical therapy and were discharged with full recovery. The average length of stay was 8.03 ± 4.97 days in our Group A series and significantly longer (9.92 ± 4.05 days) in Group B series ($p< 0.026$) (Table 2). Total duration of anesthesia did not differ statistically significantly between the study groups (154.06 ± 53.76 min in our Group A series and 167.04 ± 75.17 min in our Group B series). GGT values were significantly greater in Group A patients (377.78 ± 306.69) versus Group B (107.95 ± 107.64 U/L ($p> 0.001$). A marked reduction was noted in GGT values following surgery and ERCP (Table 2). Preoperative total bilirubin was significantly elevated in our Group A series (2.56 ± 2.25 U/L) compared to Group B series (1.39 ± 1.84 U/L; $p> 0.010$). Bilirubin values returned to normal at postoperative day 3 in both groups. Amylase values were comparable between both groups (Table 3).

DISCUSSION

Study population consisted mainly of female patients (62.5%) with a smaller percentage of male patients (37.5%). 87.5% of the patients was treated with LC and 12.5% with open conventional cholecystectomy (Table 1).

Currently, the management of obstructive jaundice remains an ongoing topic of debate in the literature. Today, single-session ERCP and LC is a safe and feasible method performed on the basis of studies cited in the literature. Aside from technical ex-

Table 2. Demographic characteristics of the study population

Variables	Group 1 (n= 31)	Group 2 (n= 25)	P
Age*	61.29 ± 19.89	53.6 ± 18.11	0.140
Gender Female	14 (45.2)	7 (28.0)	0.187
Male	17 (54.8)	18 (72.0)	
Length of hospital stay *	8.03 ± 4.97	9.92 ± 4.05	0.026 **
Total duration of anesthesia	154.06 ± 53.76	167.04 ± 75.17	0.748
Frequency of imaging	3.9 ± 3.07	5.92 ± 2.55	0.001**
Alanine aminotransferase (U/L)POD 0	122.66 ± 100.04	65.05 ± 88.18	0.005**
Alanine aminotransferase (U/L)POD1	101.19 ± 75.47	73.25 ± 102.12	0.017**
Alanine aminotransferase (U/L) POD3	74.9 ± 54.01	54.12 ± 79.91	0.008**
Aspartate aminotransferase (U/L)POD 0	81.86 ± 60.76	58.75 ± 63.18	0.029**
Aspartate aminotransferase (U/L)POD 1	74.58 ± 53.4	55.63 ± 47.19	0.038**
Aspartate aminotransferase (U/L)POD 3	48.26 ± 26.59	37.64 ± 28.56	0.024**
Gamma-glutamyl-transferasePOD O U/L	377.78 ± 306.69	107.95 ± 107.64	0.001**
Gamma-glutamyl-transferasePOD 1 U/L	318.05 ± 260.92	83.14 ± 89.89	0.001**
Gamma-glutamyl-transferasePOD 3 U/L	246.07 ± 203.9	93.4 ± 116.36	0.001**

* Mean ± Std. deviation. ** Significant at 0.05 level. † n (%).
POD: Post-operative day.

Table 3. Clinical laboratory test results by study groups

Variables	Group 1 (n= 31)	Group 2 (n= 25)	p
Creatinine POD 0 mg/dL	0.86 ± 0.29	0.75 ± 0.24	0.220
Amylase (U/L)	87.44 ± 99.32	82.34 ± 99.19	0.798
WBC count (10^9) POD0/L)	9.48 ± 4.72	9.08 ± 4.29	0.876
WBC count(10^9) POD3	10.98 ± 4.15	9.58 ± 4.27	0.245
Bilirubin total POD 0 (mg/dL)	2.56 ± 2.25	1.39 ± 1.84	0.010**
Bilirubin, total POD 1 (mg/dL)	1.84 ± 1.27	1.33 ± 1.08	0.090
Bilirubin, total POD 2 (mg/dL)	1.47 ± 1.3	0.98 ± 0.77	0.185
Bilirubin total POD 3 (mg/dL)	1.38 ± 1.3	0.8 ± 0.65	0.034**
Direct POD 0 (mg/dL) (mg/dL)	1.8 ± 1.89	0.67 ± 1.07	0.003**
Bilirubin, direct POD 1 (mg/dL)	1.15 ± 0.99	0.64 ± 0.69	0.066
Bilirubin, direct POD 2 (mg/dL)	1.03 ± 1.18	0.44 ± 0.4	0.028**
Bilirubin, direct POD3 (mg/dL)	0.76 ± 0.71	0.4 ± 0.42	0.008**

* Mean ± Std. deviation. ** Significant at 0.05 level.
POD: Post-operative day.

pertise, the procedural success depends on the papillary size, tortuosity, stenosis or abnormal papilla position. When ERCP is performed as indicated, complications can be reduced significantly. The use of conventional imaging methods and identification of the type of icterus are important for the management of patients with obstructive jaundice.

In patients discharged home without operation after acute calculous cholecystitis (ACC), the probability of a gallstone-related events by 6 weeks, 12 weeks and 1 year is 14%, 19% and 29%, respectively. Recurrent symptoms involve biliary colic in 70%, whereas biliary tract obstruction occurs in 24% and pancreatitis in 6% of the patients. Despite the frequency of ACC, significant

controversy remains regarding the diagnosis and management of ACC. The 2007 and 2013 Tokyo guidelines (TG) attempted to establish objective parameters for the diagnosis of ACC (3).

Be et al. state that although LC and therapeutic ERCP have revolutionized the management of cholelithiasis and CBD stones, the use of these modalities as a single-stage procedure remains controversial and conclude in their study that single-stage LC/ERCP provides efficient therapy for CBD stones and might be beneficial in select patients who may not tolerate a second anesthetic procedure (4).

In 2007, the Tokyo Guidelines for the management of acute cholangitis and cholecystitis (TG07) were first published in the Journal of Hepato-Biliary-Pancreatic Surgery. The Tokyo Guidelines Revision Committee (TGRC) was set up in June 2010 because of the detection of low diagnostic sensitivity of TG07 for acute cholangitis. The TGRC held meetings a total of 35 times. The updated Tokyo Guidelines (TG13) have a superior diagnostic capability compared to TG07 due to higher sensitivity (87.6%) and specificity (77.7%). Ultrasonographic Murphy's sign has a high specificity but low sensitivity (5).

As recommended by the TG13 for the management of acute cholecystitis, laparoscopic cholecystectomy is the first-line treatment in patients with Grade I (mild) acute cholecystitis. In patients with Grade II (moderate) acute cholecystitis, delayed/elective laparoscopic cholecystectomy after initial medical treatment is the first-line treatment. In non-responders to initial medical treatment, gallbladder drainage should be considered. In patients with Grade III (severe) acute cholecystitis and organ failure, appropriate organ support in addition to initial medical treatment is necessary. Urgent or early gallbladder drainage is recommended. Cholecystectomy can be performed after improvement of the acute inflammatory process (6).

There are some studies in the literature on the timing of treatment recommended by the TG13. V Amirthalingam et al. reported that the Tokyo Guidelines 2013 may be too restrictive and in patients with moderate and severe acute cholecystitis, the severity grading of AC is not the sole determinant of early LC and patient comorbidity also has an impact on clinical decisions (7).

Discussions are ongoing about the most appropriate time and the best method to remove the bile duct calculi. Intraoperative endoscopic retrograde cholangiopancreatography (IO-ERCP) should be considered as an alternative method for this purpose (8).

Two-stage approach including ERCP followed by LC within a couple of weeks is the current management of choledocholithiasis. Performing ERCP and LC in a single-session has not been fully established in major guidelines. Although relevant literature is scarce, one of the main reasons leading to the adoption of two-stage approaches is the fact that these are performed by two specialists from separate medical fields. Potential or actual organizational problems may have avoided further advances in single-session ERCP and LC. Also, restrictive nature of the current guidelines for the management of acute cholecystitis is another reason.

Maris Jones et al. have been performing one-step procedures since 1997. The results of their work were presented in 1998 at the sixth World Congress of Endoscopic Surgery, and at the American Society of Gastrointestinal Surgeons (SAGES) annual conference in 2010.

Hyperbilirubinemia and cholestasis are two closely related but distinct entities. While hyperbilirubinemia refers solely to elevated bilirubin, cholestasis manifests itself with increased GGT and ALP levels. Also, a range of causative factors overlap in the development of hepatocellular and cholestatic jaundice (9). For the management of patients with jaundice, each case should be managed with utmost care in order to determine the pathogenesis of the jaundice and employ appropriate therapeutic options.

In the present study, the common bile duct was cannulated using the standard technique in patients included in the study group. Precut technique was used for CBD cannulation in two patients in whom cannulation was particularly difficult. For the Group A patients undergoing single-stage procedure, change from left lateral position to supine position was easily done immediately after ERCP before initiation of LC. Single-stage ERCP/LC was carried out as described by the relevant literature. Our main advantage was the fact that the same surgeon performed both procedures. This approach has considerable advantages in the management of patients with obstructive jaundice by avoiding delays and organizational problems since the same surgeon is responsible for the whole treatment and follow-up of the patient, which also leads to successful patient management and monitoring.

Pencev et al. have reported that ERCP can be safely done within the first 24 hours of laparoscopic cholecystectomy but delays in removal of CBD stones may lead to complications and malignancy should be excluded in patients with persistent jaundice (10). In the present study, ERCP was repeated in one Group B patient because of persistent jaundice who was later diagnosed with primary sclerosing cholangitis.

In the study by Kimura et al., the proportion of acute cholangitis and cholecystitis after ERCP was 0.5-2.4% for cholangitis and 0.2-1.0% for acute cholecystitis (3). In our study, corresponding figures were 0.57% and 0.86% for the total number of patients undergoing ERCP, which are consistent with the literature. First ERCP and then LC were performed for the single-stage procedure in our Group A patients. Cholecystectomy operation might be relatively difficult for gas accumulation in the bowel when ERCP is prolonged. In some studies have noted in their retrospective review that ERCP can be performed first safely with

only a slight degree of small bowel dilation at the time of LC (11). LC was relatively difficult in patients with a prolonged ERCP time. This results from bowel distension after air insufflation. In order to avoid this, air was adequately aspirated while removing the duodenoscope after ERCP. However, it is not often possible to aspirate all the air in the intestines. We also employed rectal tube in the case of excessive bowel distension. LC was safely done after ERCP. Jones et al. have stated that one-step procedure has a bright future for the treatment of choledocholithiasis and do not advocate the routine use of intraoperative ERCP in uncomplicated laparoscopic or open cholecystectomies; however they consider that one-step procedure may be highly advantageous in certain cases (2). None of the patients in single-stage Group A presented with biliary episodes or complaints after discharge.

IOC was not needed at the time of LC in two-stage Group B patients. Two patients from Group B awaiting LC presented to the emergency room with biliary episodes within 6-8 weeks after ERCP and LC was performed following preliminary arrangements. The frequency of imaging methods was assessed for both groups before and after ERCP (Table 2). On average, imaging methods were used 3.9 ± 3.07 times in our Group A series after single-stage procedure and significantly more frequently (5.92 ± 2.55 times) in Group B ($p< 0.001$). Thus, the frequency of imaging was lower in our Group A series.

Sahoo et al. have randomized 83 patients with cholecystocholedocholithiasis into two groups (12). In group A, 41 patients underwent first ERCP and then LC and in group B, 42 patients underwent LC and intraoperative cholangiography and when choledocholithiasis was confirmed, these patients had ERCP by laparoendoscopic rendez-vous technique. Successful cannulation was achieved in 33 (80.5%) cases in group A and 39 cases (93%) in group B. In the same study, severe pancreatitis developed in 12% of group A patients and in none of the patients in group B. In our study, successful cannulation was achieved in 95% of two-stage Group B patients and in 100% of one-stage Group A patients; the greater success rate in Group A was related to the fact that patients with failed cannulation were not included in this group. One case of moderate pancreatitis and one case of mild pancreatitis as diagnosed by Atlanta classification occurred in Group B patients. Patients responded well to the medical therapy and were discharged with full recovery.

Mallick et al. have shown that ERCP/ LC is a safe and effective option when performed in a single-session at a tertiary care center and is associated with a reduced length of hospitalization (11). The average length of stay was 8.03 ± 4.97 days in our Group A series and significantly longer (9.92 ± 4.05 days) in Group B series ($p< 0.026$) (Table 2). However, the length of stay (in days) was calculated as the time from presentation to hospital until discharge and not the time elapsed after the procedure. This period included the time spent for ultrasonography (USG), magnetic resonance cholangiopancreatography (MRCP) and preoperative preparations. This explains the longer length of stay (LOS) in our study compared to LOS cited in the literature since all steps of patient management were included when calculating the length of hospital stay. Another reason for prolonged length of stay in our study was the inclusion of time spent for diagnosis and preparation of the patients with obstructive jaundice after taking over their management from consulting physicians. Although our institution is a secondary-care hospital, treatment of patients with obstructive jaundice is provided effectively and safely. An important factor that facilitates the organizational steps is related to the fact that the same surgeon performs both procedures for the patient.

In their study, Sahoo et al. have advocated that intraoperative endoscopic retrograde cholangiopancreatography (IO-ERCP) is an effective method that can be safely performed in routine clinical setting and is associated with a lower postoperative risk of pancreatitis and shorter hospital stay in patients with choledocholithiasis detected with IOC during LC (12). None of the patients in our single-stage Group A developed pancreatitis following ERCP or complications related to LC and single-stage was performed safely. Interestingly, all of the patients (in both groups) meeting the eligibility criteria expressed their wish to be treated with the single-stage procedure before signing the informed consent. Strict patient selection criteria were employed in our study and patients with prolonged ERCP and those who did not meet aforementioned eligibility criteria were excluded from Group A.

In their study Bansal et al. have randomized 168 patients (84 to the single-stage procedure and 84 to the two-stage procedure) and concluded that single- and two-stage treatments had similar success and complication rates but the single-stage strategy was better in terms of shorter hospital stay, reduced need for additional procedures and cost effectiveness (13). In the present study, while comparable results were obtained in both groups, previously mentioned advantages were achieved in our Group A.

Laparoscopic common bile duct exploration provides an alternative therapeutic approach that is safer and more reliable, allows for earlier recovery, and provides a cost-effective treatment of common bile duct stones (14). ERCP is an established procedure for the management of bile duct stones before and after laparoscopic cholecystectomy but laparoscopic choledochal exploration (LCE) is still evolving and experience is currently limited with very few institutions. Given the anatomical variations of the cystic duct opening into the bile duct, we believe that LCE is not appropriate for the management of choledocholithiasis. Thus, we did not perform LCE in our patients.

The single-stage LC/ERCP provides an effective treatment for cholelithiasis and choledocholithiasis and might be beneficial in select patients who may not tolerate a second anesthetic

procedure (4). Mean age of our patients was 61.29 ± 19.89 years and completion of the procedures under the same anesthesia provides improved patient satisfaction and is advantageous for elderly patients who cannot tolerate a second anesthetic procedure. Total duration of anesthesia did not differ statistically significantly between the study groups (154.06 ± 53.76 min in our Group A series and 167.04 ± 75.17 min in our Group B series). GGT values were significantly greater in Group A patients (377.78 ± 306.69) versus Group B (107.95 ± 107.64 U/L (p> 0.001). A marked reduction was noted in GGT values following surgery and ERCP (Table 2). Preoperative total bilirubin was significantly elevated in our Group A series (2.56 ± 2.25U/L) compared to Group B series (1.39 ± 1.84 U/L; p> 0.010). Bilirubin values returned to normal at postoperative day 3 in both groups. Amylase values were comparable between both groups (Table 3).

Although early and delayed CCY equally reduce the risk of subsequent recurrent biliary events, patients are at 10-fold higher risk of a recurrent biliary event while waiting for a delayed cholecystectomy compared to patients who underwent early cholecystectomy (15). In our study, recurrent biliary episodes were not detected in patients who underwent ERCP and LC at the same session.

In a randomized study with 372 patients, Nathanson et al. have suggested that 66% of CBD stones can be extracted using trans-cystic duct clearance and advocated that this method is a good choice for patients after Billroth II gastrectomy, failed ERCP access or where long delays would occur for patient transfer to other locations for the ERCP (16). In the present study, we considered that trans-cystic duct clearance would be inappropriate for our patients and avoided this strategy.

Baillie et al. have reported that same-day laparoscopic cholecystectomy following ERCP for choledocholithiasis may confer additional benefits for patients with major comorbidities (17). They propose the use of CO_2 insufflation instead of air insufflation to overcome problems associated with bowel distension. In our single-stage group, ERCP procedure was conducted using air insufflation and the air trapped in the bowel did not pose any problem during LC. However, due to safety reasons, we preferred the open technique for port access for LC. Despite safe performance of LC after ERCP, air can still be present inside the intestinal loops.

Bansal et al. have compared the outcomes of primary laparoscopic CBD exploration (LCBDE) and secondary LCBDE after failed ERCP in patients with choledocholithiasis and found that mean operative time, the degree of difficulty, length of hospital stay and cost of procedure were significantly reduced in the group undergoing primary LCBDE for difficult stones (18). In our study, one patient with a difficult stone underwent LC following failed ERCP and choledochotomy and the stone was extracted using an endoscopicstoneretrievalbasket. Limitations of our study include its retrospective design and the small sample size.

CONCLUSION

In conclusion, single-stage ERCP/laparoscopic cholecystectomy is associated with shorter hospital stay and lower frequency of imaging and can be safely used in selected cases. Additionally, none of the patients undergoing single-stage procedure was admitted to the emergency room for pancreatitis or recurrent biliary episodes. Single-stage procedure can be safely used in select patients with obstructive jaundice who may not tolerate a second anesthetic procedure.

Ethics Committee Approval: Ethics committee approval was not obtained because the study was a retrospective study.

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ORİJİNAL ÇALIŞMA-ÖZET
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Eş zamanlı ERCP ve laparoskopik kolesistektomiye karşı çift aşamalı ERCP ve 6-8 hafta takiben laparoskopik kolesistektomi: retrospektif çalışma

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ÖZET

Giriş ve Amaç: Tıkanma sarılığı hepatobiliyer sistem hastalıklarının en erken ortaya çıkan semptomlarından birisidir. Tıkanma sarılığı olan hastaların bir kısmı poliklinikten, diğer kısmı 112 ile veya ayaktan sevkle endoskopik retrograd kolanjiyopankreatografi (ERCP) yapılan merkezlere başvurmaktadır. ERCP işleminin seçilmiş merkezlerde yapılıyor olması riskli bir invaziv işlem olmasının yanında güncel yönetim, tecrübe ve yakın takip gerektiren bir işlem olmasından kaynaklanmaktadır. Gruplar single seans yapılan grup A ve ERCP takiben 6 hafta sonra laparoskopik kolesistektomi (LK) yapılan grup B olarak belirlendi. Gruplar hasta memnuniyeti, KCFT değerlerinin normale dönüşümü, toplam anestezi süresi ve görüntüleme yöntemlerinin kulanım sıklığı açısından değerlendirildi.

Gereç ve Yöntem: 01.01.2015-31.12.2016 tarihleri arasında ERCP yapılan 350 olgu arasından 31 hasta tek aşamalı ERCP ve LK için belirlenmiş uygun kriterlere göre ve 25 hasta çift aşamalı ameliyat için seçildi. Tek aşamalı olgular grup A olarak, çift aşamalı olgular grup B olarak belirlendi. Seçme kriteri olarak ERCP süresi, işlem zorluğu, görüntüleme yöntemi ile kanıtlanmış safra yolu taşları, malignite şüphesi ve bulgusunun olmaması, geçirmiş batın ameliyatı olmaması ve LK'ye kontrendike durumların olmaması olarak belirlendi.

Bulgular: Çalışmamızdaki gruba dahil edilen grupta papilla standart teknik ile kanülize edildi. Papilla kanülasyonu zor olan 2 hastada precut tekniği kullanarak koledok kanülize edildi. Serimizde ERCP işlemi sonrası laparoskopik kısmı başlanmadan önce hasta pozisyonu kolayca değiştirilebildi. Çalışmamızda eş zamanlı işlemler önce ERCP daha sonra LK şeklinde uygulandı.Tek aşamalı LK/ERCP, kolelitiazis ve koledokolitiazis için etkili tedavi sağlar ve ikinci bir anestezi prosedürüne tolerans göstermeyen seçilmiş hastalarda faydalı olabilir. Ortanca yaş grubu 61,29 ± 19,89 olup tek anestezi ile tedavisinin tamamlanması sadece hasta memnuniyeti için değil ikinci bir anestezi işlemine tolerans göstermeyen hastalar için avantajlıdır.

Sonuç: Sonuç olarak tek aşamalı ERCP ve LK hastanede kalış, daha az görüntüleme yöntemlerinin kullanım sıklığı ve toplam anestezi süresi açısından avantajlı olup seçilmiş olgularda güvenli şekilde kullanılabileceği kaydedilmiştir. Aynı zamanda tek aşamalı işlem sonrası pankreatit insidansı düşük bulunmuştur. Tek aşamalı ERCP takiben LK'nin klavuz haline gelmesi için gelecekte çok sayıda çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Endoskopik retrograd kolanjiyopankreatografi, laparoskopik kolesistektomi, manyetik rezonans kolanjiyopankreatografi, ultrasonografi

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Mini-cholecystectomy versus laparoscopic cholecystectomy: a retrospective multicentric study among patients operated in some Eastern Libyan hospitals

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ABSTRACT

Objective: This study was conducted to analyze the difference between Mini-Cholecystectomy (MC) and Laparoscopic Cholecystectomy (LC) in terms of feasibility and postoperative outcomes to determine if MC could be accepted as a good alternative procedure to LC.

Material and Methods: A retrospective comparative study of 206 consecutively operated patients of chronic cholecystitis (138 LC and 68 MC), in Al-Jalaa, Ajdabiya and Almrg Teaching hospitals between January 2014 and December 2015 was performed. All cases within the two groups were balanced for age, sex, co-morbidities, ultrasound and intraoperative findings. Exclusion criteria were acute cholecystitis, preoperative jaundice, liver cirrhosis, suspicion of malignancy, previous upper abdominal surgery and pregnancy.

Results: Mean age of the patients in the study was around 37 years. Female patients represented 88.84%. Intraoperative complications occurred in about 2% of the patients with bleeding in three cases (one in MC, two in LC) and injury to the bile ducts occurred in one case who underwent LC. Operative duration was longer in LC (mean values 64 minutes for LC and 45 minutes for MC). Rate of conversion to classical cholecystectomy in LC was 5% while it was 0% in MC. Only one case of wound infection was registered in the LC group. Postoperative hospital stay was insignificantly longer for LC versus MC (1.97 days for MC and 2.63 days for LC).

Conclusion: Mini-cholecystectomy is a feasible technique, which can be considered as a good alternative method for gallbladder removal for surgeons who have no experience with laparoscopic techniques and in peripheral hospitals where LC is not available.

Keywords: Laparoscopic cholecystectomy, mini-cholecystectomy, chronic cholecystitis, gall bladder stones

INTRODUCTION

Gallbladder diseases are considered as of the most common digestive system disorders. In spite of many trials with medical treatment, surgical intervention remains the only curative way. Cholecystectomy is the commonest abdominal surgical procedure worldwide (1). Gallbladder diseases are one of the commonest causes of admissions to surgical departments worldwide and also the commonest of the major procedures performed in daily elective surgery lists. Some literature has reported that about 77% of all operations performed at their hospital were cholecystectomies, with a female to male ratio of 4:1 (2).

First open cholecystectomy was performed by Karl Langenbuch in July 1882 (3). Before that time, and in fact even for many years afterwards, patients with symptomatic gallstone disease were treated only with ineffective medical remedies or occasionally by cholecystostomy to drain the gallbladder. The first cholecystectomy in the western hemisphere was performed four years later by Justus Ohagein, Minnesota USA. Hans Kehr of Halberstadt and Berlin was an early pioneer in biliary surgery. In 1901, he published a remarkable book describing more than 500 operations for gallstones, including 96 common bile duct operations. Kehr died of sepsis caused by a hand infection incurred after digital exploration of the common bile duct (4).

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Up to the 1980s, the conventional large subcostal incision in cholecystectomy was the standard surgical approach for treatment of gallbladder diseases, which was associated with early and late postoperative complications along with prolonged postoperative pain and hospital stay (5). Therefore, this was followed by the development of the minimally invasive surgical procedures for gallbladder disease including Mini-cholecystectomy (MC) and Laparoscopic cholecystectomy (LC). Currently, LC is the gold standard operation worldwide.

MC was first described by Dubois and Berthelot (6) in France, at the beginning of the 1980s, stating that the conventional large subcostal incision in cholecystectomy can be replaced by a much smaller incision, giving a shorter convalescence (7,8). This was preceded by more than a decade of interest among devoted specialists before being introduced into surgical practice.

On 1985, Erich Mühe in Böblingen Germany, performed the first laparoscopic cholecystectomy (3). Favorable results were reported at the same time as LC was introduced into the United Kingdom in 1990. Then it rapidly became the dominant procedure for gallbladder surgery worldwide and followed by a smoother postoperative course than the conventional method (9-11).

Recently, there are some surgical modalities under development with promising results in the industrial world. In Single Incision Laparoscopic Surgery (SILS), the approach is through the umbilicus with a single trocar and multiple ports that allow a safe cholecystectomy (12). However, Natural orifice trans luminal endoscopic surgery (NOTES) and Da Vinci surgical system (Robots) carry a high economic cost.

All these methods have the tendency to perform cholecystectomy with acceptable cosmetic results without visible scars and with decreased postoperative pain and a short hospital stay.

The aim of this study was to assess and analyze the difference between MC and LC in the surgical management of chronic cholecystitis in terms of feasibility and post-operative outcomes to determine if MC could be accepted as a good alternative procedure to the standard LC.

