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

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

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- Acknowledgment of the individuals who contributed to the preparation of the manuscript but who do not fulfill the authorship criteria.

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Manuscript Types

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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.

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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.

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

Figures and Figure Legends

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

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

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

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

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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.

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Accepted manuscripts are copy-edited for grammar, punctuation, and format. Once the publication process of a manuscript is completed, it is published online on the journal's webpage as an ahead-of-print publication before it is included in its scheduled issue. A PDF proof of the accepted manuscript is sent to the corresponding author and their publication approval is requested within 2 days of their receipt of the proof.

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FROM THE EDITOR'S DESK

Dear Authors of the Turkish Journal of Surgery,

You have now in your hands the last issue of the Turkish Journal of Surgery in 2020. This year, the unexpected Coronavirus crisis has affected almost every academical event, research, scientific institution, and etc. Like in most of the scientific journals, our routine work in the journal has considerably been disturbed by the Coronavirus outbreak. It has led to unforeseen delays in reviewing the manuscripts and preparing the issues.

This year will be remembered by the enormous efforts of the healthcare professionals. The main aim of the scientific community was to find a way out from this global problem. As part of our responsibility, we have opened our pages throughout the year to some important reviews and guidelines on the fight against the pandemic. We sincerely hope that this troublesome situation normalizes again as quickly as possible.

Once again, we present our deepest and most sincere condolences for all our losses, especially the healthcare workers.

This December 2020 issue contains remarkable studies from diverse countries. It is our great pleasure to discover the experiences of some prominent international centers, one of which is from India. Baksi et al. compared in their randomized study primary vs. delayed skin closure in patients with hollow viscus perforation (1). Surgical site infections are still a global problem despite the increasing knowledge of microbiology and advanced surgical techniques. I hope that you will find the results of this study interesting and profitable. Another article in the December 2020 issue is a meta-analysis from the United Kingdom on another very common condition (2). This study by Nevins and Kanakala focused on the topical management of chronic anal fissure. The authors assessed the results of the randomized controlled trials regarding the effectiveness and complications of two commonly applied agents. Moreover, I would like to call attention to the prospective study of Aslan et al. about the serratus anterior plane block in patients undergoing breast surgery (3). The article is especially interesting for our colleagues focusing on breast surgery.

Undoubtedly, there are much more to read in this December 2020 issue.

A chaotic and stressful year is almost over. We can do nothing but expect a more stable and healthful year from 2021.

Together with my editorial team, we wish you a happy new year in 2021 with great academical successes!

Kindest regards,

Kaya SARIBEYOĞLU

Editor,
Turkish Journal of Surgery

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1. *Baksi A, Chatterjee S, Ray U, Nilima N, Khan WF, Banerhee N. A randomized trial analyzing the effects of primary versus delayed primary closure of incision on wound healing in patients with hollow viscus perforation. Turk J Surg 2020; 36 (4): 327-332.*
2. *Nevins EJ, Kanakala V. Topical diltiazem and glyceryl-trinitrate for chronic anal fissure: A meta-analysis of randomised controlled trials. Turk J Surg 2020; 36 (4): 347-352.*
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ORIGINAL ARTICLE
Turk J Surg 2020; 36 (4): 327-332

A randomized trial analyzing the effects of primary versus delayed primary closure of incision on wound healing in patients with hollow viscus perforation

Aditya Baksi[1], Shamita Chatterjee[2], Udipta Ray[3], Nilima Nilima[4], Washim Firoz Khan[1], Niladri Banerjee[1]

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ABSTRACT

Objective: Delayed primary closure (DPC) of the skin has been suggested to decrease superficial surgical site infection (SSSI) in patients undergoing surgery for peritonitis secondary to hollow viscus perforation, but there is no consensus. The aim of this study was to compare the outcomes of primary closure (PC) and DPC of the skin in terms of SSSI, fascial dehiscence and length of hospital stay (LOS).

Material and Methods: Sixty patients, undergoing emergency surgery for perforation peritonitis, were randomized to PC (n= 30) and DPC (n= 30). Patients in the DPC group underwent skin closure four or more days after surgery when the wound was clinically considered appropriate for closure. Patients in the PC group had skin closure at the time of surgery.

Results: Incidence of SSSI was significantly less in the DPC group (7.4%) compared to the PC (42.9%) (p= 0.004). However, the median time of DPC was the 10th POD, i.e., these wounds required considerable time to become clinically suitable for closure. Incidence of fascial dehiscence was comparable between the two groups (p= 0.67). Length of hospital stay (LOS) was 13.8 days in the DPC group compared to 13.5 days in PC; the difference was not significant (p= 0.825).

Conclusion: DPC of the skin incision resulted in the reduction of SSSI. However, this did not translate into a reduction in hospital stay, as it took considerable time for these wounds to become appropriate for DPC, thus bringing into question any real advantage of DPC over PC.

Keywords: Viscus perforation, surgical site infection, peritonitis, wound infection, delayed primary closure

INTRODUCTION

Surgical site infection (SSI) is one of the commonest complications of surgery, which increases morbidity, length of hospital stay (LOS) and treatment expenses, posing a significant financial burden to patients and society. Increase in LOS results in decreased availability of beds, thus, further straining an already resource-constrained health care system. The method of skin closure - primary or delayed primary - has been implicated as an important factor in the development of post-operative SSI in contaminated and dirty wounds. However, there is no consensus among surgeons as to which is a better technique, and treatment decisions are often based on personal preference. Most randomized trials comparing primary closure (PC) and delayed primary closure (DPC) have been found to be at high risk of bias. The aim of this randomized study was to compare the outcomes of primary and DPC, in terms of superficial SSI (SSSI), fascial dehiscence and length of hospital stay (LOS), in patients undergoing emergency surgery for peritonitis secondary to hollow viscus perforation.

MATERIAL and METHODS

A randomized parallel group trial was conducted at Medical College Kolkata, a tertiary referral center in eastern India, from January 2012 to September 2013. The study was approved by the Institutional Ethics Committee and registered with the Clinical Trials Registry - India (CTRI/2018/02/011973). Patients aged 12-65 years,

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who underwent emergency surgical intervention for perforation peritonitis, diagnosed clinically with radiological evidence, were included in the trial. Informed written consent was taken from all participants or their legal guardians (for patients aged <18 years). Immunocompromised patients and patients with diabetes mellitus, chronic kidney disease, severe obesity, pre-existing skin infection and malignant hollow viscus perforation were excluded from the study. After a decision for emergency laparotomy was made, patients were invited to participate in the trial. Patients who refused were excluded and underwent primary closure of the skin, which was our standard practice before the beginning of the trial. Generation of random allocation sequence was done by an independent statistician using computer generated randomization tables in 1:1 ratio and sequentially numbered, sealed, opaque envelopes to ensure concealed allocation. Eligible participants were randomly assigned to one of the two groups, DPC and PC, by the principal investigator. No blinding techniques were applied.

Demographic and clinical data were recorded in a pre-structured proforma. All patients were resuscitated prior to surgery. Intravenous antibiotics (ceftriaxone-sulbactam 1.5 g and metronidazole 500 mg) were administered pre-operatively at the time of resuscitation and continued at least 48 hours post-operatively. Intravenous amikacin was also added if renal function was adequate. Antibiotics were upgraded depending on the clinical response of the patient, degree of contamination, concomitant infective conditions and culture report of subsequently sent wound swab.

Surgery was performed by final year residents under supervision of a senior surgeon. Midline laparotomy was done for all patients except for those who were clinically diagnosed to have localized appendicular perforation, for which, a grid-iron incision was used. After source control, thorough peritoneal lavage was done with tepid normal saline till the effluent was clear. Drains were placed at the discretion of the supervising surgeon. Fascial closure was done with no. 1 polypropylene (for midline incisions) and no. 1 polyglactin (for grid-iron incisions). After fascial closure, the anaesthetist was asked to open the sealed envelopes, and the patients were randomized to one of the two groups.

In the PC group, the skin was closed immediately with 2-0 polyamide black interrupted sutures without any subcutaneous sutures, and occlusive dressing with dry gauze was done. On post-operative day (POD) 2, the dressing was removed, and the wound was examined by one of the two senior surgeons in the team (SC or UR). If the wound was healthy, no further dressing was applied.

In the DPC group, interrupted sutures of the same material were placed but kept loose, with a knot at the end of long sutures, to prevent them from getting dislodged. Saline-soaked gauze was placed on the wound, followed by dry gauze and occlusive dressing. On POD 2, the dressing was removed, the wound examined, and the dressing changed with aseptic precaution. Twice daily dressing with saline-soaked gauze was continued till POD 4, when the wound was re-examined. In the absence of any sign of possible infection (serous or purulent discharge, flakes, necrosed or unhealthy granulation tissue), the skin was closed by tying knots on the pre-placed sutures. However, in the presence of any of the above signs, closure was deferred and twice daily dressing continued till the wound was healthy.

In both groups, stitch removal was done after ten days of skin closure. In both groups, if there were signs of SSI (purulent discharge, signs of inflammation), one or more stitches were removed, wound swab sent for culture and dressing continued, and the wound was allowed to heal by granulation. Patients were followed up at least for a month after skin closure.

Outcomes

Primary outcome was incidence of SSSI, defined as per the Centers for Disease Control and Prevention Guidelines 1999 (1). In both groups, SSSI was considered as the infection of the wound after skin closure. In the DPC group, any infection when the wound was kept open was not considered as SSSI. Secondary outcomes were incidence of fascial dehiscence, defined as a breach in the deep fascia of abdomen, and LOS, defined as total number of days from admission to discharge, including any readmission.

The sample size was calculated based on a study by Cohn et al. (2), in which the authors found 48% wound infection in patients with PC as opposed to only 12% in patients with DPC. In order to detect the specified difference, a sample size of 24 patients per group was obtained at 80% power and 95% confidence level for a two-sided test of significance. The calculation was done using nMasterv.1.0 software by the Department of Biostatistics, Christian Medical College, Vellore, India. Considering a dropout rate of 20% and rounding off to the nearest multiple of 10, a target of 30 patients in each group was set.

Intention to treat analysis was done using the EZR plugin of R console. Quantitative variables were presented as mean ± standard deviation (SD) along with range. Qualitative variables were summarized using frequency (percentages). Chi squared test or Fisher's exact test was used to investigate associations, if any, wherever applicable. Independent samples t test was used to compare a quantitative variable across DPC and PC groups. A modified intention to treat (mITT) and per protocol analysis were used. P value < 0.05 was considered significant throughout.

RESULTS

Out of the 84 patients undergoing surgery for perforation peritonitis, 24 were excluded for various reasons. Sixty patients were randomly allocated to DPC (n= 30) and PC (n= 30). One patient in the DPC group and two in the PC group died within 72 hours

of surgery, while two in the DPC group had protocol violation, thus, leaving 27 and 28 patients in the two groups, respectively, for final analysis (Figure 1).

Mean age of the patients was 37.6 ± 14 years (range 13-76 years). Majority of the patients were males (n= 51, 85%). Eighteen patients (30%) had appendicular perforation, of whom, five had midline laparotomy in view of generalized peritonitis, while the remaining 13 had grid-iron incision. Overall, 21.7% had a grid-iron incision and 78.3% had midline incisions. Baseline demographic and clinical parameters were evenly distributed between the two groups (Table 1). Median time to skin closure in the DPC group was POD 10. Time to wound closure was 10 days in nine patients, 11 days in six patients and 12 days in three patients. Notably, DPC on POD 4, as planned, was possible in only five patients.

Protocol deviation

In two patients in the DPC group, the wound was not deemed suitable for closure; the pre-placed sutures were removed, and saline dressing was continued, and the wounds allowed to heal by granulation. They were excluded in the per protocol analysis (DPC, n= 27) but included in mITT (DPC, n= 29) (Table 2).

Superficial SSI (SSSI)

In the PC group, 12 out of 28 patients (42.9%) developed SSSI, necessitating opening of one or more sutures. Subsequently, these wounds were allowed to heal by secondary intention. Four of these 12 patients needed readmission. In the DPC group, only two patients (7.4%) developed SSSI after skin closure. The difference in SSSI between the two groups was statistically significant (p = 0.004) in both mITT and per protocol analyses. The two patients, who had healing by granulation, were not considered to have SSSI as they never underwent any skin closure.

Fascial dehiscence

Three patients (n= 3, 10.7%) in the PC group had fascial dehiscence. None of the patients in the DPC group developed fascial dehiscence after skin closure. The two patients in DPC group, who had protocol violation, also developed fascial dehiscence. The difference in incidence of fascial dehiscence was not significant on mITT (p= 0.67) or per protocol analysis (p= 0.236) (Table 2).

Length of hospital stay

Mean LOS was 13.8 ± 4.2 days in DPC group and 13.5 ± 4.6 days in PC group (p= 0.825). The difference was not significant even on per protocol analysis (p= 0.64).

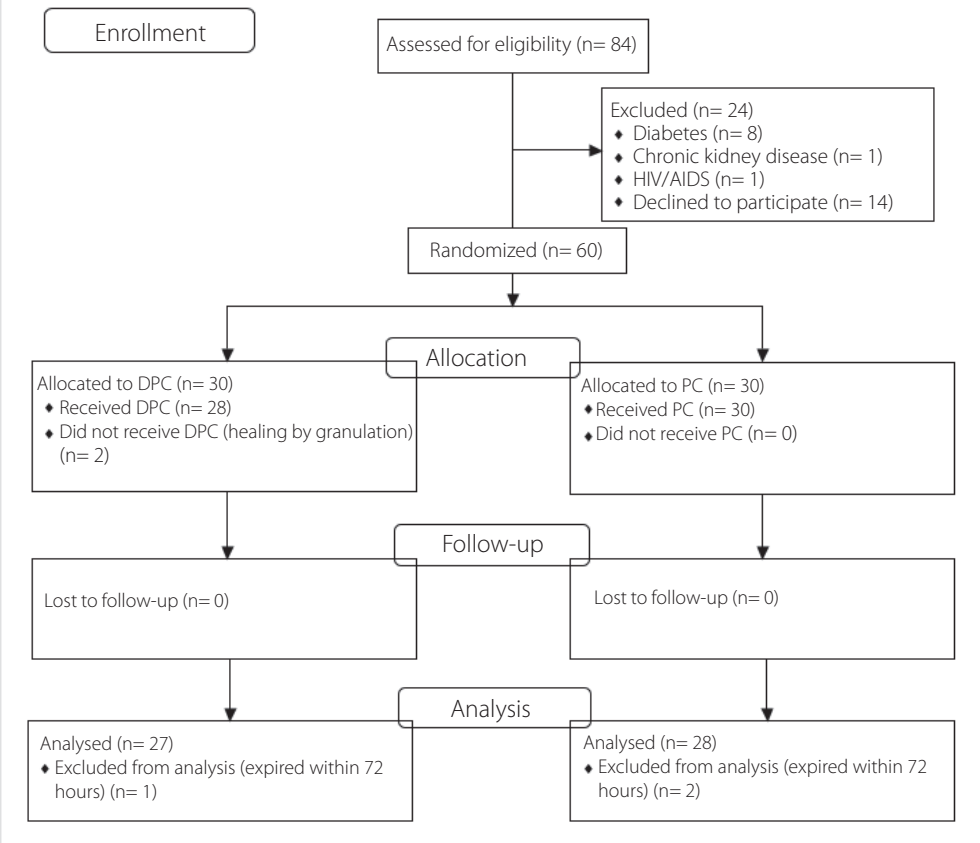

Figure 1. CONSORT flow diagram.

Table 1. Comparison of baseline demographic and clinical profiles

Characteristics	DPC (n= 30)	PC (n= 30)	p
Age in years Mean ± SD (range)	37.2 ± 13.6 (13-76)	38.1 ± 14.7 (16-75)	0.821
Sex Male, n (%) Female, n (%)	 25 (83.3) 5 (16.7)	 26 (86.7) 4 (13.3)	0.999
BMI in kg/m^2 Mean ± SD (range)	24 ± 3.5 (17.1-32.3)	24.5 ± 3 (18.2-33.2)	0.558
ASA grade, n (%) ≤2 >2	 27 (90) 3 (10)	 26 (86.7) 4 (13.3)	0.999
Duration of symptoms, n (%) ≤ 6 hours > 6 hours	 1 (3.3) 29 (96.7)	 3 (90) 27 (10)	0.612
Site of perforation, n (%) Stomach/duodenum Small bowel Appendix Large bowel	 12 (40) 8 (26.7) 9 (30) 1 (3.3)	 11 (36.7) 8 (26.7) 9 (30) 2 (6.7)	0.999
Procedure, n (%) Graham patch repair Appendicectomy Resection anastomosis Stoma Primary repair	 12 (40) 9 (30) 2 (6.7) 6 (20) 1 (3.3)	 11 (36.7) 9 (30) 3 (10) 7 (23.3) 0 (0)	0.999
Total leucocyte count Mean ± SD (range)	10.870 ± 3960 (3500-19.200)	12.006 ± 6068 (2000-28.500)	0.394

DPC: Delayed primary closure, PC: Primary closure, SD: Standard deviation, BMI: Body mass index, ASA: American society of anesthesiologists.

Table 2. Modified intention to treat findings for SSSI, fascial dehiscence and LOS across the two skin closure procedures

Outcome	DPC *	PC*	Relative risk (95% CI)	p
SSSI, n (%)	2 (7.4)	12 (42.9)	0.17 (0.04, 0.70)	0.004
Fascial dehiscence, n (%)	2 (6.9)	3 (10.7)	0.62 (0.05, 5.91)	0.670
LOS in days, mean ± SD (range)	13.8 ± 4.2 (6, 26)	13.5 ± 4.6 (4, 22)	0.26 (-2.06, 2.58)	0.825

DPC: Delayed primary closure, PC: Primary closure, SD: Standard deviation, SSSI: Superficial surgical site infection, LOS: Length of hospital stay.

DISCUSSION

Surgical wounds in patients with secondary peritonitis are considered as "dirty" (class IV) wounds typically associated with a high rate of complications, including SSSI and fascial dehiscence. DPC was first widely used for soft tissue injuries of the extremities, especially compound fractures, during World War I and subsequently went on to be used in civilian practice (3). In one of the earliest comparative trials, Bernard and Cole have found a 42% incidence of SSI in patients undergoing primary closure of wounds compared to 8% in DPC, done 24-72 hours after surgery (4). Grosfeld and Solit have found SSI rates of 34.1% and 2.3%, respectively, in patients undergoing primary and DPC of appendectomy wounds, done on POD 5 (5). However, the results of prospective studies have been variable. In an RCT, Pettigrew has found no significant difference in wound infection between primary and DPC. Patients having DPC had greater LOS and did not accept the procedure well; at follow up, 19% remembered it as an "intolerable" experience (6). Tsang et al. have studied 63 children with gangrenous or perforated appendicitis and found no difference in wound infection between the two groups. The wound was not closed in 24% of patients allocated to DPC because of significant exudate. For infected wounds,

complete wound healing time (CWHT, defined as the time from surgery to complete apposition of wound edges with cessation of wound dressing) was greater in wounds closed primarily but the difference was not significant. However, for non-infected wounds, it was significantly higher for wounds that had DPC, thus, increasing patient discomfort, nursing requirement and LOS. The authors suggested that CWHT might be clinically more meaningful than incidence of SSI (7). In our study, although incidence of SSSI was significantly less in the DPC group, LOS was comparable. Prolonged hospital stay, despite a lower incidence of SSSI, can be explained by the fact that majority of the patients in DPC group had unhealthy wounds that were deemed inappropriate for closure and needed prolonged saline-gauze dressing. Most of these patients had to wait for ≥10 days before their wounds could be closed, thus, negating the advantage of the decreased rate of wound infection after DPC. The decrease in incidence of SSSI due to DPC did not translate into a reduction in LOS. The perceived decrease in SSSI after DPC was only due to the way SSSI was defined in this study. In retrospect, we also feel that CWHT would be a more clinically relevant outcome in studies comparing primary versus DPC.

Some RCTs have found DPC to be advantageous in terms of incidence of wound infection. In a randomized trial on 51 patients, Cohn et al. have found a wound infection rate of 48% in patients having primary closure, compared to 21% in DPC. However, it is noteworthy that 46% of the patients allocated to DPC did not have DPC due to excessive discharge, and these wounds were allowed to heal by secondary intention. The difference in wound infection, though statistically significant, failed to result in any difference in LOS or hospital charges (2). Chiang et al., in a randomized trial of 70 patients, have found significantly lower wound infection and LOS in patients undergoing DPC. They performed DPC on POD 5 and did not mention if any wound was deemed unsuitable for closure (8). Duttaroy et al. have carried out DPC on POD 3 and found significantly lower SSI and LOS, compared to primary closure. Only 10.8% of patients allocated to DPC were considered unsuitable for closure on POD 3 (9). In our study, 83% of patients did not have DPC on the scheduled day due to unhealthy appearance of the wound, which Duttaroy et al. have referred to as 'pre-DPC SSI'. Our decision was based on naked eye examination and was, to some extent, subjective. However, clinical examination was the only possible way to base this decision upon, as culture from wound swabs would take 48-72 hours for an objective assessment of the wound infection, and even that is not 100% accurate. Most of our patients were referred from district hospitals and presented 24 hours after onset of symptoms, which may explain the high rate of 'pre-DPC SSI'. A multicenter randomized trial from Thailand has reported lower SSI rates, albeit non-significant, with primary closure. LOS was comparable but treatment cost was significantly higher with DPC (10).

Rucinsky et al., in a meta-analysis of 2532 patients, have found no difference in SSSI between PC and DPC (11). Henry and Moss, in a meta-analysis of 6 RCTs, have found primary closure to be associated with less treatment failure, defined as purulent drainage requiring opening of wound (for PC) or failure to close wound at scheduled time (for DPC) (12). A meta-analysis by Bhangu et al. has suggested that DPC may have a role in reducing SSI in contaminated and dirty abdominal incisions; however, there was lack of definitive evidence (13). Siribumrungwong et al., in a meta-analysis of 8 RCTs, have found no difference in SSI between PC and DPC, but hospital stay was significantly longer in patients with DPC (14). A recent meta-analysis of 12 RCTs by Tang et al. has concluded in the same lines as Bhangu et al., favouring DPC, with low-quality evidence (15).

Although several randomized trials have been conducted comparing PC and DPC, most of the studies are low quality as found in above meta-analyses. Our study is limited by a small sample size; however, it adds to the existing literature on this debate and emphasizes that there is no benefit of routinely performing DPC of dirty abdominal wounds. Future studies may be directed at patient reported outcomes like quality of life or long-term outcomes, for example incisional hernia, rather than incidence of wound infection, which, as seen in our study, may not be clinically relevant.

In conclusion, DPC of the skin in patients undergoing emergency surgery for perforation peritonitis is associated with a significant lower incidence of SSSI without any considerable decrease in LOS, as substantial time is required for the open wound to become appropriate for closure. The purported advantage of DPC, therefore, is questionable.

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ORİJİNAL ÇALIŞMA-ÖZET
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İçi boş organ perforasyonu olan hastalarda primer insizyonda gecikmeli primer kapamanın yara iyileşmesi üzerindeki etkilerini analiz eden randomize bir çalışma

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ÖZET

Giriş ve Amaç: Ciltte, ertelenen primer kapanmanın (EPK), içi boş organ perforasyonuna bağlı peritonit nedeniyle ameliyat edilen hastalarda yüzeysel cerrahi alan enfeksiyonunu (YCAE) azalttığı öne sürülmüştür, ancak bu konuda bir fikir birliği yoktur. Bu çalışmanın amacı; YCAE, fasiyal ayrılma ve hastanede kalış süresi (HKS) açısından primer kapama (PK) ve EPK sonuçlarını karşılaştırmaktı.