MATERIAL and METHODS

A multicentric retrospective comparative study was conducted on 206 consecutively operated patients of chronic gallbladder diseases (138 LC and 68 MC), in three University teaching hospitals between January 2014 and December 2015. All patients were diagnosed as having chronic gallbladder disease requiring elective cholecystectomy. The diagnosis was made after taking detailed history and clinical examination of their disease and was supported by radiological and laboratory investigations carried out to confirm the diagnosis and help in rolling out the presence of exclusion criteria that could affect the results of the study by creating patient bias.

All patients were operated by well-trained surgeons in both techniques, the surgeons were chosen according to their experience and career. All cases under the study in the two groups were balanced for age, sex, co-morbidities, ultrasound and intra operative findings. Patients with acute cholecystitis, preoperative jaundice, liver cirrhosis, suspicion of malignancy, previous upper abdominal surgery and pregnancy were excluded from the study. The included data was collected directly from patient's files.

Mini-cholecystectomy operation was performed under general anesthesia, patient in supine position. Single shot of prophylactic antibiotics was also given during the induction of anesthesia in all cases (ceftriaxone 1000 mg). The operation utilized a mini-laparotomy approach, it was defined as a small right sub-costal, midline or right para median incision of maximum 5 cm in length. Using sharp dissection, the skin, subcutaneous tissue, and anterior rectus sheaths were incised at the same wound axis followed by the separation of the rectus muscle from the sheath and retracted medially. The posterior rectus sheath and peritoneum were also incised with scissors. Then the peritoneal cavity was entered to the right of the falciform ligament. Two to three long and slim retractors were placed deep in the incision and positioned opposite to each other. The aim of these retractors was to extend the wound and open an enough approach to allow for gallbladder retraction. An abdominal gauge was inserted into the abdominal cavity and positioned deep between the retractors to push off the stomach and greater omentum on the right and for downward pushing of the right colonic flexure and loops of small bowel. After good operative exposure and isolation of the operative field from the rest of the adjacent abdominal organs, the surgeon could clearly see the inferior surface of the liver and gallbladder. Dissection of the structures in the triangle of Calot did not differ from the traditional open technique other than the necessity of remote operating and the inability to place the whole hand into the abdomen. While in Laparoscopic cholecystectomy was performed through three or four trocars, the first one was introduced using veress needle or the open technique.

We chose intraoperative outcomes as the intraoperative complication rate, operative duration, number of surgeons participating in the intervention and the rate of conversion to conventional procedure as determinants to assess feasibility. Postoperative complications and duration of hospital stay were the factors chosen for assessing postoperative outcome.

Conversion in LC means the removal of the tower of the laparoscopic aside, and complete the rest of the operation through large traditional subcostal incision as an open technique. However, in MC, it means an extension of the small incision to a large subcostal incision to complete the rest of the operation.

Approval of the publication of this study was obtained from the Ethics Committee in each hospital. Since these hospitals are teaching hospitals, informed consents to use the patient's data in academic activities and research are routinely signed by patients within the files during the time of admission and hospital stay.

Continuous variables were presented as mean, range and standard deviation, Student t-test was applied to calculate the difference between the means. 2 x 2 tables were made for binary variables and X^2 test or Fisher's exact was applied when appropriate. Differences were considered to be significant when p-value was lower than 0.05 ($p< 0.05$). All statistical procedures were made by SPSS Software v21.

RESULTS

A total of 206 patients were included into the study, among them 68 patients underwent MC while 138 underwent LC. Total mean age was 37 years with a range of 15-75 years. Mean age in both groups was 36 years for those who underwent MC and 37 for those who underwent LC (p= 0.983).

Female gender was predominant with 183/206 (88.8%) female and 23/206 (11.2%) males. Gender distribution in both groups was nearly the same of the total population with no significant difference (p= 0.82). In the MC group, females accounted for 91% (62/68) while males for 9% (6/68). In contrast, 88% (121/138) of the patients in the LC group were females and 12% (17/138) were males. Total patient basic characteristics is shown in Table 1.

Fourteen (21%) patients in the MC group had a co-morbidity while it was evident in 41(29%) of the LC group (p= 0.61). Furthermore, hypertension was diagnosed in 9 (13%) and in 21 (15%) of the MC and LC groups, respectively. Diabetes was diagnosed in 9 (13%) and in 20 (14%) in the MC and LC groups respectively. Cardiac disease was present in five patients observed only in the LC group. Statistical analysis shows no significant difference between the two groups as shown in Table 1.

Assessment of feasibility: the results of the univariate analysis showed that there is no significant difference between both techniques in terms of intra-operative complication rate, operative duration and the number of required surgeons while the rate of conversion to conventional sub-costal incision was significantly lower in the MC group. The results of univariate analysis of intra-operative outcomes is shown in Table 2.

Post-operative outcomes: the analysis showed that there is no significant difference between both techniques neither in post-operative complication rate nor in hospital stay time. The results of the univariate analysis of post-operative outcomes is shown in Table 3.

Table 1. Patient basic characteristics according to the performed procedure

	MC	LC	p
Number of cases	68	138	
Age Mean ± SD	36.1 ± 10.16	37.6 ± 11.04	**0.983**
Gender Male (%) Female (%)	 6 (8.8) 62 (91.2)	 17 (12.3) 121 (87.7)	 **0.454**
Total co-morbidity (%)	14 (20.6)	41 (29.7)	**0.164**
Hypertension (%)	9 (13.2)	21 (15.2)	**0.705**
Diabetes mellitus present (%)	9 (13.2)	20 (14.5)	**0.807**
Cardiac diseases (%)	0 (0)	5 (3.6)	**0.173**

Table 2. Results of the univariate analysis of intraoperative outcomes

	MC	LC	p
Number of cases	68	138	
Participating surgeons (mean ± SD)	2.1 ± 0.24	2.6 ± 0.54	**0.395**
Intraoperative complications rate (%)	1 (1.5)	3 (2.2)	**0.598**
Rate of conversion (%)	0 (0)	9 (6.5)	**0.032**
Operative duration in minutes (mean ± SD)	44.9 ± 6.44	63.8 ± 23.7	**0.291**

Table 3. Results of the univariate analysis of postoperative outcomes

	MC	LC	p
Number of cases	68	138	
Postoperative complications rate (%)	0 (0)	1 (0.7)	**0.673**
Hospital stay in days (mean ± SD)	1.97 ± 0.55	2.63 ± 0.79	**0.367**

DISCUSSION

MC, associated with very minimal rate of complications, is a minimally invasive cholecystectomy technique reported as a safe method in many studies worldwide (5,6,8,13). Many randomized controlled trials have compared both techniques with results in favor of LC in terms of short hospital stay and earlier return to work while operative duration was in favor of MC (1,13-15). In contrast, some other studies have shown no significant difference between MC and LC regarding these variables but they have confirmed the associated long operative duration with LC (16). A meta-analysis of randomized controlled trials in 2007 by Sanjay Purkayastha et al. showed no significant difference between MC and LC except for operative duration and hospital stay (17).

This study showed comparable results between both techniques, which is in concordance with the literature. Intra-operative complications as an important cause of morbidity associated with cholecystectomy as well as the primary cause of conversion to classical operation were comparable in both techniques with no statistical significance (p= 0.598). This is actually related to the minimal rate of intra-operative complications observed in our study, which might be a result of the improvement in surgical training programs in our hospitals.

Total operative duration from the moment of skin incision to wound closure was longer in the LC group by 19 minutes (mean duration was 45 and 64 minutes for MC and LC respectively). Setting up and testing laparoscopic equipment as well as practicing the open access method to obtain pneumoperitoneum usually adds about 15 minutes to the procedure time (16). These factors play an important role in prolonging operative duration. Statistically, there was no significant difference between both groups (p= 0.291).

Restricted operative field in MC needs less participating surgeons, which is normally around two, except in case of complication or conversion when the number increases according to the situation. Four ports LC which is the most used technique in our hospitals requires three surgeons as operator, camera man and the last for holding gallbladder fundus. In spite of the introduction of three port LC by some surgeons, which requires less participating surgeons (two surgeons), mean number of surgeons is still a little bit higher than that of MC (around 2.5). This difference of means between both techniques is not statistically significant (p= 0.395), which suggests that MC and LC has relatively the same requirements regarding human resources.

Conversion in LC means the removal of the tower of laparoscopic aside and completing the rest of the operation through large traditional subcostal incision as an open technique. However, in MC, it means an extension of the small incision to large subcostal incision to complete the rest of the operation.

The rate of conversion to classical cholecystectomy is higher in LC than in MC. Studies have reported that conversion rate in LC varies between 15-35 % (18,19). In the current study, nine cases in the LC group were converted to classical cholecystectomy. Uncontrolled bleeding, adhesions and instrumental failure were the main causes. In the MC group, there were no cases of conversion to classical technique, and subsequently statistical analysis showed significant difference in favor of MC (p= 0.024). This could be explained by the three-dimensional view offered by MC over two dimensional view in LC, which gives more orientation of the anatomy and more ability to perform safer dissection. Furthermore, LC requires much more sophisticated instruments than MC, which is vulnerable to mechanical failure as what happened in two cases in LC.

Nevertheless, the selection of cases for MC and LC tends to affect these results; thin patients have much more chance to undergo MC as no mush dissections needed either at the level of the anterior abdominal wall or at the level of cystic duct while obese patients undergo LC that add more difficulty as the hepatic hilum is usually impeded in fatty tissue. The lack of information about weight and height in patients' files prevent us from studying the effect of obesity in relation to both techniques.

This study was not large enough to compare the incidence and significance of post-operative complications with only one case of wound infection occurred in the LC group. Lujan et al. (20) have reported that post-operative complication rates is around 14% in LC and 23% in the MC. Statistically, our study showed no significant difference in the postoperative complications rate between the two groups (p= 0.673).

Postoperative hospital stay in the present study was a little bit longer for LC versus MC (the means of postoperative period were 1.97 days for MC and 2.63 days for LC). In contrast, longer hospital stay in MC is reported in the literature with signif-

icance (1,14); however another study (15) has shown that the difference is not of significance. Longer hospital stay observed in our study might be related to the difference in postoperative protocol which differs from one surgeon to the other. Statistical analysis in this study showed no significant difference between MC and LC (p= 0.367). From our experience in this study we can conclude that, mini-cholecystectomy is associated with low rate of intra-operative complications, has short operative time, and associated with a very little chance to be converted to the classical technique. Moreover, it is associated with good post-operative recovery with short hospital stay. This study calls for further studies with larger groups in multiple centers to evaluate properly the advantages of both techniques.

CONCLUSION

Mini-cholecystectomy is a feasible technique and can be considered as a good alternative method for gallbladder removal for the surgeons who have no experience with laparoscopic techniques and in the peripheral hospitals where laparoscopic cholecystectomy is not available.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of research department and medical affier office in each hospital included in this study.

Informed Consent: Because of all the hospitals included in this study are teaching hospitals, written informed consent for use the data in academic activities was obtained from patients who participated in this study as a routine at admission time.

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ORİJİNAL ÇALIŞMA-ÖZET
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Mini-kolesistektomiye karşı laparoskopik kolesistektomi: bazı Doğu Libya hastanelerinde ameliyat edilen hastaları içeren retrospektif çok merkezli bir çalışma

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ÖZET

Giriş ve Amaç: Bu çalışmada mini-kolesistektomi (MC)'nin, laparoskopik kolesistektomi (LC)'ye iyi bir alternatif yöntem olarak kabul edilip edilemeyeceğinin belirlenmesi amacıyla MC ve LC arsındaki farklılıklar fizibilite ve postoperatif sonuçlar açısından incelenmiştir.

Gereç ve Yöntem: Ocak 2014-Aralık 2015 tarihleri arasında Al-Jalaa, Ajdabiya ve Almrg Eğitim hastanelerinde 206 ardışık kronik kolesistit hastası (138 LC ve 68 MC) hastası retrospektif olarak karşılaştırıldı. İki gruptaki tüm olgular yaş için ve eşzamanlı hastalıklar için ve ultrason ve intraoperatif bulgu için dengelendi. Dışlama kriterleri akut kolesistit, preoperatif sarılık, karaciğer sirozu, malignite şüphesi, önceki üst abdominal cerrahi ve gebelik idi.

Bulgular: Çalışmaya alınan hastaların yaş ortalaması 37'dir Kadın hastalar tüm hastaların %88,84'ünü oluşturmaktadır. İntraoperatif komplikasyonlar üç olguda kanama olan hastaların %2'sinde (biri MC'de, ikisi LC'de) meydana gelmiştir, bir olguda LC'ye bağlı olarak safra kanallarında hasar meydana gelmiştir. Operasyon süresi LC'de daha uzundur (ortalama değerler LC için 64 dakika ve MC için 45 dakika). LC'de dönüşüm oranı %5 iken MC'de %0'dır. LC grubunda sadece bir yara enfeksiyonu vakası kaydedilmiştir. Postoperatif hastanede kalış süresi MC'ye karşı LC'de daha uzundur (MC için 1.97 gün ve LC için 2.63 gün).

Sonuç: Mini kolesistektomi kolay uygulanabilir bir tekniktir. LC'nin bulunmadığı periferik hastanelerde ve laparoskopik tekniklerle deneyime sahip olmayan cerrahlar için, MC safra kesesi çıkarılması için iyi bir alternatif yöntem olarak düşünülebilir.

Anahtar Kelimeler: Laparoskopik kolesistektomi, mini-kolesistektomi, kronik kolesistit, safra kesesi taşları

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Transplant nephrectomy with peritoneal window: Georgetown University experience

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ABSTRACT

Objective: Transplant nephrectomy is a technically challenging procedure with high complication rates. Morbidity and mortality are mostly due to hemorrhage or infection and are reported to be 17-60% and 1-39%, respectively. The most common surgical technique for transplant nephrectomy is sub-capsular, extraperitoneal approach which may result in fluid accumulation and subsequent super-infection. We report that intraperitoneal approach, after assuring hemostasis of the transplant pedicle, allows for passive drainage, decreases hematoma formation and minimizes the subsequent infection risk in the nephrectomy bed.

Material and Methods: From July 2009 to July 2014 a total of 38 transplant nephrectomies were performed using the intraperitoneal window technique at Georgetown University MedStar Transplant Institute (MGTI). Data was collected retrospectively.

Results: Average age at the time of transplant nephrectomy was 43.9 ± 14.3, and the majority were male (55.3%). Mean time to nephrectomy was 71.7 ± 67.4 months following transplantation. Indications for nephrectomy included pain, hematuria, fever, and recalcitrant rejection. Average operative time was 97.1 ± 28.9 minutes, average blood loss was 172.5 ± 213.6 mL. A total of 9 (24%) complications occurred. Postoperative blood transfusion was the most common complication (15.7%) followed by 2 (5.3%) re-interventions; one take back for hematoma and one percutaneous drain placement for symptomatic fluid collection. We had no infection, postoperative sepsis, ICU admissions, or mortality.

Conclusion: Transplant nephrectomy with peritoneal window is a technique with better results compared to the literature. An opening between the transplant cavity and the peritoneum allows for passive drainage of fluid and minimizes the risk of hematoma and abscess formation. This approach does not add significant time to the operation, furthermore it may decrease morbidity and mortality by reducing overall complications, namely hematoma formation and infection, which overall decreases rates of re-interventions and length of hospital stay.

Keywords: Nephrectomy, transplant, transperitoneal

INTRODUCTION

Renal transplant has a failure rate of 12-22% by three years, and 44-59% by 10 years (1). A failed transplant provokes an inflammatory response which increases morbidity and mortality. It also incites symptomatic intolerance in patients (2,3). Therefore, anywhere between 4.5-84% of those failed renal grafts require transplant nephrectomy (4). Although there are different opinions on the timing of transplant nephrectomy, current consensus is that removal of the failed graft is appropriate when symptoms are intractable (4-8).

The most common indication for transplant nephrectomy is symptomatic chronic rejection (58.2%) which can cause graft tenderness, hematuria, fever, and persistent anemia (9,10). An obvious benefit of nephrectomy is the relief of symptoms from allograft rejection or failure. Lopez-Gomez et al. have demonstrated attenuated inflammatory response after removal of a failed allograft when compared to failed graft patients treated with hemodialysis only. They have found decreased inflammatory markers, improved hypoalbuminemia, and decreased erythropoietin resistance (2). Additionally, Ayus et al. have reviewed 10.951 patients and reported that transplant nephrectomy improves survival after graft failure. After adjusting for socioeconomic status, comorbidities and donor characteristics, a 32% decrease in all-cause mortality has been found in transplant nephrectomy group compared to patients keeping the failed allograft (11).

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Although transplant nephrectomy has been shown to improve survival and relieve symptoms after failed kidney transplant, it remains a technically demanding procedure that carries high morbidity (17-60%) and mortality (1.5-14%) due the poor health and comorbid conditions that often accompany transplant patients as well as operative complications (11-13). Alberts et al. have reviewed 157 transplant nephrectomies performed from 2000 to 2012, indicating 32 surgical complications (20%), with postoperative bleeding, hematoma formation, and infection being the most common causes. Surgical re-intervention was necessary in 10% of the cases. Other reported complications are colonic perforation, cardio-pulmonary complications, and sepsis (1,15).

The most commonly performed surgical technique for transplant nephrectomy is subcapsular extra peritoneal approach. Performing the procedure in a closed extraperitoneal space may result in fluid accumulation and subsequent infection. Immune-compromised patients are inevitably prone to develop septic complications in the presence of hematoma or seroma.

We hypothesize that creating an intraperitoneal window, after assuring hemostasis of the transplant pedicle, allows for passive drainage, decreases hematoma formation and minimizes the risk of infection, sepsis, and the need for re-interventions.

MATERIAL and METHODS

From July 2009 to July 2014, a total of 38 transplant nephrectomies using the intraperitoneal window technique were performed by two transplant surgeons at Medstar Georgetown Transplant Institute. IRB approval was obtained. Inclusion criteria for the study was any adult patient with prior kidney transplant undergoing transplant nephrectomy. Patient data was collected retrospectively, including patient characteristics, allograft characteristics, nephrectomy indications, operative data, hospital course, and complications.

All transplant nephrectomies were performed using the standard subcapsular approach (Figure 1). We modified the standard double layer pedicle closure. Following excision of the specimen from the pedicle, any visible vessel was closed with figure of eight using #2-0 silk suture (Figure 2). This was followed with a double layer of running #2-0 prolene suture (Figure 3). In order to achieve adequate hemostasis, any capsular bleeding was controlled with electrocautery. Following this, the peritoneal window was created. The window was made large enough to avoid risk of internal hernia formation and bowel entrapment (Figure 4). Postoperative surgical complications were the primary outcome, and complications were graded using the Clavien-Dindo System (17).

Figure 1. The allograft is enucleated from the renal capsule attached only with the renal pedicle.

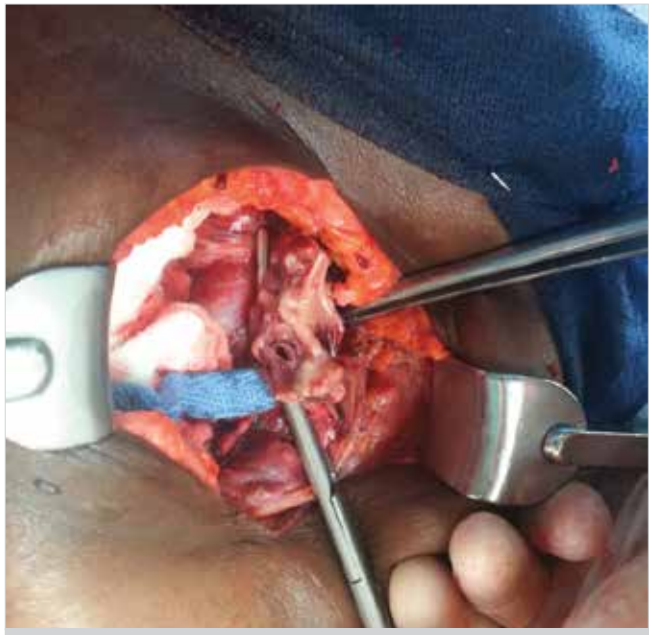

Figure 2. The pedicle is controlled with a vascular clamp and graft is excised.

Figure 3. Control of the pedicle. Visible vessels are sutured with figure of eight, using #2-0 silk followed by running #2-0 Prolene.

Figure 4. Creation of the peritoneal window. The peritoneum is incised along the length of the incision.

RESULTS

A total of 38 patients underwent transplant nephrectomy with the technique described in the 'methods' section. The average age of the patients was 43.92 ± 14.3 years and 55.3% of the patients were male (Table 1). Indications for nephrectomy included persistent and symptomatic acute and chronic transplant rejection, with fever (26.3%), pain (71.0%), hematuria (57.9%), leukocytosis (5.3%) (Table 2). The average time from transplant to nephrectomy was 71.76 ± 67.47 months. Operative time was average of 97.1 ± 28.9 minutes with an average estimated blood loss of 172.5 ± 213.6 mL. Mean length of hospital stay was 3 ± 1.7 days (Table 3).

Table 1. Patient characteristics

Characteristics	N= 38 (%)
Age	43.92 ± 14.30
Male	21 (55.3)
Comorbidities	
DM	17 (44.7)
HTN	36 (94.7)
CAD	2 (5.3)
CVA	1 (2.6)
COPD	2 (5.3)
Malignancy	2 (5.3)
Hepatitis C	3 (7.8)
Time to nephrectomy (months)	71.76 ± 67.47

DM: Diabetes mellitus, HTN: Hypertension, CAD: Coronary artery disease, CVA: Cerebrovascular accident, COPD: Chronic obstructive pulmonary disease.

Table 2. Indication for nephrectomy

Indication for nephrectomy	N= 38 (%)
Fever	10 (26.3)
Pain	27 (71.0)
Hematuria	22 (57.9)
Leukocytosis	2 (5.3)

Table 3. Operative data

Operative data	N= 38 (%)
Operative time (minutes)	97.1 ± 28.9
Estimated blood loss (mL)	172.5 ± 213.6
Hospital stay (days)	3.08 ± 1.7

A total of 9 (24%) complications occurred. Postoperative blood transfusion was the most common complication (15.7%). Two (5.6%) patients required re-intervention: one take back to operating room for hematoma wash out, one patient required percutaneous drain placement for symptomatic fluid collection. Other complications included fever (1), pneumonia (1) and ileus (1). No infections, post-operative sepsis, ICU admissions, or mortalities occurred. A total of 18.4% patients had low grade (Clavien-Dindo class 1 and 2) complications, whereas high grade complications (Clavien-Dindo class 3 or higher) occurred in 5.2% patients (Table 4).

DISCUSSION

Intraperitoneal window formation during transplant nephrectomy is a novel surgical approach designed to reduce complications and decrease morbidity and mortality. We believe creating a passage for passive fluid drainage from the nephrectomy cavity into the peritoneal cavity decreases the rate of fluid collection as well as infection risk, which are the two most common complications that occur after transplant nephrectomy.

Previous studies have discussed a wide variety of complication rates, ranging from 17%-60% (3). Three studies were focused for comparison of transplant nephrectomy complications. Mazzucchi et al. reported 70 transplant nephrectomies between 1994 and 2002, with 18.5% of complication rate with 8.6% hematoma formations, 10% fluid collections, 7.1% infections, 10% re-interventions, and 1.4% mortality. Additionally, 44.3% of patients received blood transfusions, which was not classified as a complication in the study and would increase the complication rate considerably if this was included (18).

Similarly, Secin et al. reviewed 91 transplant nephrectomies from 1970 to 2000, reporting 48.3% complication rate, including 15.4% hematoma formation, 9.9% fever, 7.6% sepsis, 4.4% wound infection, 10.9% re-interventions, and these were all were for either hematoma formation or infection. They had 7% mortality rate (4).

Table 4. Complications		
Complications	**N= 38 (%)**	
Total no. of complications	9 (23.7)	
Infection	0 (0)	
Hematoma	1 (2.6%)	
Reintervention	2 (5.2%)	
Mortality	0 (0)	
Complications grading according to Clavien-Dindo system	**N= 38 (%)**	**Actual Event**
Grade I	1 (2.6%)	Ileus
Grade II	6 (15.7%)	Blood transfusion intraoperative, fever, pneumonia
Grade III	2 (5.2%)	1 take back to OR, 1 drain placement

Lastly Alberts et al. reported 25% complication rate for 157 transplant nephrectomies from 2000-2012, with 9% infection rate, 14% hematoma rate, and 10% rate of re-intervention, most of which was for hematoma formation. Mortality rate was 3.2% (1).

When compared to our 38 patients with intraperitoneal windows, all three studies had much higher rates of complications, hematoma formations and fluid collections, infections, as well as re-intervention rate and mortality (Table 5).

Peritoneal window formation is an additional step in the surgical procedure that adds minimal amount of time to the total operation. In fact, the 38 nephrectomies with intraperitoneal window formation had a shorter average operative time (97.1 vs. 109.39 minutes), lower average estimated blood loss (172.5 vs. 509.2 mL), and shorter average hospital stay (3 vs. 7 days) than previously reported studies. Potential downsides of this technique could be bleeding into the peritoneal cavity, which is much harder to tamponade compared to the retroperitoneal space, therefore we advocate meticulous hemostasis. Other potential risk may be bowel obstruction; however, we advocate large opening of the peritoneum in order to minimize this risk.

Limitations of this study include small sample size, and inherent limitations of a retrospective analysis without control cohort.

In conclusion, intraperitoneal window formation is a novel surgical technique for transplant nephrectomy that adds minimal time to the operation and appears to have a much lower morbidity and mortality rate.

Prospective and controlled studies are necessary in order to obtain more reliable results; however, low levels of complications and zero mortality observed in this series compared to literature is suggestive of possibly superior outcome of this technique.