Gereç ve Yöntem: Perforasyon peritoniti nedeniyle acil cerrahi müdahale gerçekleştirilen 60 hasta PK (n= 30) ve EPK (n= 30) olarak randomize edildi. EPK grubundaki hastaların insizyonu, yaranın klinik olarak kapama için uygun olduğu düşünüldüğü takdirde, ameliyattan dört veya daha fazla gün sonra kapatıldı. PC grubundaki hastalarda, insizyon ameliyat sırasında kapatıldı.

Bulgular: YCAE insidansı EPK grubunda (%7,4) PK'ye (%42,9) kıyasla anlamlı olarak daha düşüktü (p= 0,004). Bununla birlikte, EPK'nin medyan süresi 10. gün idi, yani bu yaraların klinik olarak kapanmaya uygun hale gelmesi için belirgin bir zaman gerekiyordu. Fasiyal ayrılma insidansı iki grup arasında benzer seviyedeydi (p= 0,67). Hastanede kalış süresi (HKS) EPK grubunda 13,8 gün iken PK'de 13,5 gündü; bu fark anlamlı değildi (p= 0,825).

Sonuç: Cerrahi kesinin EPK'si, YCAE'nin azalmasına neden oldu. Bununla birlikte, bu yaraların EPK'ye uygun hale gelmesi belirgin bir zaman aldığından ve bu durum da EPK'nin PK'ye göre gerçek bir avantajı olup olmadığını sorgulanır kıldığından, bu durum hastanede kalış süresinde azalmaya dönüşmedi.

Anahtar Kelimeler: Organ perforasyonu, cerrahi alan enfeksiyonu, peritonit, yara enfeksiyonu, ertelenen primer kapanma

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ORIGINAL ARTICLE
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Risk factors for postoperative ileus following loop ileostomy closure

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ABSTRACT

Objective: The most common intra-abdominal complication following loop ileostomy closure (LIC) is postoperative ileus (POI). The aim of the study was to determine the risk factors of POI development following LIC and make recommendations for its prevention.

Material and Methods: In this study, patients having undergone LIC with peristomal incision following distal colorectal surgery were included. Clavien-Dindo classification was used to evaluate postoperative complications. POI and postoperative leakage were defined based on clinical and radiological criteria. The Centers for Disease Control and Prevention 2017 criteria were used to diagnose surgical site infection (SSI). Postoperative bleeding was diagnosed one day after surgery if there was a >2 g/dL or ≥15% decrease in the hemoglobin level.

Results: Seventy-nine patients were included into the study. In nine of the patients POI developed, six had SSI, five had postoperative bleeding, and two had anastomosis leakage. In the univariate analysis; age <60 years (p= 0.02), presence of comorbidity (p= 0.007), using an open technique in the first surgery (p= 0.02), performing total colectomy in the first surgery (p= 0.048), performing hand-sewn anastomosis of LIC (p= 0.01), and postoperative blood transfusion (p= 0.04) were found to be risk factors for POI. Performing hand-sewn anastomosis of LIC (p= 0.03) and using an open technique in the first surgery (p= 0.03) were found to be independent variables for POI risk.

Conclusion: Using an open technique in the first surgery and performing a hand-sewn anastomosis of LIC may increase POI.

Keywords: Ileostomy reversal, small bowel obstruction, colorectal surgery, hand-sewn anastomosis, laparoscopy

INTRODUCTION

Loop ileostomy closure (LIC) is associated with postoperative morbidity, reoperation, and mortality at rates of up to 45%, 7%, and 3.7%, respectively (1-7). The most common complications are anastomosis leakage, gastrointestinal hemorrhage, surgical site infection (SSI), and postoperative ileus (POI). POI is the most common complication following LIC with a rate of 4.1% - 32.6% (2-4). POI is the biggest obstacle for a successful enhanced recovery after surgery protocols (8,9), and it is the most important cause of hospitalization within the first 30 days postoperatively (10). POI rises healthcare costs by increasing the risk of hospital-acquired infections (5,6), and it usually improves with conservative treatment (11).

The incidence of POI following LIC and its risk factors vary in the literature. The aim of this study was to determine the risk factors of POI development following LIC and make recommendations for its prevention.

MATERIAL and METHODS

This retrospective study was approved by the Ethics Committee of Inonu University (decision no: 2017/26-2). We scanned the medical records of adult patients who had undergone elective ileostomy closure after distal colorectal surgery in Inonu University General Surgery Clinic between January 2009 and September 2018. Patients who had undergone LIC with peristomal incision following distal rectal/anal anastomosis were included into this study. Patients undergoing additional surgery

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during LIC and simultaneous ileostomy-colostomy at other localizations and those whose incisions were left to recover by secondary wound healing or whose wounds were closed with Bogota bag were excluded from the study.

Surgical Technique

All procedures were performed under general anesthesia. Surgical site was cleaned with povidone iodine antiseptic solution (Kansuk laboratory, Turkey), and the patients were covered with sterile surgical drapes; 1 gr IV cefazolin was administered 30 minutes before the surgery for antibiotic prophylaxis and was terminated at postoperative 24 hours. In case surgery duration exceeded four hours and intraoperative bleeding was 1500 ml, an additional 1 gr of IV cefazolin was administered. A peristomal circular elliptical incision was used to mobilize the fascia and the peritoneal adhesions surrounding the mouth of the loop ileostomy. According to the surgeon's preference, side-to-side anastomosis was performed using a linear stapler (DST Series 80 mm-3.8 mm, Covidien, USA) while end-to-end anastomosis was hand-sewn with an absorbable 3/0 suture (Vicryl, Ethicon Inc., Cincinnati, OH, USA). Lambert sutures were placed with a non-absorbable 3/0 suture (Prolene, Ethicon, USA) according to the surgeon's preference. The intestine was then replaced into the abdominal cavity, and the abdominal fascia was closed with a non-absorbable 2/0 suture (Prolene, Ethicon, USA). Subcutaneous tissues were closed with absorbable 3/0 suture (PDS, Ethicon, USA), while the skin was closed using the primary or purse suture technique with a non-absorbable 3/0 suture (Prolene, Ethicon, USA), according to the surgeon's preference. Penrose drain was placed under the skin according to the surgeon's preference and was removed on the first postoperative day. Liquid diet was started on the first postoperative day, and wound dressing was done with povidone iodine solution for the first 48 hours.

Definitions

Distal rectal or anal anastomosis was defined as anastomosis performed below the pelvic peritoneal reflection. Clavien-Dindo classification was used to evaluate postoperative complications (POC). POI was defined clinically (intolerance to oral intake, abdominal distension, nausea, vomiting, abdominal pain, inability to remove gas-stool, and fever) and radiologically (dilatation of small bowel loops and air-fluid level in abdominal X-ray or computed tomography) during the postoperative 30-day period. Postoperative leakage was diagnosed clinically (nausea, vomiting, abdominal pain, and fever) and radiologically (air-fluid level in the small intestines on abdominal X-ray, small intestine level on abdominal computed tomography, and presence of intra-abdominal purulent or fecaloid content). Postoperative bleeding was diagnosed one day after surgery if there was a >2 g/dL or ≥15% decrease in the hemoglobin level. The Centers for Disease Control and Prevention (CDC) 2017 criteria were used to diagnose SSI12. SSI was classified according the CDC classification system as follows: (1) superficial incisional involving only the skin or subcutaneous tissue of the incision; (2) deep incisional involving the fascia and/or muscular layers in the primary incision (deep incisional primary) in a patient having undergone an operation involving one or more incisions and an SSI identified in the secondary incision (deep incisional secondary) in an operation with more than one incision; and (3) organ space involving any part of the body opened or manipulated during the procedure, excluding the skin incision, fascia, or muscle layers. In the presence of more than one SSI type, the more complex SSI type was selected.

Age, sex, comorbidity, American Society of Anesthesiologists score, first operation, pathology of the first specimen, neoadjuvant and adjuvant therapy, LIC duration, type of anastomosis, duration of the operation, amount of intraoperative bleeding, POC, length of hospital stay, and mortality were recorded.

Statistical Analysis

Data were analyzed using the SPSS 22 software. Shapiro-Wilk test was used for testing normality. Chi-square and Mann-Whitney U tests were used for categorical and continuous variables, respectively. Logistic regression analysis was performed for variables that had P-values < 0.05 in the univariate analyses. P-values < 0.05 were considered statistically significant.

RESULTS

Ileostomy was closed in 142 patients who had colorectal surgery. A total of 79 patients having undergone LIC following distal rectal or ileoanal anastomosis were included. Patients who had undergone end-ileostomy closure (n= 29), non-colorectal LIC (n= 14), non-distal rectal and ileoanal anastomosis LIC (n= 8), and additional surgery during LIC (n= 12) were excluded. Median age was 55 (18-93) years, and 62.0% of the patients were males. Loop ileostomy was performed in 81.0% of the patients due to colorectal cancer, using the laparoscopic technique in 68.4% of them. The median interval between loop ileostomy creation and closure was 202 (14-576) days. A total of 16.5% of the patients received neoadjuvant chemoradiotherapy, and 50.6% of them received adjuvant chemotherapy. Median operation duration of LIC was 54 (40-80) minutes. A total of 77.2% of LIC surgeries was performed with a stapler. Demographic characteristics of the patients included in the study are shown in Table 1.

Twenty-two intra-abdominal complications (Clavien-Dindo 2, 3A, 3B) developed in 14 patients (17.7%) within the first 30 days postoperatively. POI was observed in nine patients (11.4%). POI was diagnosed clinically and radiologically in seven patients and all recovered with medical treatment. POI developed in two patients who experienced anastomosis leakage on the sixth and tenth postoperative days. One of these patients underwent primary repair and the other underwent loop ileostomy. Post-

Table 1. Patients demography

Parameters	n= 79	%
Age (years) (median, range)	55 (18-93)	
Gender (n, %)		
Male	49	62.0
Female	30	38.0
Comorbidity (n, %)	31	37.8
Hypertension	18	21.9
Diabetes Mellitus type 2	10	12.2
Chronic obstructive pulmonary disease	5	6.1
Coronary artery disease	4	4.8
Epilepsy	1	1.2
Loop ileostomy etiology (n, %)		
Rectum Cancer	58	73.4
Rectal villous adenoma	6	7.6
FAP	5	6.3
FAP + Rectum Cancer	4	5.1
Ulcerative colitis	3	3.8
Others	3	3.8
First surgical technique for LIC (n, %)		
Open	25	31.6
Laparoscopy	54	68.4
Interval between ileostomy creation and closure (day) (median, range)	202 (14-576)	
Operation duration (minute) (median, range)	54 (40-80)	
Postoperative complications (n, %)		
Ileus	9	11.4
Gastrointestinal hemorrhage	5	6.3
Surgical site infection	6	7.6
Anastomosis leak	2	2.5
Lenght of stay (day) (median, range)	6 (3-14)	

FAP: Familial adenomatous polyposis, Others: FAP + Colon Cancer, Colonic inertia, Diverticulitis, LIC: Loop ileostomy closure.

operative lower gastrointestinal bleeding was observed in five patients (hematochezia in two patients and melena in three patients). Only three of these patients gave blood transfusions (three, three, and four units of erythrocyte transfusion). Skin incision was closed with primary sutures in 75 patients and purse sutures in four patients. SSI developed in six patients whose incision had a primary closure (superficial SSI in two patients, deep SSI in one patient, and organ/space SSI in three patients). However, incision closure type was not associated with SSI (8.0% vs. 0%, p= 1.00). Length of hospital stay was six days longer in patients with POI. Six patients were re-hospitalized after discharge. Three of them had SSI, one had an anastomosis leak, one had POI, and one had abdominal pain. No patient died within the first postoperative 30 days.

In the univariate analysis, age <60 years (p= 0.02), presence of comorbidity (p= 0.007), using an open technique in the first surgery (p= 0.02), performing total colectomy in the first surgery (p= 0.048), performing hand-sewn anastomosis of LIC (p= 0.01), and postoperative blood transfusion (p= 0.04) were found to be risk factors for POI (Table 2). Performing hand-sewn anastomosis of LIC (OR: 6.250, p= 0.03) and using an open technique in the first surgery (OR: 6.400, p= 0.03) were found to be independent variables for POI risk (Table 3).

DISCUSSION

POI is defined as the transient inhibition of normal gastrointestinal motility after abdominal surgery. The function of the small intestine recovers within 24 hours, stomach function within 36-48 hours, and colon function within 48-72 hours, postoperatively. Thus, in uncomplicated POI, gastrointestinal motility recovers within three days. If the recovery of the gastrointestinal motility exceeds three days, it is considered to be complicated and paralytic ileus or mechanical bowel obstruction is considered to have occurred (13). POI is characterized clinically by abdominal pain and distension, nausea, and vomiting, as well as the inabil-

Table 2. Risk factors for postoperative ileus

Parameters	POI n= 9	No-POI n= 70	p
Age (n, %)			0.02
≥60	0 (0)	28 (100.0)	
<60	9 (17.6)	42 (82.4)	
Gender (n, %)			0.76
Male	6 (12.2)	43 (87.8)	
Female	3 (10.0)	27 (90.0)	
Comorbidity (n, %)	7 (24.1)	22 (75.9)	0.007
ASA score (n, %)			0.61
I	0 (0)	7 (100.0)	
II	7 (12.3)	50 (87.7)	
III	2 (13.3)	13 (86.7)	
First operation (n, %)			0.02
Open	6 (24.0)	19 (76.0)	
Laparoscopic	3 (5.6)	51 (94.4)	
First operation type (n, %)			0.048
Total colectomy	3 (30.0)	7 (70.0)	
Low anterior resection	6 (8.7)	63 (91.3)	
First pathology (n, %)			0.30
Benign	3 (20.0)	12 (80.0)	
Malign	6 (9.4)	58 (90.6)	
Neoadjuvant chemoradiotherapy (n, %)	1 (7.7)	12 (92.3)	0.60
Adjuvant chemotherapy (n, %)	3 (7.5)	37 (92.5)	0.22
Interval between ileostomy creation and closure (month) (n, %)			1.00
≤2	1 (12.5)	7 (87.5)	
>2	8 (11.3)	63 (88.7)	
Operation duration (minute) (median, range)	45 (40-50)	55 (45-80)	0.36
Intraoperative blood loss (ml) (median, range)	20 (10-30)	20 (5-40)	0.63
Anastomosis type (n, %)			0.01
Stapled	4(6.6)	57 (93.4)	
Hand-sewn	5 (66.7)	13 (32.3)	
Drain (n, %)	1 (3.4)	28 (96.6)	0.09
Postoperative blood transfusion (n, %)	2 (40.0)	3 (60.0)	0.04
Clavien-Dindo classification (n, %)			<0.001
2	7	4	
3A	0	1	
3B	2	0	

POI: Postoperative ileus, ASA: American Society of Anesthesiologists.

ity to eliminate gas or stool and radiologically by dilatation and air-fluid levels in the small intestine (3). POI is one of the most common complications following LIC (4,14). In our study, POI was found to be the most common complication following LIC. Performing hand-sewn anastomosis of LIC and using an open technique in the first surgery were found to be independent risk factors for POI.

In laparoscopic surgery, POI is less common and its duration is shorter since laparoscopic surgery causes less inflammatory cell activation compared to open surgery (15,16). However, results of numerous studies comparing adhesion formation after laparoscopic or open surgery are contradictory (17). The risk of adhesive small bowel obstruction has been found to be lower following laparoscopic colorectal surgery in a prospective co-

Table 3. Multivariate analyzes* of risk factors for postoperative ileus

Parameters	Multivariate analysis 95% C.I.			
	OR	Lower	Upper	p
First operation (Laparoscopy)	6.400	1.201	34.103	0.03
Anastomosis type (Stapled)	6.250	1.1158	33.279	0.03

*: Age, first operation, first operation type, anastomosis type and postoperative blood transfusion were included into the multivariate analyzes.
C.I.: Confidence interval, OR: Odds ratio.

hort study and meta-analysis (18,19). However, the same finding could not be demonstrated in the randomized controlled trial (classic trial) of Guillou et al (20). In our study, compared to open surgery, POI was less frequent when the initial procedure was performed laparoscopically (5.6% vs. 24.0%, p= 0.02). Using an open technique in the first surgery was found to be an independent risk factor for POI (p= 0.03).

There are two techniques used in LIC: stapled anastomosis and hand-sewn anastomosis. Stapled anastomoses are performed in a side-to-side anastomosis, whereas end-to-end technique is generally used in the hand suture groups (21). Due to the fact that the distal limb is not functional for some time, anastomosis is generally made on a relatively small caliber of the distal limb, if restored in an end-to-end configuration. Therefore, perioperative edema might compromise the luminal diameter causing an early bowel obstruction (22). It has been suggested that stapled closure of a loop ileostomy may reduce POI since the lumen created using a stapled side-to-side anastomosis may be wider than that created by hand-sewn closure (23,24). In one randomized controlled trial and three meta-analyses, it has been reported that POI risk is lower for stapler anastomosis (p= 0.02, p= 0.01, p< 0.001, p= 0.01; respectively) (21,22,25). In our study, side-to-side anastomosis was done with a stapler, and end-to-end anastomosis was done by hand. We found that stapler anastomosis was an independent risk factor for POI (OR: 6.250, p= 0.03).

Grass et al. have found that advanced patient age increases POI risk (p= 0.049) (1). In the study by Man et al., prolonged ileus has been observed to be more common in patients aged ≥ 80 years (p= 0.02)26. Contrary to the literature, the risk of POI was higher in patients aged < 60 years in our study (17.6% vs. 0%, p= 0.02, respectively); however, patient age < 60 years was not an independent risk factor for POI.

Distal colorectal resection or total colectomy/proctocolectomy is important in the development of POI. It has been reported that FAP increases POI risk (p= 0.001) and is an independent risk factor for POI (p= 0.004) (27). In our study, it was found that total colectomy/proctocolectomy owing to FAP increased the risk of POI (30.0% vs. 8.7%, p= 0.048), but was not an independent risk factor for POI.

There are no specific guidelines or timing for assessing the most suitable LIC duration (28). Although there are studies reporting 1-12 weeks for early LIC and 2-6 months for late LIC, LIC duration is usually performed after 8-12 weeks (29-31). Early LIC is associated with more overall complications and wound complications after closure, and it may delay the completion of adjuvant chemotherapy (28,32). Therefore, early LIC is not generally recommended for patients with rectal cancer (28). Conversely, having ileostomy during adjuvant chemotherapy has been shown to increase stoma output, leading to dehydration, electrolyte disturbances, and renal failure (28,33). In a recent meta-analysis, it has been found that LIC during or after adjuvant chemotherapy does not change the risk of POI (34). In our study, loop ileostomy was closed in eight patients within ≤2 months following the first surgery, and in 71 patients >2 months following the first surgery. LIC duration was 10 months or more in 13 of the 71 patients. Early LIC of these patients was delayed due to their comorbid conditions, infection or excoriation of the skin of stoma circumference. We found that LIC duration (≤2 months vs >2 months) did not change the risk of POI (p= 1.00). Since 50.6% of our patients received adjuvant chemotherapy, LIC was closed after adjuvant chemotherapy. We found that adjuvant chemotherapy did not change the risk of POI (p= 0.22).

Our study has some limitations: (1) All data that may affect the risk of POI could not be obtained owing to the retrospective nature of the study, (2) Colorectal surgery was performed for many reasons in the patients (heterogeneous sample), which can change the POI rate and risk factors (3) Small patient sample may have reduced the effectiveness of some subgroup analyses, (4) The study was performed in a single center and therefore, POC and their management may differ from other centers.

CONCLUSION

POI is an important complication after LIC. Using an open technique in the first surgery and performing a hand-sewn anastomosis of LIC may increase POI.

Ethics Committee Approval: The approval for this study was obtained from Inonu University Non-Interventional Clinical Research Ethics Committee (Decision No: 2017/26-2, Date: 05.12.2017).

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ORİJİNAL ÇALIŞMA-ÖZET
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Loop ileostomi kapatılması sonrası postoperatif ileus için risk faktörleri

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ÖZET

Giriş ve Amaç: Loop ileostomi kapatılması (LİK) sonrası en sık görülen karın içi komplikasyon postoperatif ileus'tur (POİ). Çalışmanın amacı, LİK sonrası gelişen POİ için risk faktörlerini belirlemek ve onun önlenmesi için önerilerde bulunmaktır.

Gereç ve Yöntem: Bu çalışmaya distal kolorektal cerrahi sonrası peristomal insizyon ile LİK uygulanan hastalar dahil edildi. Postoperatif komplikasyonları değerlendirmek için Clavien-Dindo sınıflaması kullanıldı. POİ ve postoperatif kaçak klinik ve radyolojik kriterlere göre tanımlandı. Cerrahi alan enfeksiyonu (CAE) tanısında Hastalık Kontrol ve Önleme Merkezleri-2017 kriterleri kullanılmıştır. Cerrahi sonrası birinci günde hemoglobin seviyesinde > 2 g/dL veya ≥ %15'ten fazla azalma olması durumunda postoperatif kanama teşhisi konuldu.

Bulgular: Yetmiş dokuz hasta çalışmaya dahil edildi. Dokuz hastada POİ, altı hastada CAE, beş hastada postoperatif kanama ve iki hastada anastomoz kaçağı gelişti. Tek değişkenli analizde; yaş <60 yaş (p= 0,02), komorbidite varlığı (p= 0,007), ilk cerrahide açık teknik kullanılması (p= 0,02), ilk cerrahide total kolektomi yapılması (p = 0,048), LİK anastomozunun elle yapılması (p= 0,01) ve postoperatif kan transfüzyonu (p= 0,04) POİ için risk faktörleri olarak bulundu. LİK anastomozunun elle yapılması (p= 0,03) ve ilk cerrahide açık teknik kullanılması (p= 0,03) POİ riski için bağımsız değişkenler olarak bulundu.

Sonuç: İlk ameliyatta açık bir tekniğin kullanılması ve loop ileostomi kapamanın elle yapılması postoperatif ileusu artırabilir.

Anahtar Kelimeler: Leostomi kapama, ince bağırsak tıkanıklığı, kolorektal cerrahi, elle anastomoz yapma, laparoskopi

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Transoral endoscopic thyroidectomy vestibular approach (TOETVA): Our outcomes from Turkey

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ABSTRACT

Objective: The Transoral Endoscopic Thyroidectomy Vestibular Approach (TOETVA) was described in 2016 and had its case series published. This study aimed to present the largest TOETVA case series performed in Turkey.

Material and Methods: Data from 52 patients who underwent TOETVA procedure between February 2018 and October 2019 were analyzed retrospectively. Demographic data, duration of operation, blood loss, rate of conversion to open surgery, radiological findings, pathological outcomes, and complications were analyzed.

Results: All patients were female. Mean duration of the operation was 192 ± 45 minutes, mean blood loss was 39 ± 47 mL, and the ratio of surgical site infection was 6% (3/50). In two (4%) patients, TOETVA was converted to open surgery. Temporary and permanent recurrent laryngeal nerve (RLN) paralysis was observed in 2 (4%) and 0 patients, respectively. Temporary and permanent hypoparathyroidism was observed in 10 (20%) and 0 patients, respectively.