Ethics Committee Approval: Institutional Review Board (IRB) approval was obtained.

Informed Consent: Due to the retrospective design of the study, the informed consent was not obtained.

Peer-review: Externally peer-reviewed.

Author Contributions: Consept - M.C., S.G.; Design - M.C., S.G., O.M.A.; Supervision - M.C., S.G.; Resource - R.R., E.A., W.C., E.M., J.M.; Materials - R.R., E.A., W.C., E.M., J.M.; Data Collection and/or Processing - R.R., O.M.A., E.A., W.C., E.M., J.M.; Analysis and Interpretation - O.M.A., S.G., M.C.; Literature Search - R.R., E.A., W.C., E.M.; Writing Manuscript - R.R., O.M.A., S.G.; Critical Reviews - M.C., S.G., O.M.A.

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

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ORİJİNAL ÇALIŞMA-ÖZET
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Peritoneal drenaj ile transplant nefrektomi: Georgetown Üniversitesi sonuçları

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ÖZET

Giriş ve Amaç: Transplant nefrektomisinin morbidite ve mortalitesi %60 ve %39'a kadar çıkmakta olup genellikle kanama, enfeksiyon veya sepsise bağlı gelişmektedir. En çok kullanılan teknik subkapsüler, ekstraperitoneal yaklaşımdır. Bu yaklaşım seroma ya da hematom birikimini, dolayısıyla enfeksiyon riskini yükseltebilmektedir.

Gereç ve Yöntem: Temmuz 2009-Temmuz 2014 tarihleri arasında, Georgetown Üniversitesi MedStar Transplant Enstitüsü (MGTI)'nde 38 transplant nefrektomi olgusu gözden geçirildi. Retrospektif data analizi uygulandı.

Bulgular: Toplam 9 (%24) komplikasyon gelişti. Transfüzyon en sık görülen komplikasyon idi (%15,7) ve 2 (%5,3) hastaya yeniden girişim yapıldı. Enfeksiyon, sepsis, yoğun bakım yatışı ya da ölüm gözlenmedi.

Sonuç: İntraperitoneal tekniğin pasif drenaj ve/veya absorbsiyon yolu ile hematom ya da enfeksiyon oluşumunu, dolayısıyla mortalite ve morbiditeyi azalttığı görüşündeyiz.

Anahtar Kelimeler: Nefrektomi, transplant, transperitoneal

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Impact of routine histopathological examination of appendectomy specimens on patient management: a study of 4012 appendectomy specimens

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ABSTRACT

Objective: For a suspected diagnosis of acute appendicitis, appendectomy is one of the most common emergency abdominal operations performed. However, the need for routine histopathological examination (HPE) of all appendectomy specimens has recently been questioned. The aim of this study was to assess whether a routine HPE of appendectomy specimens is needed and whether routine HPE has an impact on further management of patients.

Material and Methods: From January 2009 to June 2017, all histopathology reports of 4012 consecutive appendectomy specimens for a clinical suspicion of acute appendicitis were retrospectively analyzed in two university hospitals.

Results: Out of the 4012 cases, 3530 (88%) patients showed findings consistent with acute appendicitis on HPE. Perforation rate was 5.8% and was significantly higher in male patients ($p< 0.001$) and higher in the > 30 years age group ($p= 0.024$). Negative appendectomy rate was 5.6% and was significantly higher in female patients ($p< 0.001$). There were 256 (6.4%) patients who demonstrated unusual findings in their HPE, which included chronic appendicitis (n= 207; 5.2%) patients, *Enterobius vermicularis* (n= 14), *Schistosoma* (n= 8), Crohn's disease (n= 1), neuroma (n= 10), carcinoid tumour (n= 5) and mucinous cystadenoma (n= 5), mucocele (n= 4) and mucinous cystadenocarcinoma (n= 2).

Conclusion: HPE of the appendix does not only confirm the diagnosis of acute appendicitis, but also detects other unusual diagnoses that may have an impact on a patient's management. A number of patients with unusual histopathological findings require anti-helmentic treatment, colectomy, gastroenterology follow-up or periodic surveillance. Hence, all appendectomy specimens must be submitted for routine HPE.

Keywords: Appendectomy, appendicitis, histopathological examination

INTRODUCTION

Acute appendicitis is the most common abdominal emergencies encountered in general surgical services. The overall lifetime risk of acute appendicitis is about 7.0%, with 8.6% for males and 6.7% for females (1). Diagnosis of acute appendicitis is a major challenge, even for experienced surgeons since typical presentations only appear in about 60% of the patients (2). In addition, many conditions mimic acute appendicitis in their presentation especially in women, causing diagnostic difficulties and increasing the rate of negative appendectomies (3). Thus, histopathological examination (HPE) is still considered the most accurate method for confirming appendicitis diagnosis.

There has been a debate in the literature concerning the routine or selective HPE of appendectomy specimens (3). However, a policy of selective HPE may miss significant pathology, which may have an impact on patient management. Furthermore, HPE of appendectomy specimens may detect other unusual findings such as parasitic infections, endometriosis or granulomatosis (4).

The aim of this study was to assess whether a routine HPE of appendectomy specimens is needed and whether routine HPE has an impact on further management of patients.

MATERIAL and METHODS

From January 2009 to June 2017, all histopathology reports of 4012 consecutive appendectomy specimens for a clinical suspicion of acute appendicitis were retro-

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spectively analyzed in two university hospitals. The research was performed according to the World Medical Association Declaration of Helsinki.

Patient details such as age, sex, and histopathological diagnosis were recorded. Exclusion criteria were appendectomies performed in conjunction with bowel resections or other pelvic surgeries and paediatric ages < 13 years. Appendectomy performed for a suspicion of acute appendicitis where HPE showed normal appendix was considered negative appendectomy.

Statistical Analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS Inc.; Chicago, IL, USA), version 18.0 software program. The data was analyzed using the Chi-square test. A p value < 0.05 was considered to indicate statistical significance.

RESULTS

Of the 4012 appendectomy specimens were sent for HPE during the study period, 1846 (46%) were males and 2166 (54%) were females, with a median age of 23 (range, 13-91) years. The most common age group for appendectomy in this study was 13-20 years (39.9%) closely followed by the 21-30 year age group (37.2%), together constituting 77.1% of total specimens. The distribution of histopathological diagnosis is shown in Table 1.

Out of the 4012 cases, 3530 (88%) patients showed findings consistent with acute appendicitis on HPE that includes early acute appendicitis, acute suppurative appendicitis, gangrenous appendicitis and perforated appendicitis. The histopathological finding of acute appendicitis was highest in the second decade of life, followed by those in their third and fourth decades of life, at 88.8%, 88.0%, and 87.2%, respectively. About 77.4% of acute appendicitis cases were found in the age group of 13 to 30 years (Table 2).

Table 1. Histopathological diagnoses encountered in the appendectomy specimens

Diagnosis	Number	Percentage
Early acute appendicitis	526	13.1
Acute suppurative appendicitis	2774	69.1
Gangrenous appendicits	26	0.6
Perforated appendicits	204	5.1
Chronic appendicits	207	5.2
Normal appendix	226	5.6
Crohn's disease	1	0.02
Schistosoma infection	8	0.2
Enterobius vermicularis	14	0.3
Carcinoid	5	0.1
Cystadenocarcinoma	2	0.04
Cystadenoma	5	0.1
Mucocele	4	0.1
Neuroma	10	0.2
Total	4012	100

In the 3530 patients with acute appendicitis, there were 204 patients with perforated appendicitis with an overall perforation rate of 5.8%. Male patients had a significantly higher perforation rate than female patients (n= 148; 8.8% vs. n= 56; 3.0%; p< 0.001). The age group of > 30 years had a higher perforation rate than that of the age group of ≤ 30 years (7.4% vs. 5.3%; p= 0.024). The perforation rate gradually increased with patient age from the second decade (4.7%) till the seventh decade (11.1%) and then decreased to zero in patients older than 70 years of age (Table 3).

Table 2. Distribution of the incidence of acute appendicitis, normal appendix, and unusual finding according to patient age

		Acute appendicitis (n= 3530)		Normal appendix (n= 226)		Unusual findings (n= 256)	
Age group	Proportion of patients (%)	(%) within the age group	(%) within the diagnosis	(%) within the age group	(%) within the diagnosis	(%) within the age group	(%) within the diagnosis
13-20	39.9	88.8	40.2	5.9	41.6	5.3	33.2
21-30	37.2	88	37.2	5.8	38.5	6.2	36.3
31-40	15	87.2	14.8	4.7	12.4	8.2	19.1
41-50	4.8	86.5	4.7	6.7	5.8	6.7	5.1
51-60	1.8	86.1	1.8	4.2	1.3	9.7	2.7
61-70	0.8	84.4	0.8	3.1	0.4	12.5	1.6
71-80	0.3	69.2	0.3	0	0.0	30.8	1.6
81-91	0.2	85.7	0.2	0	0.0	14.3	0.4

Table 3. Distribution of the incidence of acute appendicitis and perforation rate with patient age

Age group	Proportion of acute appendicitis (%) (n= 3530)	Perforated appendicitis (n= 204)	
		(%) within the age group	(%) within the diagnosis
13-20	40.2	4.7	32.8
21-30	37.2	5.9	38.2
31-40	14.8	6.9	17.6
41-50	4.7	8.4	6.9
51-60	1.8	9.7	2.9
61-70	0.8	11.1	1.5
71-80	0.3	0.0	0.0
81-91	0.2	0.0	0.0

The HPE of the appendix was normal in 226 (5.6%) of the 4012 patients who were operated on with a clinical suspicion of acute appendicitis. Negative appendectomy rate (NAR) was significantly higher in female (n= 161; 7.4%) than in male (n= 65; 3.5%) patients (p< 0.001). However, there was no significant statistical difference in the NAR when the ≤ 30 year age group compared to > 30 year age groups (5.9% vs. 4.9%; p= 0.274).

Of the 4012 patients who had appendectomy for preoperative suspicion of acute appendicitis, 256 (6.4%) had unusual findings in their HPE. There were 103 (5.6%) males and 153 (7.1%) females (p= 0.055). Median age was 25 (range, 13-81) years. Unusual histopathological finding was highest in the seventh, eighth and ninth decades of life, at 12.5%, 30.8%, and 14.3%, respectively. About 69.5% of unusual finding cases were found in the age group of 13 to 30 years (Table 2). The rate of unusual finding was higher in the > 30 year age group compared to ≤ 30 year age group (8.5% vs. 5.8%; p= 0.003).

The most common unusual finding in the HPE of appendectomy specimens was chronic appendicitis seen in 207 (5.2%) patients. Parasitic infections were discovered in 22 patients, of these 14 were *Enterobius vermicularis* and eight were *Schistosoma*. Crohn's disease was reported in one case.

Of the 26 (0.6%) appendiceal tumours, the most common appendiceal tumour was neuroma, found in 10 patients, followed by carcinoid tumour (n= 5) and mucinous cystadenoma (n= 5). Mucocele was found in four and mucinous cystadenocarcinoma in two; one of them complicated by pseudomyxoma peritonei.

DISCUSSION

For a clinical diagnosis of acute appendicitis, appendectomy is one of the most common emergency abdominal operations performed (5).

In this study, 88% of the appendectomy specimens had histological evidence of acute appendicitis, comparable with other studies (65-91%) (4). The incidence of acute appendicitis in our study was higher in the second and third decade, about 76.4% of acute appendicitis occurring below 30 years of age, similar to other studies (6,7).

While other studies (2,7,8) have shown male predominance, our study showed slightly female predominance with a female to male ratio of 1.1:1, consistent with the study of Shreshtha et al. (9).

In our study, the perforation rate of 5.8% and was comparable to that reported by Charfi et al. (10) (6.4%) and Chandrasegaram et al. (8) (7.4%). However, several studies (1,2,7,11) have reported much higher rates of 11-22.5%. By contrast, Shrestha et al. (9) and Jat et al. (12) have found a low rate of 1.9% and 2%, respectively. Most studies have demonstrated that the incidence of appendicular perforation increases with age (2,7,8), which is consistent with the present study.

NAR in the present study was 5.6%. In 2011, Swank et al. (4) reviewed the literature and found that NAR was between 8 and 32% in 55 and 138 appendectomies, respectively (4). Recently, Emre et al. (1) have reported a NAR of 6 % and Jat et al. (12) have reported a rate of 3%. van Rossem et al., (11) hav reported a NAR of 2.2 %. It has been shown that routine diagnostic imaging (US or CT) lowers NAR in patients with suspected appendicitis to 1.7-6.2% (13), which was consistent with our findings.

NAR in the present study was significantly higher in female patients, consistent with other studies (2,7-9). This is likely due to the difficulties in diagnosing acute appendicitis in female patients because of the added possibility of gynaecological conditions that mimic acute appendicitis (8).

Although acute appendicitis is the most common histopathological finding affecting the appendix, chronic appendicitis was the most common unusual finding on HPE of the appendectomy specimens in the current study. Chronic appendicitis does not present with typical symptoms of acute appendicitis and diagnosis is frequently made following an appendectomy and based on HPE (14). In our study, the rate of chronic appendicitis was 5.2%. Shreshtha et al. and Dincel et a. havel reported lower rates of 2.6% and 0.2%, respectively (9,14). In a study conducted by Rehman et al., 7.9% of a total of 316 patients has been found to have chronic appendicitis (15).

E. vermicularis is the most prevalent parasitic infection of the gastrointestinal tract. The incidence of *E. vermicularis* ranges from 0.6% to 3.8% in all appendectomy specimens; however, the rates of inflammation in appendices infested with these parasites is 13% to 37% (16). Appendectomy only treats the consequences but not the cause of the disease. For this reason, these patients should also receive anthelmintic treatment (oral mebendazole) (14). In the present study, fourteen patients (0.3 %) had *E. ver-*

micularis in their specimens, with the incidence being slightly lower than that of other published studies.

Schistosomiasis is another uncommon cause of appendicitis. Patients with Schistosomal appendicitis should be treated with praziquantel after surgery (14). The incidence of Schistosomal appendicitis was reported to be 0.1% by Dincel et al. (14) and 2.3% by Gali et al. (17). In the current study, 8 (0.2%) cases had Schistosomiasis.

Crohn's disease of the appendix is usually associated with Crohn's disease of the ileum and caecum. Isolated Crohn's disease of the appendix is rare and often mimics acute appendicitis in clinical presentation. Crohn's disease has been found to be the cause of acute appendicitis in 0.2% to 1.8% of all appendectomies. Appendectomy is considered adequate if the disease is restricted to the appendix. However, patients with ileocaecal involvement may need further ileocaecal resection. Patients with Crohn's disease need further gastroenterology follow-up postoperatively (18). In the present study, only one patient had Crohn's disease in their appendectomy specimen.

Appendiceal tumours, found in less than 3% of all appendectomies, are usually asymptomatic and are usually identified either intraoperatively or during the HPE (19). Carcinoid tumour of the appendix is the most common type of primary malignant tumour of the appendix. It represents 60% of all appendiceal tumours and is discovered in 0.3% to 2.3% of the appendectomy specimens (1,14). In the current study, we had slightly lower incidence of appendiceal carcinoids (0.1%) compared to other studies. Carcinoids are rarely diagnosed preoperatively, and they are commonly identified as an incidental finding during appendectomy. They are mostly benign, < 1 cm in size, and rarely metastasize. For carcinoids < 1 cm in size, the risk of metastasis is exceedingly low and simple appendectomy is considered curative. However, with carcinoids ≥ 2 cm, the risk of metastasis increases up to 85% and patients usually proceed to right hemicolectomy (1,14,16,17,19).

Mucocele of the appendix is a rare disease characterized by a distended, mucus-filled appendix. Retention cyst, mucosal hyperplasia, mucinous cystadenoma, and mucinous cystadenocarcinoma are the histological types of mucocele of the appendix. It is found in 0.2% to 0.7% of all appendectomy specimens (14,20,21). Mucoceles are frequently discovered incidentally during appendectomy (19). Mucinous cystadenoma is treated by simple appendectomy whereas a cystadenocarcinoma should undergo a right hemicolectomy. During the follow-up period, patients should undergo radiological (US & CT) and colonoscopic investigations since mucinous cystadenoma is strongly associated with colonic and ovarian malignancy (14,16,19). In this study, eleven (0.27%) patients had mucocele in their appendectomy specimens and this incidence was comparable with other studies.

Appendiceal neuromas (fibrous obliteration of the appendix) are rare and characterized by fibrous obliteration on HPE of the appendix. The majority of appendiceal neuromas are often incidentally discovered (22). The incidence of appendiceal neuromas in our study was only 0.2%, which is lower than that reported by Yilmaz et al. (21) (3.7%) and Emre et al. (1) (4.5%).

CONCLUSION

HPE of the appendix does not only confirm the diagnosis of acute appendicitis but also detects other pathological lesions that may not be obvious intraoperatively, and furthermore, routine HPE has a direct impact on patient management such as anti-helmentic treatment, further resection, endoscopic and gastroenterology follow-up or periodic surveillance. Hence, we conclude that all appendectomy specimens must be submitted for routine HPE regardless of the gross appearance of the specimen at operation.

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Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013).

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ORİJİNAL ÇALIŞMA-ÖZET
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Apendektomi örneklerinin rutin histopatolojik incelemesinin hasta yönetimine etkisi: 4012 apendektomi örneği

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ÖZET

Giriş ve Amaç: Akut apandisit tanısı şüphenilen durumlarda apendektomi en yaygın acil abdomen ameliyatlarından birini oluşturmaktadır. Ancak, tüm apendektomi örneklerinin rutin histopatolojik değerlendirilmesi (HPE) son yıllarda tartışılan bir konu olmuştur. Bu çalışmanın amacı, apendektomi örneklerine HPE yapılmasının gerekli olup olmadığını ve HPE'nin detaylı hasta yönetiminde bir etkiye sahip olup olmadığını ortaya koymaktı.

Gereç ve Yöntem: Ocak 2009-Haziran 2017 tarihleri arasında akut apandisit klinik şüphesiyle 4012 ardışık apendektomi örneklerinin histopatolojik raporları iki üniversite hastanesinde retrospektif olarak incelendi.

Bulgular: Toplam 4012 olgu içerisinde, 3530 (%88)'u, HPE'de akut apandisit ile uyumlu bulgular gösterdi. Perforasyon oranı %5,8 ve anlamlı derecede erkeklerde (p< 0,001) ve > 30 yaş grubunda daha yüksekti (p= 0,024). Negatif apendektomi oranı %5,6 idi ve kadın hastalarda anlamlı şekilde daha yüksek bulundu (p< 0,001). 256 (%6,4) hastanın HPE'sinde olağandışı bulgulara rastlandı; bunlar sırasıyla kronik apandisit hastaları (n= 207; %5,2), *Enterobius vermicularis* (n= 14), *Schistosoma* (n= 8), Crohn's hastalığı (n= 1), nöroma (n= 10), karsinoid tümör (n= 5), musinöz kistadenoma (n= 5), mukosel (n= 4) ve musinöz kistadenokarsinoma (n= 2) idi.

Sonuç: Apandiste yapılan hem akut apandisit tanısını doğrular hem de hasta yönetimine etki edebilecek diğer olağandışı tanıları tespit eder. Olağandışı histopatolojik buğusu olan birkaç hasta anti-helmentik tedavi, kolektomi, gastroenteroloji takibi veya periyodik takip gerektirmektedir. Bu yüzden, tüm appendektomi örneklerine rutin HPE yapılmalıdır.

Anahtar Kelimeler: Apendektomi, apandisit, histopatolojik değerlendirme

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ORIGINAL ARTICLE
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Effects of erythropoietin on bacterial translocation in a rat model of experimental colitis

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ABSTRACT

Objective: In this experimental study, it was aimed to assess the effects of erythropoietin (EPO) on bacterial translocation in a rat model of colitis.

Material and Methods: The rats were randomly assigned into control, colitis and EPO-treated groups (n= 8 in each group). Saline solution (NS) was administered to control rats via rectal route. A trinitrobenzene sulfonic acid and ethanol mixture (TNBS-E) was used to induce colitis in the experiment groups. No treatment was administered to colitis group after induction. Starting at one day after induction of colitis with TNBS-E, EPO (1000 IU/kg) was administered subcutaneously for three days to the rats in the EPO-treated group. Colonic inflammation was assessed by gross and microscopic examination on day five. Blood samples were obtained to evaluate bacterial translocation while hepatic, mesenteric tissue samples and mesenteric lymph node (MLN) samples were collected for tissue culture. Tissue myeloperoxidase (MPO) levels, and tumor necrosis factor alpha (TNF- α) and endotoxin levels in the sera were studied.

Results: Significant gross and microscopic differences were found in the comparison between colitis and EPO-treated groups ($p< 0.05$). MPO level was significantly lower when compared to the colitis group ($p< 0.05$). Serum TNF-α and plasma endotoxin levels were significantly lower in the EPO-treated group than the colitis group ($p< 0.05$). Bacterial translocation was lower in the liver, spleen, MLNs and systemic blood in the EPO-treated group when compared to the colitis group ($p< 0.05$).

Conclusion: In TNBS-E-induced rat model of colitis, EPO significantly decreased inflammation and bacterial translocation based on histopathological, biochemical and microbiological parameters.

Keywords: Erythropoietin, experimental colitis, bacterial translocation

INTRODUCTION

Inflammatory bowel diseases (IBD) is a group of diseases progressing with chronic inflammation in the gastrointestinal system (GIS). Ulcerative Colitis (UC) is a recurrent non-transmural inflammatory disorder confined to the colon while Chorn Disease (CH) is a recurrent disorder that is associated with the transmural inflammation of the whole gastrointestinal tract. Current hypothesis about the etiology of IBD postulates that the disease stems from immune system dysregulation in the gastrointestinal tract in patients with genetic predisposition (1). In patients with genetic predisposition, together with environmental factors, the excessive inflammation without control leads to the intestinal migration of the inflammatory cells, and progressive tissue damage develops due to the effects of cytokines in the gastrointestinal tract (GIT) (2).

IBD is associated with an increase in epithelial permeability resulting in chronic stimulation of the mucosal immunity by bacterial products. It is suggested that the increase in mucosal permeability may be the primary defect in IBD (3). Intestinal epithelial cells involve control mechanisms to inhibit inappropriate immune response activation. However, the bacterial products passing across the mucosal barrier directly contact with immune cells, promoting a classical immune response. The impaired response by mucosal immunity and cytokine release result in chronic mucosal damage (1). This may lead passage of enteric bacteria and bacterial substances into sterile extraintestinal sites through the intestinal wall.

Erythropoietin (EPO) is a glycoprotein growth hormone with a molecular weight of 34 kDa which stimulates the growth of erythroid progenitor cells (4). It is primarily produced in kidneys (4). It is released from the kidneys as a response to hypoxia and

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stimulates the hematopoietic system. EPO is produced in mammalian cell culture by recombinant DNA technology and is used for the treatment of anemia caused by renal failure or cancer chemotherapy (5).

Erythropoietin is a growth hormone which primarily stimulates the growth of erythroid progenitor cells. It has been shown that EPO decreases apoptosis in neurons in rat models (6). In experimental colitis models, EPO has been shown to decrease the effects of inflammatory bowel disease (7-9).

EPO has also been determined to decrease bacterial translocation in rats with induced obstructive jaundice (10). Another study in rat models has demonstrated that EPO administration after hemorrhagic shock enhances barrier function of the mucosa and reduces bacterial translocation (11).

However, there are no studies in the literature investigating EPO effects on bacterial translocation in experimental colitis model. Our study aimed to assess the effects of EPO on bacterial translocation in IBD, and anti-inflammatory effects of erythropoietin based on colitis pathophysiology.

MATERIAL and METHODS

Animals

The present study was conducted on 24 male Wistar-Albino rats aged 28-32 weeks (weighing 220-280 g). The rats were acclimatized over a week before the experiments. All rats were kept at 21°C and fed with standard rat chow. Prior to the experiments, the rats were fasted for 12 hours with only water allowed. This experimental study was conducted at the Hakan Çetinsaya Experimental and Clinical Research Center (ECRC) of Erciyes University School of Medicine. The study was approved by the Medical Faculty Ethics Committee.

Experimental Design

The animals were randomly assigned into three groups (eight animals per group):

- Group 1 (control group): the rats in this group received saline solution (SS) via rectal route.
- Group 2 (colitis group): colitis was induced by TNBS-E administration and no treatment was given.
- Group 3 (EPO-treated group): EPO was administered after induction of colitis.

Experimental Procedure

In all rats, sedation was achieved by halothane, and spontaneous respiration was maintained throughout the procedure. The animals were weighed after sedation. In order to induce colitis, a 3.5-F plastic cannula was inserted 5 cm into the rectum. Colitis was triggered by slow instillation of trinitrobenzene sulfonic acid (TNBS) (50 mg/kg) in 0.25 mL ethanol (50%) into the colon through this cannula. Then, the rats were placed in supine position until recovery from sedation in order to prevent leakage. The control group received only 0.9% NaCl solution through the rectal cannula. The colitis group was administered TNBS (50 mg/kg) in 0.25 ml (50%) ethanol intracolonically to induce colitis. In the EPO-treated group, starting at one day after the induction of colitis with intracolonically administered TNBS-E, Erythropoietin Beta (Neorecormon, Roche, Mannheim, Germany) 1000 IU/kg was administered subcutaneously for three days. Identical amounts of subcutaneous sterile saline solution were simultaneously administered to the controls and rats in the colitis groups.

All injections were administered upon cleansing of the injection site with a 10% povidone-iodine antiseptic solution. All rats received standard rat pellets for five days. On day five after colitis induction, anesthesia was achieved with 50 mg/kg ketamine and 8 mg/kg xylazine via intraperitoneal route. A midline incision was made after removal of abdominal hair and skin preparation with 10% povidone-iodine. Blood sampling was performed from vena cava (3 mL) and portal veins (2 mL) for tumor necrosis factor alpha (TNF-α), and plasma endotoxin assays and blood culture tests. Using sterile forceps, the liver, spleen and mesenteric lymph nodes were crushed followed by homogenization and transfer into a medium to isolate bacteria immediately. Then the colon was removed from mid-transverse segment to rectum. The rats were sacrificed by ether inhalation at lethal doses.

Serum TNF-α Assay

The sera were obtained by centrifugation 4000 rpm over 10 minutes. Sera were stored in Eppendorf tubes at -80°C until assays. Serum TNF-α level measurement was performed using a Rat TNF-α Elisa kit (Rat TNF-α Invitrogen ELISA Kit, USA). TNF-α level is expressed as pg/mL.

Plasma Endotoxin Assay

Plasma endotoxin measurement was performed in samples obtained from the portal vein using modified (quantitatively) Limulus-amebocyte-lysate test (Sunred). Plasma endotoxin level is given as pg/mL.

Determination of Bacterial Translocation

Blood culture tests were performed using an automated blood culture system. The blood samples were transferred to BacT/Alert culture bottles. After inoculation, the bottles were incubated at 35-37°C. During incubation, the bottles were mixed by shaking and controlled at 10-minute intervals throughout incubation. CO_2 production in fluid media was continuously measured by colorimetric principle and monitored by a reflectometer available in the system. The system provided a visual and audio signal if a positive result was detected. The samples found positive were inoculated onto blood agar and eosin methylene blue agar (EMB agar) and were incubated for 24 hours at 37°C. After incubation, microbial identification was performed according to conventional methods. After seven days, samples with no positive signal were accepted as negative. Tissue samples were inoculated into sterile bottles containing brain-heart infusion broth which were then

incubated over 24-to-48 hours at 37°C. Then the samples were incubated in blood agar and EMB agar broths over hours at 37°C. Microbial identification was performed according to conventional methods.

Evaluation of Colonic Damage

The distal colon obtained from rats was opened in a longitudinal manner. The colon was washed out by using normal saline in order to remove feces. Then the colon segments were examined by a pathologist.

Gross Examination of Colon

Gross changes in the colon mucosa were assessed in five categories previously defined by Campos et al. (12). Macroscopic morphology scores are shown in Table 1.

Microscopic Examination of the Colon

Microscopic evaluation of the colonic mucosa was performed as described by Yamamoto et al. After fixation with a 10% formaldehyde solution for 24 h, the tissue samples were placed into ethanol (70%). Then the sections (4 µm in thickness) prepared from paraffin-embedded tissue samples were stained by H&E. The sections were examined by a pathologist blinded to the groups. Microscopic changes were graded from 0-3 (Table 2) (13).

Measurement of Tissue Myeloperoxidase Activity

In the colon mucosa, MPO activity was measured after preparation of the colon homogenates via Elisa method by a Rat MPO ELISA Kit (Cell Sciences, USA) as defined by Krawisz et al. (14). Briefly, the colon mucosa sample underwent homogenization using ice-cold solution containing PBS (PH: 6.0) and hexadecyl trimethyl ammonium bromide. After triple freeze-thaw cycles, the homogenate was centrifuged at 40.000 rpm for 15 minutes at 4°C. Then O-Dianisidine -H_2O_2 buffer was mixed to the supernatant. The absorbance (λ= 460 nM) was measured over 2 minutes to detect changes. MPO activity was defined as amount of H_2O_2 (1 mMol) degraded in one minute. The result is given as unit per gram tissue weight (U/g tissue).

Table 1. Classification of macroscopic findings in the colonic mucosa

Grade	Finding
0	Preserved mucosal layer normal in appearance
1	Erythematous areas without edema, congestion or superficial ulceration
2	Linear superficial ulcerations (7-15 mm); with depressed, erythematous or darker mucosal, granular bottom
3	Ulcerated area (15-45 mm) with irregular bottom; granular with rounded shaped island of normal or edematous mucosa among ulcerated mucosa
4	Extensive, irregular and multiple ulcers (> 45 mm); thinned intestinal wall; granular irregular bottom

Table 2. Classification of microscopic findings in the colonic mucosa

Grade	Finding
0	Normal epithelium, no cellular swelling, normal crypt appearance, low monocyte infiltration, low or absent neutrophil infiltration
1	Indicates loss of single epithelial cells. Moderate epithelial swelling, single inflammatory cell infiltration of crypts, mild monocyte–neutrophil infiltration
2	Multiple epithelial cell loss, epithelial flattening, cryptitis and moderate monocyte–neutrophil infiltration
3	Marked epithelial ulceration, crypt abscesses and a marked increase in monocytes and neurophils

Statistical Analysis

Data analysis was performed by SPSS Statistics 21.0 statistical software package (IBM,Corp., Armonk,NY,USA). Normality was tested using Shapiro-Wilk normality in numeric variables. One-way analysis of variance was used to compare the variables with normal distribution among the groups. Multiple comparisons with the Student-Newman-Keuls test were used for the groups showing a difference in the result of one-way analysis of variance. Kruskal-Wallis test was used for variables with skewed distribution. Multiple comparisons with the Student-Newman-Keuls test were used for the groups showing a difference in Kruskal-Wallis analysis. A two proportions test was used to evaluate bacterial translocation. Summary of the statistics of the variables with normal distribution was presented as mean ± SD, while the summary of the statistics of the variables without normal distribution was expressed as median (minimum-maximum) values. A $p<0.05$ value was set for statistical significance.

RESULTS

Colonic Damage

Macroscopic Evaluation Results

In this study, colonic macroscopic damage score values were statistically expressed as median (min-max) values: 3.0 (3.0-4.0) in the TNBS-E-induced colitis group, 2.0 (2.0-3.0) in the EPO + colitis (treatment) group and 0.0 (0.0-1.0) in the control group, showing significant differences among groups ($p< 0.001$). Normal colonic epithelium was observed in the control group. While widespread irregular ulcers and transmural inflammation were observed in the colitis group, only minimal damage and mild inflammation were found in the surface epithelium in the EPO-treated group.

Microscopic Evaluation Results

In this study, colonic microscopic damage score values were statistically expressed as median (minimum-maximum) values: 2.0 (2.0-3.0) in the TNBS-E-induced colitis group, 1.0 (1.0-2.0) in the EPO + colitis (treatment) group and 0.0 (0.0-1.0) in the con-

trol group (p< 0.001). Normal colonic epithelium was observed in the control group. While widespread mucosal damage and transmural infiltration of neutrophils, monocytes, and lymphocytes were observed in the colitis group, mild epithelial damage and inflammation were observed in the EPO-treated group. Microscopic images are shown in Figure 1.

Serum TNF-α Results

Plasma TNF-α value is expressed as mean ± SD. TNF-α value was 27.91 ± 2.19 pg/mL in the EPO-treated group, 33.55 ± 1.95 pg/mL in the colitis group, and 23.88 ± 2.07 pg/mL in the control group. It was found to be significantly lower in the EPO-treated group than the colitis group (p< 0.001). These values are shown in Figure 2.

Plasma Endotoxin Results

Plasma endotoxin value is expressed as mean ± SD. Endotoxin level was 20.15 ± 1.33 pg/mL in the EPO-treated group, 26.45 ± 2.55 pg/mL in the colitis group, and 15.88 ± 2.07 pg/mL in the control group. It was found to be significantly lower in the EPO-treated group than the colitis group (p< 0.001). These values are shown in Figure 3.

Myeloperoxidase Results

Tissue MPO level is expressed as median (min-max). MPO level was 24.1 (20.9-27.5) U/gr in the EPO-treated group, 57.6 (24.1-88.6) U/gr in the colitis group and 15.5 (5.1-26.2) U/gr in the control group. It was found to be significantly lower in the EPO-treated group when compared to the colitis group (p= 0.021). There was no significant difference between the treatment and control groups. These values are shown in Figure 4.

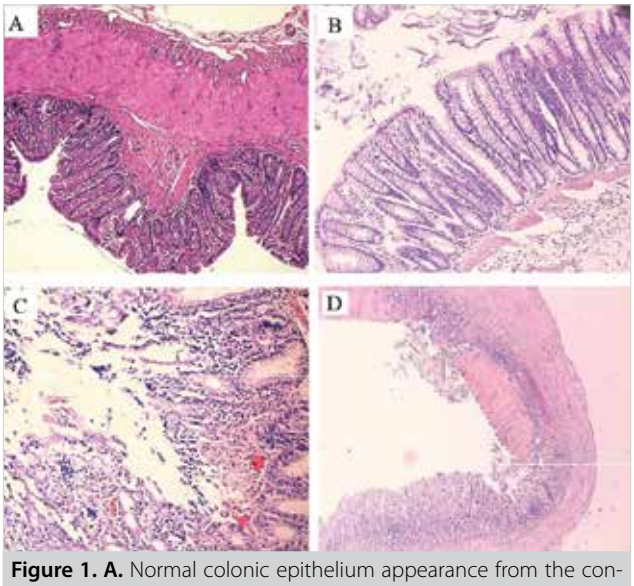

Figure 1. A. Normal colonic epithelium appearance from the control group (Grade 0). **B.** In the treatment group, moderate edema in the epithelium, mild inflammation and neutrophil infiltration in the lamina propria (Grade 1). **C.** In the colitis group, epithelial cell loss, cryptitis, erosion, appearance of the lymphoid follicle and mucosal ulceration (Grade 2). **D.** In the colitis group, prominent epithelial ulceration, crypt abduceri and significant increase of monocytr and neutrophil levels (Grade 3).

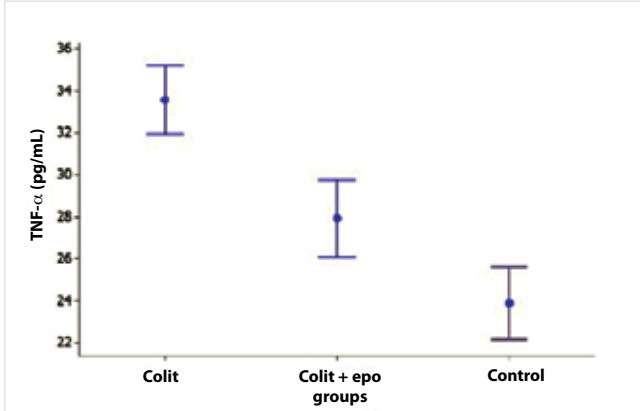

Figure 2. Comparison of the groups in terms of TNF-α values.

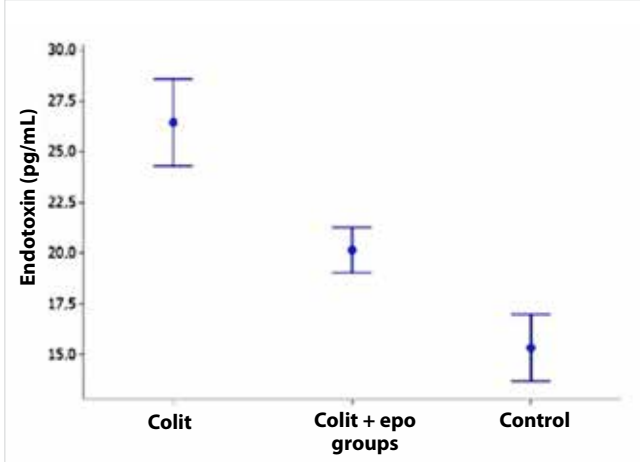

Figure 3. Mean endotoxin values (pg/mL) and confidence intervals by groups (p< 0.001).

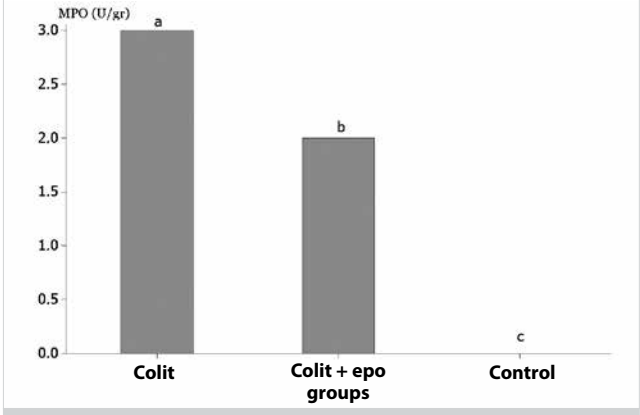

Figure 4. MPO values by groups (U/gr) (p< 0.05).

Table 3. Bacterial translocation by groups. A two proportions test was used for the comparison. The number of positive tests was tested for all animals (8 animals in each group) ($p< 0.05$)

Tissue	Control group	Colitis group	Colitis + Epo group	p
MLN	0	8	3	< 0.001
Spleen	0	8	2	< 0.001
Liver	0	7	3	0.002
Systemic blood	0	5	0	0.004

MLN: Mesenteric lymph nodes, Epo: Erythropoietin.

Bacterial Translocation Results

It was failed to detect positive growth in the control group. There was a significant increase in the frequency of bacterial translocation to the liver, spleen, MLNs and blood in the group with trinitrobenzene sulfonic acid-ethanol-induced colitis ($p< 0.05$). However, there was significant decrease in bacterial translocation to the liver, spleen, MLN and blood by treatment with EPO when compared to colitis group. Bacterial translocation incidences in different groups are shown in Table 3. The bacteria included *Escherichia coli*, *Enterococcus* spp., *Proteus* spp. and *K. pneumoniae*.

DISCUSSION

Inflammatory bowel diseases (IBD), namely Crohn's Disease and Ulcerative Colitis, are chronic inflammatory diseases involving gastrointestinal (GI) tract. Defective immune system regulation due to environmental and genetic factors, abnormal GI luminal factors associated with microorganisms in the GI lumen flora and antigens in dietary intake, and a defective GI barrier that allows the penetration of colonic mucosa by GI luminal factors are among the factors that underlie the etiology of IBD (15).

TNBS-induced colitis model is a chronic inflammation and ulceration model that occurs after delayed hypersensitivity induced by the haptene. The mucosal barrier is disrupted by ethanol, leading to ulceration and inflammation in a dose-dependent manner. It was shown that the colitis in the TNBS model is similar to the colitis in humans, and it was especially pointed out as a convenient model for the development and trial of new drugs for the treatment of the disease (16).

In the literature, experimental colitis was induced by different doses of TNBS in a 5% ethanol solution. Doses of 5, 50, 100, and 150 mg/kg TNBS in 0.25 mL ethanol were tested, and the optimal dose for colitis induction was found to be 50 mg/kg TNBS in a 0.25 mL 50% ethanol solution (17). In this study, we used 50 mg/kg TNBS in a 0.25 mL 50% ethanol solution to induce colitis, based on this information. Togashiet al., in their study, have measured in vivo mucosal sulfhydryl compounds in a TNBS-E-induced experimental colitis model and has shown that advanced mucosal damage occurs one or two days after induction (18). Three days after TNBS administration, inflammation and ulceration of the colon were demonstrated endoscopically (19).

Several protective effects of EPO against ischemia were demonstrated in cell cultures and animal models, including anti-apoptotic, antioxidant, and neuroprotective effects (20,21). There are studies indicating that EPO decreases the damage caused by ischemia/reperfusion in kidneys (22) and colon (23). Large amounts of EPO receptors were identified on macrophages. In experimental colitis models, EPO has been shown to inhibit NF-κB activation and pro-inflammatory gene expression of myeloid cells in the lamina propria, leading to a decrease in the severity of colitis (9).

Taşdemir et al., in their study investigating the effects of melatonin and erythropoietin in a DNBS-induced experimental colitis model, have administered subcutaneous EPO on the 2nd and 3rd day following rectal DNBS administration, and the animals have been examined under anesthesia on the 4th day (24). In a study by Cuzzocrea et al., investigating the effects of EPO on inflammatory bowel disease, colitis was induced by dinitrobenzene sulfonic acid (DNBS), EPO (1000 IU/kg) was administered daily as SC bolus injections from day 2 onwards and the effects of EPO were evaluated on the 4th day (9).

In our study, after induction of colitis with TNBS, we administered EPO (1000 IU/kg/day s.c.) from the 2nd to the 4th day, and on the 5th day, we collected tissue and blood samples from the rats under anesthesia.

In order to evaluate the effects of EPO on pro-inflammatory cytokines, blood TNF-α levels and tissue MPO levels were measured in this study. TNF-α is one of the major cytokines implicated in IBD and TNF-α levels were found to be elevated in IBD (25). Hence, it was demonstrated that TNF-α monoclonal antibodies are effective in the treatment of IBD by preventing the binding of TNF-α to its receptor, and they are used as therapeutic agents for the treatment of patients non-respondent to current treatment (26).

In the study by Küçük et al., bacterial translocation has been assessed in an experimental model of colitis regarding the effects of Met-RANTES. They have demonstrated that TNF-α levels were increased by increasing inflammation and Met-RANTES treatment resulted in decreased serum TNF-α levels and bacterial translocation (27). Another study by Nairiz et al. investigating the effects of EPO on experimental colitis has demonstrated that in inflamed colons of TNBS-subjected mice, there was a significant decrease

in Nos2, TNF-α, IL-6, IL-12p35 and IL-23p19 mRNA expression levels associated with EPO treatment. Furthermore, the supernatants of colon samples from TNBS-subjected mice receiving EPO had significantly reduced levels of TNF-α, IL-6, IL-12p70 and IL-23 (9). In this study, we compared the colitis and EPO-treated groups in terms of serum TNF-α levels. We found significantly lower levels of TNF-α in the EPO-treated group than those in the colitis group ($p< 0.05$) (Graph 3). High TNF-α level is a common feature of all colitis models in rats. Our study demonstrates that severe inflammation and increased bacterial translocation were in parallel with elevated TNF-α levels in the colitis group. The detection of low TNF-α levels in the EPO-treated group shows the anti-inflammatory effect of EPO.

MPO is a lysosomal enzyme found in phagocytic cells. It is abundant in the azurophilic granules of polymorphonuclear leukocytes and activated leukocytes entering the tissue release enzymes, including MPO, elastase, protease, and lactoferrin. Therefore, MPO activity may be used as a quantitative indicator of neutrophil sequestration. Neutrophil activity has been shown to increase in IBD and elevated MPO levels have been considered as an indicator of neutrophil migration (28).

Cuzzocreaet al., in their study investigating the effects of erythropoietin on experimental colitis, have shown that EPO treatment decreases inflammation in the colon by microscopic examination of the colonic tissue. MPO activity in the inflamed colon has been measured and significant differences found between the colitis and EPO groups (8).

Consistent with the literature, we also found that MPO levels were significantly higher in rats with induced colitis when compared to the controls ($p< 0.05$). Tissue MPO levels were significantly lower in the group receiving EPO treatment in comparison to the colitis group ($p< 0.05$) and the values were higher in the EPO-treated group when compared to the control group but the difference was not significant (Figure 4).

Histopathologically, there were macroscopic and microscopic improvements in the EPO-treated group when compared to the colitis group. These results demonstrate that EPO reduces mucosal damage by means of its anti-inflammatory effect.

There are some defense mechanisms that prevent the passage of bacteria in the normal intestinal flora across the intestinal mucosa. These include the physical barrier function of the mucosal epithelium, the mucus layer between bacteria in the lumen and the intestinal epithelium, blockage of epithelial adhesion sites on the bacterial wall by secreted IgA and the presence of intestinal peristalsis. These local defense mechanisms maintain the normal intestinal flora (29). Under normal conditions, normal flora bacteria in the intestinal lumen cannot pass the mucosal barrier. Intestinal bacterial translocation is defined as the passage of gastrointestinal micro-flora to local mesenteric lymph nodes (MLN) through lamina propria and to other organs such as the liver and spleen thereafter (30).

In cases such as IBD, acute pancreatitis, severe burns, intestinal obstruction and shock, bowel barrier function and mucosal integrity are impaired, which causes the bacteria to be released from the intestine and spread to other organs (31).

The presence of bacterial translocation in IBD has also been shown in experimental colitis models. Halaçlar et al., in their study, have investigated the effects of glucagon-like peptide 2 (GLP 2) on bacterial translocation in an experimental colitis model. In this study, bacterial translocation to the liver, spleen, MLNs and systemic blood has been investigated by culturing tissue and blood samples after the induction of colitis with TNBS. *Escherichia coli*, *Enterococcus faecalis*, *Staphylococcus aureus* and *Enterobacter agglomerans* have been identified as the translocated bacteria (32).

Kao et al. have investigated the effect of EPO on intestinal bacterial translocation in a case of shock. After inducing hemorrhagic shock in rats, intravenous rHuEPO (1000U/kg) have been administered together with saline solution, and bacterial translocation has been assessed by cultured mesenteric lymph nodes. It has been reported that EPO reduced bacterial translocation associated with ischemic-reperfusion damage by reducing the tissue damage caused by hemorrhagic shock and saline resuscitation (11).

We also performed blood and tissue cultures to determine bacterial translocation in the course of colitis. TNBS-E-induced colitis caused a significant increase in the frequency of bacterial translocation in our study while EPO treatment reduced bacterial translocation. The translocated bacteria and translocation frequencies in each group are shown in Table 3.

Endotoxin is a component of the lipopolysaccharide structure present in the cell walls of all gram-negative bacilli. Rather than through its direct effect, endotoxin triggers a strong response by stimulating hormonal and chemical mediators. Endotoxemia originating from the intestine is particularly observed in patients with IBD, burns, trauma, liver failure or acute pancreatitis (33). In our study, plasma endotoxin levels were significantly elevated in the rats with induced colitis compared to the control group. The endotoxin level was shown to be significantly lower in the EPO-treated group ($p< 0.05$) (Figure 3).

The effects of EPO in the experimental colitis model were investigated and the following findings were obtained. A significant improvement in macroscopic scores and histopathological appearance was found in the EPO-treated group ($p< 0.05$). There was a significant increase in tissue MPO levels increased in the colitis group whereas a significant decrease in the EPO-treated group ($p< 0.05$). Plasma endotoxin levels increased in the EPO-treated group while they significantly decreased in the

EPO-treated group (p< 0.05). TNF-α levels were elevated in the EPO-treated group while they significantly decreased in the EPO-treated group (p< 0.05). Bacterial translocation observed in the colitis group was significantly reduced in the EPO-treated group (p< 0.05).

CONCLUSION

In light of these results, the decrease in bacterial translocation in the EPO-treated group could be explained not only by the anti-inflammatory effect of EPO, but also by its protective effect on the intestinal mucosa and its decreasing effect on intestinal permeability. EPO treatment, if supported by further experimental and clinical studies, may become an alternative approach in IBD.

Ethics Committee Approval: The study was approved by the Medical Faculty Ethics Committee (Date: 14.11.2012 No: 12/112).

Informed Consent: Due to the retrospective design of the study, the informed consent was not obtained.

Peer-review: Externally peer-reviewed.

Author Contributions: Consept - T.A., A.A., Z.Y., E.S.; Design - T.A., A.A.; Supervision - T.A., A.A., Y.D., Z.Y., E.S.; Resource - T.A., Y.D., B.P., M.B.; Materials - T.A., Y.D., M.G.; Data Collection and/or Processing - T.A., Y.D., M.B., M.G., B.P.; Analysis and Interpretation - T.A., Z.Y., E.S., B.Ö., M.B., M.G., B.P.; Literature Search - T.A., B.Ö., E.S.; Writing Manuscript - T.A., A.A., Y.D., B.Ö., E.S.; Critical Reviews - T.A., A.A., Y.D., B.Ö., E.S., Z.Y., M.B., B.P., M.G.

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ORİJİNAL ÇALIŞMA-ÖZET
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Sıçanlarda oluşturulan deneysel kolit modelinde eritropoietinin bakteriyel translokasyon üzerine etkisi

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ÖZET

Giriş ve Amaç: Bu çalışmanın amacı kolit sürecinin patofizyolojisinden yola çıkarak, ratlarda oluşturulan deneysel kolit modelinde eritropoietinin (EPO) bakteriyel translokasyonu üzerine etkisini araştırmaktır.

Gereç ve Yöntem: Gruplar randomize olarak her biri sekiz rattan oluşan üç gruba (kontrol, kolit ve tedavi) ayrıldı. Kolit grubuna trinitrobenzensülfonik asit ve etanol karışımı (TNBS-E) rektal yoldan verilerek kolit oluşturuldu. Tedavi grubuna ise TNBS-E ile kolit oluşturulduktan bir gün sonra başlanarak üç gün boyunca günde bir defa subkutan olarak 1000 IU/kg EPO verildi. Beşinci gün kolondaki inflamasyon makroskobik ve mikroskobik olarak değerlendirildi . Bakteriyel translokasyonu değerlendirmek için kan alındı ve doku kültürü amacıyla karaciğer, dalak, mezenterik lenf nodlarından (MLN) doku örneklemeleri yapıldı. Doku düzeyinde miyeloperoksidaz (MPO), serumda ise tümör nekroz faktörü-alfa (TNF-α), endotoksin düzeylerine bakıldı.

Bulgular: Kolit ve tedavi grupları karşılaştırıldığında gruplar arasında makroskobik ve mikroskobik açıdan belirgin farklılık mevcuttu ($p< 0.05$). Tedavi grubunda ölçülen MPO düzeyleri kolit grubuna göre anlamlı düzeyde düşüktü ($p< 0.05$). TNF-α ve plazma endotoksin düzeyleri tedavi grubunda kolit grubuna göre belirgin şekilde düşüktü ($p< 0.05$). Kolit grubuyla karşılaştırılınca, tedavi grubunda karaciğer, dalak, MLN'ler ve sistemik kanda bakteriyel translokasyon düşüktü ($p< 0.05$).

Sonuç: Deneysel olarak TNBS-E ile oluşturulmuş kolit modelinde uygulanan EPO, histopatolojik, biyokimyasal, mikrobiyolojik parametrelere bakıldığında inflamasyonu ve bakteriyel translokasyonu belirgin düzeyde azaltmıştır.