Conclusion: TOETVA procedure is the most recently defined NOTES technique for endocrine surgery. In experienced healthcare centers, TOETVA can achieve outcomes similar and even better than the ones obtained with open surgery. The complication rates, durations of operation, surgical site infection, and blood loss parameters that we observed in our experience are similar to the ones reported in the literature.

Keywords: Minimally invasive surgery, natural orifice endoscopic surgery, thyroidectomy

INTRODUCTION

Thyroid hypertrophy, thyroid nodules, and thyroid cancers are the main diseases that require thyroidectomy worldwide (1). Recognized as the pioneering figure of thyroid surgery, Kocher defined the transcervical approach thyroidectomy for such patients for the first time in 1898 (1). The anterior cervical incision is still being used at most healthcare centers (1). While this approach ensures perfect vision and direct access in the central neck area, it also causes an incision scar on the neck, which has a negative effect on patients' quality of life (2). The frequency of thyroid pathologies is increasing especially in the population of young patients (3). Since external appearance is becoming more important in social life, thyroid surgeons have begun to prefer operations with remote access to the neck area. (3). Foremost among these approaches are the transaxillary approach, the bilateral axillo-breast approach (BABA) and the facelift approach (4-6). However, these techniques force surgeons to make large subcutaneous surgical dissections in order to hide the incision scar. This is because in these types of surgeries, there is, inevitably, a visible scar left by a minimal incision or a concealed incision accompanied by large subcutaneous tissue dissection (7).

The introduction of the natural orifice transluminal endoscopic surgery (NOTES), which is performed through natural body orifices without leaving a scar, was an exciting development for many surgeons (8,9). NOTES techniques developed for thyroid surgery were sublingual and transtracheal approaches. However, these techniques were abandoned due to severe tissue damage, high complication rates, and high rates of conversion to open surgery, as well as surgical difficulties caused by movement restriction in the small surgical site (10-12). Following these develop-

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ments, Anuwong (13) defined the transoral endoscopic thyroidectomy vestibular approach (TOETVA) in 2016, and the transoral endoscopic parathyroidectomy vestibular approach later on. This technique can assist to provide access to both thyroid lobes via minimal subcutaneous dissection, besides offering a better vision as well. Furthermore, it leaves no scars because it is a real NOTES procedure (13).

This study aimed to compare the literature with data from patients who underwent surgery using the TOETVA technique at the general surgery clinic of Kepez State Hospital and the Antalya Training and Research Hospital (Antalya, Turkey).

MATERIAL and METHODS

Patients

The records of 52 patients who underwent surgery using the TOETVA procedure at the general surgery clinic of Kepez State Hospital and the Antalya Training and Research Hospital (Antalya, Turkey) between February 2018 and October 2019 were included in the study. The data was evaluated retrospectively. The criteria for patients suitable for TOETVA procedures include the following: 1) Patients with a history of hypertrophic scar and who do not want any scars left on their neck, 2) patients with a long diameter of the thyroid gland less than 10 cm, 3) a solid benign thyroid nodule of ≤6 cm, 4) T1 differentiated thyroid cancer cases confirmed by preoperative imaging that have a solid malign thyroid nodule of ≤2 cm and that lack lateral neck lymph node metastasis or tracheal invasion. Thyroid gland and thyroid nodule diameters were evaluated by ultrasonography. The criteria of the patients unsuitable for TOETVA procedure are: 1) History of a maxillofacial or neck surgery, 2) previous radiotherapy on the head, neck and upper mediastinum, 3) clinically active hyperthyroidism, 4) substernal goiter, 5) proven lateral neck lymph nodule metastasis, 6) suspicion of invasion in adjacent organs such as the esophagus, trachea and recurrent laryngeal nerve (RLN), 7) compromised oral hygiene, 8) unsuitability for general anesthesia, and 9) patients who do not want the procedure to be applied. These criteria have been compiled from the studies conducted by the clinics with high levels of experience with TOETVA (13). All patients were informed about the TOETVA procedure, and written consents were obtained. This study was approved by the institutional review board (IRB) of University of Health Sciences Antalya Training and Research Hospital (IRB number: 02/05/2019-12/22).

The first 30 patients were operated by two surgeons (B.D., M.İ.T.). Preoperatively, all patients underwent physical examination; serum parathormone (PTH), serum calcium and thyroid function tests; fine needle aspiration cytology; and thyroid ultrasonography. Patients considered to simultaneously have both parathyroid and thyroid pathology also underwent Tc-99m MIBI parathyroid scintigraphy to detect localization. Patients who previously had treatment on the lower jaw and teeth were sent to have a dental examination, while those who had a previous nasal operation were sent to have otorhinolaryngological examination. In order to avoid postoperative infection and decrease microbial concentrations in the patients, all patients were instructed to mouthwash their mouths with chlorhexidine twice a day three days before the operation.

Surgical Technique

Nasotracheal or orotracheal intubation with adhesive electrodes was applied in all of the patients under general anesthesia. While the patients were in supine position, a slight extension of the neck was ensured by placing a low pillow under the shoulders. Endotracheal tube and anesthesia equipment were placed on the left corner. Amoxicillin-clavulanic acid was administered at 1.2 g 30 minutes before the incision. In order to protect the eyes and nose, they were covered and closed with textile and Tegaderm film roll (3M Company, Saint Paul, MN, USA). The anterior neck area and the oral cavity were disinfected with 10% povidone-iodine.

First, a 10 mm-incision was applied through the middle of the vestibulum, and the submandibular site was accessed using a cautery and curved clamp to pass through the jaw. For hydrodissection, diluted adrenaline solution (1:500 000) was used. This solution was injected from the vestibular area toward the frontal side of the neck using a Veress needle; thus, there was constituted subplatysmal a working site. An olive dissector was used to blindly dissect the anterior part of the neck. A 10-mm trocar and 30° fiberoptic were inserted through the incision. Insufflation was applied to achieve a carbon dioxide (CO_2) pressure of 6 mmHg. Two 5-mm trocars were inserted in the lateral of the intersection between the canine and first premolar teeth (Figure 1). A working site was created on the subplatysmal area. The upper

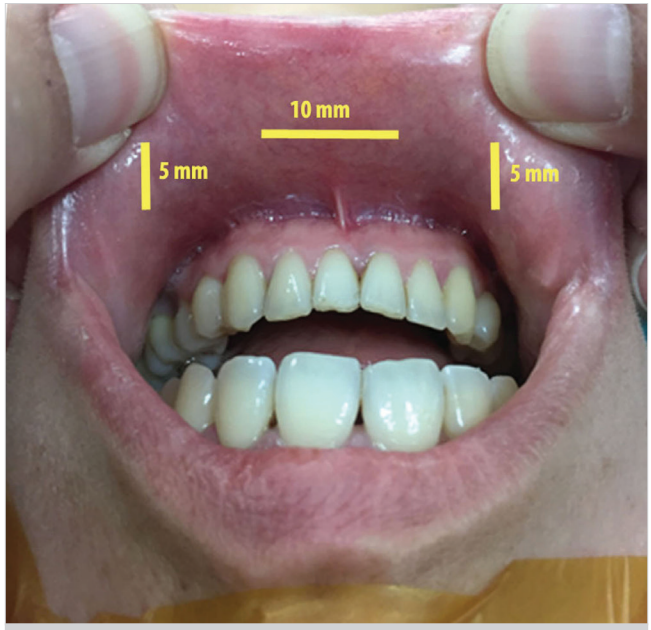

Figure 1. Port placement.

border of this subplatysmal flap was the larynx, its lower border was the suprasternal notch, and its lateral borders were between the anterior edges of the two sternocleidomastoid muscles. This method enabled perfect craniocaudal vision. So as to see the thyroid and trachea, strap muscles were separated from the midline, and retracted toward the lateral sides transcutaneously using 2/0 silk and absorbable synthetic sutures. First, the isthmus of the thyroid was identified, and then, isthmusectomy was completed by dissecting from the trachea. The upper pole vessels were sealed using ultrasonic or bipolar energy devices. For RLN identification and dissection, the gland was retracted to the medial. Intraoperative intermittent neuromonitoring (IONM) was used as a standard in all patients. IONM measurement records were retrieved before and after lobectomy. The dissection was performed in the craniocaudal direction. All parathyroids were identified and spared. Specimens were removed through the 10-mm trocar using an endobag (Figure 2). Linea alba cervicale and in-mouth incision were closed using absorbable sutures. In all of the patients, pressure dressing was applied for 24 hours in a way that covered the jaw and upper area of the neck. Oral intake was initiated on the first postoperative day, and oral antibiotics were prescribed for five days (Figure 3) (14).

Statistical Analysis

Data were prospectively collected and retrospectively analyzed. All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) Statistics for Windows, version 21 (IBM Corp., Armonk, N.Y., USA). To describe the basic features of the data, descriptive statistics such as mean, median, standard deviation, and ratio, were used.

RESULTS

Demographic and clinical data of the patients are presented in Table 1. All patients were female, and median age was 44 years (21-76). Their mean body mass index was 27.1 ± 4.4 kg/m^2. Preoperative benign pathology was detected in 38 (76%) of the patients, and 40 (80%) of these patients underwent total thyroidectomy, while 10 (20%) underwent hemithyroidectomy. There were 12 (24%) patients with malignancy or suspicious for malignancy. Of these patients, 11 (91.7%) underwent total thyroid-

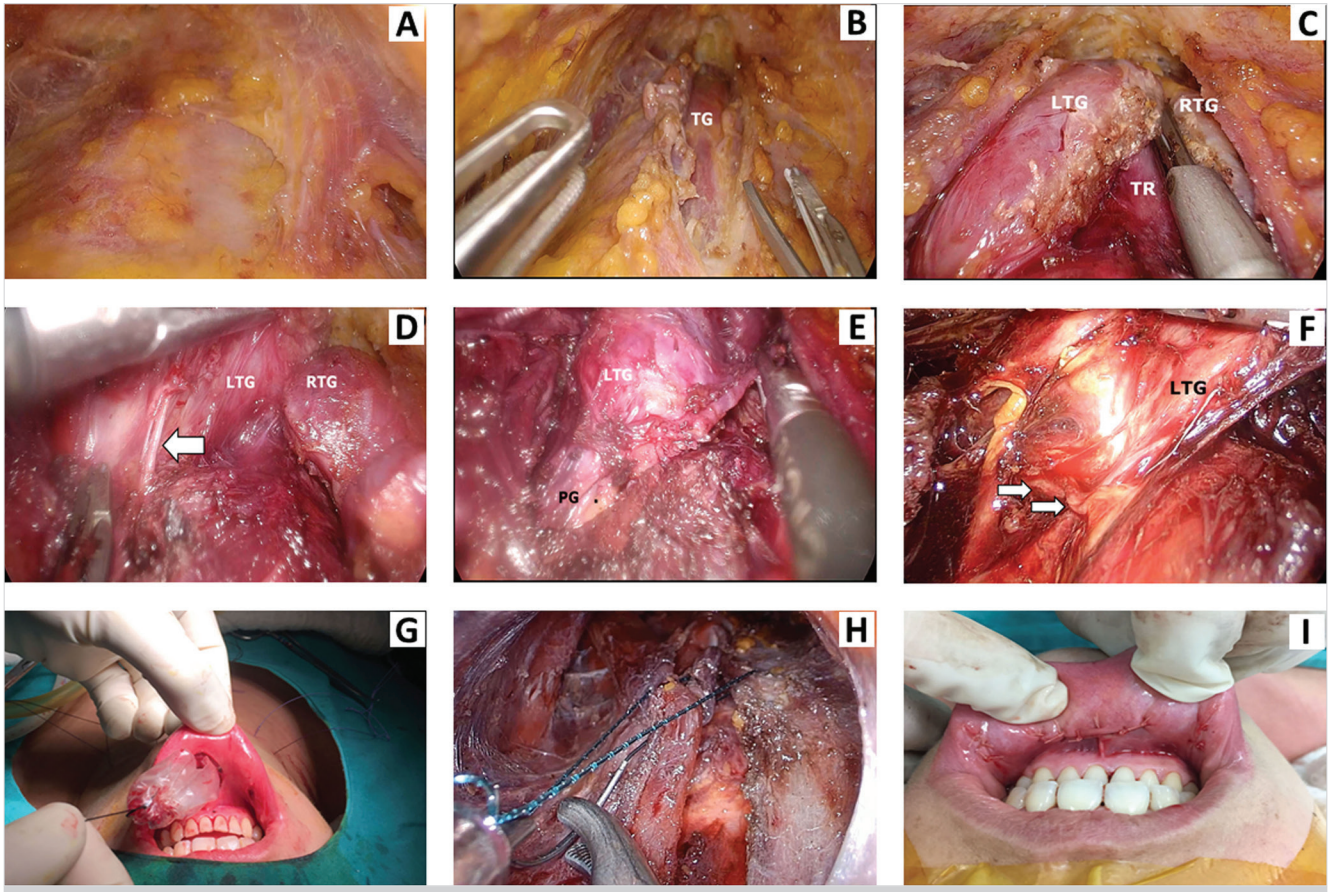

Figure 2. A. Subplatysmal working site; **B.** Strap muscles being separated in the middle line; **C.** Isthmectomy; **D.** Upper pole dissection, external branch of the superior laryngeal nerve (white arrow); **E.** Upper parathyroid gland; **F.** Recurrent laryngeal nerve (white arrows); **G.** Specimens being removed into endobag; **H.** Closure of strap muscles; **I.** Closure of port spots.
TG: Thyroid gland, LTG: Left thyroid gland, RTG: Right thyroid gland, TR: Trachea, PG: Parathyroid gland.

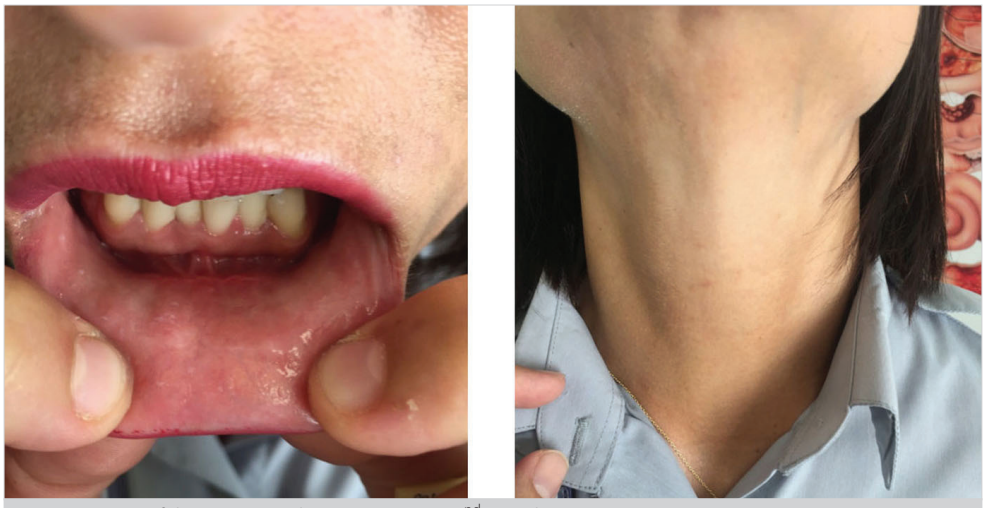

Figure 3. View of the patient in the postoperative 2nd month.

Table 1. Demographic and clinical data

	(n= 50)
Age, year, median	44 (21-76)
Sex Female Male	 50 (100%) -
Preoperative pathology n (%) Bening Malignant/suspected	 38 (76%) 12 (24%)
Dominant nodule diameter, cm, mean (SD)	2.2 (1.5)
Body mass index, kg/m^2, mean (SD)	27.1 (4.4)

ectomy, whereas 1 (8.3%) underwent hemithyroidectomy. Two (4%) patients were converted to open surgery due to serious adhesions. These patients were excluded from the assessment. Total duration of the operation was 192 ± 45 minutes. Malignancy related to the thyroid gland was reported in 21 (42%) of the patients. There was no need for complementary surgery in any of the patients (Table 2).

Nasal bleeding caused by nasotracheal intubation was intraoperatively observed in two of the patients, and the bleeding was taken under control with nasal tamponade. Flap perforation was observed in two patients, which was repaired through reconstruction. Blood loss of over 50 mL was observed in two of the patients, and hemostasis in these patients was ensured using 5-mm clips in addition to energy devices. There are some complications in TOETVA, such as mental nerve injury and subcutaneous-mediastinal emphysema that were different from those in open thyroid surgery. These complications can negatively affect the quality of life. However, these complications were not observed in our case series. Surgical site infection was observed in 3 (6%) patients. They were treated with oral antibiotic therapy, and they did not require hospitalization. Temporary unilateral RLN paralysis was postoperatively observed in 2 (4%) patients, and these patients spontaneously recovered in two weeks. On the other hand, none of the patients showed bilateral or permanent RLN damage. Temporary hypoparathyroidism was detected in 10 (20%) of the patients. None of the patients showed permanent hypoparathyroidism (Table 2).

DISCUSSION

After the first endoscopic parathyroidectomy had been performed by Gagner in 1996 (15), different endoscopic methods (axillary, breast areola, retro-auricular, anterior chest approach, etc.) were defined for benign thyroid nodules and certain differentiated thyroid cancers (16,17). Transaxillary thyroidectomy and BABA are frequently practiced in Eastern countries, where a scar on the neck area is considered undesirable (4,5). Although extracervical total endoscopic approaches are viewed as minimally invasive methods, they are also criticized for requiring large subcutaneous dissection and leaving scars on the areas outside the neck (18). With the introduction of the NOTES technique for the first time in thyroid surgery, it became possible to apply procedures that left no scars (11). However, differences in their insertion places and the complications that occurred led surgeons to search for more ergonomic, reliable and effective procedures. The TOETVA procedure was developed as a result of this pursuit (19). TOETVA has proven to be successful and reliable in experimental studies on animals and cadavers (18).

Contrary to the clean scar in open thyroid surgery, the surgeries performed in the oral cavity are classified as clean-contaminated scars. Although the rate of surgical site infection in open thyroid surgery is 0.1%-2%, in surgeries performed in the oral cavity, it can rise to 12% (19,20). To avoid this, it is recommended to use an antiseptic mouthwash started preoperatively, along with prophylaxis that covers gram-positive and anaerobic bacteria. (18). In our study, surgical site infection developed in 3 (6%) of

Table 2. Operative data, postoperative data and complications

	(n= 50)
Operation, n (%)	
Hemithyroidectomy	10 (20%)
Total thyroidectomy	40 (80%)
Operation duration, minute, mean (SD)	
Hemithyroidectomy	141 (25)
Total thyroidectomy	205 (40)
Total duration	192 (45)
Blood loss, mL, mean (SD)	39 (47)
Transition to open surgery, n (%)	2 (3.3%)
Hospitalization, day, mean (SD)	1.6 (0.5)
Thyroid pathology, n (%)	
Benign	29 (58%)
Micropapillary thyroid cancer	7 (14%)
Papillary thyroid cancer	12 (24%)
Medullary thyroid cancer	1 (2%)
Hurthle cell carcinoma	1 (2%)
Complications n (%)	
RLN paralysis	
Temporary	2 (4%)
Permanent	0
Hypoparathyroidism	
Temporary	10 (20%)
Permanent	0
Hematoma	0
Seroma	3 (6%)
Infection	3 (6%)
Intra-operative hemorrhage	2 (4%)
Nasal bleeding	2 (4%)
Flap ischemia/perforation	2 (4%)
Mental nerve injury	0
Subcutaneous/mediastinal emphysema	0
Tracheal injury	0
Esophageal injury	0

RLN: Recurrent laryngeal nerve.

the patients, and our surgical site infection rate is compatible with the literature.

Mental nerve damage occurring in up to 87% of extra-vestibular transoral thyroidectomy methods has obliged surgeons to use approaches that ensure access through the anterior of mandibular (21). In the vestibular approach defined by Nokaja et al. (22) that involves a 2.5 cm incision (transoral video-assisted neck surgery (TOVANS), mental nerve damage that lasted for more than six months was observed in all of the eight patients. Wang et al. (23) replaced the port that is in the middle of vestibulum with a 10-mm port, brought it closer to buccogingival sulcus, and placed the two 5-mm ports to the lateral as much as possible. Although there is information in the study regarding paresthaesia on the gonion, it was necessary to change the insertion spots of the ports, since the 5-mm ports passed through the mental nerve line. Finally, in the TOETVA approach performed by Anuwong (19) in 2016, the 5-mm lateral ports were brought closer to the edge of the lower lips, and mental nerve damage was reported in none of the 60 patients. In our study, no mental nerve damage observed in any of the 50 patients that underwent the TOETVA method defined by Anuwong.

Complications caused by CO_2 insufflation, such as massive subcutaneous emphysema and hypercarbia, have been observed in high intracavitary pressures (24). While studies conducted on humans report that pressures under 10 mmHg are reliable, the TOETVA procedure uses a pressure of 6 mmHg (19,25). Another complication caused by insuflattion is CO_2 embolism associated with venous injuries that remain open. In a case report published in the literature, Kim et al. (26) injured the anterior jugular vein during the preparation of the skin flap. Because CO_2 in the working site entered into the opened vein, CO_2 embolism was occurred. In our study, none of the patients developed any complications caused by CO_2 insufflation.

Another complication of endoscopic and open thyroidectomy is RLN injury. In open surgery, temporary RLN injury varies between 2 and 12%, while permanent injuries vary between 0.2 and 6% (19). Endoscopic minimally invasive thyroidectomy (eMIT) and TOVANS, which are two endoscopic thyroidectomy approaches, have been reported to have RLN injury rates of 25% and 12.5%, respectively (21,22). In the 200 patients on which Anuwong et al. performed TOETVA procedure, the rate of temporary RLN paralysis was 2.6%, while permanent paralysis was not seen in any of these patients (14). In our study, temporary RLN paralysis was observed in 2 (4%) patients, while RLN paralysis was not seen in any of the patients. This result is compatible with the literature. Although many studies demonstrating that the use of IONM will be beneficial in reducing RLN paralysis have been published, these studies have included small numbers of cases (27).

According to the literature, the prevalence of temporary and permanent hypoparathyroidism in open surgery is from 0.3% to 49% and from 0% to 13%, respectively (28,29). On the other hand, in TOETVA, temporary hypoparathyroidism has been observed in two (3.3%) of the 60 patients in the study by Anuwong (19) and in one (6.6%) of the 15 patients in the study by Dionigi et al. (18). Permanent hypoparathyroidism has been identified in neither one of these two studies. In our study, temporary hypoparathyroidism was detected in 10 (20%) patients, while permanent hypoparathyroidism was detected in none of the patients. In our opinion, the reason for the high rate of temporary hypoparathyroidism is that this was our first experience.

The present study has some limitations. One of these is the type of study; as it is a retrospective study, this might lead to case selection and assessment bias. Second, the sample size included

in our study was small. Third, outcomes of the referred studies might differ from those of our study owing to causes such as patient selection, sample size, and variations in regional treatment guidelines. Additionally, there were few published articles on TOETVA. Therefore, the average values of previous studies still do not have a standard value and the outcomes of the literature are heterogenic.

CONCLUSION

TOETVA is the most recent NOTES technique defined for thyroid surgery. Since the large majority of the patients are young females, it is very important in terms of both cosmetics and psychology that no scar is left on their neck. Because this procedure is a sensitive surgical procedure performed on a limited dissection site, it requires a high level of endoscopic surgical experience. We observed complication rates that were similar to, and even lower, than those in open surgery. These results support the view that this method can be safely applied.

Ethics Committee Approval: The approval for this study was obtained from Antalya Local Ethics Committee for Clinical Research (Decision No: 12/22, Date: 02.05.2019).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - B.D.; Design - B.D., M.İ.T.; Supervision - B.D., M.İ.T., U.R.G., N.H.B.; Data Collection and/or Processing - B.D., M.İ.T., U.R.G., N.H.B.; Analysis and/or Interpretation - B.D., U.R.G.; Literature Review - B.D.; Writing Manuscript - B.D.; Critical Reviews - B.D., M.İ.T., U.R.G., N.H.B.

Conflict of Interest: All authors declare that they have no competing interests.

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ORİJİNAL ÇALIŞMA-ÖZET
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Vestibüler yaklaşımlı transoral endoskopik tiroidektomi

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ÖZET

Giriş ve Amaç: Vestibüler yaklaşımlı transoral endoskopik tiroidektomi (TOETVA) 2016 yılında tanımlanmış ve vaka serileri yayınlanmıştır. Bu çalışmada amacımız Türkiye'de gerçekleştirilen en büyük TOETVA vaka serisini sunmaktır.

Gereç ve Yöntem: Şubat 2018 ile Ekim 2019 arasında TOETVA işlemi uygulanan 52 hastanın verileri retrospektif olarak incelendi. Demografik veriler, operasyon süresi, kan kaybı, açık cerrahiye dönüşüm oranı, radyolojik bulgular, patolojik sonuçlar ve komplikasyonlar analiz edildi.

Bulgular: Hastaların tamamı kadındı. Ortalama operasyon süresi 192 ± 45 dakika, ortalama kan kaybı 39 ± 47 mL ve cerrahi alan enfeksiyon oranı %6 (3/50) 'ydı. İki hastada (%4) açık cerrahiye dönüş yapıldı. Geçici ve kalıcı rekürren laringeal sinir (RLN) paralizisi sırası ile 2 (%4) ve 0 hastada gözlendi. Geçici ve kalıcı hipoparatiroidizm sırası ile 10 (%20) ve 0 hastada gözlendi.

Sonuç: TOETVA işlemi endokrin cerrahisi için en son tanımlanan NOTES tekniğidir. Deneyimli sağlık merkezlerinde, açık cerrahi ile elde edilenlere benzer ve hatta daha iyi sonuçlar elde edilebilir. Deneyimlerimizde gözlemlediğimiz komplikasyon oranları, ameliyat süreleri, cerrahi alan enfeksiyonu ve kan kaybı parametreleri literatürle benzerdir.

Anahtar Kelimeler: Minimal invaziv cerrahi, doğal açıklık endoskopik cerrahi, tiroidektomi

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ORIGINAL ARTICLE
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Topical diltiazem and glyceryl-trinitrate for chronic anal fissure: A meta-analysis of randomised controlled trials

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ABSTRACT

Objective: Surgical management of chronic anal fissure can result in permanent fecal incontinence. Topical treatments have a lower risk of severe complication and are less expensive than surgical intervention. Rates of healing and compliance with topical agents vary in the reported literature. The aim of this study was to compare healing rates, incidence of headaches, and recurrence rates of chronic anal fissure in patients treated with topical diltiazem (DTZ) and topical glyceryl-trinitrate (GTN), with a view of identifying which agent should be used as first line non-operative therapy.

Material and Methods: Randomized controlled trials (RCTs), published since January 2000, comparing topical DTZ and GTN for treatment of chronic anal fissure were identified and compared. End points included healing rates, headache due to treatment, and late recurrence (>12 weeks). A random effects meta-analysis model was used to compare outcomes.

Results: All studies used 2% DTZ and 0.2% or 0.5% GTN, and treatment was continued twice daily for between 6-12 weeks. Nine RCTs compared rates of healing with topical DTZ (n= 379) and GTN (n= 351), there was no difference between the two groups [RR 1.04 (0.93-1.16), p= 0.48]. Eight RCTs reviewed incidence of headaches, DTZ was better tolerated [RR 0.15 (0.07-0.34), p< 0.00001]. Four RCTs reported late recurrence rates, DTZ was superior [RR 0.51 (0.27-0.96), p= 0.04].

Conclusion: Topical DTZ and GTN result in comparable healing rates; however, DTZ is superior with regards to headaches and late recurrence rates. DTZ should therefore be considered as first line non-operative treatment for chronic anal fissure.

Keywords: Chronic anal fissure, topical therapy, diltiazem, glyceryl-trinitrate

INTRODUCTION

Anal fissure is a lineal tear in the anal canal distal to the dentate line (1). Chronic anal fissure (CAF) is associated with hypertonia of the internal sphincter resulting in mucosal ischaemia and failure to heal, which results in severe anal pain (2,3). Resolution of the symptoms can be achieved by lowering the resting anal tone, and increasing blood flow. Historically, this was achieved by division of the muscle fibers, in the form of a lateral sphincterotomy. This was the mainstay of treatment, however, lateral sphincterotomy causes significant morbidity with reported incontinence rates of up to 30% (4).

Topical treatment of CAF with Diltiazem (DTZ) and Glyceryl-trinitrate (GTN) can result in good outcome, without the risk of surgery and incontinence. In the UK, topical GTN is considered first line therapy for CAF, and clinicians are advised to use analgesics concurrently for the management of side effects such as headache, DTZ is only considered after this (5). This meta-analysis of randomized controlled trials (RCTs) aimed to assess healing, headache and recurrence rates of CAF in adult patients treated with topical DTZ and GTN.

MATERIAL and METHODS

The search engines Ovid Medline, Embase, PubMed, Scopus and Google Scholar were used to identify publications. Search terms used were "chronic anal fissure", "glyceryl-trinitrate", "diltiazem", "healing," "side effect," "randomized" in exploded and linked combinations. Complete articles published in English since January 2000 were considered for inclusion. Articles identified were RCTs which compared out-

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comes of topical DTZ vs topical GTN in the management of CAF. All articles pertaining to acute anal fissure, systemic therapies, or surgical therapies were excluded. This search strategy is summarized in Figure 1. Primary outcomes included rates of healing, headaches and reported recurrence, which were collected by a single author (EJN).

A meta-analysis was performed by combining the results of outcome variables. Data were summarized using risk ratio. Heterogeneity among the studies was estimated using chi-squared (χ^2) tests which were reported as the I^2 statistic to estimate the percentage of total variation across studies attributable to study heterogenicity. A random effects meta-analysis model was used to account for the possible clinical diversity and methodological variation amongst the studies. All p-values were 2-sided. A significant difference was defined as $p< 0.05$. Statistical analysis was conducted with Review Manager Version 5.3 (Cochrane Collaboration, Software Update, Oxford, UK).

Ethical approval for this research was not required owing to it being a meta-analysis of previously published (and approved) RCTs.

RESULTS

A total of 9 RCTs were identified, they incorporated 385 patients who were treated with DTZ and 371 in the GTN group (Table 1). All studies used between 6 and 12 weeks of treatment using 2% DTZ and 0.2% or 0.5% GTN twice daily. Follow up ranged from 6 weeks to 52 weeks following completion of treatment.

Across the 9 studies, 277/379 (73.1%) of the patients treated with DTZ had healed. A total of 244/351 (69.5%) of the patients treated with GTN had healed. There was therefore no significant difference in healing rates between the two groups (p= 0.48) (Figure 2).

Eight studies reported rates of headaches during treatment. Only 31/359 (8.6%) of those treated with DTZ reported headache. The

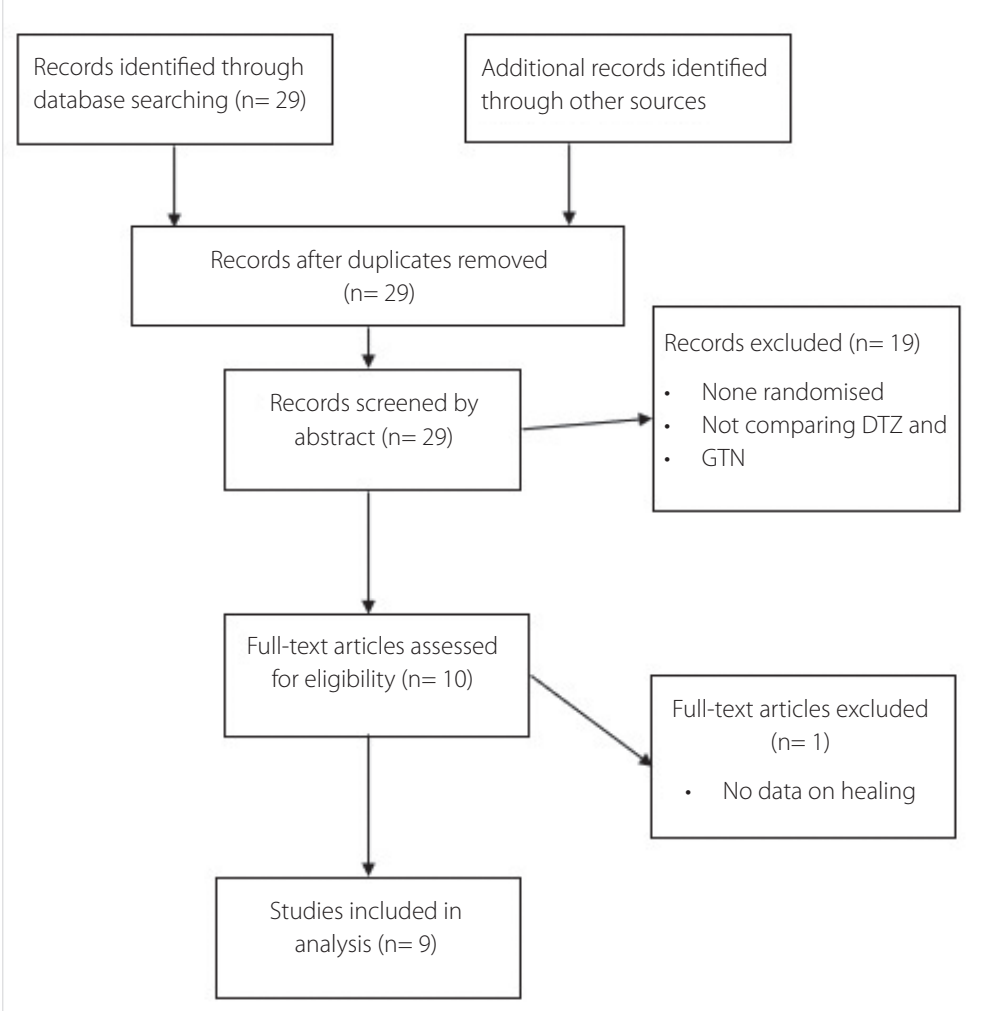

Figure 1. PRISMA diagram demonstrating search strategy to identify RCTs comparing DTZ and GTN for management of CAF.

Table 1. Data extracted from RCTs comparing GTN and DTZ for CAF

Author	DTZ group	GTN group	Treatment length	Follow up	Blinding	Randomisation protocol	Source of funding
Bielecki 2002[5]	22	21	BD 8/52	8/52	?		?
Kocher 2002[6]	31	29	BD 6-8/25	12/52	Double	Computer generated	?
Shrivastava 2006[7]	30	30	BD 6/25	3/12	?	Drawing lots	?
Jawaid 2009[8]	40	40	BD 8/52	8/52	?	Computer generated	?
Sanei 2009[9]	51	51	BD 12/52	8-12/52	Double	Computer generated	?
Suvarna 2010[10]	100	100	BD 6/52	52/52	?	Sequential order	None
Ala 2012[11]	36	25	BD 8/52	8/52	Double	Computer generated	?
Bansal 2016[12]	25	25	BD 6/52	3/12	?	Computer generated	?
Venkatesh 2019[13]	50	50	BD 8/52	6/52	?	?	None
Total	385	371					

?: Paper does not specify.

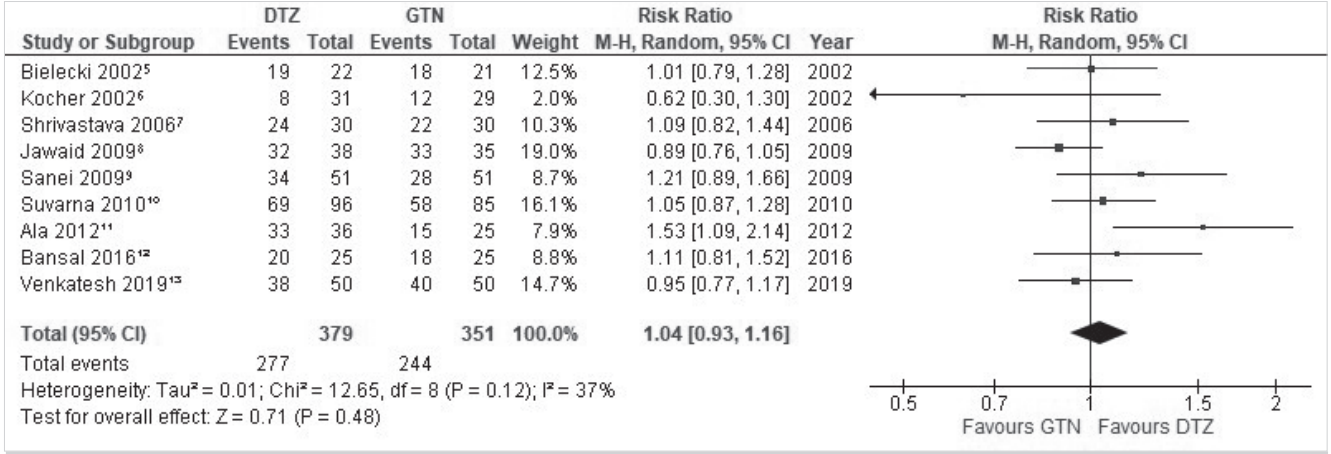

Figure 2. Forrest plot demonstrating rates of healing in patients with CAF treated with DTZ and GTN.

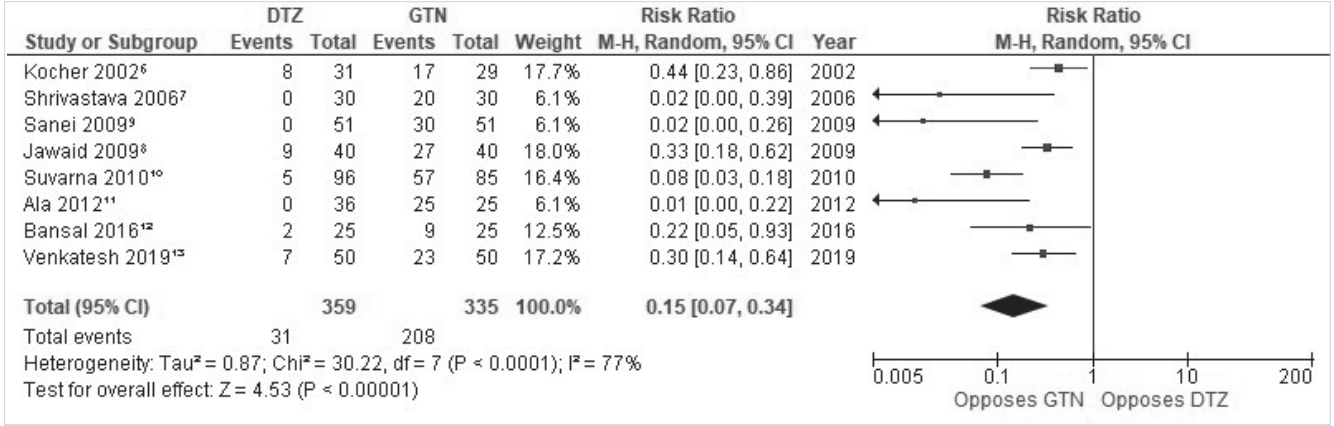

Figure 3. Forrest plot demonstrating rates of headache in patients with CAF treated with DTZ and GTN.

rates of headache in those treated with GTN was significantly worse, 208/335 (62.1%) (p< 0.0001) (Figure 3).

Four RCTs reviewed late recurrence rates (>12 weeks) of CAF following completion of treatment. Recurrence rates were higher in the group treated by GTN compared to DTZ, 23/123 (18.7%) vs 13/143 (9.1%) respectively (p= 0.04) (Figure 4).

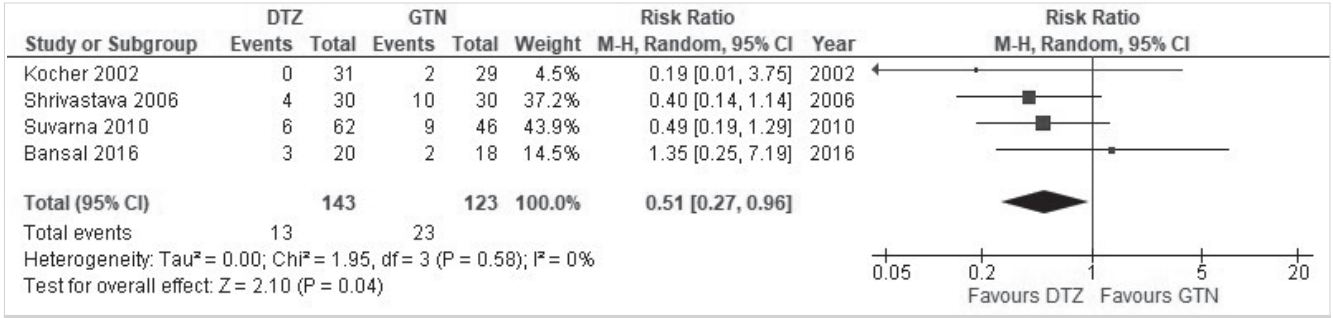

Figure 4. Forrest plot demonstrating rates of late recurrence in patients with CAF treated with DTZ and GTN.

DISCUSSION

Due to the risk of fecal incontinence and the financial cost of operative management, there has been a shift from operative intervention for the treatment of CAF to non-operative treatment modalities. Surgery is now typically reserved for treatment resistant CAF (15). Moreover, systemic therapy for CAF is poorly tolerated due to side effects (2,16). For this reason topical therapies, with low side effect profiles, have been assessed.

Nine RCTs published since 2000 have been identified which compared topical DTZ and GTN. This meta-analysis has demonstrated comparable healing rates with DTZ (73.1%) when compared to GTN (69.5%). However, recurrence rates were twice as high in the GTN group. Moreover, rates of headache were significantly higher in the GTN cohort. Furthermore, Ala et al. have demonstrated faster symptom resolution with DTZ when compared to GTN (12). All of these reasons point towards the use of DTZ as first line therapy for the topical management of CAF. This report validates previously published reviews which have also demonstrated favorable outcomes with topical DTZ rather than GTN (17,18).

Importantly, the NHS drug tariff for DTZ is less than that for GTN. The tariff for DTZ cream is £17.59 (DTZ 2% cream 30 g), and DTZ ointment is even less, £13.44 (DTZ 2% ointment 30 g). 0.4% GTN ointment (Rectogesic 30 g) is significantly more expensive and costs £39.30 (19). This should be considered as another reason for considering DTZ as first line therapy.

Limitations

This meta-analysis has reviewed all randomized controlled trials reviewing DTZ and GTN for CAF. All publications used very similar treatment regimens (Table 1); however, not all publications reported a standard definition for CAF, this may be one of the reasons for the slight variation in reported results across studies.

In addition, RCTs included in the present analysis used either 0.5% or 0.2% GTN. All 8 RCTs that compared rates of headache demonstrated favorable outcomes in the DTZ group. Therefore, we believe that even the lower dose preparation is less likely to be tolerated when compared to DTZ. It is, however, possible that this dose variability may have impacted upon other outcomes in the present analysis, such as recurrence or healing. Nevertheless, two previously published RCTs have failed to demonstrate that increasing concentrations of GTN affect healing rates in CAF (20,21).

Despite all of the trials included in this study being RCTs, there remains significant risk of bias (Table 1). Only 3 of the studies reported if the assessors or patients were blinded; and we must therefore assume that the rest were not, therefore there is significant risk of observer bias in these trials. Two also failed to report their randomization methods, which again questions their validity. Furthermore, only 2 publications report their funding sources.

CONCLUSION

This meta-analysis has identified comparable healing rates for DTZ and GTN. However, DTZ results in fewer headaches and fewer late recurrences. DTZ should therefore be considered as first line non-operative treatment for chronic anal fissure.

Ethics Committee Approval: Ethical approval for this research was not required owing to it being a meta-analysis of previously published (and approved) RCTs.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - E.J.N., V.K.; Design - E.J.N., V.K.; Supervision - E.J.N., V.K.; Resource - E.J.N., V.K.; Data Collection and/or Processing - E.J.N., V.K.; Analysis and Interpretation - E.J.N., V.K.; Literature Review - E.J.N., V.K.; Writing Manuscript - E.J.N., V.K.; Critical Reviews - E.J.N., V.K.

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

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ORİJİNAL ÇALIŞMA-ÖZET
Turk J Surg 2020; 36 (4): 347-352

Kronik anal fissür tedavisinde topikal diltiazem ve gliseril-trinitrat: Randomize kontrollü çalışmaların meta-analizi

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ÖZET

Giriş ve Amaç: Kronik anal fissürün cerrahi tedavisi kalıcı fekal enkontinansa neden olabilir. Topikal tedavilerde ciddi komplikasyon riski daha düşüktür ve bu tedaviler cerrahi müdahaleden daha ucuzdur. Literatürde topikal ajanlarla iyileşme ve uyum oranları değişiklik göstermektedir. Bu çalışmanın amacı, topikal diltiazem (DTZ) ve topikal gliseril-trinitrat (GTN) ile tedavi edilen hastalarda iyileşme oranlarını, baş ağrısı vakaları ve kronik anal fissür nüks oranlarını birinci basamak non-operatif tedaviler kapsamında karşılaştırmaktır.

Gereç ve Yöntem: Ocak 2000'den beri yayımlanan, kronik anal fissür tedavisi için topikal DTZ ve GTN'yi karşılaştıran randomize kontrollü çalışmalar (Randomized Controlled Trials) tespit edilerek karşılaştırılmıştır. Karşılaştırma noktaları iyileşme oranları, tedaviye bağlı baş ağrısı ve geç nüks etme (> 12 hafta) olarak belirlenmiştir. Sonuçları karşılaştırmak için bir randomize meta-analiz modeli kullanılmıştır.

Bulgular: Tüm çalışmalarda %2 DTZ ve %0,2 veya %0,5 GTN kullanılmıştır ve tedavi 6-12 hafta boyunca günde iki kez uygulanmıştır. Dokuz çalışmanın topikal DTZ (n= 379) ve GTN (n= 351) ile iyileşme oranları karşılaştırıldığında, iki grup arasında fark olmadığı görülmüştür (RR 1,04 [0,93-1,16], p= 0,48). Baş ağrısı vakalarının incelendiği 8 çalışmada, DTZ'nin daha iyi tolere edildiği görülmüştür (RR 0,15 [0,07-0,34], p< 0,00001). Geç nüksetme oranlarının karşılaştırıldığı 4 çalışmada, DTZ'nin daha iyi olduğu tespit edilmiştir (RR 0,51 [0,27-0,96], p= 0,04).