Anahtar Kelimeler: Eritropoietin, deneysel kolit, bakteriyel translokasyon

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Retrospective evaluation of candidemic patients among general surgery department in a tertiary care university hospital

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ABSTRACT

Objective: *Candida* species are among the most important causes of hospital acquired blood borne infections, and with high rates of mortality and morbidity, these infections are still a major problem today. History of gastrointestinal surgery, administration of total parenteral nutrition and/or wide spectrum antibiotics and immune suppression following organ transplantations are considered serious risk factors for these infections. This study aimed to evaluate the patients from our general surgery department with diagnosed candidemia; by means of strain, treatment and prognosis.

Material and Methods: Patients with positive blood cultures for *Candida* species who were treated in the wards and Ege University Faculty of Medicine general surgery department of surgical intensive care units of our between 2012 and 2017 were retrospectively analyzed by means of strain, treatment and prognosis.

Results: A total of 50 patients were enrolled in the study. Mean age was 58.96 years and 54% of the patients were female. There were nine patients with organ transplantation (four liver and five kidney transplantations), six with intestinal perforation and three with anastomotic leakage. Isolated strains were *Candida albicans* (36%; 18/50), *Candida tropicalis* (14%; 7/50), *Candida glabrata* (12%; 6/50), *Candida parapsilosis* (8%; 4/50), *Candida kefyr* (6%; 3/50), *Candida krusei* (4%; 2/50), *Candida pulcherrima* (2%; 1/50), *Cryptococcus neoformans* (2%, 1/50), *Geotrichum capitatum* (2%, 1/50), *Candida* spp. (unidentified, 14%; 7/50) with decreasing frequency. The highest antifungal sensitivity rates (> 90%) were measured for amphotericin B, voriconazole and echinocandins among all isolates. One-month mortality rate was 43.4% (20/46). Documented eradication was achieved among 24 of the 33 patients who had control blood culture samples (72.7%), and mean eradication time was 7.6 days. Echocardiography was performed in 14% (7/50) and ophthalmic examination in 8% (4/50).

Conclusion: Although *C. albicans* appears to be the dominant strain in patients with candidemia, frequencies of other strains are increasing. Early diagnosis and treatment of patients with candidemia is of vital importance due to high mortality and morbidity rates.

Keywords: Candidemia, prognosis, treatment, risk factors

INTRODUCTION

Candidemia demonstrated as an important part of invasive fungal infections and also a significant factor for the high mortality rates, prolonged length of hospital stay and high health-related costs, ranks between the fourth and seventh mostly seen disease among the blood stream infections in the United States and Europe (1). Candidemia incidence has been shown as 1.23 to 12.3 per 1000 admissions from our country which can be varied due to regional differences in terms of mortality rates, isolated pathogens, risk factors and antifungal susceptibility rates (2-5).

This study aimed to evaluate the pathogens, treatments and prognosis of the patients followed by the General Surgery Department of our hospital.

MATERIAL and METHODS

In our study, the patients with positive blood cultures for *Candida* who were followed up by the Ege University Faculty of Medicine, General Surgery Department (Inpatient Clinic/Intensive Care Unit/Transplantation Unit) between the years of 2012-2017 were evaluated in terms of pathogen, treatment and prognosis, retrospectively. At least one positive blood culture for *Candida* spp. was accepted as candidemia and only adult patients (≥ 18-year-old) were included into our study. Sociodemographic features, risk factors, blood culture results, 30-day (due to all causes) mortality rates and antifungal treatment regimens were screened via the

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patients' files. Sabouraud dextrose agar (Acumedia; Michigan, USA) was used for the culture, and identification of the species was performed by conventional methods (Dalmou method) with micromorphologic features, ID32C (bioMerieux; France) with carbohydrate assimilation features and MALDI-TOFF MS with proteomic features. Antifungal susceptibilities were investigated via E-test method, and minimum inhibitor concentration levels were used according to the CLSI guideline (6,7).

Statistical Package for Social Sciences (SPSS) version 22.0 (IBM Corp.; Armonk, NY, USA) program was used to analyze our data. P value below 0.05 was accepted as statistically significant.

No ethics committee approval was sought due to the retrospective design of the study. Our study was performed in accordance to the ethical standards of the Helsinki Declaration which was accepted by the World Health Community in 1975 (revised in 2008).

RESULTS

A total number of 50 patients (54% female) were recorded during the six-year period. Mean age was 58.96 ± 2.36 years. Comorbidities were recorded as nine organ transplantations (four liver transplantation, five renal transplantation), six intestinal perforations, four intraabdominal abscesses, and three anastomosis leakages (Table 1). Parenteral nutrition rate was 88% (44/50).

Isolated pathogens from the blood cultures were *Candida albicans* (36%; 18/50), *Candida tropicalis* (14%; 7/50), *Candida glabrata* (12%; 6/50), *Candida parapsilosis* (8%; 4/50), *Candida kefyr* (6%; 3/50), *Candida krusei* (4%; 2/50), *Candida pulcherrima* (2%; 1/50), *Cryptococcus neoformans* (2%, 1/50), *Geotrichum capitatum* (2%, 1/50) , *Candida* spp. (14%; 7/50), respectively (Figure 1).

The highest sensitivity rate (> 90%) among all isolates was observed for amphotericin B, voriconazole, caspofungin and echinocandin. Fluconazole resistance was investigated among the antifungal susceptibility tested ones, and resistance rate was observed as 2/16 (12.5%) for both *C. albicans* and non albicans isolates. Fluconazole resistance was observed one out of three antifungal sensitivity tested *C. glabrata* isolates, which supports the fact that fluconazole resistance rate is increasing globally among them in recent years.

Table 1. Comorbidities

Comorbidities	Rates (n, %)
Organ transplantation	9 (18%)
Renal transplantation	5 (10%)
Liver transplantation	4 (8%)
Intestinal perforation	6 (12%)
Intraabdominal abscess	4 (8%)
Anastomosis leakage	3 (6%)

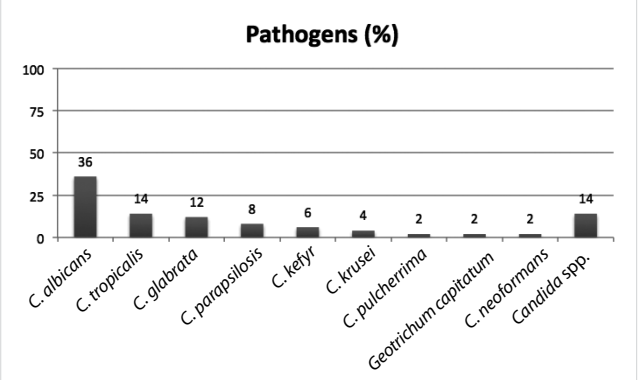

Figure 1. Pathogens.

A total number of four patients were discharged or transported to another hospitals, and thus the rest of the patients' all-cause mortality rate (for one month) was noted as 43.4% (40/46). Antifungal treatment was not started in nine patients and mortality was observed in five. Four patients, in whom antifungal treatment was not started, were discharged or transported, and hence their follow up cannot been done. In subgroup analysis of different treatment regimens, mortality (one-month) rates were recorded as (5/9; 55.6%) for fluconazole, (8/27; 29.6%) for anidulafungin, (1/3; 33.3%) for caspofungin, (1/1; 100%) and (0/1, 0%) for liposomal amphotericin B plus fluconazole, respectively. Mortality rate (one-month) was found as statistically significant for the anidulafungin treatment given and non-given group (8/27-12/19; p= 0.024).

Treatment was changed in five patients (anidulafungin treatment was changed in four and fluconazole treatment was changed in one patient), and among them, only one mortality was observed whose treatment was switched to liposomal amphotericin B from fluconazole.

Microbiologic eradication was noticed in 24/33 patients whose control cultures were performed with a mean duration of 7.6 days. Mortality rate (one-month) was found as statistically significant for the microbiologic responsive and nonresponsive group (4/24-7/9; p= 0.002).

Mean duration of treatment was noted as 17.9 ± 2.26 (min 1, max 58 days) in the treatment given patients. Echocardiography was performed in 14% (7/50) and ophthalmoscopic examination was done in 8% (4/50) during the follow up period of candidemia patients. Infective endocarditis was spotted in one out of seven patients via echocardiography, and none of the four patients had septic emboly in whom ophthalmoscopic examination was carried out.

DISCUSSION

Although the mostly seen pathogen is *C. albicans* in candidemia patients, the incidence of non-albicans *Candida* isolates has increased in recent years (1-3,13). Urethral catheterization,

total parenteral nutrition, history of wide spectrum antibiotic usage, blood transfusion, central venous catheters are accepted as the important risk factors for candidemia (8). In our study, although the mostly detected pathogen was *C. albicans* (36%) in candidemia patients similar to the literature data, non-albicans *Candida* was also seen with high numbers (50%). History of gastrointestinal surgery, total parenteral nutrition, organ transplantation and immunosupression were the main risk factors for candidemia in our study.

In recent years, fluconazole resistance is seen in high rates for non-albicans *Candida* spp. like *C. glabrata* besides the natural resistant *C. krusei*, and Mencarini et al. have shown fluconazole resistance rate as 30% for *C. glabrata* from Italy (9). In our study, although the numbers were low, we found fluconazole resistance as 33% similar to the literature thus, we believe that echinocandins should be preferred to fluconazole in candidemia patients with *C. glabrata*.

Karadag et al. have revealed a mortality rate as 30% for a total number of 89 candidemia patients from our country (10). Different mortality rates have been seen in the literature from our country like Kocak et al. who have confirmed a mortality rate as high as 58% for 38 candidemia patients (11). In our study, one-month mortality rate with all causes was spotted as 43.4% for 46 followed-up patients. Antifungal treatment was not started in nine patients, and mortality was observed as 100% in the rest of the four patients who were discharged or transported to other hospitals (5/5). These results also show that early diagnosis and treatment for candidemia patients are vitally important due to high mortality rates. In subgroup analysis, mortality rate (one-month) was found as statistically significant for the anidulafungin treatment given and non-given group (8/27-12/19; p= 0.024).

Five main subjects underlined to increase survival rates in candidemia patients are appropriate antifungal treatment, control blood culture follow-up, echocardiography control, ophthalmoscopic examination and removal of central venous catheter, respectively (12). Another important result of our study revealed that echocardiography and ophthalmoscopic examination were performed only in 14% (7/50) and 8% (4/50) of the candidemia patients.

The most important limitations of the study included its retrospective design and the fact that antifungal susceptibility test could not be performed in all samples.

CONCLUSION

In conclusion, appropriate antifungal treatment has a vital importance in candidemia patients due to high mortality rates despite the current diagnostic and therapeutic options. Although the mostly seen pathogen is *C. albicans* in candidemia patients, the incidence of non albicans *Candida* isolates is increasing. Due to high resistance for fluconazole, we believe that echinocandins like anidulafungin are more appropriate choices of antifungal treatment rather than fluconazole especially for the hemodynamically unstable intensive care unit patients. In addition to this, echocardiography and ophthalmoscopic examination should be kept in mind for the follow-up of candidemia patients.

Ethics Committee Approval: No ethics committee approval was sought due to the retrospective design of the study.

Informed Consent: Due to the retrospective design of the study, the informed consent was not obtained.

Peer-review: Externally peer-reviewed.

Author Contributions: Consept - U.Ö., M.I.T.; Design - U.Ö.; Supervision - M.I.T., Resource - D.Y.M., S.H.P., C.K., S.E., Materials - D.Y.M., S.H.P.; Data Collection and/or Processing - U.Ö., D.Y.M.; Analysis and Interpretation - U.Ö.; Literature Search - U.Ö.; Writing Manuscript - U.Ö.; Critical Reviews - M.I.T., D.Y.M.

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

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ORİJİNAL ÇALIŞMA-ÖZET
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Bir üçüncü basamak tıp fakültesi hastanesi genel cerrahi bölümünde takip edilen kandidemili olguların retrospektif değerlendirilmesi

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ÖZET

Giriş ve Amaç: *Candida* türleri, hastane kaynaklı kan yoluyla bulaşan enfeksiyonların başlıca sebepleri olmakla birlikte yüksek oranda morbidite ve mortalite sebebiyle günümüzde hala bir sorun teşkil etmektedir. Gastrointestinal cerrahi işlemi öyküsü, total parenteral beslenme ve/veya geniş-spektrumlu antibiyotik kullanımı ve organ transplantasyonu sonrası immünsüpresyon bu enfeksiyonlar için risk ciddi risk faktörleri olarak kabul edilmektedir. Bu çalışmada genel cerrahi bölümümüzde kandidemi tanısı almış hastaların suş, tedavi ve prognoz açısından değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: 2012-2017 yılları arasında Ege Üniversitesi Tıp Fakültesi Genel Cerrahi servisinde veya yoğun bakım ünitesinde tedavi gören ve kan kültürlerinde *Candida* türleri bulunan hastalar retrospektif olarak suş, tedavi ve prognoz açısından değerlendirildi.

Bulgular: Çalışmaya toplamda 50 hasta dahil edildi. Ortalama yaş 58.96 ve hastaların %54'ü kadındı. Organ transplantasyonu geçirmiş dokuz hasta vardı (dört karaciğer, beş böbrek transplantasyonu), altı hastada intestinal preforasyon ve üçünde anastomoz kaçağı tespit edildi. Izole edilen suşlar sıklığı azalan şekilde sırasıyla *Candida albicans* (%36; 18/50), *Candida tropicalis* (%14; 7/50), *Candida glabrata* (%12; 6/50), *Candida parapsilosis* (%8; 4/50), *Candida kefyr* (%6; 3/50), *Candida krusei* (%4; 2/50), *Candida pulcherrima* (%2; 1/50), *Cryptococcus neoformans* (%2, 1/50), *Geotrichum capitatum* (%2, 1/50), *Candida* spp. (tanımlanamayan, %14; 7/50) idi. Tüm suşlar arasında en yüksek antifungal duyarlılık oranları (> %90) amfoterisin B, vorikonozol ve ekinokandinler için ölçüldü. Bir aylık mortalite oranı %43,4 (20/46) olarak bulundu. Belgelenmiş eradikasyon, kontrol kan örneği olan 33 hastadan 24 (%72,7)'ünde elde edildi ve ortalama eradikasyon süresi 7,6 gündü. Ekokardiyografi ve oftalmik muayene sırasıyla %14 (7/50) ve %8 (4/50) hastada uygulandı.

Sonuç: Kandidemi hastalarında en dominant tür *C. albicans* olsa da, diğer suşların sıklığı da artmaktadır. Erken tanı ve kandidemi hastalarının tedavisi yüksek mortalite ve morbidite oranları açısından büyük öneme sahiptir.

Anahtar Kelimeler: Kandidemi, prognoz, tedavi, risk faktörleri

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An outcome analysis of videoscopic assisted retroperitoneal debridement in infected pancreatic necrosis: a single centre experience

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ABSTRACT

Objective: Infected pancreatic necrosis (IPN) is a dreadful complication of moderately severe and severe acute necrotising pancreatitis (ANP). Videoscopic assisted retroperitoneal debridement (VARD) is a minimally invasive surgical option for predominantly left sided, posterior and laterally located disease in patients not responding to conservative and percutaneous options. This study aimed to present an outcome analysis of VARD in the management of IPN at our tertiary care centre.

Material and Methods: The present retrospective analysis of prospectively entered data included 22 patients diagnosed as ANP with IPN from January 2015 to December 2017. These patients were admitted in the surgical gastroenterology unit of our tertiary care centre. The outcome of these patients managed with VARD was evaluated.

Results: The aetiology of ANP was idiopathic, and gallstones were found in 7 patients each and alcohol in 8. Twelve patients were managed with a single VARD procedure; whereas, 10 required a re-debridement due to suboptimal improvement. Eighteen out of 22 patients survived whereas 4 succumbed to major postoperative bleeding/severe sepsis and multiorgan failure (Mortality 18.2%). Hospital stay after the index procedure was between 6 to 11 weeks.

Conclusion: VARD is a safe and effective surgical option for the management of IPN that worsens or fails to respond to conservative and percutaneous drainage options after a minimum of 4 weeks of moderately severe and severe ANP. It decreases postoperative morbidity and mortality and avoids major laparotomy, and hence, it can be considered in a selected group of patients.

Keywords: Videoscopic assisted retroperitoneal debridement, acute necrotising pancreatitis, infected pancreatic necrosis, step up approach

INTRODUCTION

Infected pancreatic necrosis (IPN) is one of the most feared complications occurring in approximately 8-12% of patients with moderately severe and severe acute pancreatitis, leading to increased morbidity and mortality (1,2). 'Step up approach' for the treatment of IPN has been a paradigm shift in its management (3). Videoscopic assisted retroperitoneal debridement (VARD) is one of the minimally invasive surgical options in the step up approach, used for predominantly left sided, posterior and laterally located disease in patients not responding to conservative, endoscopic and/or percutaneous options (3). The present study analyzes our indications, techniques and outcomes of VARD in the management of moderately severe and severe acute necrotising pancreatitis (ANP) with IPN and provides a brief review of current literature.

MATERIAL and METHODS

The study was performed after the approval of research protocols by the institutional ethics committee in accordance with international agreements (World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects," amended in October 2013, www.wma.net)

This observational study is a retrospective evaluation of prospectively entered data of 22 patients admitted with moderately severe and severe ANP with IPN who were managed with VARD from January 2015 to December 2017 in the surgical gastroenterology unit of our tertiary care centre. Severity was assessed as per the 2012 revision of Atlanta classification with modified Marshall scoring system for organ

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dysfunction. ANP was defined as inflammation associated with pancreatic parenchymal and/or peripancreatic necrosis. Moderately severe acute pancreatitis was defined as transient organ failure (< 48 hours) and/or local or systemic complications; whereas severe acute pancreatitis was defined as persistent (> 48 hours) organ failure (single/multiple) (3). IPN was diagnosed by the presence of clinical features of sepsis/ air foci on contrast enhanced computed tomography (CECT) abdomen or positive cultures in percutaneously drained collections.

The data was retrieved with regards to patient's demographic profile, etiology, site of necrosum, duration of conservative treatment, drainage, number of VARD procedures done, morbidity, hospital stay and outcome. The patients were evaluated by CECT abdomen at approximately 1 week from the onset of symptoms and on demand during the hospital stay. Our approach to the management of this patient group is as shown in the algorithm (Figure 1).

VARD was decided upon after the patients failed to improve or deteriorated (persistent or worsening of multiorgan failure, sepsis, CECT evidence of persistent necrosum) at least 4 weeks after the onset of ANP in spite of treatment with intravenous antibiotics, maximised supportive care in the intensive care unit and percutaneous catheter drainage. In all patients, a 12 Fr catheter was placed percutaneously from the left posterior subcostal approach in the necrotic cavity under computed tomography guidance at least 48 hours prior to VARD procedure.

VARD was then performed with the patient in supine position, under general anaesthesia with the left side elevated by 30 degrees. The representative image of IPN on CECT as shown in was studied and a guided 5 cm left subcostal incision was taken (Figure 2 and 3). The dissection was deepened along the percutaneous catheter until necrotic material was visualised. Gross solid necrotic material was removed under direct vision (Figure 4). A 0° laparoscope was then introduced into the cavity and air insufflated, if required, after temporarily closing the sheath (Figure 5). The remaining necrotic material was then removed under videoscopic guidance and a thorough normal saline wash was given to remove the loose necrosum (Figure 6). Two drains were left in the cavity, 1 superficial and 1 deep, for irrigation and drainage. The patients were taken to the intensive care unit (ICU) after the procedure, and antibiotics, enteral feeding and supportive care were continued. Postoperative lavage 6 litres/day was given with normal saline until the draining fluid was clear. Postoperative hospital course was recorded for the need of repeat VARD or other surgical/endoscopic/percutaneous interventional radiology procedures, postoperative complications, duration of hospital stay, bowel function and management of patient till discharge. All patients were discharged with drains after check CECT scans which also guided drain removal. The patients were followed up at 1 month and 3 months after discharge and then as required. The representative image of one such patient who had undergone VARD followed by repeat procedure via laparoscopic transperitoneal transmesocolic approach is as depicted in Figure 7.

The complications were defined as follows: Postoperative pancreatic fistula (POPF) was defined as per international study group of pancreatic surgery (ISGPS) as drain output of any measurable volume of fluid with an amylase level > 3 times the upper limit of normal serum amylase, associated with a clinically relevant development/condition related directly to the postoperative pancreatic fistula (4). Superficial incisional, deep incisional and organ space surgical site infections were defined according to the 1992 modified definitions of nosocomial surgical site infection by centre for disease control (CDC) (5). Paralytic ileus was defined as hypomotility of the gastrointestinal (GI) tract in the absence of mechanical bowel obstruction for more than 3 days following the procedure (6). Hemorrhagic complications were divided into intraluminal gastrointestinal haemorrhage or intraabdominal haemorrhage (7). Postoperative course, complications and their management protocol in our department is as shown in Figure 8. All the data was tabulated and analysed.

RESULTS

The demographic data of the 22 patients who underwent VARD is listed in Table 1. Mean age of the patients was 48.6 years, 16 of which were male. Mean body mass index was 27.8. Nine patients had diabetes mellitus; whereas, 7 had hypertension. Aetiology was alcohol (8), gall stones (7) and idiopathic (7). All 22 patients had moderately severe or severe acute necrotising pancreatitis. All patients had pancreatic and peripancreatic necroses with minimal fluid documented on CECT scan. Prior CT guided percutaneous catheter drainage was done in all the patients.

The time from diagnosis of ANP to VARD ranged from 32 to 35 days. All patients had a subcostal retroperitoneal approach during the first VARD procedure. 10 patients required a repeat VARD procedure on account of CECT abdomen showing residual or newly formed collection or worsening organ failure. Out of these 10 patients, 5 required one more procedure in the form of laparoscopic (3) or open (2) transperitoneal transmesocolic drainage for central necrotic collection which persisted after the second VARD procedure. Hospital stay after the index procedure was between 6 to 11 weeks.

Thirty two postoperative complications with 4 fatalities were observed, of which 13 were minor and 19 were major complications. Four patients had massive bleeding postoperatively, 3 from a branch of splenic artery and 1 from the gastroduodenal artery. Angioembolisation was done postoperatively and although the bleeding was controlled in these 4 patients, they succumbed to hypovolemia/ongoing sepsis and multiorgan failure. All of these 4 patients had undergone repeat VARD procedures. Nine patients developed superficial surgical site infections whereas 4 developed paralytic ileus.

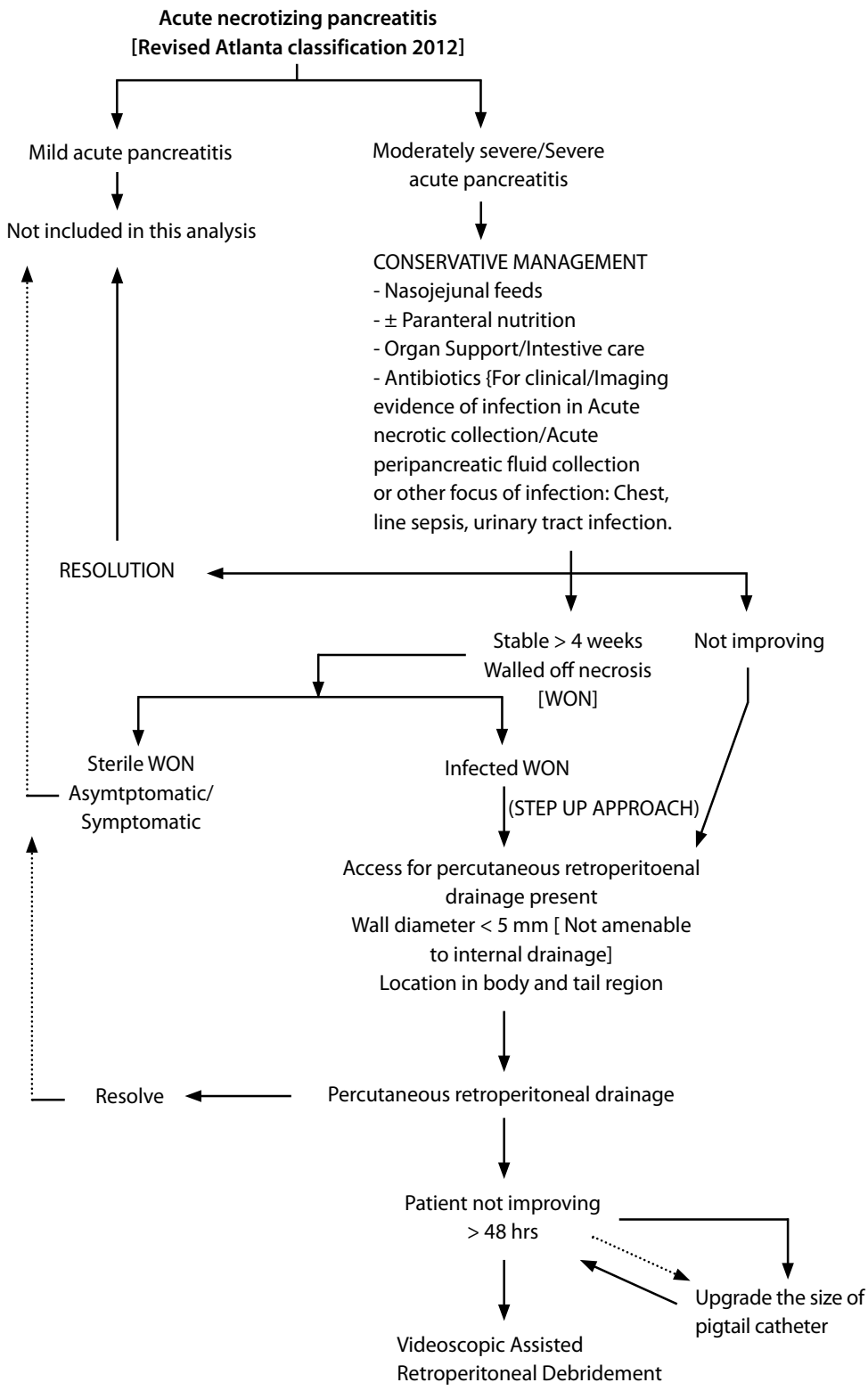

Figure 1. Algorithm showing our approach to the management of moderately severe and severe acute necrotising pancreatitis as well as patient selection for videoscopic assisted retroperitoneal debridement.