Sonuç: Her ne kadar Topikal DTZ ve GTN arasında iyileşme oranları arasında bir fark olmasa da baş ağrısı ve geç nüksetme değişkenlerinde DTZ'nin daha iyi olduğu görülmüştür. Bu nedenle DTZ, kronik anal fissür için birinci basamak non-operatif tedavi olarak düşünülmelidir.

Anahtar Kelimeler: Kronik anal fissür, topikal tedavi, diltiazem, gliseril trinitrat

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ORIGINAL ARTICLE
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Single incision laparoscopic abdominal surgeries: case series of 155 various procedures, an observational cohort study

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ABSTRACT

Objective: Over the last decade, surgeons have started to think of the ways in which to further reduce the trauma of surgery and improve cosmesis. Consequently, many surgeons have yielded to single incision laparoscopic surgeries (SILS) in order to maximize operative and postoperative outcomes. This study aimed to highlight the feasibility and challenges of different procedures by presenting our data about different fields of abdominal SILS practices with long term follow-up.

Material and Methods: We retrospectively analysed an observational cohort of 155 patients who underwent surgery for different indications using the SILS technique.

Results: Of the 155 SILS procedures: 75 (48.4%) were cholecystectomies; 22 (14.2%) were splenectomies; 17 (11%) were hernia repairs; 11 (7.1%) were appendectomies; 8 (5.2%) were partial colon resections; 8 (5.2%) were adrenalectomies; 6 (3.8%) were distal pancreatectomy & splenectomies; 3 (1.9%) were subtotal gastrectomies; 3 (1.9%) were partial liver resections; and 2 (1.3%) were Nissen fundoplications. Ten (6.5%) early and 3 (1.9%) late postoperative complications were detected. No mortality or late morbidity (> 30 days) was detected due to SILS procedures.

Conclusion: SILS is a feasible technique in experienced hands for specific procedures. Meticulous patient selection is also important for good cosmetic results and outcomes.

Keywords: Appendectomy, cholecystectomy, laparoscopic surgery, laparoscopy, single incision, splenectomy

INTRODUCTION

Starting in the nineteenth century (the golden era), surgery began to evolve from radical surgical procedures to minimally invasive procedures. K. Semm described the first laparoscopic appendectomy in 1983 (1-3), and it was followed by the first laparoscopic cholecystectomy in 1985 (4). These procedures are currently the gold standard approaches since they provide better cosmetic results; less postoperative pain; shorter hospital stay; and faster recovery. In addition, laparoscopy has also been a standard in various different surgeries such as: colorectal surgery; splenic surgery; urinary surgery; and lung surgery. In the last decade, surgeons have started to suggest different approaches to further reduce the trauma of surgery using natural orifices (invisible scars) and improve cosmesis (5). However, that was not feasible due to the lack of the instrumental and technological innovations until recent years. Therefore, many surgeons in this field turned their attention to single incision laparoscopic surgeries (SILS), which is a principal first-step for natural orifice surgery (NOS). The ulterior motive of effort was further maximizing cosmetic results; the operative and postoperative outcomes; and patient comfort. In this observational cohort study, it was aimed to present our SILS series in different fields of abdominal surgical practice with long term follow-up and to highlight the feasibility of different procedures.

MATERIAL and METHODS

We retrospectively evaluated an observational cohort of 155 patients who underwent SILS between January 2009 and December 2012 in our clinic for different diagnoses. Demographic data, perioperative data (indications for surgery, sur-

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gery type, blood loss, conversion to open or conventional laparoscopic surgery) and postoperative data (early postoperative complication, late postoperative complication and length of hospital stays) were all prospectively recorded in a chart specifically designed for SILS cases. Patients' exclusion criteria for SILS procedure were previous abdominal surgery, patients with an ASA grade IV and V classification, patients with a contraindication for laparoscopic surgery depending on the procedure (i.e., oversized spleens, perforated appendicitis), and age>70.

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. The study was approved by the local ethical committee of the home institution.

All procedures were performed by the same surgeon who is an expert in laparoscopic surgery over 10 years and specifically in SILS surgery for 5 years. The surgeon performs around 250-300 laparoscopic surgeries (both CL and SILS) a year with different indications.

All patients who underwent splenectomy were vaccinated with Pneumovax 23 (Merck & Co., Inc., Whitehouse Station, New Jersey, United States) two weeks prior to surgery, and a prophylactic antibiotic was administered (1g intravenous ampicillin-sulbactam) before surgery. An intravenous contrast enhanced abdominal multislice computed tomography scan was performed to measure the pre-operative splenic dimensions and to search for susceptible accessory spleens. Adrenalectomy candidates were discussed in a multidisciplinary meeting by the surgeons and the endocrinologists prior to surgery. All surgical procedures, other than retroperitoneal adrenalectomies, were carried out with access through the umbilicus using the SILS port and articulated devices specifically designed for SILS surgery. Conversion was defined as either conversion to conventional laparoscopy (CL) or open surgery. Early postoperative complication was defined as a possible minor or major complication that occurred until the end of the postoperative day two (within 48 hours after surgery). Late postoperative complication was defined as any possible minor or major complication developing between postoperative day three and day thirty. Late complication was defined as any possible minor or major complication developing after postoperative day thirty.

Statistical Analysis

Categorical and continuous variables were summarized using descriptive statistics like mean and median, range, frequency, and percentage. Statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS) version 24 (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp., United States).

RESULTS

Of the 155 SILS procedures: 75 (48.4%) were cholecystectomy; 22 (14.2%) were splenectomy; 17 (11%) were hernia repair; 11 (7.1%) were appendectomy; 8 (5.2%) were partial colon resection; 8 (5.2%) were adrenalectomy; 6 (3.8%) were distal pancreatectomy & splenectomy; 3 (1.9%) were subtotal gastrectomy; 3 (1.9%) were partial liver resection; and 2 (1.3%) were Nissen fundoplication. The demographic and surgical data of the patients is presented in the table. Operative blood loss was negligible (less than 20 mL) in cholecystectomy; hernia repair; appendectomy; partial colon resection; and Nissen fundoplication group. There was only one conversion to laparotomy in the splenectomy group due to splenic artery haemorrhage which resulted from a malfunctioning vascular stapler. We reasoned that this was because of the thick fat pad around the splenic hilum where the stapler was applied. The patient was administered two units of erythrocyte suspension. A total of 10 (6.5%) early postoperative complications were detected. Only one was a severe complication that was detected in a patient with immune thrombocytopenic purpura who underwent splenectomy. During the first twenty-four hours, the patient was hypotensive, tachycardic, and a rapid decline was detected in the haemoglobin and haematocrit levels. The patient was re-operated on under laparotomy and resultant bleeding due to iatrogenic parenchymal lacerations was put under control. One patient with a cystic stump leak after cholecystectomy was managed conservatively with drainage. No major late postoperative complications were detected; however, port site hernias were detected in 3 (1.9%) patients. Low-level drain amylase elevation occurred in 6 of our patients, of whom 3 were in the pancreatectomy group. These patients were observed by following the daily drain level and the drain amylase level. All surgical drains were removed within two weeks when pancreatic drain level was detected below 50mL and the amylase level was normal. Median follow-up time was 8 years. There was only one mortality and no late morbidity (late incisional hernias, adhesion ileus, re-operation for recurrent disease or any cause related to initial operation).

DISCUSSION

Over the last four decades, surgeons have sought less invasive procedures and been more sensitive regarding human anatomy. Laparoscopic surgery concept which started in the early 1980s also aimed for better cosmesis, less pain, faster postoperative recovery, and less trauma to the patient by achieving similar oncologic and surgical results. Therefore, the current laparoscopic surgical procedures are the gold standard in many surgical fields. The number of less invasive methods has rapidly increased over the last decade. The goal is to achieve surgical procedures which are ultimately scar-free. Early experimental attempts of NOS encountered some limitations and disadvantages (6). The instruments specifically designed for NOS are vital, as the tools used in

Table 1. Demographic, perioperative, and postoperative features of the SILS patients cohort

Age (Median)	Sex (M/F)	Operation Type	Indication	Operation Time (min)	Blood Loss (ml)	Conversion	Early PO Complication	Late PO Complication	LoHS (day)
45 (19-70)	35/40	Cholecystectomy	Gallstones (n= 73)	50.7 ± 14.7 (SD)	0	No	Cystic stump leak (n= 1)	Port site hernia (n=1)	1 ± 0.2 (SD)
			Gallbladder Polyp (n= 2)						
32.5 (18-57)	6/16	Splenectomy	ITP (n= 21)	68.4 ± 29.5 (SD)	80 ± 135.5 (SD)	Yes (n= 1)	LL-DAE (n= 1)	No	2.4 ± 1.3 (SD)
			Wandering Spleen (n= 1)				Arterial haemorrhage (n= 1)		
38 (23-70)	13/4	Hernia Repair	Inguinal Hernia (n= 12)	46.6 ± 15.5 (SD)	0	No	No	No	1
			Umbilical Hernia (n= 3)						
			Incisional Hernia (n= 2)						
33 (19-56)	6/5	Appendectomy	Acute Appendicitis (n= 11)	37.2 ± 9.4 (SD)	0	No	No	Port site hernia (n= 1)	1
50 (39-65)	4/4	Partial Colon Resection	Sigmoid Colon Tumor (n= 6)	93.7 ± 16.9 (SD)	0	No	No	No	6.2 ± 1 (SD)
			Right Colon Tumor (n= 1)						
			Rectosigmoid Tumor (n= 1)						
43.5 (35-55)	3/5	Adrenalectomy	(TP) Conn Syndrome (n= 1)	71.2 ± 15.1 (SD)	36.2 ± 10.6 (SD)	No	LL-DAE (n= 1)	No	4.2 ± 1.7 (SD)
			(TP) Adrenal Carcinoma (n= 1)						
			(RP) Cushing (n= 2)						
			(RP) Non-functional Adenoma (n= 2)						
			(RP) Metastatic Adrenal Carcinoma (n= 1)				Port site infection (n= 1)		
			(RP) Pheochromocytoma (n= 1)						
52.5 (41-60)	3/3	Distal Pancreatectomy & Splenectomy	Insulinoma (n= 2)	298.3 ± 22.3 (SD)	75 ± 18.7 (SD)	No	LL-DAE (n= 3)	No	3.3 ± 1.4 (SD)
			Pancreas Adenocancer (n= 1)						
			Neuroendocrine Tumor (n= 1)						
			Renal Cell Cancer Metastasis (n= 1)				Gastric atonia (n= 1)		
			Pancreas Pseudocyst (n= 1)						
52 (43-58)	2/1	Subtotal Gastrectomy	Gastric Cancer (n= 3)	245 ± 65 (SD)	170 ± 131.1 (SD)	No	LL-DAE (n= 1)	Port site hernia (n= 1)	5.3 ± 0.7 (SD)
49 (44-57)	2/1	Partial Liver Resection	Hemangioma (n= 2)	125 ± 18 (SD)	116.7 ± 76.4 (SD)	No	No	No	3
			Hepatic Adenoma (n= 1)						
49.5 (37-62)	1/1	Nissen Fundoplication	Hiatal Hernia (n= 2)	110 ± 14.1 (SD)	0	No	No	No	1

*Age was presented as median. Operation time (minutes), intraoperative blood loss (millilitres), and length of hospital stay (days) were presented as mean with standard deviations.
M: Male, F: Female, PO: Post-operative, LoHS: Length of Hospital Stay, SD: Standard Deviation, ITP: Immune Thrombocytopenic Purpura, LL-DAE: Low Level Drain Amylase Elevation, TP: Trans-peritoneal, RP: Retro-peritoneal.

routine practices have limited range of motion inside the abdomen. Contamination and viscerotomy closure are other major concerns. Therefore, surgeons have stepped back and started to perform surgeries using another less invasive method; SILS.

Single incision laparoscopic surgery was proven to be as feasible as CL surgeries in many different fields of surgical practice (7-17). The most significant advantages of SILS are better cosmesis, less pain, and faster recovery (7,9,12). Our series of SILS cases also present shorter hospital stays especially for the major abdominal surgeries such as splenectomies, colon resections, pancreatico-splenectomies, subtotal gastrectomies, and partial liver resections.

SILS appendectomies are the practice-procedures of single incision surgeries. The learning curve is fast, easy, and beneficial when considering engaging with more complex procedures. In a meta-analysis that included 1.489 patients from eleven randomized controlled trials comparing SILS appendectomy with CL appendectomy (13), the authors suggest that SILS patients have significantly shorter hospital stay (p= 0.003) and return to activity faster (p= 0.002). However, they experienced a longer operating time (p< 0.0001) and a higher rate of conversion (p< 0.00001). There were no differences in visual analogue pain scores, overall complication rates, and cosmesis. Only one late postoperative complication of a port site hernia from umbilical access was detected in our series of 11 SILS appendectomies.

Cholecystectomies are one of the most frequently performed procedures using the SILS method. A clinical comparative study of SILS and CL cholecystectomies in Turkey and Spain (9) has shown that the rates of satisfaction and aesthetic results are significantly higher for SILS patients with other similar perioperative outcomes. This study has stressed that conversion to CL surgery should be performed when there are doubts over safety. Haueter R. et al. conducted a literature search for randomized controlled trials comparing SILS and CL cholecystectomies including thirty-seven studies with 3,051 patients (11). The meta-analysis revealed that body image scores, cosmesis scores and wound satisfaction scores were more favourable for SILS at all time points (short-term, mid-term, long-term). Postoperative pain was lower at the twelfth hour (p= 0.007.) Duration of surgery was longer for SILS (mean difference 13.56 min: p< 0.001) and SILS required more additional ports (odds ratio 6.78: p< 0.001). But most of all, incisional hernia rate was higher after SILS (4% for SILS and 1.1% for CL; OR 2.50, p= 0.03.) We only have one (1.3%) port site hernia in seventy-five SILS cholecystectomies which is a comparable rate with CL procedures. Meticulous anatomical closure is probably the most important fact at this point. Studies showed that bile duct injury rate was 0.7%, and 0.5% for SILS and CL techniques respectively. Although no bile duct injury was detected, we found a low-level cystic stump leak in one patient on postoperative day two, and the patient was followed up conservatively. Serous drainage was detected on postoperative day seven, and the drain was thus removed. The possible cause of cystic stump leak may be the oedema and the elevation of the intraductal biliary fluid pressure caused by surgical trauma around the biliary tract after cystic duct.

Barbaros et al. have reported the first SILS splenectomy (18). Since then, we have conducted twenty-one splenectomies. Indication for surgery was the immune thrombocytopenic purpura for all patients other than one patient with wandering spleen syndrome. It should be kept in mind that the procedure is ideal for normal- to mid-sized spleens, and not suitable for haematological malignancies. Barbaros et al. (8) have compared the outcomes of the single port and three port laparoscopic splenectomies in another study. Visual analogue pain scores were better ($p < 0.05$); however, surgery time was longer (112 ± 14 minutes for SILS vs. 71 ± 18 minutes for CL; $p < 0.05$) for the SILS group (8).

Hernia repair using SILS is also feasible. However, it provides no additional advantage in comparison with the CL procedure. Shanshan Luo et al. showed in their meta-analysis that SILS approach had similar outcomes with significantly longer operative time (14).

We performed eight partial colon resections using SILS port with no early or late complications. Six were for a sigmoid colon tumor, one for a right colon tumor, and one was for a rectosigmoid tumor. Recently, three meta-analyses presenting outcomes of SILS compared to CL surgery for colorectal disease have highlighted the same results (15-17) SILS cases had significantly shorter hospital stay with comparable outcomes to CL in terms of operating time, conversion rate, re-operation rate, postoperative complications, and mortality. Furthermore, pathological and oncological parameters such as the average dissected lymph node and resection margins were similar (15-16). There was no recurrence or mortality during the median follow-up of 8-years.

Adrenalectomy is also another field of SILS procedure. Although the adrenal gland is a small organ, it is located in the retroperitoneal region neighboured by important anatomical structures, which makes this procedure notably challenging. Retraction of the surrounding organs such as the liver is often challenging. We performed two transperitoneal, and six retroperitoneal adrenalectomies due to different indications. Only two minor complications were detected, one of which was a port site hernia and the other was a low-level of elevation in drain amylase which was hence normalized one week after surgery.

Advanced procedures like pancreatico-splenectomy for pancreatic cancer, gastrectomy for gastric cancer, and partial liver resection for hepatic cancer can be carried out using SILS (10). Besides, surgeons must consider their own knowledge and ex-

pertise in these fields even with open or CL techniques prior to performing these procedures with the SILS technique. Yet, it is still not preferred due a plethora of challenges which include oncological safety concerns. We found no major complications in patients who underwent pancreatico-splenectomy (n= 6), subtotal gastrectomy (n= 3), and partial liver resection (n= 3) surgeries. There was only 1 mortality in a subtotal gastrectomy patient. The patient admitted to clinic with pleural effusion, respiratory distress and stage IV disease in his 4-year follow-up. Careful patient selection is of central importance.

Cosmesis is the most commonly highlighted advantage of SILS. We previously reported better cosmesis and higher rates of satisfaction with SILS technique compared with CL (9). Evans L. and Manley K. have reported that SILS demonstrates a clear advantage in terms of the cosmetic outcome when compared with CL in their systematic review and meta-analysis (12). They have also emphasized that this is a quantifiable advantage as all studies included in the meta-analysis used a specific type of cosmetic/satisfaction scores. There are debates on cosmesis specifically for procedures like colon or liver resections when we need to enlarge or make another incision in order to retrieve the specimen. So, there is uncertainty as to whether it is a SILS procedure anymore. In addition, the evaluation of long-term cosmesis showed that it is significantly affected by port-site hernias. Significantly higher rates of port-site hernias have been reported (odds ratio 2.5; p= 0.03) in SILS compared with CL procedures (11,12,15).

As reported in earlier studies, SILS presents technical difficulties when performing the procedure (7,8,10). Namely because this procedure is performed via a single port that all instruments supported by the same fulcrum, the clashing of instruments inside or outside the surgical area is of concern. Even though there are different angled or articulated instruments on the market to solve this problem, it is still a hassle as many of the meta-analyses reported significantly longer operative times with SILS. Another factor that affects the learning curve of the surgeons is adapting to the use of their cross-hand for the procedures. Right hand for left side, and vice-versa for manipulation, dissection, and traction. More practice is the key at this point. Another concern is the visual area of the surgical field. It is less of an issue for small field surgeries like appendectomies or cholecystectomies. However, things get more complex in colon resections (especially wide segmental resections for transverse colon) because these procedures need to be performed in different regions of the intra-abdominal cavity. The traction of the surrounding tissues and organs is also a concern. Different methods such as suturing the tissue to abdominal wall, puppeting with the sutures, metallic or magnetic clips to fix the structures to the abdominal wall, and rubber bands to hang the structures for different procedures were described so far (7-10). All these methods work for a variety of surgeries. Therefore, in any case, surgeons must be creative to solve the traction problem intraoperatively depending on the circumstances.

There are some limitations of our study. First, this is an observational cohort study with different varieties of surgical procedures. It should be better to compare one kind SILS operation with CL. However, we published our SILS cholecystectomy series and SIL splenectomy series compared with our CL series before. Therefore, we wished to present different procedures of SILS cases in order to present feasibility of different operations. Second, it would be better to present data of our case after December 2012. As we plan to do this study as an observational cohort between 2009 and 2012, we did not collect all data of the SILS cases after December 2012. So, we think that it would be better to present long term follow-up of these patients.

CONCLUSION

In conclusion, SILS is a feasible technique in experienced hands. Careful patient selection is also an important factor for comparable cosmetic results and outcomes. Even though SILS is still not widely accepted, it will be used in multifarious fields in the near future. It should be considered as a leap forward towards NOS with the utilization of innovative devices and technologies in laparoscopic surgery.

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ORİJİNAL ÇALIŞMA-ÖZET
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Tek delikten laparoskopik karın cerrahisi: farklı prosedürleri içeren 155 vakalık gözlemsel kohort serisi

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ÖZET

Giriş ve Amaç: Son 10 yılda cerrahlar, cerrahi travmayı azaltmanın ve kozmetiği arttırmanın yolunu düşünmeye başladılar. Neticede birçok cerrah perioperatif sonuçları iyileştirmek için tek delikten laparoskopik cerrahiye (TDLC) yöneldi. Bu çalışmada farklı tekniklerle yaptığımız TDLC batın ameliyatlarının uygulanabilirliği, uzun dönem takiplerini, tekniğin avantajları ve zorluklarını sunmayı amaçladık.

Gereç ve Yöntem: Ocak 2009-Aralık 2012 arasında farklı endikasyonlarla ameliyat edilen 155 TDLC batın ameliyatının verileri prospektif olarak toplandı ve retrospektif incelendi.

Bulgular: Hastaların ortalama takip süresi 8 yıldı. 155 TDLC'nin 75'i (%48,4) kolesistektomi, 22'si (%14,2) splenektomi, 17'si (%11) herni tamiri, 11'i (%7,1) apendektomi, 8'i (%5,2) parsiyel kolon rezeksiyonu, 8'i (%5,2) adrenalektomi, 6'sı (%3,8) distal pankreatektomi ve splenektomi, 3'ü (%1,9) subtotal gastrektomi, 3'ü (%1,9) parsiyel karaciğer rezeksiyonu ve 2'si (%1,3%) Nissen fundoplikasyonuydu. 10 (%6,5) erken ve 3 (%1,9) geç postoperatif komplikasyon görüldü. Ameliyata bağlı mortalite görülmedi.

Sonuç: TDLC deneyimli ellerde uygulanabilir bir yöntemdir. Dikkatli hasta seçimi iyi cerrahi ve kozmetik sonuçlar için çok önemlidir.

Anahtar Kelimeler: Apendektomi, kolesistektomi, laparoskopik cerrahi, laparoskopi, tek delik, splenektomi

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Outcomes of pain management in chronic pancreatitis: experience from a tertiary care hospital in India

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ABSTRACT

Objective: Chronic pancreatitis (CP) is a progressive inflammatory disorder that leads to irreversible destruction of exocrine and endocrine parenchyma. Little is known about outcomes of CP in the Indian subcontinent. We aim to study the treatment outcomes of CP in terms of pain severity in a tertiary hospital in India.

Material and Methods: This is a prospective cohort study of 75 patients diagnosed with CP. Data regarding patient demographics, symptoms, and imaging findings were recorded. Pain severity was recorded objectively by the visual analogue scale (VAS). Cambridge score was calculated, and patients were classified into mild, moderate and severe categories. Patients were treated appropriately, and pain scores were monitored at 3 months and 6 months after initial visit.

Results: Alcohol was the most common etiology (54%) followed by idiopathic/unknown causes (34%). Cambridge score or morphology on imaging did not affect pain severity ($p>0.05$). History of smoking and larger duct diameter decreased the effectiveness of treatment in reducing pain while higher post prandial sugar levels increased effectiveness ($p<0.05$). Pain relief did not differ between the treatment groups including analgesics, endoscopic or surgery ($p>0.05$).

Conclusion: CP presents earlier in the Indian population and represents a unique population with a greater proportion of idiopathic cases than western countries. Rather than pancreatic morphology or Cambridge score alone, a combination of morphology, pain severity and functional status can be utilized for formulating an individualized treatment plan. Present treatment strategies prove effective in treatment of CP.