Figure 2. Representative image of infected pancreatic necrosis on contrast enhanced computed tomography.

Figure 3. 5 cm left subcostal incision.

Figure 4. Gross solid necrotic material being removed under direct vision.

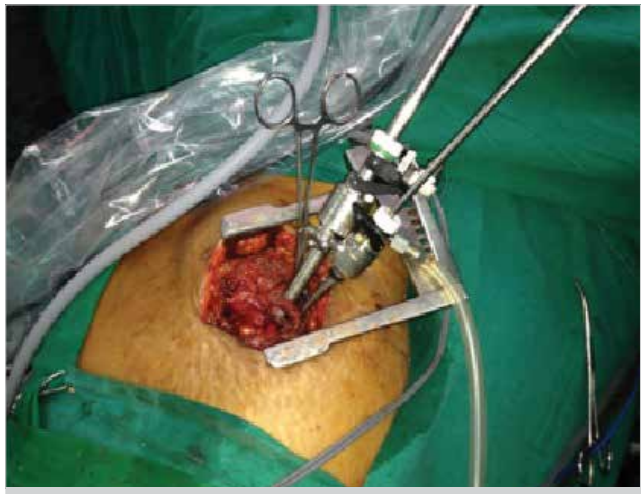

Figure 5. 0° laparoscope introduced into the retroperitoneum.

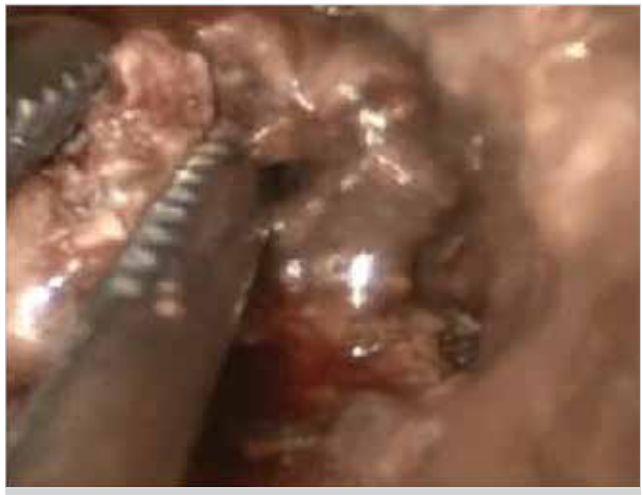

Figure 6. Necrotic material being removed under laparoscopic guidance.

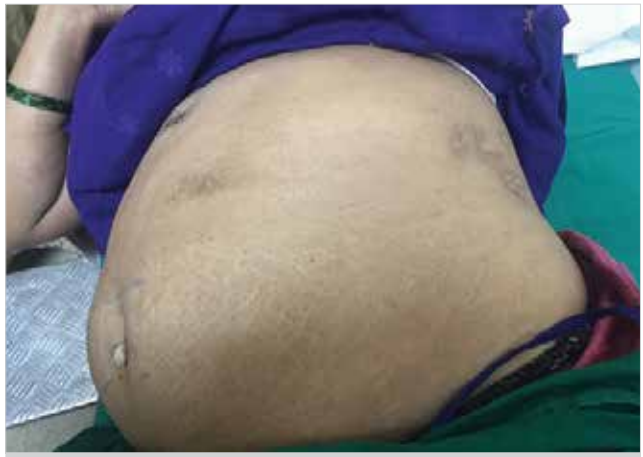

Figure 7. Final postoperative picture with healed incisions.

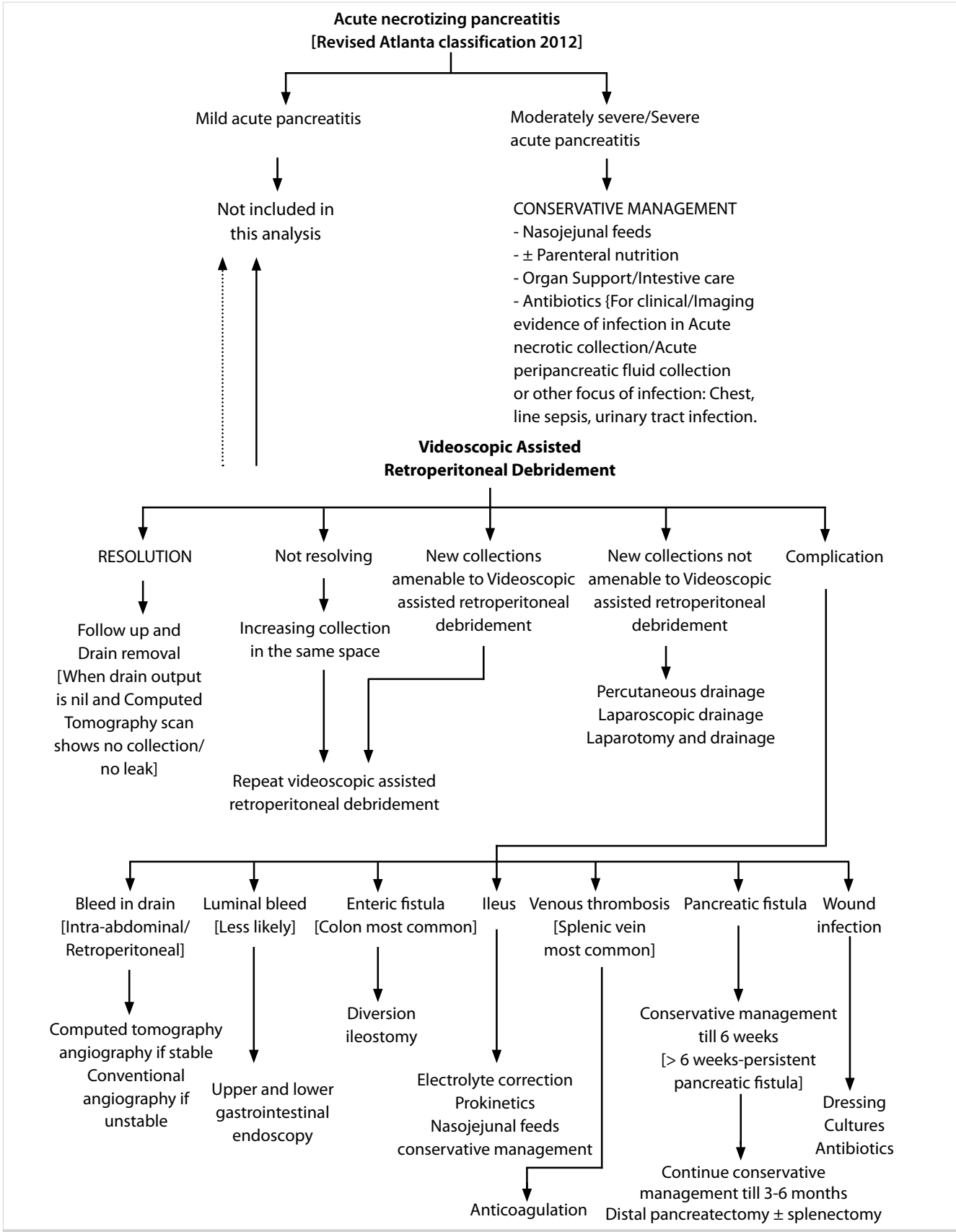

Figure 8. Algorithm depicting the postoperative course, complications and their management following videoscopic assisted retroperitoneal debridement.

Table 1. Patient characteristics, etiology, disease details, treatment details, outcome		
Patient characteristics		
Median age and range (years)		48.6 (39-68)
Sex (Male/Female)		16/6 (72.7%/27.3%)
Mean Body mass index (BMI)		27.8
Co morbid conditions		
Diabetes mellitus		9 (40.9%)
Hypertension		7 (31.8%)
Aetiology of pancreatitis		
Alcohol		8 (36.4%)
Gallstones		7 (31.8%)
Idiopathic		7 (31.8%)
Site of necrosis		
Body		8 (36.4%)
Tail		14 (63.6%)
Duration of conservative treatment prior to VARD		32.6 (32-35 days)
Mean (Range {in days})		
VARD attempts		
1		12 (54.5%)
2		10 (45.5%)
In patient stay		
Mean (Range {in days})		51.3 (42-72 days)
Post op complications	**Clavien Dindo Class**	
Failure to resolve after first attempt	3b	10 (45.5%)
Surgical site infection	1	9 (40.9%)
Bleeding from splenic artery	4	3 (13.6%)
Bleeding from gastroduodenal artery	4	1 (4.5%)
Paralytic ileus	4a	4 (18.2%)
Post operative pancreatic fistula	4a	4 (18.2%)
Colonic fistula	4a	1 (4.5%)
Mortality	5	4 (18.2%)

WARD: Videoscopic assisted retroperitoneal debridement.

Of the 18 patients that survived, 4 developed Grade C postoperative pancreatic fistula which were managed by Roux en Y fistulojejunostomy in 2 and distal pancreatectomy in 2 after 6 months of expectant management. In the remaining 14 patients, drain output gradually diminished and drains were removed after a follow up CECT scan. One patient developed colonic fistula which was managed by diversion loop ileostomy.

DISCUSSION

ANP occurs in 5-10% cases of acute pancreatitis (8). Of these, moderately severe and severe acute pancreatitis (SAP) are life threatening conditions associated with high mortality and morbidity (5). The presence of IPN further doubles mortality in SAP (9).

Conventional surgical intervention by open or laparoscopic necrosectomy for IPN is associated with a mortality rate of 25% to 40% (10). The open approach is also associated with relatively higher rates of complications such as bleeding (1-23%), colonic fistula (1-17%) and pancreatic fistula (3-72%) (11). A systematic review by Nieuwenhuijs et al. has concluded that the mortality rates of ANP treated with open abdominal surgery with continuous postoperative lavage remains high, mainly due to multiorgan failure despite optimal surgical and medical treatment. (12) Shifting to VARD as a treatment option might help decrease the morbidity and mortality associated with these open surgeries (13,14). Connor et al. have also proposed that minimally invasive retroperitoneal necrosectomy is a new technique that has shown promising results, and could be preferable to open pancreatic necrosectomy in selected patients (15).

The PANTER trial has shown that a minimally invasive step up approach, as compared with open necrosectomy, reduces the rate of the composite end point of major complications or de-

ath among patients with necrotising pancreatitis and infected necrotic tissue (16). Thus, less invasive options such as percutaneous drainage, endoscopic transgastric and laparoscopic transperitoneal necrosectomy have been applied for this indication (9). We also prefer the step up approach at our centre, depending on the location of the necrosum, route of access and local expertise.

The percutaneous endoscopic approaches for necrosectomy were described in the early part of the 21st century, but were associated with many drawbacks viz: time consuming, multiple interventions, incomplete necrosectomy and bleeding (17,18). Carter et al. have proposed that minimally invasive approach for pancreatic necrosectomy has encouraging results but needs further evaluation with larger studies (19). VARD has thus evolved as a result of allowing minimal invasive approach to drain infected pancreatic necrosis without removing the entire solid necrosum in a "step up fashion" (20). VARD can be considered as a hybrid between open necrosectomy and a percutaneous endoscopic approach (1).

VARD is done in cases of established infected pancreatic necrosis after giving a maximised trial of conservative management with intravenous antibiotics, organ support [respiratory, vasopressor, dialysis], and percutaneous drainage techniques (21). Radiological evidence of walled off pancreatic necrosis [WOPN] is essential to plan this minimally invasive procedure (1). The technique involves the placement of a 12-14 french percutaneous catheter in the necrotic cavity through the left retroperitoneum 24-48 hours prior to the VARD procedure. During the procedure, through a small left subcostal incision, the necrotic cavity is reached by following the percutaneous catheter and solid but loose necrosum is removed under vision. This is followed by the insertion of 0° laparoscope and carbon dioxide gas inflated for better vision. The loosely adherent necrosum is further removed, thorough wash given and 2 drains kept (superficial and deep) for postoperative lavage (13).

Variations in the technique described in the literature include variations in the size of incisions, ranging from sinus tract endoscopy to as big as 15 cm translumbar incisions. Also the use of wide range of videoscopes such as laparoscope, nephroscope, cystoscope, mediastinoscope have been described (18). There are wide variations in approach to the necrosum, postoperative operative lavage fluids as well as their volumes infused per day (14,16).

VARD provides an excellent alternative to necrosectomy by laparotomy. Our early results on a few patients as described are comparable to those reported in the literature (9). Horvath et al. have evaluated the safety and efficacy of VARD for IPN in 40 patients using a multicentre, prospective, single arm phase 2 study and concluded that VARD is safe as well as efficacious for IPN (7). Most published data regarding minimally invasive necrosectomy have a postoperative hospital stay ranging between 50 and 64 days which are comparable to our study (17). Re-intervention rates for further necrosectomy may be needed in as high as 73% whereas in our study it was 45.5% (17). The rates of individual complications viz infection, bleeding, fistula as well as mortality were comparable to our study (18.2%) (22). Overall morbidity in different studies has shown wide variation from 0 to 93% and mortality ranging from 10 to 27%. (3) Other studies have shown postoperative bleeding rates (7.5%) compared to ours (18.2%) and similar pancreatic fistula rates (18.2%) (3). Interestingly, our enteric fistula rate (4.5%) was less as compared to others (23,24).

The advantages of VARD include less perioperative stress on an already sick patient, benefit of both limited open and laparoscopic approach, simplicity and cost effectiveness, the disadvantage being the need of undergoing multiple repeat procedures. Also, life-threatening complications are still possible, necessitating close vigilance by a multispecialty team in an intensive care setting.

Study Limitations

The limitations of our study were the relatively small sample size, single centre data and that there were no comparative group of patients.

CONCLUSION

VARD is a safe and effective surgical option for the management of IPN that worsens or fails to respond to conservative and percutaneous drainage options. Necrosum is debrided and drained using a hybrid open - laparoscopic approach alongside the percutaneously placed catheter. It decreases postoperative morbidity and mortality and avoids major laparotomies and hence, should be considered in the management of this selected group of patients.

Ethics Committee Approval: The study was performed after the approval of research protocols by the institutional ethics committee in accordance with international agreements (World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects," amended in October 2013, www.wma.net)

Informed Consent: Written informed consent was obtained from all patients involved in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - P.W., P.V.; Design - P.W., P.V.; Supervision - G.D., P.P., R.N., P.W., P.V.; Materials - P.W., P.V.; Data Collection and/or Processing - D.B.; Analysis and/or Interpretation - D.B.; Literature Search - D.B.; Writing Manuscript - D.B.; Critical Reviews - G.D., P.P., R.N., P.W., P.V.

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ORİJİNAL ÇALIŞMA-ÖZET
Turk J Surg 2019; 35 (3): 214-222

Enfekte pankreatik nekrozda videoskopik yardımlı retroperitoneal debridmanın sonuç analizi: tek merkezli çalışma

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ÖZET

Giriş ve Amaç: Enfekte pankreatik nekroz (EPN), orta derecede şiddetli ve şiddetli akut nekrotizan pankreatit (ANP)'in korkutucu komplikasyonudur. Videoskopik yardımlı retroperitoneal debridman (VYRD), konservatif ve perkütan seçeneklere yanıt vermeyen hastalarda ağırlıklı olarak sol taraflı, posterior ve lateral yerleşimli hastalık için minimal invaziv bir cerrahi seçenektir. Bu çalışmanın amacı, üçüncü basamak tedavi merkezimizde EPN yönetiminde kullanılan VRYD'nin sonuç analizini sunmaktı.

Gereç ve Yöntem: Prospektif olarak girilen verilerin retrospektif analizini içeren bu çalışmaya Ocak 2015 ve Aralık 2017 tarihleri arasında EPN'li ANP tanısı alan 22 hasta dahil edildi. Bu hastalar üçüncü basamak tedavi merkezimizin cerrahi gastroenteroloji bölümüne yatırıldı. VYRD ile tedavileri yapılan hastalardan alınan sonuçlar değerlendirmeye tabi tutuldu.

Bulgular: ANP etyolojisi yedi hastada idiyopatik olmakla birlikte yedi hastada safra kesesi taşı ve sekiz hastada alkol kaynaklıydı. On iki hasta tek bir VRYD müdahalesi ile tedavi edilirken 10 hastada yetersiz iyileşme sebebiyle ikinci debridmana gerek duyuldu. Yirmi iki hastadan 18'i kurtulurken dört hastada majör postoperatif kanama/şiddetli sepsis ve çoklu organ yetmezliği gelişti (mortalite: %18.2). Hastanede yatış süresi 6-10 hafta arasındaydı.

Sonuç: Dört hafta süren orta şiddetli veya şiddetli ANP sonrasında konservatif ve perkütan drenaj seçeneklerine yanıt vermeyen veya daha da kötüleşen EPN tedavisinde VRYD güvenilir ve efektif bir cerrahi seçenektir. Postoperatif morbidite ve mortaliteyi azaltıp majör laparotomi ihtimalinin önüne geçtiği için seçilmiş hasta gruplarında göz önünde bulundurulabilir.

Anahtar Kelimeler: Videoskopik yardımlı retroperitoneal debridman, akut nekrotizan pankreatit, enfekte pankreatik nekroz, step up yaklaşımı

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ORIGINAL ARTICLE
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Laparoscopic resection of choledochal cysts in adults: a series from Turkey

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ABSTRACT

Objective: Choledochal cyst is a congenital disease in which surgical treatment is preliminary because of the potential for malignancy. In recent years, increase in technological developments and laparoscopic experience have popularised the use of laparoscopy in adult choledochal cyst surgery. This study aimed to present the results of eight adult patients undergoing laparoscopic choledochal excision surgery.

Material and Methods: Patients who underwent laparoscopic choledochal cyst excision and hepatico-jejunostomy anastomoses between the years 2013 and 2018 were evaluated retrospectively. Demographic characteristics, preoperative and postoperative findings, pathological results and final condition of the patients were examined.

Results: Of the eight patients, three were males and five were females. Median age was 41.5 years (22-49). One of the patients had Type IVa and the rest had Type I choledochal cysts. Laparoscopic choledochal cyst excision, cholecystectomy, and hepatico-jejunostomy anastomoses were performed on all of the patients. One patient was converted to open surgery. Three patients had postoperative biliary leakage. Duration of the operations was determined as median 330 (240-480) minutes and blood loss was 50 (10-100) mL. Hospitalization of the patients was median 6 (4-23) days and follow-up time was median 20 (2-65) months. In the late period, cholangitis occured in a patient who was treated with medical therapy and there was no mortality in the follow-up period.

Conclusion: We suggest that laparoscopic choledochal cyst excision in adults may be an alternative to open surgery due to the satisfactory results in the late period in spite of early problems like self-limiting bile leakage.

Keywords: Laparoscopy, Hepatico-jejunostomy, minimally invasive surgery, cyst excision

INTRODUCTION

Choledochal cyst is a congenital disease which presents with cystic dilatation of the biliary tract. The incidence is one in 100.000 and 80% presents in childhood (1,2). Although choledochal cysts were first classified by Alonso-Lej, original classification used today was categorised by Todani (3). According to this classification, there are five types of choledochal cysts and the most common one is type 1; followed by types 4, 5, 3 and 2 in decreasing frequency. Abdominal pain, jaundice and choledochal enlargement, which are usually identified as symptoms triad, are detected in only 6% of the patients (4). Treatment of choledochal cyst is surgical excision and bilioenteric reconstruction due to recurrent cholangitis, biliary stone formation, pancreatitis and risk of malignancy. Recently, minimally invasive approaches have been used in the treatment of choledochal cysts with acceptable morbidity and mortality (5).

Our aim in this study was to emphasize the availability of laparoscopic choledochal cyst excision.

MATERIAL and METHODS

Eight patients scheduled for laparoscopic cyst excision and bilio-enteric reconstruction due to choledochal cyst in our clinic between February 2013 and May 2018 were inluded into the study. The study was conducted in accordance with the Declaration of Helsinki. Patients were operated with their informed consent in technical details as previously described (6) (Figure 1 and 2). Patient demographics, body mass indexes, history of additional diseases, history of previous operations, types of cysts, operation

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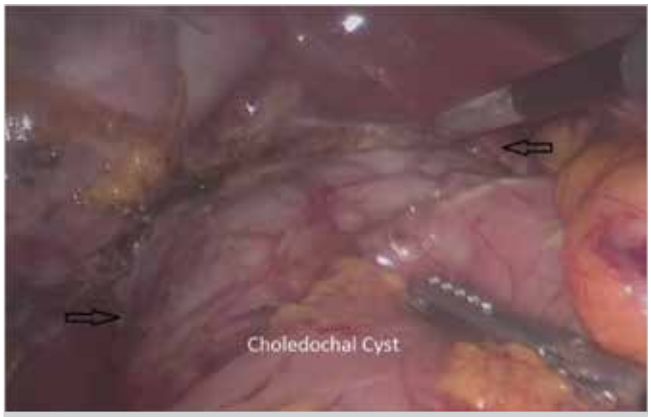

Figure 1. Choledochal cyst.

Figure 2. Hepatico- jejunostomy.

times, amount of blood losses, length of hospital stay, early and late complications, pathology findings and final conditions of the cases were reviewed.

Statistical Analysis

Descriptive statistics were performed for all data. Values were reported in median and range or mean and percentages. The data was analyzed using Microsoft Excel 2013 program.

RESULTS

Sixty-two percent of the patients were females, and mean age was median 41.5 (22-49) years. There were no known comorbidities for all patients. There was a previous laparoscopic cholecystectomy history in one patient. One of the patients had Type IVa and the rest had Type I choledochal cysts. Choledochal excision and hepatico-jejunostomy anastomoses procedure were performed for all patients as surgical treatment. In all patients, surgical procedure was completed laparoscopically. However, after completing the surgical procedure, bile leak was detected from hepatico-jejunostomy anastomoses intraoperatively in a patient and converted to open surgical procedure for revision (14%). Hepatico-jejunostomy anastomosis of the patient was renewed and the operation ended after no problem was detected. Mean duration of the operation was median 330 (240-480) minutes and blood loss was median 50 (10-100) mL. All patients were followed for one day postoperatively in the intensive care unit, and no blood replacement was necessary for any patient. Postoperative bile leak developed in three patients. One of these patients required drainage with relaparoscopy and spontaneous cessation of the biliary leakage occurred in the follow-up. Drainage was discontinued on postoperative 3rd and 4th days in the other two patients with bile leak. Postoperative pneumonia developed in one patient, and the patient was discharged without any problems after medical treatment. Hospitalization time of our patients was median 6 (4-23) days. Examination of the pathologic lesions revealed that all patients were compatible with choledochal cyst while one patient had an additional gallbladder tumor. Liver resection and lymphadenectomy were performed in a second session to the patient whose tumor was T2. Pathologic examination revealed no tumoral tissue in the liver, and all of the lymph nodes were reactive. Follow-up period of the patients was median 20 (2-65) months. In follow-up, cholangitis occured in one patient who was treated with medical therapy, and there was no mortality in the follow-up period (Table 1).

DISCUSSION

Although choledochal cysts are rare, it is a congenital disease in which surgical treatment has priority because of the risk for malignancy. It is usually seen in childhood, but 20% is detected in adult ages (2). It is detected more in females as in our study. In the surgical treatment of choledochal cysts, hepatico-jujenostomy or hepatico-duodenostomy anastomoses are preferred following choledochal excision. However, considering that pancreaticobiliary reflux after hepatico-duodenostomy anastomoses increases the risk of malignancy in the hepatic hillus, hepatico-jejunostomy anastomoses has become the preferred surgical procedure as it is in our study (7). Laparoscopic cyst excision and bilio-enteric reconstruction are used more frequently nowadays with the developments in minimally invasive surgery. With this application, it has been reported that abdominal wall complications (wound infection and incisional hernia) and peroperative blood loss are reduced. It has also been reported that laparoscopy provides a more detailed image due to its enlargement feature (8,9). However, the application of laparoscopy to biliary reconstructive surgery has been limited in part because of the complexity of these procedures and the need for rigorous surgical technique (8,10). To the best of our knowledge, this is the largest experience in minimally invasive surgery on choledochal cysts in Turkey.

Another limitation of the laparoscopic surgery practice is that it has longer operating times than open surgery. Our median operation time was 330 minutes, and it was reported in the literature with the range of 228 and 395 minutes (7-15). Liuetal et al. have reported that when compared with open surgery, the laparoscopic approach shows a longer operative time (249 ± 58 vs. 132 ± 15 min). Their study has revealed that time of laparos-

Table 1. Demographic, preoperative and postoperative findings

Age	Sex	History of abdominal operation	Type	Blood Loss (mL)	Operation Time (min)	Convertion	Complication	Hospital stay (day)	Follow up (month)	Morbidity
40	M	None	I	80	260	No	None	6	65.3	None
22	F	CIS	I	50	360	No	Pneumonia (2)	6	40.1	None
43	F	CIS Appendectomy	I	100	480	No	None	4	41.1	None
45	F	Cholecystectomy	I	70	240	Yes	None	8	23.8	None
23	F	None	I	50	380	No	Bile leak (2)	7	16.7	None
48	F	Appendectomy	I	10	420	No	None	4	12.8	None
49	M	None	IVa	30	300	No	Bile leak (3b)	23	10.2	Cholangitis
28	M	None	I	20	280	No	Bile leak (2)	6	1.8	None

Complication classification was made according to Clavien-Dindo Classification.

copic procedure decreases after twenty cases and lasts for up to 190 minutes (9). Therefore, they have shared the idea that after completing the learning curve, laparoscopic procedures would have similar operative times with open operations.