Keywords: Chronic pancreatitis, pain, Cambridge score, treatment

INTRODUCTION

Chronic pancreatitis (CP) is a progressive inflammatory disorder of the pancreas that leads to irreversible destruction of both exocrine and endocrine parenchyma (1). It commonly affects middle aged individuals with a slightly higher incidence in males (2). There is an increasing trend in the incidence and prevalence of CP over the last decade worldwide (3-5). At present, the US healthcare system spends over 150 million dollars toward the management of CP (6). Nearly 2/3rd of the patients have history of heavy alcohol consumption (150-175 g/d) for over a decade (7). Other common etiological factors include smoking, auto-immune, and idiopathic causes (2). Abdominal pain is the most common presenting symptom of CP which is caused due a multitude of reasons including recurrent or chronic inflammation of parenchyma, localized complications, or neurological mechanisms with nervous system changes (8). It is crucial to treat CP as soon as possible, because repeated episodes of inflammation can cause irreversible damage and make treatment less effective (9). Pain can severely reduce the quality of life and increase healthcare costs considerably in affected patients (8). Due to these reasons, it is considered as a significant health concern worldwide (10). There are many treatment strategies described in the literature for CP, and all involve a multidisciplinary team comprising surgical, gastroenterological, and radiologic team. Most therapeutic strategies are targeted towards alleviating pain. The initial mainstay of treatment includes symptomatic medication, most commonly NSAIDs (non-steroidal anti-inflammatory drugs) (8). Patients who do not respond to medication are subjected to either endoscopic or surgical treatment (11,12).

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Compared to a prevalence of 10/100,000 in western countries, India, as well as other Asian countries, has an increased prevalence of CP (13). Recently, CP in India has shown a change, with an increased incidence in older patients, an increase in incidence of milder disease, increasing longevity, and increasing association with alcoholism and smoking (14). In addition to the etiologies described above, tropical pancreatitis is unique to Asian countries which comprises 3-5% of the patients (15). These patients have a more aggressive course, affecting younger patients and commonly resulting in pancreatic cancer (16). At present, there is sparse literature concerned about the treatment outcomes of patients with CP in the Indian subcontinent. Herein, we aimed to describe the clinical course and treatment outcomes of patients diagnosed with CP at a tertiary hospital in India. We primarily focused on pain severity as the main outcome before and after treatment. We also studied the factors affecting pain severity before and after treatment.

MATERIAL and METHODS

This is a prospective cohort study conducted at the Department of General Surgery, King Edward Memorial Hospital, Mumbai, India a tertiary care hospital. Patients diagnosed with chronic pancreatitis were enrolled between June 2016 and January 2017. A written informed consent was obtained from all eligible patients. The study was approved by the institutional ethics committee (IEC number: EC/76/2016) and all procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional) and with the Helsinki Declaration of 1975, as revised in 2000. This study was structured utilizing the STROBE (strengthening of observational studies in epidemiology) guidelines (17).

The study included patients with CP diagnosed by contrast-enhanced computer tomography (CECT abdomen) and/ or magnetic resonance cholangiopancreatography (MRCP) and relevant clinical symptoms including severe abdominal pain, malabsorption, and/or features of diabetes mellitus. Patients who had underlying pancreatic malignancy were excluded. Details in regard to history were recorded including age, sex, presenting symptoms, duration of symptoms, number of prior admissions for similar symptoms, history of alcohol intake and smoking, gall bladder disease, and history of diabetes mellitus. Pain severity was objectively measured using the visual analog scale (VAS) and graded from 0-10 (18). Anorexia or malnutrition was defined as a body mass index (BMI) of < 18. CECT-abdomen was used to record the following findings including pancreatic atrophy, calcification, features of acute pancreatitis, portal vein thrombosis, and ascites. Basic laboratory investigations carried out included fasting blood sugar, post-prandial blood sugar, serum lipase, aspartate transaminase (AST), alanine transaminase (ALT), and fecal fat test.

Patients were treated with either symptomatic management only, or endoscopic and/or surgery and symptomatic treatment post intervention, depending on the treating surgeon's assessment of symptoms and morphological findings on CECT, MRI, or EUS (endoscopic ultrasound). Symptomatic treatment included NSAIDs with or without opioid analgesics for pain, pancreatic enzyme supplementation and diet modification as the standard of care. Patients were instructed to attend follow-up visits at monthly intervals, irrespective of their symptoms. Patients who did not respond symptomatically to conservative therapy was offered either endoscopic or surgical treatment depending on disease morphology. Response to therapy was measured by pain severity (VAS score) which was measured at 3 and 6 months after initial visit.

Statistical Analysis

Continuous data including age, duration of symptoms, number of admissions, fasting and post-prandial blood sugar, serum lipase, ALT and AST, pancreatic duct diameter, and pain score was described as means with range. Categorical variables including gender, presenting complaints, history of alcohol intake, smoking, gall stone disease, Cambridge score, CECT findings, and treatment provided was described as frequency with percentages.

Initial univariate linear regression was used to study the clinical factors associated with pain severity (VAS) at first visit. Predictor variables were selected based on their unadjusted log-rank statistical significance ($p <= 0.250$) on the univariate analyses for all the potential confounders (e.g. age, duration of symptoms, number of prior admission, etc.) separately, for the initial multivariate model. A backward step-wise elimination procedure, based on the Akaike Information Criteria and statistical significance ($p <= 0.05$), was then used to achieve the final multivariate model presented.

Wilcoxon rank-sum test was used to study the change in pain severity from first visit to 3- and 6-months post initial visit. Mixed effects multiple linear regression model fit by REML (Restricted maximum likelihood) was used to account for the correlation due to multiple visits by same patient: pre-treatment, 3-months and 6-months clinic visit. Univariate and multivariate analyses were performed as described previously. All statistical analysis was performed using StataSE software (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC) and statistical significance was defined as $p< 0.05$.

RESULTS

A total of 100 patients were enrolled in the study. Out of the 100 patients, 25 were excluded with the following reasons: 8 patients did not receive treatment at our hospital and 17 patients were lost to follow-up. Seventy-five patients underwent treatment and were followed until 6 months and were included into the study. The study flow diagram is shown in Figure 1.

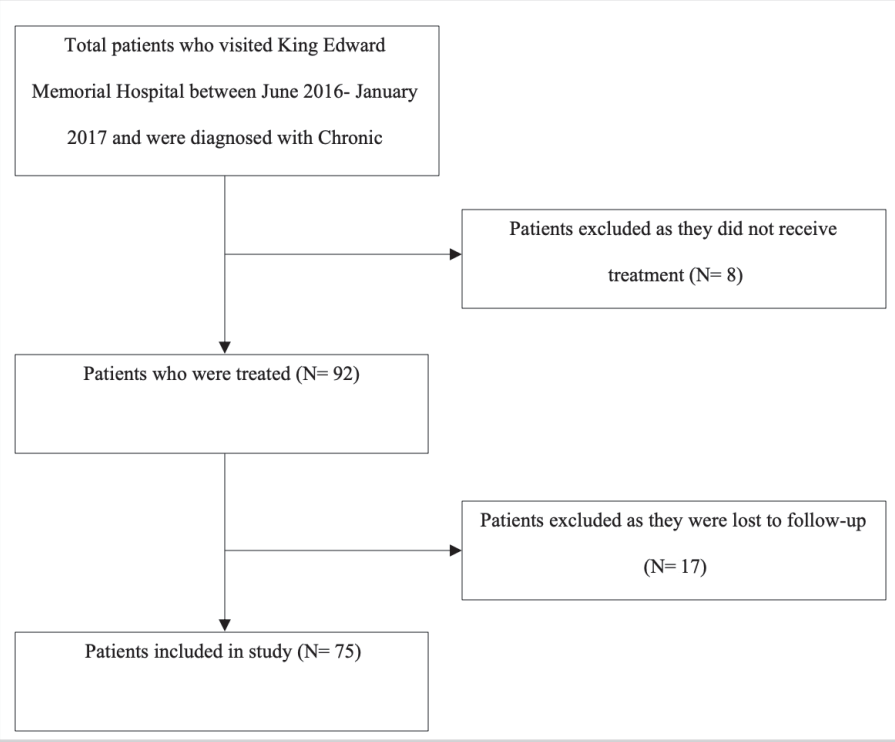

Figure 1. Study flow diagram.

Baseline demographics of the 75 patients are shown in Table 1. Thirty-four patients (45%) were alcoholic and 13 patients (17%) were smokers. Four patients (5%) had prior history of gall stone disease. Patients had a mean symptom duration of 2.5 years (range: 3 months – 15 years). Mean number of admissions prior to initial visit was 3 (range 1-3).

Eight patients (11%) underwent endoscopic intervention including pancreatic duct stenting and/or ESWL (extracorporeal shortwave lithotripsy). Sixteen patients (21%) underwent surgery including lateral pancreaticoduodenectomy (14/75, 19%) and distal pancreatectomy (2/75, 3%). Indication for surgery was intractable pain (16/16, 100%). Of this, 14 patients had a dilated pancreatic duct size greater than 6 mm, and two patients had a pseudocyst. (Table 1). Out of the patients who underwent surgery, 1 (6%) patient developed post-operative pancreatic fistula. The surgical drain was kept in-situ for a month post-surgery until the drain output reduced, and then it was removed. One patient developed superficial wound infection (6%), which healed with adequate wound dressing. Median length of stay for all patients was 7 days. All patients were discharged home with adequate chest physiotherapy exercises. None of the patients required any re-operation. There was no 30- and 90- day readmission or mortality.

At first visit, malabsorption was associated with a greater pain severity (Regression coefficient: 2.3, p= 0.015). Prior history of diabetes mellitus (Regression coefficient: -1.3, p= 0.03) and higher post-prandial blood sugar (Regression coefficient: -0.008, p= 0.03) was associated with less pain. (Table 2). On multivariate analysis, malabsorption (Regression coefficient: 4.5, p= 0.008) continued to be associated with greater pain and history of diabetes mellitus (Regression coefficient: -2.3, p= 0.01), and high postprandial blood sugar (Regression coefficient: -0.1, p= 0.04) was associated with less pain (Table 2).

Mean pain score at initial visit was 6.24 (range: 0-10) and at 3 months follow-up, it was 0.94 (range: 0-6) and at 6 months follow up, it was 0.78 (range: 0-6). There was a significant change in pain severity at 3- and 6- month follow-up compared to pre-treatment pain scores (p< 0.0001, p< 0.0001). Pain severity remained similar at 3- and 6-months (p= 0.863) (Table 3). The change in pain severity along with 95% confidence interval is shown in Figure 2.

Patients were likely to have decreased response to treatment if they had a history of smoking (Regression coefficient: 1.03, p= 0.01), greater pancreatic duct diameter (Regression coefficient: -0.09, p= 0.01) or postal vein thrombosis (Regression coefficient: -0.81, p= 0.04) on univariate analysis (Table 4). On multivariate analysis, history of smoking (Regression coefficient: 1.04, p= 0.004) and duct diameter (Regression coefficient: 0.087, p= 0.01) continued to decrease response to treatment. Portal vein thrombosis did not show a significant relationship on multivariate analysis. Higher post prandial blood sugar increased pain response to treatment (Regression coefficient: -0.005, p= 0.049) on multivariate analysis.

Table 1. Patient characteristics

Parameter	Mean with range or n (%)
Sample size (n)	75
Age (years)	35 (17-67)
Gender	
Male	56 (75%)
Female	19 (25%)
Presenting symptoms	
Abdominal pain	75 (100%)
Vomiting	60 (80%)
Anorexia/ malnutrition (BMI<18)	37 (49%)
Malabsorption	70 (93%)
Duration of symptoms	2.5 years (3 months-15 years)
Number of prior admissions	3 (1-12)
H/o alcohol consumption	39 (52%)
H/o smoking	13 (17%)
H/o Gall stone disease	4 (5%)
H/o Diabetes Mellitus	12 (16%)
Lab parameters	
Fasting blood sugar (mg/dl)	82 (44-188)
Post-prandial blood sugar (mg/dl)	136 (88-305)
Serum lipase (U/L)	375 (12-4300)
Fecal fat test	19 (25%)
AST (U/L)	36 (13-124)
ALT (U/L)	33 (10-124)
Cambridge score	
Mild	10 (13%)
Moderate	15 (20%)
Severe	50 (67%)
CECT findings	
Atrophy	49 (65%)
Calcification	59 (79%)
Portal venous thrombosis	16 (21%)
Ascites	3 (4%)
Acute pancreatitis	12 (16%)
Pancreatic duct diameter	
< 6mm	42 (56%)
> 6mm	33 (44%)
Conservative treatment	
NSAIDs	74 (99%)
Opioid analgesics	29 (39%)
Enzyme supplementation	75 (100%)
10.000U	44 (59%)
25000U	29 (39%)
40.000U	1 (1%)
Endoscopic intervention	8 (11%)
Surgery	16 (21%)
Lateral pancreaticojejunostomy	14 (19%)
Distal pancreatectomy	2 (3%)

AST: aspartate transaminase, ALT: alanine transaminase.

Pain reduction did not depend on whether patients received medical, endoscopic (Regression coefficient: -0.42, p= 0.34), or surgery (Regression coefficient: 0.37, p= 0.16) treatment. However, among those that received only conservative therapy, patients who received opioids in addition to NSAIDs had better pain relief (Regression coefficient: -0.44, p= 0.001). However, on multivariate analysis, opioid addition to NSADIS lost statistical significance (Regression coefficient: 0.38, p= 0.26).

DISCUSSION

Our study adds to the current literature on the outcomes of patients with CP in the Indian subcontinent. Mean age of presentation was 35 years, which is much earlier compared to the worldwide median age of 51-58 years (19,20). According to two other studies conducted in India, the age of the patients with CP was between 15 and 38 years, and 33 years respectively (21,22). The earlier course of this disease could be due to the higher proportion of idiopathic or tropical variant of CP that is common in the Indian subcontinent, which presents with large pancreatic calculi that affect young malnourished individuals and have a more aggressive course (13,16,21). In our study, though 45%, 14%, and 5% of patients had alcoholic, smoking or gall-bladder disease as potential etiologies, the remaining 34% did not have any discernable etiology and could be considered idiopathic. According to Yadav et al, alcohol is the most common risk factor, but recently alcohol use and smoking levels have been relatively stable or have declined (23). Several other studies have similarly shown an increased prevalence of idiopathic CP in the Indian population (15,21,22). This study showed a greater male-to-female ratio of 3:1 which is similar to previous studies (24).

Abdominal pain was the most common presenting symptom of CP. Malnutrition was present in 49% of the patients. In a similar study conducted in Ireland, 78% of the patients had pain, 15% had vomiting, and 35% had malnutrition (25). Patients were symptomatic for around 2-3 years before they visited our hospital, which is also similar to other studies (26). Most of them were not appropriately managed prior to initial visit even though they had prior in-patient admissions for similar symptoms. This signifies misdiagnosis or delayed diagnosis of CP. Nearly 2/3rd of CP patients had a severe Cambridge score. This could imply that mild/early CP is under-diagnosed among patients of CP. A panel of pancreatic function tests along with clinical features and morphological changes among patients suspected of CP may be required for the diagnosis of early CP (27).

Pancreatic calcification was present in 79% of the patients which is higher than the expected 30-50% (28). In previous studies conducted in India, there was 95-97% calcification and there was no difference between different etiologies (22). Pancreatic atrophy was present in 65% of the patients, which signifies the severity and chronicity of the disease. Large duct disease was present in 44% of patients, which signifies advanced disease (26).

Even though pain is said to have quicker onset in younger patients (<35 years) (29), our study showed that pain severity did

Table 2. Factors affecting VAS pain score at diagnosis

Parameter	Univariate regression coefficient	p	Multivariate regression coefficient	p
Age	-0.02	0.31		
Gender	-0.67	0.22		
Presenting symptoms				
Vomiting	-0.63	0.29		
Anorexia or malnutrition (BMI<18)	0.32	0.50		
Malabsorption	2.3	**0.015**	**4.5**	**0.008**
Duration of symptoms	1	0.99		
Number of prior admissions	0.13	0.18		
H/o alcohol consumption	-0.07	0.88		
H/o smoking	0.82	0.19		
H/o Gall stone disease	-1.3	0.22		
H/o Diabetes Mellitus	-1.3	**0.03**	**-2.3**	**0.01**
Lab parameters				
Fasting blood sugar (mg/dl)	-0.01	0.07		
Post-prandial blood sugar (mg/dl)	-0.008	**0.03**	**-0.1**	**0.04**
Serum lipase (U/L)	-0.0001	0.71		
Fecal fat test	-0.22	0.67		
AST (U/L)	0.009	0.38		
ALT (U/L)	-0.01	0.35		
Cambridge score	0.09	0.65		
CECT findings				
Atrophy	-0.69	0.173		
Calcification	-0.04	0.94		
Portal venous thrombosis	1.04	0.07		
Ascites	0.79	0.52		
Acute pancreatitis	-1.07	0.101		
Pancreatic duct diameter	0.08	0.13		

Table 3. Pain score change at first visit, 3 and 6 months

Parameter	Mean with range	p
Pain score at first visit (P_{T0})	6.24 (0-10)	
Pain score at 3 months (P_{T3})	0.94 (0-6)	
Pain score at 6 months (P_{T6})	0.78 (0-6)	
Pain score at 3 months compared to diagnosis (P_{T3} - P_{T0})		**< 0.0001**
Pain score at 6 months compared to diagnosis (P_{T6} - P_{T0})		**< 0.0001**
Pain score at 6 months compared to 3 months (P_{T6} - P_{T3})		0.863

not vary based on age. Patients having malabsorption had more pain severity at diagnosis. This could be explained by the severity of pancreatic exocrine insufficiency causing fat indigestion and pain due to repeated inflammation of the parenchyma and surrounding nerve tissue (8). Presence of diabetes mellitus resulted in decreased pain severity at diagnosis. Diabetes causes neuropathy and could explain the alteration in pain severity in the sample. Cambridge score or morphology including atrophy, calcification, duct diameter on imaging was not associated with pain severity of CP. Similarly, Frøkjær and Wilcox et al. were not able to demonstrate a significant relationship between pain and morphological changes like fibrosis and atrophy in pancreatic parenchyma (30,31). Studies have compared duct diameter with pain severity with similar results (32).

There was significant improvement in pain severity at 3- and 6-months after initiating treatment. There was no relapse in

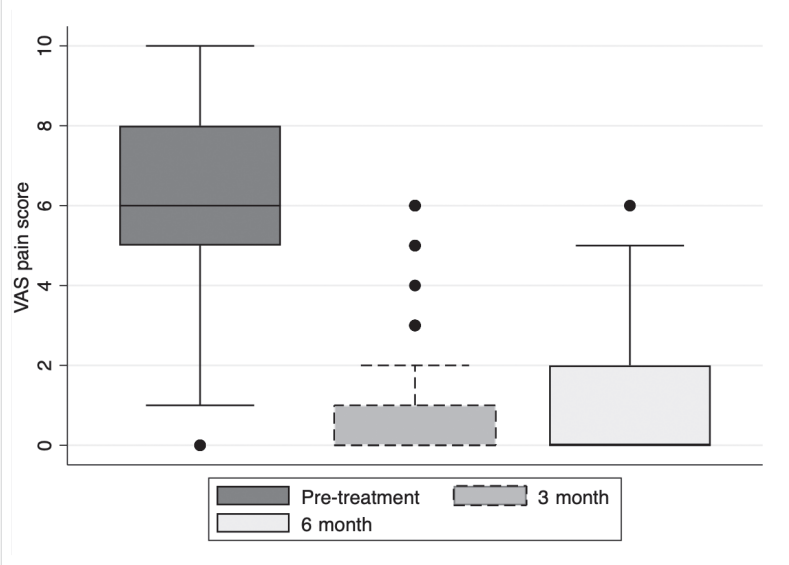

Figure 2. Distribution of pain severity among CP patients at the initial visit, 3 and 6 months follow-up.

Table 4. Factors affecting change in pain severity up to 6 months

Parameter	Univariate Regression Coefficient	p	Multivariate Regression Coefficient	p
Age	-0.0005	0.96		
Gender	-0.45	0.24		
Symptoms				
Vomiting	-0.48	0.25		
Anorexia or malnutrition	0.61	0.06		
Malabsorption	1.2	0.05		
H/o prior admission	0.05	0.46		
H/o alcohol intake	0.06	0.86		
H/o smoking	1.03	**0.01**	1.04	**0.004**
H/o gall stone disease	-1.01	0.20		
H/o Diabetes Mellitus	-0.85	0.98		
Period of symptoms	0.001			
Lab values				
Serum lipase	0.0001	0.66		
Fecal fat test	-2.79	0.45	1.164	**0.027**
AST	0.009	0.20		
ALT	-0.008	0.41		
Fasting blood sugar	-0.008	0.13		
Post prandial blood sugar	-0.005	0.05	-0.005	**0.049**
CECT findings				
Atrophy	-0.09	0.80		
Pancreatic calcification	-0.03	0.93		
Pancreatic duct diameter	0.09	**0.01**	0.087	**0.01**
Acute pancreatitis	-0.36	0.44		
Portal venous thrombosis	0.81	**0.04**		
Ascites	0.11	0.90		
Cambridge score	0.05	0.73		
Treatment type				
Analgesics	Reference			
Endoscopic intervention	-0.42	0.34	-0.25	0.69
Surgery	0.37	0.16	0.27	0.39
Medical management				
NSAID	Reference			
NSAID & opioids	-0.44	**0.001**	0.38	0.26

symptoms at 6 months compared to 3 months. History of smoking was likely to decrease response to therapy for patients undergoing treatment. Smoking is considered to aggravate chronic pain according to previous studies, which could explain the heightened pain compared to others (33). Increased pancreatic duct diameter morphology caused more pain post-treatment compared to others. Large duct disease signifies advanced disease and could be the reason for this finding (16). Higher post prandial blood sugar increased response to treatment. This could be explained by the underlying neuropathy that affects pain experienced by the patients.

Our results showed that pain response was comparable among different treatment groups; either medical, endoscopic or surgery. For those patients only receiving analgesics, addition of opioids to NSAIDs increased pain relief. This is in accordance with the WHO principles of the "pain relief ladder". This is based on the principle of the serial addition of drugs of increasing analgesic potency, until pain relief is established (34). However, on performing multivariate analysis, opioid addition did not increase pain relief.

In our study, all patients initially received analgesics, and those that did not respond to medication at first follow-up visit (1-month) were selected for intervention. Endoscopic and various surgical drainage procedures are available for patients with intractable pain who do not respond to conservative management. The cause of pain is still an area of controversy but various mechanisms have been described, such as large duct disease due to proximal structuring of duct or main duct stones causing pancreatic ductal hypertension, defective blood supply to the pancreas due to fibrosis, or chronic inflammation of adjacent nerve plexus (35). In our study, 95% of the patients who needed surgery had evidence of large duct disease. This is indicative of intraductal hypertension causing atrophy and ischemia of the gland, which can aggravate pain. Drainage procedure like lateral pancreatojejunostomy, or decompression like distal pancreatectomy helps relieve this pressure within the ductal system and cause pain relief. The similar could be said for endoscopic stenting or lithotripsy which attempt to relieve ductal obstruction (35). Various studies have shown that surgery is associated with better pain relief compared to endoscopic procedures. In addition, patients usually undergo multiple endoscopic procedures compared to surgery (36). We believe that the similar pain response to the three treatment modalities in our study may be due to the fact that treatments were overlapping among few patients. However, at the same time our results show that a uniform strategy of management can result in consistent pain relief among all patients.

Some of the limitations of the study include a small sample size and lack of long-term follow up beyond 6 months. Further follow-up of patients could help study relapse and long-term outcomes of treatment strategies. Our only outcome was pain, and we did not look at other outcomes like malnutrition, quality of life or functional status. The study was only observational and not controlled which could decrease the validity of results. Larger clinical trials may be performed in the Indian population to compare treatment strategies and long-term outcomes of such patients.

To conclude, CP presents earlier in the Indian population and is commonly under-diagnosed. This represents a unique population with a greater proportion of idiopathic cases than western countries. Abdominal pain and malnutrition are the most debilitating features of CP and must be primarily focused in such patients. Rather than pancreatic morphology on imaging or Cambridge score alone, a combination of morphology, pain severity and functional status of the pancreas may be utilized for formulating an individualized treatment plan. The current treatment strategies employed are effective in controlling pain in patients with CP.

Ethics Committee Approval: The approval for this study was obtained from Seth GS Medical College and KEM Hospital Ethics Committee (Decision No: 562/16, Date: 20.06.2016).

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ORİJİNAL ÇALIŞMA-ÖZET
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Kronik panktreatitte ağrı yönetiminin sonuçları: Hindistan'da üçüncü basamak bir hastane deneyimi

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ÖZET

Giriş ve Amaç: Kronik pankreatit (KP), geri dönüşü olmayan ekzokrin ve endokrin parenkim tahribatına yol açan progresif bir enflamatuvar hastalıktır. Hindistan bölgesinde KP sonuçları çok az bilinmektedir. Bu çalışmanın amacı, Hindistan'da üçüncü basamak bir hastanede ağrı ciddiyeti açısından KP tedavisinin sonuçlarını araştırmaktı.

Gereç ve Yöntem: Bu çalışma, KP tanısı almış 75 hastayı içeren prospektif kohort çalışmadır. Hastaların demografik özellikleri, semptomları ve görüntüleme bulguları kaydedildi. Ağrı ciddiyeti, vizüel analog skala (VAS) kullanılarak objektif bir şekilde kaydedildi. Cambridge skoru hesaplandı ve hastalar hafif, orta ve şiddetli kategorilerine ayrıldı. Hastalar buna uygun olarak tedavi edildi ve ağrı skorları başvuru sonrası 3. ve 6. aylarda tekrar değerlendirildi.

Bulgular: En yaygın etiyoloji alkoldü (54%) ve bunu idiyopatik/bilinmeyen sebepler takip etti (%34). Cambridge skoru ve görüntülemede morfoloji ağrı, şiddetine etki etmedi ($p > 0,05$). Sigara içme ve daha büyük kanal çapı, tedavinin ağrıyı azaltma etkinliğini düşürürken daha yüksek postprandial şeker etkinliğin derecesini arttırdı ($p < 0,05$). Analjezikler, endoskopik veya cerrahi tedavi gruplarında ağrı giderme açısından bir fark saptanmadı ($p > 0,05$).

Sonuç: Hindistan nüfusunda KP daha erken görülmekle birlikte Batı ülkelerine kıyasla idiyopatik olguların oranı daha yüksektir. Pankreatik morfoloji ya da sadece Cambridge skorundan ziyade kişiselleştirilmiş bir tedavi planı oluşturma açıısndan morfoloji, ağrı şiddeti ve işlevsel durum kombinasyonu kullanılabilir. Mevcut tedavi stratejileri KP tedavisinde etkilidir.

Anahtar Kelimeler: Kronik pankreatit, ağrı, Cambridge skoru, tedavi

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ORIGINAL ARTICLE
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The effect of pre-procedure anxiety on sedative requirements for sedation during upper gastrointestinal endoscopy

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ABSTRACT

Objective: Sedation for upper gastrointestinal endoscopy, commonly used for diagnosis and treatment of gastrointestinal diseases, has been increasing widespread. Sedative agent requirements during sedation or anesthesia can be affected by many factors such as age and sex. In the present study, we aimed to evaluate the effects of pre-procedural anxiety levels on sedative requirements during upper gastrointestinal endoscopy.

Material and Methods: 300 patients between the ages of 18-70 years were studied. Baseline anxiety levels were measured before the procedure using Spielberger's State-Trait Anxiety Inventory (STAI) form X1. Propofol was administered to have BIS values between 65-85 during sedation. Doses of propofol, total procedure time, satisfaction of the patients and endoscopists and BIS values were recorded.

Results: Pre-procedural anxiety was 44 (40-48 [20-70]). We found significant correlations between pre-procedure anxiety and the usage of propofol (mg, mg/kg, mg/kg/dk) at BIS values between 65-85, [respectively, ($p= 0.451$, $p< 0.001$), ($p= 0.455$, $p< 0.001$), ($p= 0.428$, $p< 0.001$)]. No correlation was found between pre-procedure anxiety and procedural or sedation complications (respectively $p= 0.111$, $p= 0.424$ and $p= 0.408$, $p= 0.363$). We found significant negative correlations between pre-procedure anxiety and the satisfaction of the patients/endoscopist [respectively, ($p= -0.477$, $p< 0.001$), ($p= -0.495$, $p< 0.001$)].

Conclusion: Based on the results of this study, we suggest that there is a significant association between the pre-procedural anxiety levels and use of sedative drugs in patients undergoing upper gastrointestinal endoscopy.

Keywords: Sedation, anxiety, upper gastrointestinal endoscopy

INTRODUCTION

Upper gastrointestinal (GI) endoscopy is commonly used in the diagnosis and treatment of upper GI disorders. Although the technique is considered to be safe and well tolerated, it is associated with significant patient discomfort and intolerance if sedation is not performed.

Although sedation performed during upper GI endoscopy increases the costs of the procedure, it is obvious that sedation increases the success rate and makes this procedure more tolerable (1,2). Sedation does not only increase patient satisfaction and tolerance to the procedure, but also makes the patient more persuadable for a repeat procedure (3). Despite this, upper GI endoscopy is still accepted as an invasive procedure with the potential for discomfort, embarrassment, and disappointment related to unexpected findings. As a result, the presence of anxiety in these patients is not surprising. However, the relationship between the severity of anxiety and individual characteristics of the patients remains unclear. Patient characteristics such as age and sex are suggested to influence the level of anxiety (4,5). It is also likely that the level of anxiety affects both the patient and the endoscopists before and after the procedure, as well as the anesthesiologists who deliver sedation. Previous studies have evaluated the relationship between the level of anxiety and the requirement for sedative or anesthetic agents in patients undergoing sedation or anesthesia; however, there is no consensus on this subject (6-9).

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The present study aimed to evaluate the relationship between the level of pre-procedural anxiety in patients undergoing upper GI endoscopy and the requirement of sedative agents, patient satisfaction, and complications.

MATERIAL and METHODS

After obtaining institutional ethics committee approval, informed written consent was obtained from all patients. It has been registered with the Australian New Zealand Clinical Trial Registry (ACTRN12615000369527). Three hundred patients, between the ages of 18-70 years with an ASA physical status I and II, scheduled to undergo planned upper GI endoscopy were studied. Patients with a history of any upper GI surgery, a history of a psychiatric disease, insufficient gastric preparation, a predicted difficult airway or allergy to propofol were excluded from the present study. In addition, non-elective patients were excluded from the study. Fasting periods were in accordance with ASA guidelines. All patients were instructed to upper GI endoscopy preparation is applied as a standard in the endoscopy unit.

Baseline anxiety levels were measured before the procedure while patients waited in the reception area. Each patient was asked to complete Spielberger's State-Trait Anxiety Inventory (STAI) form X (10). STAI measures both state and trait anxiety. STAI-X is subdivided into two different scales, STAI-X1 and -X2, used to evaluate state anxiety and trait anxiety, respectively. STAI-X1 (State Anxiety) contains 20 items based on a 4-point Likert scale and asks the respondent how they feel "right now". The total score may range from 20 to 80, with higher scores representing more severe anxiety (11). STAI has no established categories, but a cutoff score of 40 has been used to identify patients with high/very high anxiety. The validity and reliability of the Turkish versions of these instruments have been conducted (12,13). Immediately after the admission into the reception area, the patients were asked to fill out the STAI-X1 questionnaire. Data were collected by an anaesthetist (MSU) who was blind to the sedation procedures.

A 20-gauge IV catheter was inserted in the right forearm before the patient arrived in the operating room. 0.9 % saline infusion was used to keep the IV line open. BIS monitoring (BIS Monitor, Aspect 2000TM XP, USA) was applied to all patients in addition to routine monitoring (consisting of a pulse oximeter, 3-lead ECG and a non-invasive blood pressure cuff). After baseline measurements (haemodynamic profiles and BIS values) were obtained, the patient was placed in the left lateral position. Supplemental oxygen (4 l.min-1) was administered through a nasal cannula. One milligram of midazolam was administered intravenously. Next, an initial intravenous dose of propofol (0.3-0.5 mg/kg of body weight) was administered, followed by repeated 10-20 mg doses so as to BIS values 65-85 or the patient expressed discomfort. Other medications, including analgesics, were not used in the present study. All sedation procedures were practiced by an anaesthetist (MS) who was blind to pre-procedure anxiety scores. If there were any symptoms of respiratory depression or airway obstruction, a simple jaw thrust or chin lift maneuvers was performed.

All endoscopies, also blinded to the anxiety scores, were performed by one of the three endoscopists, each of whom had performed more than 300 endoscopies before participating in the study. Endoscopist satisfaction were evaluated immediately after procedure using a 10-cm visual analog scale. Patient satisfaction was measured using a 10-cm visual analog scale in patients with a modified Aldrete score higher than or equal to 9.

Doses of propofol, total procedure time, satisfaction of patients and endoscopists and BIS values (Basal, after initial dose of propofol, at the second minute of the procedure, at the end of procedure) were recorded. Complications associated with the procedure (Abdominal distension, abdominal pain, nausea and vomiting) were also analyzed. We also recorded any complications associated with sedation (i.e. oxygen saturation < 90%, blood pressure < 90/50 mm Hg, heart rate < 50 bpm).

Statistical Analysis

The main association that we examined was between the usage of propofol at BIS values between 65-85 and pre-procedure anxiety. Based on our prior study's (with 50 patients) data, we presumed a correlation coefficient of 0.19. We needed at least 283 patients to set a significance level of 0.05 (two-sided) and achieve a power of 0.90. To compensate for possible dropouts, we enrolled 300 patients.

Statistical analyses were performed with SPSS 15.0 software (SPSS Institute, Chicago, IL, USA). The association between the usage of propofol at BIS values between 65-85 and pre-procedure anxiety was assessed by Spearman correlation coefficient. Categorical variables were analyzed using the chi-square test and were given as numbers. A P-value less than 0.05 was considered statistically significant.

RESULTS

All patients successfully completed STAI-X1. Patients' demographics, basal anxiety scores and hemodynamic profiles are summarized in Table 1. Pre-procedural anxiety was 44 (40-48 [20-70]). The duration of procedure was 4 (3-5 [3-7]) min.

Sedation results (BIS values and propofol doses) for 300 patients are summarized in Table 2. Propofol doses of the 300 patients were 70 (60-80 [20-150]) mg, 1.00 (0.75-1.29 [0.25-2.44]) mg/kg and 0.24 (0.16-0.33 [0.04-0.81]) mg/kg/min.

We found significant correlations between pre-procedure anxiety and the usage of propofol (mg) at BIS values between 65-85, p= 0.451 and p< 0.001 (Figure 1a). We found significant correlations between pre-procedure anxiety and the usage of propofol (mg/kg) at BIS values between 65-85, p= 0.455 and p< 0.001

Table 1. Patients' demographics, basal anxiety scores and haemodynamic profiles for 300 patients. Values are as median (IQR[range]), number or number (proportion)

Age (year)	40 [28-52 (18-70)]
Gender (Male:Female)	201 (67%) : 99 (33%)
Height (cm)	165 [160-170 (142-195)]
Weight (cm)	70 [60-80 (40-102)]
Body mass index (kg/m^2)	25.6 [22.0-28.7 (15.4-39.5)]
ASA physical status (I/II)	200 (66.7 %): 100 (33.3%)
Pre-procedurel anxiety	44 [40-48 (20-70)]
Basal HR (beats/min)	87 [78-96 (55-119)]
Basal SBP (mmHg)	120 [111-130 (92-149)]
Basal DBP (mmHg)	69 [60-74 (45-97)]
Basal MBP (mmHg)	84 [77-91 (59-112)]
Duration of procedure (min)	4 [3-5 (3-7)]

HR:Heart rate, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MBP: Mean blood pressure.

Table 2. Sedation results (BIS values and propofol doses). Values are median (IQR [range])

BIS-basal	96 [94-97 (92-99)]
BIS-beginning of procedure	69 [66-72 (61-78)]
BIS-at the second min of procedure	72 [70-75 (67-80)]
BIS-end of procedure	76 [75-79 (70-85)]
Propofol doses	
mg/kg	1.00 [0.75-1.29 (0.25-2.44)]
mg/kg/dk	0.24 [0.16-0.33 (0.04-0.81)]
mg (total dose)	70 [60-80 (20-150)]

(Figure 1b). We found significant correlations between pre-procedure anxiety and the usage of propofol (mg) at BIS values between 65-85, p= 0.428 and p< 0.001 (Figure 1c).

Procedural, sedation complications and satisfaction of the patients and endoscopists are summarized in Table 3. While procedural complications occurred in 54 (18%) patients, sedation complications occurred in only 7 (2.3%) patients. No correlation was found between pre-procedure anxiety and the procedural or sedation complications (respectively p= 0.111, p= 0.424 and p= 0.408, p= 0.363). Pre-procedure anxiety and satisfaction of the patients are shown in Figure 2a. We found significant negative correlations between pre-procedure anxiety and satisfaction of the patients, p= -0.477 and p< 0.001. Pre-procedure anxiety and satisfaction of the endoscopist are shown in Figure 2b. We found significant negative correlations between pre-procedure anxiety and satisfaction of thr endoscopist, p= -0.495 and p< 0.001. During the study period, no patient required assisted ventilation or intubation.

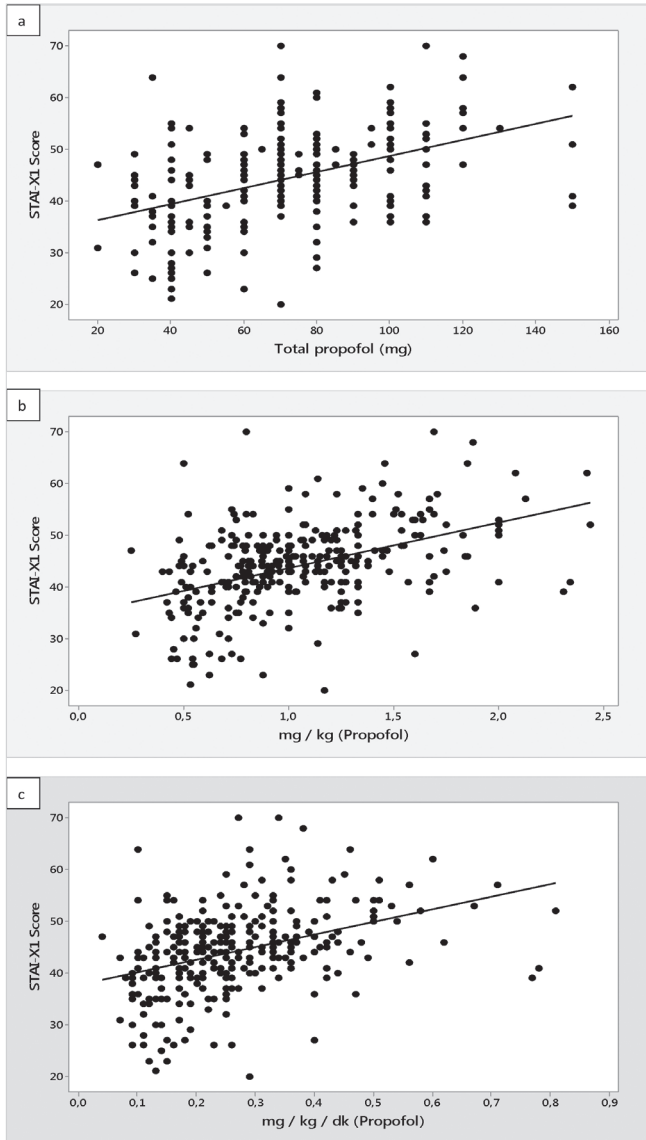

Figure 1. A. Spearman's correlation coefficient between pre-procedure anxiety and the usage of propofol (mg) at BIS values between 65-85. **B.** Spearman's correlation coefficient between pre-procedure anxiety and the usage of propofol (mg/kg) at BIS values between 65-85. **C.** Spearman's correlation coefficient between pre-procedure anxiety and the usage of propofol (mg/kg/min) at BIS values between 65-85.

DISCUSSION

The findings of the present study suggest a relationship between a high level of pre-procedural anxiety and an increased propofol requirement for sedation during upper GI endoscopy. In addition, a negative correlation was suggested between a high level of pro-procedural anxiety in patients undergoing upper GI endoscopy and the satisfaction of both the patient and the endoscopist.

Table 3. Complications and satisfaction of patients and endoscopists. Values are number (proportion) or median (IQR [range])

Procedural complications	54 (18%)
Abdominal distension	33 (11%)
Abdominal pain	20 (6.7%)
Nausea and vomiting	1 (0.3%)
Sedation complications	
Blood pressure< 90/50 mmHg	6 (2%)
Heart rate < 50 bpm	1 (0.3%)
Satisfaction of patients	8 [8-10 (5-10)]
Satisfaction of endoscopist	9 [9-10 (5-10)]
mg (total dose)	70 [60-80 (20-150)]

Anxiety is defined as an unpleasant emotional status or circumstance. A state of anxiety is defined as subjective feelings of apprehension, nervousness, worry, and tension when subjected to an anxiety provoking stimulus, whereas trait anxiety is defined as individual differences in the disposition of responses to stressful situations. Various studies have suggested a strong correlation between state and trait anxiety (8,13,14). Previous studies that evaluated the relationship between anxiety and the requirement for anesthetic agent have found different results.

In a study that evaluated the effects of preoperative anxiety on intraoperative anesthetic agent requirements in 57 women that underwent laparoscopic tubal ligation under propofol-based anesthesia reported that state anxiety had no effect on propofol doses, either during the induction or maintenance of anesthesia (7). However, a high level of trait anxiety was shown to be associated with propofol doses both during the induction and maintenance of anesthesia. As in the present study, bispectral index monitoring was used to maintain the hypnotic component of the anesthetic state in that study. Different from this study, however, the present study found a significant correlation between the level of state anxiety and propofol doses. We consider that the difference can be explained by the inclusion of only female patients and the relatively small sample size in the present study.

Another study that evaluated the effects of preoperative anxiety on the requirement for propofol and sevoflurane reported that higher propofol doses were required to achieve light (BIS: 85) and moderate (BIS: 75) levels of sedation in patients that had high anxiety scores (both state and trait) (15). However, the propofol doses required to achieve deeper sedation were only related to the level of trait anxiety.

One study did not report a significant relationship between the level of state and trait anxiety and propofol doses used to induce sedation in 25 patients who underwent extraction of the third molar tooth under intravenous sedation (8). This study also performed BIS to monitor the continuity of sedation. In addition, patients with a high level of anxiety were more predisposed to have unwanted body movements under sedation, and it is obvious that these movements would decrease the satisfaction of the operators.

In a study of patients undergoing sedation for oocyte retrieval, which is another discomforting procedure for the patients, as is upper GI endoscopy, propofol doses used to achieve sedation were compared between patients with high versus low levels of anxiety, and the doses of propofol were significantly higher in patients with higher levels of anxiety (9). Different from our study, this study used target-controlled infusion (TCI) system, but they did not use BIS to monitor the level of sedation. In addition, they used a simpler scale to assess anxiety levels in their patients as compared to the STAI anxiety scale used in the present study.

The studies mentioned so far are thought to have differences due to their limitations such as small sample size and methodological differences like a lack of BIS monitoring for the depth of sedation (7-9,14).

Using a superior methodological approach compared to these studies, one study that evaluated the effects of pre-procedural

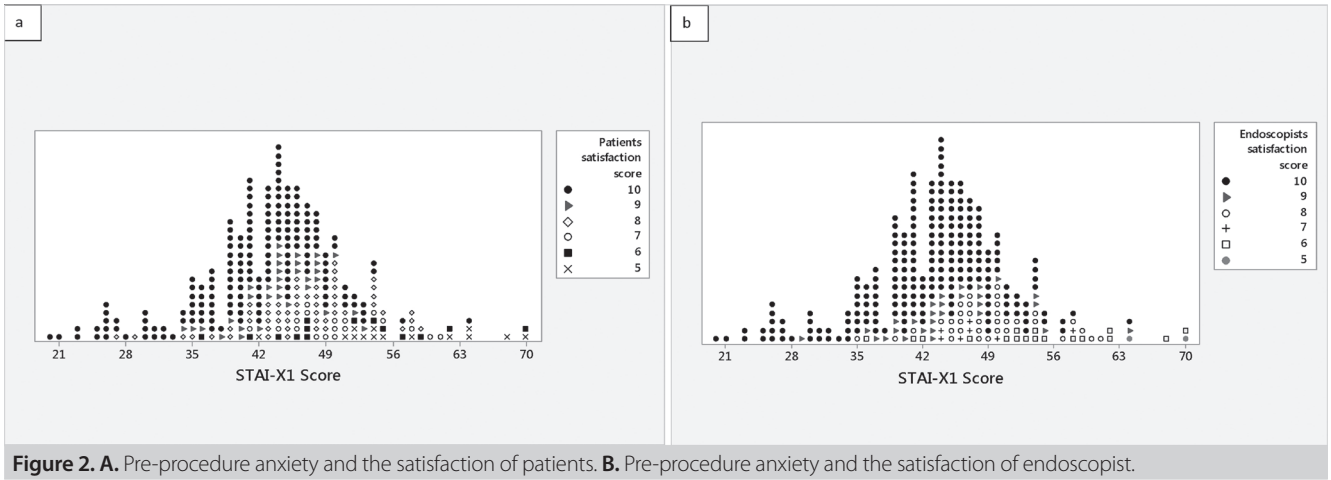

Figure 2. A. Pre-procedure anxiety and the satisfaction of patients. **B.** Pre-procedure anxiety and the satisfaction of endoscopist.

anxiety on the use of sedative agents in patients undergoing colonoscopy under sedation reported that pre-procedural anxiety had no effect on sedative agent requirement (6). Similar to our findings, this study did not report a significant correlation between pre-procedural anxiety and procedural complications. However, the present study showed a decrease in patient satisfaction with increasing levels of anxiety, while their study did not report a relationship between the level of anxiety and patient satisfaction. Different from our study, they used the TCI system and not BIS monitoring. In addition, they used an anxiety assessment scale, which is different than that which was used in the present study.