In our study, the amount of blood loss was median 50 mL. In the study by Liu et al., the laparoscopic group and open surgery group have been compared and the mean amount of blood loss was found as 72 ± 26 mL in the laparoscopic group and as 174 ± 51 mL in the open group (9). In a study by Senthilnathan et al., 110 patients undergoing laparoscopic surgery have been studied and mean blood loss was 66.2 ± 24.3 mL (8). Tian and colleagues have determined this amount as 252.3 ± 162.5 mL (13). Based on these results, it is seen that the amount of blood loss in our study is compatible with the literature.

In our study, length of hospitalization was median six days. In the study of Lu et al with 34 patients, it has been reported as 4.7 ± 1.3 days, and besides that, in the study of Jang and colleagues with 82 patients, it has been found as 8.6 ± 5.2 days and 8.3 ± 3.2 days in the study of Tian et al (11-13).

Although literature reveals bile leak rate between 3.6% and 12.8%, it is still the most common complication. However, it usually resolves without any intervention (8-15). The rate of bile leakage in our study seems to be higher than the literature (38.5%). However, two of the three cases with bile leak were spontaneously resolved on postoperative third and fourth days without any additional intervention.

Other complications mentioned in the literature include intra-abdominal collection, hemorrhage, pancreatic fistula, pancreatitis, intestinal obstruction, stricture in hepatico-jejunostomy anastomosis, and wound complications (12). In our series, only one patient (type IVa) was admitted to our hospital with late cholangitis and treated medically.

CONCLUSION

We suggest that laparoscopic choledochal cyst excision in adults may be an alternative to traditional open surgery due to the satisfactory results in the late period in spite of the early problems like self-limiting bile leakage.

Ethics Committee Approval: This study is registered at Inonu University Human Ethical Committee as a research. The registration identification number is 2014/33.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - E.G.; Design - E.G., F.S.; Supervision - F.S, C.K.; Resource - E.G., M.K.Ç; Materials - E.G., M.K.Ç; Data Collection and/or Processing - E.Ç; Analysis and/or Interpretation - C.G.; Literature Search - M.C.A.; Writing Manuscript - E.G., F.S.; Critical Reviews - C.K.

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ORİJİNAL ÇALIŞMA-ÖZET
Turk J Surg 2019; 35 (3): 223-226

Erişkinlerde laparoskopik koledok kist rezeksiyonu: Türkiye'den bir seri

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ÖZET

Giriş ve Amaç: Koledok kistleri malignite potansiyeli nedeniyle cerrahi tedavinin ön planda olduğu konjenital bir hastalıktır. Son yıllarda teknolojik gelişmeler ve laparoskopik tecrübede artış erişkin koledok kist cerrahisinde laparoskopinin kullanımını yaygınlaştırmaktadır. Bu çalışmada amacımız laparoskopik koledok eksizyonu yapılan sekiz erişkin hastanın sonuçlarını sunmaktır.

Gereç ve Yöntem: Kliniğimizde 2013-2018 yılları arasında laparoskopik koledok kist eksizyonu ve hepatiko-jejunostomi uygulanan hastalar retrospektif olarak değerlendirildi. Hastaların demografik özellikleri, peroperatif ve postoperatif bulguları, patolojik sonuçları ve son durumları irdelendi.

Bulgular: Çalışmaya dahil edilen sekiz hastanın üçü erkek, beşi kadın idi. Yaşların median değeri 41.5 (22-49) idi. Hastaların bir tanesinde tip IVa, diğerlerinde ise tip 1 koledok kisti saptandı. Hastaların tamamına laparoskopik koledok eksizyonu, kolesistektomi ve heptiko-jejunostomi yapıldı. Bir hastada açık cerrahiye geçildi. Üç hastada postoperatif safra kaçağı oldu. Operasyon süreleri median 330 (240-480) dakika ve kan kaybı 50 (10-100) mL olarak saptandı. Hastaların yatış süreleri median 6 (4-23) gün ve takip süreleri median 20 (2-65) ay olduğu tespit edildi. Geç dönemde; bir hastada medikal tedavi ile düzelen kolanjit atağı gözlendi, mortalite ise görülmedi.

Sonuç: Kendini sınırlayan safra kaçakları dışında erken dönemde önemli sorun yaşamamamız ve geç dönemdeki tatminkar sonuçlar nedeniyle laparoskopik koledok kist eksizyonunun erişkinlerde açık cerrahiye bir alternatif olabileceğini söyleyebiliriz.

Anahtar Kelimeler: Laparoskopi, hepatiko-jejunostomi, minimal invaziv cerrahi, koledok kist eksizyonu

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CASE SERIES
Turk J Surg 2019; 35 (3): 227-230

Laparoscopic management of hydatid cysts with biliary communication: clips may rescue when suture fails - report of three cases

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ABSTRACT

Hydatid disease is a parasitic zoonosis caused by the larval form of the Echinococcus worm. Hepatic hydatidosis is the most common form of the disease in humans. Centrally located, large hydatid cysts have the tendency to rupture into the adjoining bile duct and form a fistulous communication. Suture closure of the cysto-biliary communication detected during surgery is recommended to avoid postoperative complications related to bile leak. In the era of minimally invasive surgery, laparoscopic management of the cysto-biliary communication can be challenging, and laparoscopic suturing may not always be feasible. Postoperative endoscopic biliary decompression is necessary in such situations, but it has its own set of potential risk and complications. This case report aimed at presenting a simple and easy technique for laparoscopic closure of the cysto-biliary communication when suture ligation is technically not possible.

Keywords: Hydatid cyst, laparoscopic, cysto-biliary communication, clipping, bile leak

INTRODUCTION

Echinococcal hydatid disease is a parasitic zoonosis endemic in the Indian subcontinent. The liver is the most commonly affected organ (50%-70%), but other organs such as the lungs, spleen, and brain can also be involved (1,2). Cysto-biliary communication (CBC) is the most common complication of hepatic hydatid cyst, and its management may pose a challenge during minimally invasive surgery (3). Suture ligation of any detectable CBC is advised; however, it may not always be possible (4).

This study aimed at reporting three cases of hepatic hydatid cyst in whom CBC was detected intraoperatively, but laparoscopic suture ligation was not feasible. Laparoscopic clip application was performed to occlude CBC, thus avoiding the need for conversion (to open surgery) or any postoperative intervention.

CASE REPORTS

Case 1

A 62-year-old man presented with complaints of discomfort in the right hypochondrium for one month. There was no associated nausea, vomiting, jaundice, or weight loss. General examination of the patient was unremarkable. On abdominal examination, a globular, non-tender lump was palpable in the right hypochondrium. Blood investigations including liver function tests were normal. Abdominal computed tomography (CT) revealed a hydatid cyst size of 12 × 11 × 16 cm involving the left lobe of the liver extending up to the perihilar region (Figure 1).

Laparoscopic hydatid cyst deroofing was performed, and daughter cysts and hydatid sand were evacuated. A small (5 mm) CBC with ongoing bile leak was discovered in the cyst cavity. Laparoscopic suturing of the CBC was attempted; however, it was unsuccessful due to the difficult fistula site. Metallic clips were applied to occlude CBC (Figure 2). Postoperative course was uneventful with no bile leak. The patient remained symptom-free at three months follow-up.

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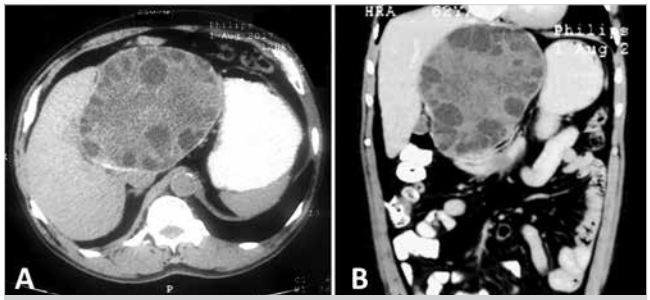

Figure 1. Computed tomography scan of the abdomen showing a large hepatic hydatid cyst in close relation to the hilum.

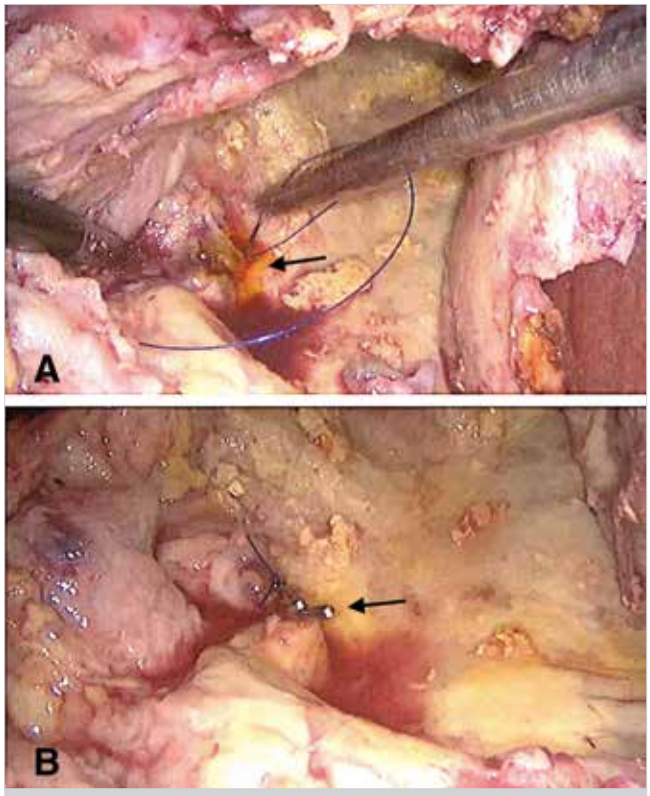

Figure 2. Laparoscopic image showing bile leak from a cysto-biliary fistula. Suture ligation is being attempted **(A).** Application of metallic clips successfully occluded the fistula **(B).**

Case 2

A 65-year-old woman presented with complaints of upper abdominal pain for two years with no other relevant history. General examination of the patient was unremarkable. On abdominal palpation, a tender hepatomegaly was found. Hemogram and bilirubin level were normal; however, serum alkaline phosphatase level (440 IU/L) was elevated. CT scan revealed two hydatid cysts in segments VI and VIII (sizes 7 × 6 × 6 cm and 4 × 4 × 6 cm, respectively) of the liver lying in close proximity to the right biliary system (Figure 3). Magnetic resonance cholangiopancreatogram showed a dilated common bile duct (14 mm) with intraluminal filling defects and a 9 mm focal defect in the posterior cyst wall, suggesting CBC (Figure 4). Endoscopic retrograde cholangiopancreatogram (ERCP) was planned for biliary decompression in view of a possible CBC, followed by laparoscopic hydatid cyst management. At ERCP, cholangiogram revealed few filling defects in CBC. On balloon sweep, few membranes were cleared from the CBC, and a 10 Fr plastic stent was placed in the right biliary system. Cyst contents were bile stained intraoperatively (Figure 5), and a CBC was present in the segment VI cyst. Laparoscopic suturing was not possible due to the limited intracavitary space. Finally, clips were applied laparoscopically, and the CBC was occluded. The patient recovered well and remained symptom-free six months post-surgery. An informed consent for publication was obtained from all three patients discussed in this study.

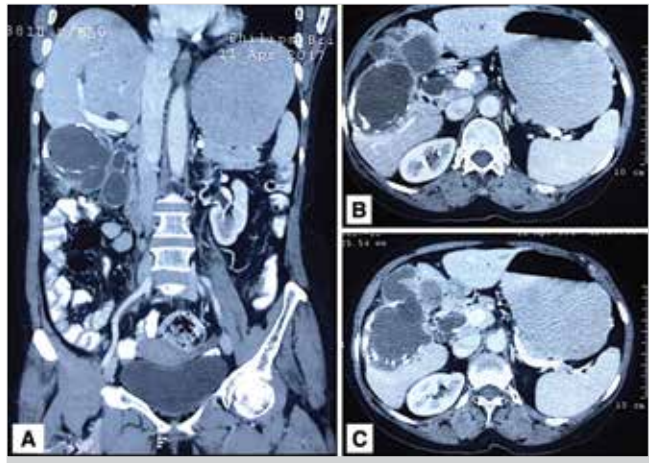

Figure 3. Computed tomography scan showing two hydatid cysts in segments VI and VIII of the liver lying in close proximity to the right biliary system **(A).** Coronal section view. Transverse section view **(B,C).**

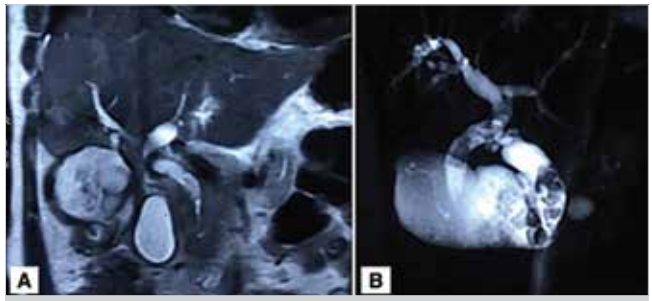

Figure 4. Magnetic resonance image of the abdomen showing hydatid cyst in segment VI of the liver lying in close proximity to the bile duct **(A).** Magnetic resonance cholangiopancreatogram showing dilated biliary system with filling defects (daughter cysts) in the common bile duct **(B).**

Case 3

A 35-year-old woman was admitted for pain in the right hypochondrium and nausea for three months. General examination and her abdominal findings were normal except for a small paraumbilical hernia. Blood investigations (including liver function

Figure 5. Bile stained hydatid cyst contents, suggesting a cysto-biliary fistula.

tests) were within normal limits. Abdominal CT demonstrated a hydatid cyst size of 9.5 × 7.4 × 7 cm in relation to segment VI of the liver. Laparoscopic hydatid cyst surgery and paraumbilical hernia repair were performed in a single setting. A small (5 mm) CBC was noted along the medial Wall of the cyst cavity intraoperatively. Laparoscopic suturing of the CBC was attempted but could not be performed due to the difficult location of the CBC. Laparoscopic endoclipping of the CBC was performed with metallic clips. She had an uneventful postoperative course and remained symptom-free at eight months follow-up.

Technique

Between 2009 and 2017, 54 cases of laparoscopic hydatid cyst deroofing were performed in our center out of which intraoperative CBC was detected in 20 patients. Laparoscopic suturing was performed in 12 cases, open surgery in three cases, and postoperative biliary stenting in two patients. Laparoscopic clip occlusion was performed in the above three cases.

CBC site was clearly delineated after deroofing and evacuation of the cyst contents. The fistula site was grasped with a tip of a Maryland dissector and lifted slightly. Two metal clips (Ligaclip Extra, Ethicon Endo-surgery, LLC, Guaynabo, Puerto Rico, USA) were then applied over the fistula site. Cessation of the bile leak indicated successful occlusion of the fistula (Supplementary video file 1). A surgical vacuum drain was placed in all three cases.

DISCUSSION

Hepatic hydatid disease is a significant problem in endemic areas including India (1-3). The cyst gradually enlarges and compresses the surrounding hepatocytes and biliary radicles. Long standing bile duct compression by the hydatid cyst may result in intrabiliary cyst rupture, leading to the formation of CBC (5). CBC incidence has been reported in up to 25%-30% of cases (1-3). Diagnosis of CBC is usually made preoperatively, but sometimes, it can get unmasked during surgery. Occult CBC remains undetected even during surgery and is manifested in the postoperative period as biloma or external biliary fistula (6). Postoperative management of such leaks is challenging and may require invasive procedures, such as endoscopic biliary stenting and percutaneous drain placement. A major laparotomy may rarely become necessary. Thus, intraoperative detection and management of CBC are crucial.

Preoperative factors indicating the likelihood of CBC include deranged liver function tests (increased bilirubin or alkaline phosphatase level), leukocytosis (> 10.000 mm^3), perihilar or central location, large size (> 10 cm), and dilated biliary radicles on imaging (7,8). Infrequently, it may be delineated on CT or magnetic resonance imaging (9).

All CBCs detected intraoperatively should be meticulously addressed. With the advent of minimally invasive approaches, laparoscopic hydatid cyst deroofing is increasingly performed offering several advantages (10). However, management of concomitant CBC can sometimes be challenging with this approach. Difficult fistula site, limited intracavitary space, and surgeon's inexperience may occasionally render laparoscopic CBC suturing unachievable. In all three of our cases, laparoscopic suture ligation was not possible due to the difficult location and limited access. Metal clips were applied, and bile leak stopped instantaneously, thus avoiding any postoperative morbidity and need of postoperative ERCP. Clip slippage is a potential drawback; however, no such complication was encountered in the present case series.

CONCLUSION

Laparoscopic suturing of CBC encountered during hydatid cyst surgery may be technically challenging. Laparoscopic clipping can successfully occlude CBC in difficult cases. It is a cheap, reproducible and effective technique of CBC management.

Informed Consent: Written informed consent was obtained from patient who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - S.K., A.C.; Design - S.K., A.C., N.C., R.K.; Supervision - S.K., A.C.; Resource - R.K., N.C.; Materials - S.K., R.K., A.C.; Data Collection and/or Processing - S.K., R.K., N.C., A.C.; Literature Search - S.K., R.K., N.C.; Writing Manuscript - S.K., R.K., N.C.; Critical Reviews - S.K., A.C.

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

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OLGU SERİSİ-ÖZET
Turk J Surg 2019; 35 (3): 227-230

Safra yolları ile ilişkili hidatik kistlerinin laparoskopik tedavisi: dikişler başarısız olduğunda klipler faydalı olabilir - üç olgu sunumu

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ÖZET

Hidatik hastalık, Echinococcus solucanının larval formunun neden olduğu parazit bir zoonozdur. Hepatik hidatidoz insanlardaki en yaygın formdur. Merkezi yerleşimli büyük hidatik kistler, bitişik safra kanalına rüptür olma eğilimi gösterir ve fistül bir iletişim oluşturur. Safra sızıntısı ile ilişkili postoperatif komplikasyonları önlemek için, cerrahi sırasında tespit edilen sistobiliyer bağlantıların sütür ile kapatılması önerilir. Laparoskopik yöntem ile sistobiliyer müdahale zor olabilir ve laparoskopik dikiş her zaman uygun olmayabilir. Bu gibi durumlarda postoperatif endoskopik safra dekompresyonu gerekir, ancak bunun da kendi potansiyel risk ve komplikasyonları vardır. Bu çalışmada, dikiş ligasyonunun teknik olarak mümkün olmadığında sistobiliyer bağlantıların laparoskopik yöntemle kapatılması için basit ve kolay bir teknik sunmaktayız.

Anahtar Kelimeler: Hidatik kist, laparoskopik, sistobiliyer iştirak, klipleme, safra kaçağı

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CASE SERIES
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Minimally invasive parathyroidectomy using intraoperative ultrasonographic localization for primary hyperparathyroidism in pregnancy: report of two cases

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ABSTRACT

Primary hyperparathyroidism (pHPT) in pregnancy is a rare entity associated with increased maternal and fetal mortality and morbidity. Diagnosis of pHPT is challenging in pregnancy. Approximately 80% of the cases are asymptomatic, while the most common symptoms are nausea, vomiting, polyuria, polydypsia, and cloudy vision in symptomatic patients. Since the most common cause of pHPT in pregnancy is adenoma, such in the general population, focused anterior or lateral approach is recommended due to shorter operation time, less risk for the fetus, and lower complication risk. Performing intraoperative ultrasonography to do the incision just over the adenoma provides quicker access to the adenoma and intraoperative parathormone assay confirms the surgical cure. Laryngeal mask anesthesia causes lesser sore throat, laryngospasm, coughing, and rapid recovery as compared to endotracheal intubation anesthesia. This study aimed to present the management of two pregnant patients diagnosed with pHPT and who underwent minimally invasive parathyroidectomy under intraoperative ultrasonography and laryngeal mask anesthesia at the second trimester of gestation. To the best of our knowledge, parathyroidectomy under laryngeal mask anesthesia in pregnancy has never been described before.

Keywords: Intraoperative ultrasonography, laryngeal mask anesthesia, minimally invasive parathyroidectomy, pregnancy, gestational hyperparathyroidism

INTRODUCTION

Primary hyperparathyroidism (pHPT) in pregnancy is a rare but serious entity associated with increased maternal and fetal mortality and morbidity. The exact incidence remains unclear due to asymptomatic cases and many similar symptoms are shared by hyperparathyroidism and pregnancy such as hyperemesis, vomiting, bone pain and fatigue (1). Nephrolithiasis, acute pancreatitis and rarely hypercalcemic crisis are the most serious complications for pregnant woman during intrauterine growth retardation, preterm labor and neonatal tetany for the fetus (2-4). Management of the pregnant women with hyperparathyroidism is also challenging, and maternal and fetal morbidity and mortality can be prevented with prompt treatment approaches.

This study aimed to present management of two pregnant patients who were diagnosed with pHPT and underwent minimally invasive parathyroidectomy under laryngeal mask anesthesia (LMA) in the second trimester of gestation.

CASE REPORTS

Case 1

A 25-year-old pregnant woman (G1P0) was admitted to hospital with a complaint of severe nausea and muscle cramp at the 19th week of gestation. She had no history of any previous disease, operation, family history of chronic diseases and medication. Physical examination was insignificant. In initial laboratory tests, serum calcium level was 11.8 mg/dL (reference range= 8.5-10.5 mg/dL), phosphorus was 2 mg/dL (reference range= 2.5-4.5 mg/dL) and albumin level was within normal limits. On additional tests, parathormone (PTH) level was found 192 pg/mL (reference range= 18-78 pg/mL) and 24h urinary calcium as 680 mg (reference range= 100-150 mg). Neck

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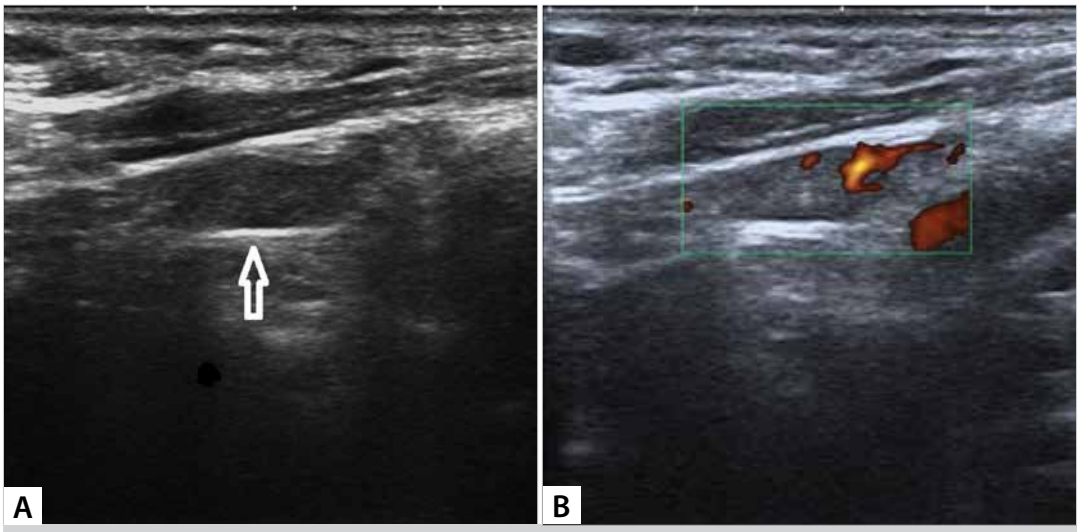

Figure 1. On ultrasound, 16 x 11 mm sized, well-circumscribed hypoechoic solid parathyroid adenoma was seen **(A).** Peripheral and polar blood flow of the lesion were detected **(B).**

ultrasonography (USG) revealed a solitary left inferior parathyroid adenoma 1.6 cm in diameter (Figure 1). Surgery was recommended for the patient and risks of both the disease and operation were informed. After oral and intravenous rehydration without forced diuresis and an overnight fasting, the patient was operated under LMA. Intraoperative USG was used for prompt detection of the incision site just over the adenoma to prevent both the patient and the fetus from adverse effects of prolonged anesthesia. Focused lateral approach (FLA) was applied, and sufficient intraoperative PTH drop was achieved 10 minutes after excision of the adenoma (from 185 pg/mL to 56 pg/mL).

Postoperative maternal and fetal health was well, and the patient was discharged 2 days after the operation with normal serum calcium and PTH levels. Histopathological examination confirmed the diagnosis of solitary parathyroid adenoma (Figure 2). At the 39th week of gestation, she delivered a healthy male infant with no evidence of neonatal tetany or LMA related complication.

Figure 2. Parathyroid adenoma, 1.6 cm in size.

Case 2

A 36-year-old pregnant woman (G3P2) who was at the 24th week of gestation was referred to our department due to elevated serum calcium level which was detected in regular outpatient visit. The patient denied any history of previous disease, operation and family history of chronic diseases. Physical examination was unremarkable. Laboratory tests revealed hypercalcemia with a serum calcium level of 12.4 mg/dL (reference range= 8.5-10.5 mg/dL) and phosphorus of 2.3 mg/dL (reference range= 2.5-4.5 mg/dL). PTH level was found as 286 pg/mL (reference range= 18-78 pg/mL) and 24h urinary calcium as 340 mg (reference range= 100-150 mg). Neck USG showed a solitary parathyroid adenoma 2.1 cm in diameter at the inferior margin of the right thyroid lobe (Figure 3). After oral and intravenous rehydration without forced diuresis and an overnight fasting, the patient was operated under LMA, and intraoperative USG was used to determine the incision site. The patient also underwent FLA, and intraoperative PTH decreased sufficiently (from 274 pg/mL to 36 pg/mL).

Postoperative obstetric USG confirmed presence of fetal cardiac activity. The patient had an uneventful recovery and was discharged on postoperative day 2 with normal levels of serum calcium and PTH. Histopathological examination revealed a solitary parathyroid adenoma (Figure 4). At the 37th week of gestation, she delivered a healthy female infant with no evidence of complication related to hypercalcemia or LMA.

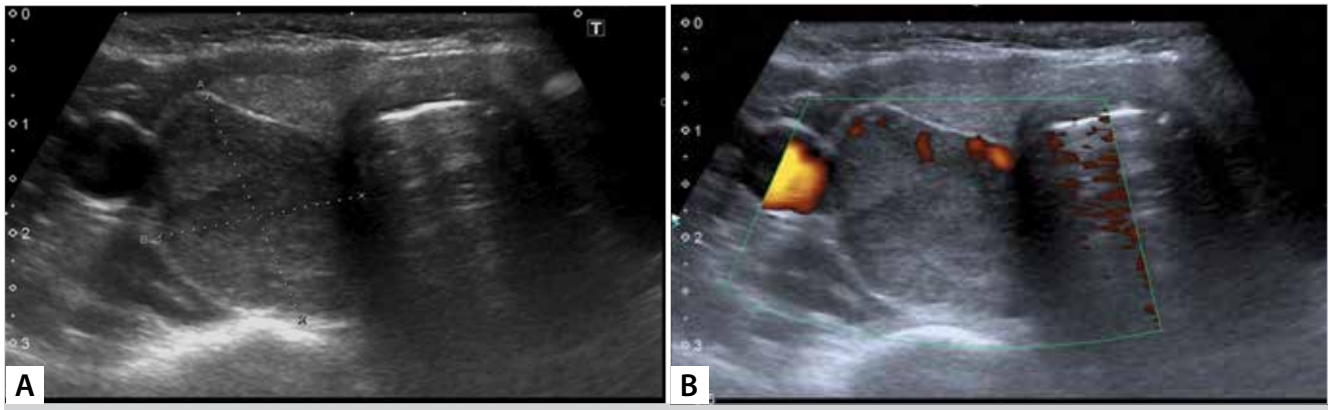

Figure 3. A hypoechoic well-circumscribed lesion 21 x 18 mm in size in the right thyroid capsule was observed on ultrasound. It was noticeable that the lesion is slightly heterogeneous **(A).** Doppler ultrasound examination revealed peripheral vessel sign of the adenoma **(B).**

Figure 4. Excised adenoma, 2.1 cm in diameter.

Written informed consents were obtained from the patients for publication of this case report and any accompanying images.

DISCUSSION

pHPT can be a serious, life threatening condition for both the fetus and the mother. If undiagnosed and untreated, it has been reported to lead to maternal complications which are hyperemesis, nephrolithiasis, maternal hypertension, preeclampsia, depression, constipation, bone fractures, pancreatitis, heart rhythm problems, and more common hypercalcemic crisis in almost 2/3 of the cases (5).

Fetal death, fetal growth retardation, preterm delivery and decreased birth weight are the most serious risks for the fetus and increase three to five times more in pregnant women with pHPT (6). In a study, thirty-two pregnant women diagnosed with pHPT had a history of miscarriage rate up to 50% in their previous pregnancy. This rate is six times more than accepted in the whole population (7). Postpartum neonatal tetany may occur in the first 2 weeks of delivery and affect approximately half of the children of those untreated pregnant women. Intrauterine parathyroid suppression is the main reason of neonatal tetany. In the literature, most of the patients recovered, while hypocalcemia remained permanent in some reported cases (6,8).

Prompt diagnosis and treatment can prevent such complications for both the fetus and the pregnant women.

Diagnosis of pHPT is challenging in pregnancy. Approximately 80% of the cases are asymptomatic, while the most common symptoms are nausea, vomiting, polyuria, polydipsia, and cloudy vision in symptomatic patients. Many of these symptoms may erroneously be accepted as corollary of pregnancy (8). Physiologic changes in pregnancy such as hemodilution related hypoalbuminemia, calcium transfer to the fetus bone and increased renal clearance of calcium play a role on decreased calcium level of the mother. Pregnancy does not affect PTH level; but, clinicians should consider pHPT in the presence of an elevated PTH and serum calcium levels. One should consider the diagnosis of pHPT in pregnancy in the presence of an elevated ionized serum calcium and PTH levels in the absence of other causes of hypercalcemia.

USG of the neck is the first-line tool for preoperative localization of the diseased gland(s) in pregnancy since other methods such as 99mTc-sestamibi and computed tomography carry the risk of ionizing radiation to the fetus. On the detection of parathyroid lesions, USG has a sensitivity of 65-75% and specificity of 90-94% in experienced hands and that ratio increases in the solitary adenoma cases (9). The most common cause of pHPT in pregnancy is solitary adenoma. PTH level assay in USG-guided aspirate of suspicious parathyroid adenoma has also been reported as an alternative method for diagnosis (2).

Since pHPT during pregnancy is rare, the management is also challenging and no definite treatment guidelines have been established. Treatment should be individualized according to the severity of patients' complaints, the severity of hypercalcemia and the gestational age.

Hyperparathyroidism in the first trimester should be managed medically (10). A pregnant woman with mild hypercalcemia (<11 mg/dL) can also be managed medically.

Rehydration (oral/intravenous) with or without forced diuresis is the mainstay of initial management with close monitoring of the fetus and the mother. A few drugs (calcitonin, cinacalcet) are available for the treatment of pHPT in pregnancy but more evidence about their safety for fetus are needed. Bisphosphonates are contraindicated in pregnancy.

Surgery is the only curative treatment and is indicated when serum calcium levels are above 11 mg/dL or ionized calcium level exceeds 2.75 mmol/L during the second trimester. An image-guided, focused parathyroidectomy during the second trimester is the gold standard management of pPHT during pregnancy because organogenesis is complete and the risk of anesthesia-induced preterm delivery is very low (11).

The treatment of pHPT in the third trimester is also challenging, and risk and benefit of surgery should be assessed individually. Parathyroidectomy should be performed at any time regardless of the gestational age if the patient has severe hypercalcemia (12).

Since the most common cause of pHPT in pregnancy is adenoma, focused anterior or lateral approach is the preferred intervention due to shorter duration of operation, less risk for fetus, and lower complication risk (2,6). We used ultrasonography to do the incision just over the adenoma for quicker access and intraoperative parathormone assay to confirm surgical success.

We preferred LMA for parathyroidectomy in pregnant women in the second trimester. LMA causes lesser sore throat, laryngospasm, and cough; and supplies rapid recovery as compared to endotracheal intubation anesthesia (13). Operation after an overnight fasting is sufficient to prevent regurgitation and aspiration which are possible complications of LMA in pregnancy. Lower abdominal pressure in the second trimester than in the third trimester also decreases the risk of LMA- related complications. To the best of our knowledge, parathyroidectomy under LMA in pregnancy has never been described before. We recommend the use of LMA in elective parathyroidectomy in the second trimester.

CONCLUSION

Although pHPT is rare in pregnancy, prompt diagnosis and management are mandatory. Focused parathyroidectomy with the use of intraoperative USG is a safe and effective treatment with confirmation by intraoperative PTH assay in the second trimester. In addition, LMA, which is a less invasive method than endotracheal intubation anesthesia, may be an alternative choice in pregnant patients undergoing focused parathyroidectomy.

Informed Consent: Written informed consent was obtained from all the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - M.H., S.K.; Design - E.O.G., H.G.; Supervision - M.H., H.G.; Resource - S.G.H., E.O.G.; Materials - S.G.H., S.K.; Data Collection and/or Processing - T.A., S.K.; Analysis and/or Interpretation - H.G., F.T.; Literature Search - T.A., F.T.; Writing Manuscript - S.K., M.H.; Critical Reviews - M.H., H.G., F.T.

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

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OLGU SERİSİ-ÖZET
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Gebelikte primer hiperparatiroidi için intraoperatif ultrasonografi kullanarak minimal invaziv paratiroidektomi: iki olgu sunumu

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ÖZET

Gebelikte primer hiperparatiroidizm (pHPT) nadir görülen bir durumdur ve artmış maternal ve fetal mortalite ve morbidite ile ilişkilidir. Gebelikte pHPT'nin teşhisi zordur. Olguların yaklaşık %80'i asemptomatiktir, semptomatik hastalarda ise en sık görülen semptomlar bulantı, kusma, poliüri, polidipsi ve bulanık görmedir. Gebelikte pHPT'nin en yaygın nedeni genel popülasyonda olduğu gibi adenom olduğu için; daha kısa operasyon süresi, fetus için daha az risk ve daha düşük komplikasyon riski nedeniyle odaklanmış anterior veya lateral yaklaşım önerilmektedir. Adenomun hemen üzerinde insizyon yapabilmak için intraoperatif ultrasonografi yapılması, adenomun daha hızlı tespitini sağlar ve intraoperatif parathormon testi ile cerrahi tedavi doğrulanır. Laringeal maske anestezisi endotrakeal entübasyona göre daha az boğaz ağrısı, laringospazm ve öksürüğe neden olur ve hızlı iyileşme sağlar. Bu yazıda, gebeliğin ikinci trimesterinde pHPT tanısı konmuş ve intraoperatif ultrasonografi ve laringeal maske anestezisi altında minimal invaziv paratiroidektomi uygulanmış olan iki gebe hastanın tedavisi sunulmaktadır. Bildiğimiz kadarıyla, gebelikte laringeal maske anestezi altında paratiroidektomi daha önce tanımlanmamıştır.

Anahtar Kelimeler: Gebelik, gestasyonel hiperparatiroidi, intraoperatif ultrasonografi, laringeal maske anestezi, minimal invaziv paratiroidektomi

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CASE REPORT
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A rare breast tumor: primary neuroendocrine carcinoma

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* This study was presented at the 19th National Congress of Surgery, 16-20 April 2014, Antalya, Turkey.

ABSTRACT

Breast cancer is the most frequently seen cancer in females but primary neuroendocrine carcinoma of the breast, which was defined as a separate entity in the 2003 World Health Organisation tumour classification, is seen extremely rarely. This entity, which is still not well-defined and has not been well-researched, demonstrates a more aggressive course than invasive ductal carcinoma. As metastatic breast neuroendocrine tumours are more widespread and the treatment strategy is different, preoperative differential diagnosis is important. The basic diagnostic method is pathological examination. If a neuroendocrine pattern is determined in microscopy, then immunohistochemical study of neuroendocrine markers should be made. It is necessary to be vigilant in terms of synchronous tumours and metachronous tumours which may develop in the postoperative period as the incidence of synchronous and metachronous cancers in patients with neuroendocrine tumours is higher compared to the general population. The case presented here is of a 73-year old patient who presented with complaints of a breast lump, which was thought to be invasive breast cancer, and as a result of the operation with pathological and immunohistochemical examination, primary neuroendocrine carcinoma of the breast was determined. With more advanced evaluations, no synchronous or metachronous tumours were determined.

Keywords: Breast cancer, neuroendocrine carcinoma, treatment, surgery

INTRODUCTION

Neuroendocrine cancers of the breast refer to a heterogenous group of tumours which comprise less than 1% of all breast tumours (1). They show similar morphological features to neuroendocrine neoplasmas of the intestine and lungs. For diagnosis of a neuroendocrine tumour, at least 50% of the tumour cell must express one or more of the neuroendocrine markers (neuron specific enolase, chromogranin, synaptophysin) (2,3). These tumours, which are more often seen in elderly patients, have a high tendency to local and distant recurrence and show an aggressive course with low general survival rates (2,4). Synchronous tumours are an almost inseparable part of neuroendocrine breast tumours (5). The treatment for a primary neuroendocrine tumour of the breast is firstly surgery then, depending on the status, hormonotherapy, chemotherapy or radiotherapy can be added (6).

CASE REPORT

A 73-year old female presented at the clinic with complaints of pain and swelling, redness of the skin and bruising in the right breast. The patient had noticed the swelling in the breast one month previously, and the redness and brusing of the skin had occurred in the last week. The patient was the mother of two children, each of whom she had breast-fed for approximately one year. She had never used any oral contraceptive agent or hormone replacement therapy. She had passed through menopause 30 years previously. On physical examination, a hard immobile mass, 4 x 2 cm in size, was palpated in the right breast 2 cm from the areola at 11 o'clock. There was an area of redness and ecchymosis of pink-purple colour on the skin of the breast over the mass. In the right axillary region, lymphadenopathy was palpated. Tumour markers were negative.

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On ultrasonography (USG) of the right breast, malignant lymph nodes were determined in the right axilla and a mass lesion, 31 x 23 mm in size, located 2 cm from the areola at 11 o'clock, in a hypoechoic pattern with no evident vascularity on the colour Doppler USG examination, with irregular borders which could not be clearly differentiated from the pectoral muscle with no posterior acoustic shadow observed. On mammography, a macrolobular mass lesion was observed 3 x 2 cm in size in the superior-external quadrant of the right breast (Figure 1).

Tru-cut biopsy was applied to the mass lesion under USG guidance. In histopathological examination, a tumour was observed showing infiltration in the form of large solid islands in the fibrous stroma. In the centre of these solid islands, scattered rosette-like structures were seen and occasionally cells which resembled signet rings. In immunohistochemical staining with GCDFP15, CK7 and NSE, there was cytoplasmic positive reactivity in a section of the neoplastic cells, 95% estrogen receptor (ER) positive reactivity, 85% progesterone receptor (PR) positive reactivity and CK20 and C-erb b2 negative reactivity. In p53 staining, myoepithelial layer was not observed. With these findings, invasive ductal carcinoma displaying neuroendocrine characteristics, was reported as histological Grade 1. No other primary tumours were determined outside the breast from the cranial, neck, thoracic and abdominal computed tomography (CT) examination and gastrointestinal endoscopy, so a modified radical mastectomy (MRM) was applied to the patient. Pathology examination results of the biopsy material were histological Grade 3 according to the World Health Organisation 2010 classification. Tubule formation was graded as 3, nuclear pleomorphism as 2 and mitosis as 3 (under 12/10 magnification). The invasive tumour was 4 cm in diameter (pT2).

Figure 1. Mass appearance on mammography.

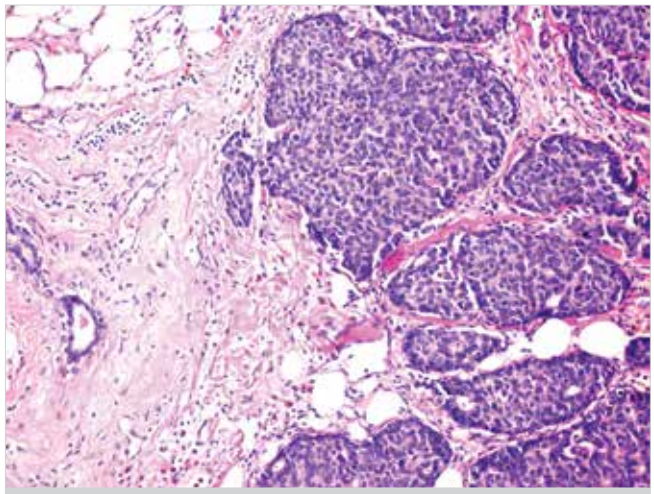

Figure 2. Invasive ductal carcinoma of the breast with neuroendocrine differentiation (H&E x200).

In the examination of the axillary dissection material, 14 reactive lymph nodes were determined (pN0). In the immunohistochemical examination with neuron specific enolase (NSE), cytoplasmic positive reactivity was determined in most of the cells. The Ki 67 proliferation index was below 5%. With these findings, the patient was evaluated with stage 2A (pT2N0M0) of luminal A type invasive ductal carcinoma showing neuroendocrine differentiation (Figure 2 and 3). As no synchronous tumour was determined, it was accepted as a primary solid neuroendocrine carcinoma of the breast. Anastrozol, (1 mg/day Arimidex) as an aromatase inhibitor, was started and with no recommendation for adjuvant chemotherapy or radiotherapy, the patient was followed up for four years with no problems.

DISCUSSION

Neuroendocrine tumours, which are found all over the body, originate from submucosal neuroendocrine cells. The majority of these cells are localised in the gastrointestinal and bronchopulmonary system. Primary neuroendocrine carcinoma of the breast comprise 1% of all neuroendocrine carcinomas (7) and less than 0.1% of all breast tumours (1).

Histogenesis of the tumour has not been fully clarified as yet. Very few researchers have hypothesised that rather than the carcinoma

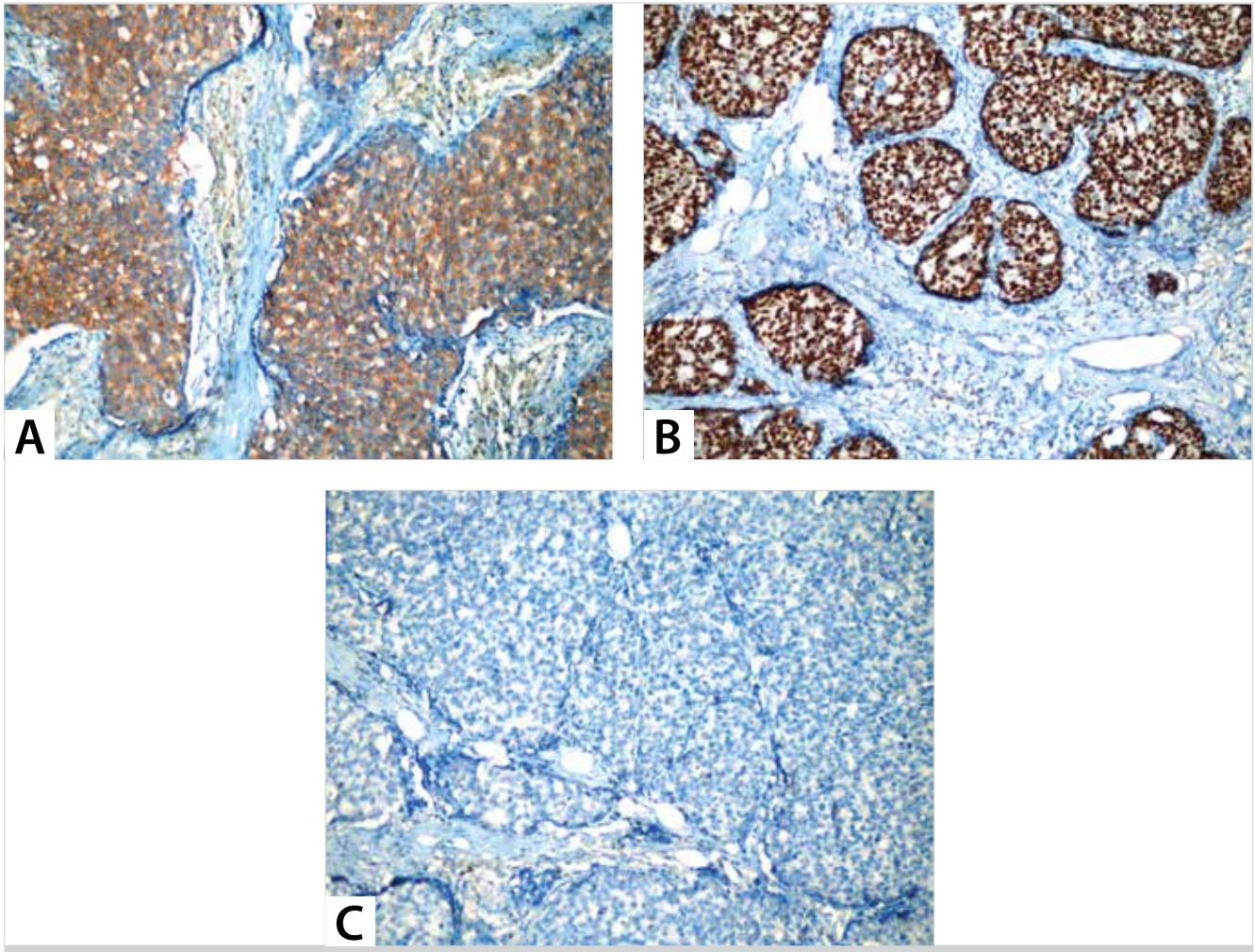

Figure 3. Immunohistochemical positive immunoreactivity for NSE (A, x200) and ER (B, x200) and negative immunoreactivity for HER-2 (C, x200).

originating from endocrine cells which are present in the breast, it shows endocrine differentiation of the breast. The majority; however, consider that they have originated from the differentiation of the neuroendocrine carcinoma phenotype of the multipotent stem cells (8).

Neuroendocrine cells can be determined in a random way in 10-50% of the breast tumours (9). This focal neuroendocrine differentiation pattern is found in invasive ductal, mucinous or signet ring cell carcinoma (10). According to the World Health Organisation 2003 tumour classification, to be able to make a diagnosis of a neuroendocrine breast tumour, one of the neuroendocrine markers such as neuron specific enolase, chromogranin-A, synaptophysin or CD56, must be revealed immunohistochemically in more than 50% of the tumour cells. Primary neuroendocrine carcinoma of the breast includes solid neuroendocrine carcinoma, atypical carcinoid tumour, small cell tumour/oat cell carcinoma and large cell carcinoma (11). The case prresented here was the solid type.

Studies have been carried out related to molecular subtyping. In a study by Weigelt et al. (12), five of six cases were found to be luminal A type and one case was luminal B type. In a single case report by Watrowski et al. (13), the case was luminal B type and molecular classification was reported to be helpful in the treatment strategy. The case presented here was luminal A type.

Compared with the general population, there is a high incidence of synchronous and metachronous cancers in patients with neuroendocrine tumours (14). In a study by Lopez-Bonet et al. (5), a second tumour has been found in 5 of 12 cases. In the case presented here, no secondary tumour was determined and it was accepted as a primary neuroendocrine carcinoma of the breast.

In the literature, the majority of these cases are 60-70 years of age. There is no specific clinical or radiological characteristic different from other breast malignancies (11). According to Samli et al. (15), the complaints related to this disease are breast cellulitis, mastitis, abscess and inflammation of the breast. Tumours are not seen bilaterally and are more often located in the left breast. In

the case presented here, the patient was 73 years of age and had complaints of redness and bruising on the skin of the breast. The tumour was determined as a hard, immobile mass in the right breast.

Neuroendocrine carcinoma displays a more aggressive course than invasive ductal carcinoma (4,8). Five-year local and distant recurrence rates have been found to be 15% and 34%, respectively (4). Mucinous differentiation and ER/PR positivity are good prognostic factors (8). The most common sites of metastasis are the bones and liver (4).

The surgical treatment for primary neuroendocrine cancer of the breast ranges from lumpectomy to MRM (6). In cases of large, multifocal or retro-areolar tumours, MRM is preferred (4). If there is ≥ 10% expression of Ki67 protein, which is used to define the aggressiveness and proliferation activity of the tumour, then adjuvant chemotherapy may be given. Hormonotherapy with tamoxifen or aromatase inhibitors is applied to patients with ER and/or PR positivity. Radiotherapy is used for patients who undergoing breast-conserving surgery and/or patients who have 3 or more axillary lymph node metastases (5). In the current case, MRM was applied as a surgical procedure. Ki67 expression was below 10% and oestrogen and progesterone receptors were positive. Therefore, as the patient was postmenopausal, aromatase inhibitor was administered without adjuvant chemotherapy.

CONCLUSION

When a diagnosis is made of a primary neuroendocrine cancer of the breast, it is necessary to make an evaluation in respect of synchronous and metachronous tumours to be able to adapt the prognosis and treatment strategy for the patient.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - H.P., M.Z.S., O.K.; Design - M.F.B., H.E.E. K.K.B.; Supervision - H.P., M.F.B., H.E.E.; Materials - M.Z.S., O.K., K.K.B.; Analysis and/or Interpretation - H.P., M.Z.S., H.E.E.; Literature Search - O.K., K.K.B., H.P.; Writing Manuscript - H.P., O.K.; Critical Reviews - H.E.E., M.Z.S., K.K.B.

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OLGU SUNUMU-ÖZET
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Nadir bir meme tümörü: primer nöroendokrin karsinom

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ÖZET

Meme kanseri, kadınlarda en sık görülen kanser olmasına rağmen, Dünya Sağlık Örgütü'nün 2003'teki tümör sınıflandırmasında farklı bir antite olarak tanımlanan memenin primer nöroendokrin karsinomu; oldukça nadir görülür. Henüz iyi tanınmamış ve üzerine çalışılmamış olan bu antite, invaziv duktal karsinomadan daha agresif bir seyir göstermektedir. Metastatik meme nöroendokrin tümörleri, daha yaygın olduğundan ve tedavi stratejileri farklı olduğundan preoperatif ayırıcı tanı önemlidir. Temel tanı yöntemi patolojik incelemedir. Mikroskopide nöroendokrin patern saptanırsa immünohistokimyasal olarak nöroendokrin markerlar çalışılmalıdır. Senkron tümörler ve postoperatif dönemde gelişebilecek metakron tümörler yönünden uyanık olunmalıdır. Çünkü genel nüfus ile karşılaştırıldığında nöroendokrin tümörlü hastalarda senkron ve metakron kanserlerin insidansı daha yüksektir. Kliniğimize memede kitle şikayeti ile başvuran, invaziv meme kanseri düşünülerek opere edilen ve patolojik inceleme ve immünohistokimyasal yöntemler sonucunda memenin primer nöroendokrin karsinomu saptanan 73 yaşındaki bir hastayı sunuyoruz. Daha ileri değerlendirmeler ile herhangi bir senkron veya metakron tümör tespit edilmemiştir.

Anahtar Kelimeler: Meme kanseri, nöroendokrin karsinom, tedavi, cerrahi

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