BIS monitoring is used to optimize the depth of sedation at the beginning and maintenance of sedation in the endoscopic procedure, and this method increases patient satisfaction and tolerability of the procedure and also decreases patient awareness during the procedure (16,17). Furthermore, BIS can be a useful monitoring guide for the titration of propofol by physicians who are competent in airway and hemodynamic management (18). Along with these advantages, BIS monitoring during sedation has been shown to reduce propofol doses (19).

Study Limitations

The present study has some limitations. First, we did not use the TCI system to monitor propofol use and consumption. Second, BIS scores could have been maintained within a narrower range instead of 65-85 or the patients could have been divided into two groups as 65-75 and 75-80 points. Third, we could have also evaluated trait anxiety and not only state anxiety. However, we do not expect a significant influence on the results due to the fact that previous studies reported a strong correlation between state anxiety and trait anxiety (14-16).

CONCLUSION

In conclusion, we suggest the presence of a significant relationship between high levels of anxiety and the use of sedative agents in patients undergoing upper GI endoscopy. For this reason, pre-procedural anxiety levels of the patients must be taken into consideration while using sedative agents to induce sedation during upper GI endoscopy.

Ethics Committee Approval: The approval for this study was obtained from Necmettin Erbakan University Ethics Committee for Clinical Research with non-Pharmaceutical Products and non-Medical Device (Decision No: 14567952-050/, Date: 28.11.2014).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - M.S., M.U.; Design - M.S.; Supervision - M.S., M.U.; Resource - M.S., M.U.; Materials - M.S., M.U.; Data Collection and/or Processing - M.S., M.U.; Analysis and Interpretation - M.S.; Literature Review - M.S.; Writing Manuscript - M.S., M.U.; Critical Reviews - M.S..

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ORİJİNAL ÇALIŞMA-ÖZET
Turk J Surg 2020; 36 (4): 368-373

Pre-prosedürel anksiyetenin üst gastrointestinal endoskopi sırasında uygulanan sedasyonda sedatif ajan gereksinimi üzerine etkisi

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ÖZET

Giriş ve Amaç: Gastrointestinal hastalıkların tanı ve tedavisinde yaygın olarak kullanılan üst gastrointestinal endoskopide sedasyon yaygınlaşmaktadır. Sedasyon veya anestezi sırasında sedatif ajanların gereksinimleri yaş ve cinsiyet gibi birçok faktör tarafından etkilenebilir. Bu çalışmada, üst gastrointestinal endoskopide işlem öncesi anksiyete düzeylerinin sedatif gereksinimlere olan etkilerini değerlendirmeyi amaçladık.

Gereç ve Yöntem: 18-70 yaş arasındaki 300 hasta çalışmaya alındı. Bazal anksiyete düzeyleri, işlem öncesi Spielberger'in Devlet Sürekli Anksiyete Envanteri (STAI) X1 formunu kullanarak ölçülmüştür. Sedasyon sırasında BID değerleri 65-85 arasında tutuldu. Propofol dozları, toplam işlem süresi, hasta ve endoskopist memnuniyeti ve BIS değerleri kaydedildi.

Bulgular: İşlem öncesi anksiyete 44 idi (40-48 [20-70]). BIS değerleri 65-85 arasında tutulduğunda, işlem öncesi kaygı ile propofol kullanımı (mg, mg/kg, mg/kg/dk) arasında anlamlı korelasyon bulduk [Sırasıyla, (p= 0,451, p< 0,001), (p= 0,455, p< 0,001), (p= 0,428, p< 0,001)]. İşlem öncesi anksiyete ile işlemsel veya sedasyon komplikasyonları arasında korelasyon saptanmadı (Sırasıyla p= 0,111, p= 0,424 ve p= 0,408, p= 0,363). İşlem öncesi kaygı ile hasta/endoskopistin memnuniyeti arasında anlamlı negatif korelasyon bulduk, [Sırasıyla, (p= -0,477, p< 0,001), (p= -0,495, p< 0,001)].

Sonuç: Bu çalışmanın sonuçlarına dayanarak, üst gastrointestinal endoskopi uygulanan hastalarda işlem öncesi anksiyete düzeyleri ile sedatif ajan kullanımı arasında anlamlı bir ilişki olduğunu düşünmekteyiz.

Anahtar Kelimeler: Sedasyon, anksiyete, üst gastrointestinal endoskopi

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ORIGINAL ARTICLE
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The effect of postoperative serratus anterior plane block on postoperative analgesia in patients undergoing breast surgery

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ABSTRACT

Objective: This study aimed to evaluate the effect of serratus anterior plane block (SAP) on postoperative morphine consumption. We aimed to determine the differences between both similar blocks and evaluate the effect of the methods of application of this block on patients' postoperative pain scores and morphine consumption.

Material and Methods: This study is a single-center, prospective and observational study performed with 40 volunteer patients with American Society of Anesthesiologists (ASA) I-III, who were 18-70 years of age, scheduled for breast surgery. A total of 40 patients who underwent general anesthesia were divided into two groups each with 20 patients. While SAP block was applied to the study group, no block was applied to the control group. SAP block was made by injecting a total of 40 ml of 0.25% bupivacaine between 2 muscles after the test dose was injected with saline. All patients were followed up for 12 hours postoperatively with patient-controlled analgesia (PCA) pump. Morphine consumption, visual analogue score (VAS) values and side effects were recorded at the postoperative 1st, 6th and 12th hours.

Results: There was no significant difference between the two groups in terms of hemodynamic parameters and demographic data. Postoperative morphine consumption and postoperative analgesic requirement were significantly lower in the SAP block group ($p< 0.001$). Postoperative VAS values were significantly lower in the SAP block group ($p< 0.001$). No complication was observed related to the block.

Conclusion: It was found that the SAP block reduced morphine consumption, significantly decreased VAS values, and reduced side effects due to opioids postoperatively.

Keywords: Serratus anterior plane block, breast surgery, postoperative pain management

INTRODUCTION

Serratus anterior plane (SAP) block has efficacy including thoracic anterior wall, lateral wall and axilla (1). Female patients with breast surgery were included in this study. Breast cancer in women is often treated surgically. Although the incision line varies according to the type of surgery, it is usually long. It is thought that both postoperative pulmonary complications increase and mobilization of the patients decreases due to the surgical site in the thorax. After surgery, the pain patterns of these patients change, and anesthetists have a lot to do for the treatment of pain.

Postoperative pain is still considered a major problem in surgical clinics though many treatments and drug options have been developed. Although pharmacological treatments have been developed, it is difficult for physicians to control the side effects. In addition to pharmacological treatment, various methods can be applied postoperatively in breast surgery. These techniques include thoracic epidural block, intercostal nerve block, thoracic paravertebral block, pectoral nerve block, SAP block and local infiltration.

Today, postoperative pain management is updated with regional anesthesia techniques. The development of ultrasound and more frequent use of it in clinics leads to the development of new regional anesthesia techniques. The pectoral nerve block and serratus anterior plane block described by Blanco et al. are among these techniques (1,2). Regional anesthesia is defined as blocking the functioning of the nerves in certain parts of the body for a while without causing loss of consciousness and thus eliminating the sense of pain (3).

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The pectoral nerve block and the SAP block aim to decrease the patient's postoperative pain scores (1,2). Patient satisfaction is increased and analgesic consumption is reduced with these techniques.

In this study, the effect of SAP block on postoperative morphine consumption was evaluated. We aimed to determine the effect of differences between both similar blocks and the methods of application of this block on patients' postoperative pain scores and morphine consumption and to find the most effective method.

Regional techniques are generally used as a preemptive method in breast surgeries, but we tried to demonstrate the difference from similar studies by applying SAP block postoperatively. We aimed to reduce postoperative complaints of the patients and the side effects seen in additional analgesic use.

MATERIAL and METHODS

This is a single-center, prospective and observational study that was conducted in University Hospital. The study started after the decision of the Clinical Research Ethics Committee of Cumhuriyet University Faculty of Medicine dated 19.03.2019 and numbered 2019-03/03. This study included 40 volunteer patients aged between 18-70 years, who underwent modified radical mastectomy under elective conditions and who were between the American Society of Anesthesiologists (ASA) I-III and 18-70 years old. The patients were electively evaluated at the preoperative anesthesia outpatient clinic. Patients with diabetes mellitus and neoadjuvant chemotherapy were excluded from the study since their pain sensation could be impaired. Written and verbal consents were obtained in accordance with the Helsinki Declaration for anesthesia applications and research. These consents were taken from all of the patients participating in the study but serratus anterior plane block was performed to twenty of them. So, the patients were blinded. Randomization was based on a computer-generated code that was prepared at a remote site and sealed in opaque, sequentially numbered envelopes. Before the operation, preoperative procedures performed in routine were applied to all patients. Patients fasted 8 hours before the operation and the crystalloid replacement was made as 2 mg/kg/h.

Premedication was performed with midazolam (Zolamid, DEFARMA-Turkey) in a dose of 70 mcg/kg intramuscularly to reduce preoperative anxiety in all patients. Heart rate (HR), electrocardiograms (ECG) in the DII derivation, noninvasive mean arterial blood pressures (MAP) and peripheral oxygen saturation (SpO_2) were followed up before and during surgery.

General anesthesia was applied to all patients as an anesthesia method. Peripheral venous access was provided with 18 gauge. After making necessary measurements and preparations, 1 mcg/kg fentanyl (Fentanyl Citrate® Hospira, USA), 2-3 mg/kg propofol (Propofol®, Fresenius Kabi, Melsungen, Germany) and 0.6 mg/kg rocuronium (Esmeron®, Organon) (Kloosterstraat, Netherlands) were administered intravenously (IV). The patients were ventilated with 100% oxygen for 5 minutes and intubated with an appropriate endotracheal tube. After endotracheal intubation, all patients were given 48% nitrogen oxide, 2% sevoflurane (Sevorane®, Abbott, Chicago, USA) and 50% oxygen for anesthesia maintenance.

Following the completion of the surgical procedure, we divided the patients into two groups regardless of their demographic and surgical features. The patients in the study group were under general anesthesia in supine position at the end of the surgery. The intercostal midaxillary line level was sterilized. Sonovisible needle (Stimuplex ®D 0.71 x 80 mm, 22G, Braun, Germany) was inserted through the skin, subcutaneous and latissimus dorsi muscles, respectively by using ultrasound (US). Between the serratus anterior and latissimus dorsi, the needle was placed in the craniocaudal direction. Aspiration was performed and no blood or air was seen. After 2 mL of saline was injected as the test dose between the two muscle plans, the serratus anterior plan blockage was applied by injecting 0.25% bupivacaine (Buvasin, VEM, Turkey) in a dose of 40 mL. No intervention was applied to the control group.

This randomized, controlled and prospective study is single-centered and the same anesthesiologist made the blocks to all patients, and there is no practitioner difference between the patients who were blocked. All the patients in the study were blinded. Then, a 10 mg/kg dose of paracetamol infusion was sent to all patients before being awakened. The duration of the surgeries in both groups, and additionally, the duration of the block application in the study group was recorded.

All patients were extubated after intravenous administration of Sugammadex (Bridion, Merck Sharp Dohme, New Jersey, USA) at a dose of 4 mg/kg. Patients with an Aldrete score of 9 and above were taken to the recovery unit after anesthesia (PACU). All patients received patient-controlled analgesia (PCA) pump in the recovery unit. Patient-controlled analgesia was prepared with IV morphine to be used in both groups in the postoperative period. PCA was prepared with 0.5 mg concentration in 1 milliliter of morphine hydrochloride (Morphin HCl®, Galen drug). The PCA pump device (CADD-legacy® PCA pump Model 6300-100 ml Cassette, USA) was set as 1 mg bolus, 8 minutes lockout time, 6 pushes in 1-hour dose limit.

The patients were followed up in the surgical service where they were hospitalized. Visual analogue score (VAS) and morphine consumption were recorded at the postoperative 1st, 6th and 12th hours. In addition to analgesic, paracetamol (Parole, Atabay, Turkey) 10 mg/kg IV infusion was given to patients with VAS over 5. The time the analgesic drug was given was recorded. Side effect profiles of the patients related to morphine were recorded as nausea, vomiting and constipation.

Patients with ASA 4 and above, who had infection in the region where the block would be applied, who had coagulopathy, liver and kidney failure, patients that could not cooperate, patients that did not want to be a volunteer, patients who described allergies to the drugs used, and those that had neuropathy were not included into the research.

Statistical Method

Data obtained from this study were analyzed on SPSS (ver: 22.0) statistic program on the computer. When the parametric test assumptions were fulfilled (Kolmogorov-Smirnov), variance analysis in significant repeated measurements of the difference between the two means in independent groups and Bonferroni tests were used. When the parametric test assumptions were not fulfilled, Whitney U test, Friedman test and Wilcoxon test were used. In the evaluation of the data obtained by counting, chi-square test was applied in 2x2 and multi-wells. The error level was taken as 0.05. In this study, when $\alpha = 0.05$ $\beta = 0.10$ $1-\beta = 0.90$, it was decided to add 20 individuals to each group and the power of the test was found to be p= 0.9092.

RESULTS

When the demographic data of the 40 patients included in the study were evaluated, the age, weight, height and ASA classifications of both groups are shown in Table 1. There were 20 patients in both groups. Mean age in the control group was 41.3 ± 15.27 years, and 48.80 ± 15.06 years in the study group, and there was no statistically significant difference between the groups (p>0.05). Arithmetic weight averages of the patients were 74.60 ± 10.75 and 73.50 ± 14.68 in the control and study groups, respectively, and there was no significant difference between the groups (p>0.05). The height averages of both groups were 159.55 ± 3.52 cm and 159.75 ± 3.40 cm in the control and study groups, respectively, and there was no significant difference between the groups (p> 0.05). When the ASA scores of the patients were evaluated, it was found as 2.00 ± 0.79 in the control group, and 2.25 ± 0.64 in the study group, and p= 0.31 between the two groups.

Intraoperative heart rate (HR) of the patients was recorded at basal (0^{th} minute), 30^{th} minute, 1^{st} hour and 2^{nd} hour. Based on these values, no statistically significant difference was found between consecutive and simultaneous measurements in the control and study groups (p> 0.05).

Intraoperative peripheral oxygen saturation (SpO_2) of the patients was recorded at basal (0^{th} minute), 30^{th} minute, 1^{st} hour and 2^{nd} hour. Based on these values, no statistically significant difference was found between consecutive and simultaneous measurements in the control and study groups (p> 0.05).

Intraoperative mean arterial pressure (MAP) of the patients was recorded at basal (0^{th} minute), 30^{th} minute, 1^{st} hour and 2^{nd} hour. There was a significant difference between the groups at the 2^{nd} hour of MAP values. No statistically significant difference was found between other consecutive and simultaneous measurements in the control and study groups (p> 0.05). These MAP values are shown in Table 2.

When the surgery durations of the patients were compared, mean surgery duration was 133.25 ± 40.7 minutes in the control group and 117.25 ± 43.30 minutes in the study group, and there was no statistically significant difference between the two groups (p> 0.05). When the first analgesic application time was compared in both groups, a statistically significant difference was found between the groups (p< 0.05). Mean time of the first analgesic requirement was found to be 1.29 ± 0.78 hours in the control group and 5.50 ± 0.71 hours in the study group (Table 3).

Additional analgesics were performed in 9 patients in the control group and in 2 patients in the study group. While 11 of the 40 patients required additional analgesics, 29 patients did not need additional analgesics. When these data were evaluated, p= 0.013 was found. There was a significant difference between the groups (Table 4).

In the data of the 40 patients evaluated, constipation was observed in 1 patient in the study group and 6 patients in the control group. In addition, nausea was observed in 2 patients in the control group. According to these data, p= 0.028 and there was a statistically significant difference between the groups (Table 5).

When the patients' 1^{st}, 6^{th} and 12^{th} hours of morphine consumption were recorded and evaluated cumulatively, there was a significant difference in both groups (p< 0.05). In the control group, 2.35 ± 0.56 mg of morphine was consumed in the first hour, and

Table 1. Demographic data of the patients

	Control Group (n= 20)		Study Group (n= 20)		
	Mean ± SD	**Minimum-Maximum**	**Mean ± SD**	**Minimum-Maximum**	**p**
Age (year)	41.30 ± 15.27	22-69	48.80 ± 15.06	19-69	0.13
Weight (kg)	74.60 ± 10.75	59-96	73.50 ± 14.68	42-100	0.79
Height (cm)	159.55 ± 3.52	155-166	159.75 ± 3.40	152-165	0.86
ASA	2.00 ± 0.79	1-3	2.25 ± 0.64	1-3	0.31

kg: Kilogram, cm: Centimeter, ASA: American society of anesthesiologists, SD: Standard deviation, n: Number of the patients.

Table 2. Comparison of the intraoperative hemodynamic data

Measurement time	Control Group (n= 20) Mean ± SD	Study Group (n= 20) Mean ± SD	p
HR Basal	81.55 ± 8.89	82.80 ± 9.12	0.663
HR 30. Minute	73.30 ± 7.40	75.80 ± 8.16	0.317
HR 1. Hour	73.10 ± 7.63	73.53 ± 7.60	0.862
HR 2. Hour	74.42 ± 6.79	74.50 ± 7.76	0.979
MAP Basal	94.25 ± 15.75	103.35 ± 14.20	0.072
MAP 30. Minute	86.95 ± 13.98	94.10 ± 12.32	0.094
MAP 1. Hour	84.7 ± 13.58	90.21 ± 13.58	0.285
MAP 2. Hour	83.08 ± 12.26	90.70 ± 7.10	0.207
SpO_2 Basal	95.10 ± 2.75	94.90 ± 2.73	0.774
SpO_2 30. Minute	93.55 ± 1.05	94.05 ± 2.82	0.835
SpO_2 1. Hour	93.3 ± 1.26	94.11 ± 2.02	0.279
SpO_2 2. Hour	92.67 ± 1.37	92.80 ± 2.10	0.859

HR: Heart rate, MAP: Mean arterial pressure, SpO_2: Peripheral oxygen saturation, SD: Standard deviation, n: Number of the patients.

Table 3. Comparison of the patients' mean surgery durations and the first analgesic requirements

	Control Group (n=20) Mean ± SD	Study Group (n= 20) Mean ± SD	p
Surgery duration (minute)	133.25 ± 40.7	117.25 ± 43.30	0.236
First analgesic need (hour)	1.29 ± 0.78	5.50 ± 0.71	0.032

SD: Standard deviation.

Table 4. Comparison of the postoperative additional analgesic requirement

Absent present			Additional Analgesic Requirement		Total	p
Group	Control	Number	11	9	20	0.013
		Ratio (%)	55%	45%	100%	
	Study	Number	18	2	20	
		Ratio (%)	90.0%	10.0%	100%	
Total		Number	29	11	40	
Ratio (%)		72.5%	27.5%	100%		

Table 5. Comparison of the side effects seen in the postoperative period

None		Side Effects				
		None	Nausea	Constipation	Total	p
Control	Number	12	2	6	20	0.028
	Ratio(%)	60%	10%	30%	100%	
Study	Number	19	0	1	20	
	Ratio(%)	95%	0%	5%	100%	
Total	Number	31	2	7	40	
	Ratio(%)	77.5%	5.0%	17.5%	100%	

Table 6. Comparison of the postoperative morphine consumption and VAS values

	Control Group (n= 20) Mean ± SD	Study Group (n= 20) Mean ± SD	p
Morphine 1st hour (mg)	2.35 ± 0.56	1.08 ± 0.61	< 0.001
Morphine 6th hour (mg)	8.53 ± 2.61	4.95 ± 1.73	< 0.001
Morphine 12th hour (mg)	14.23 ± 3.76	9.48 ± 2.47	< 0.001
VAS 1st hour	6.10 ± 1.07	3.40 ± 1.14	< 0.001
VAS 6th hour	3.50 ± 0.69	2.35 ± 0.67	< 0.001
VAS 12th hour	1.60 ± 0.60	1.60 ± 0.50	0.901

mg: Milligram, VAS: Visual Analogue Scale, N: Number of the patients, SD: Standard deviation.

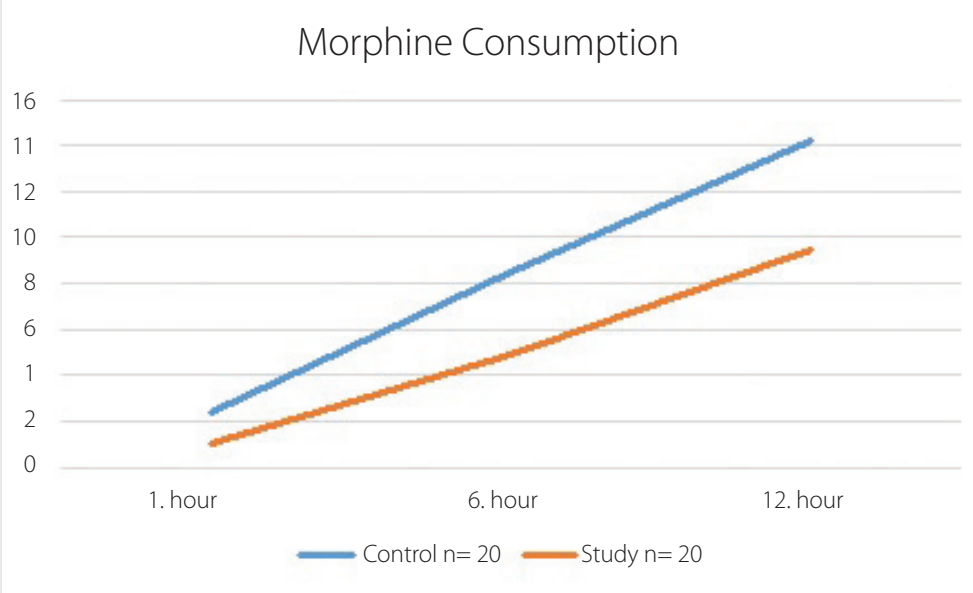

Figure 1. Morphine consumption of the patients.

1.08 ± 0.61 mg of morphine was consumed in the study group. While 6th-hour morphine consumption was 8.53 ± 2.61 mg in the control group, it was 4.95 ± 1.73 mg in the study group. At the 12th hour, morphine consumption was 14.23 ± 3.76 mg and 9.48 ± 2.47 mg, respectively, for the control and study groups. When the 1st, 6th and 12th-hour VAS values of the patients were evaluated, the 1st and 6th-hour VAS values were found to be significantly different (p< 0.05). No significant difference was found between the 12th-hour VAS values (Table 6) (Figure 1,2). In addition, the application time of the block was found to be 246 ± 101 seconds on average.

DISCUSSION

Breast cancer is the most common cancer that affects women, making up 31% of all new cancer cases in women. Depending on the patients' condition, severe acute pain and chronic pain may occur after breast cancer surgeries ranging from 25% to 60% (4). Through effective awareness campaigns carried out in Turkey in recent years, more diagnoses of patients and more surgeries have been realized.

In breast surgeries, thoracic epidural, ipsilateral or bilateral paravertebral block, intercostal block, pectoral nerve block (PECS) and serratus anterior plane (SAP) block can be applied (5-7). Since thoracic epidural has been in use for relatively longer years, it is more preferred in clinics. Due to its side effects such as sympathetic blockade, hypotension, and motor blockade due to its proximity to the medulla spinalis, the popularity of this regional method has decreased in recent years (5). Because of the pneumothorax risk of paravertebral and intercostal blocks due to its proximity to the thorax, these methods also started not to be chosen by physicians (6,7). We have chosen ultrasound-guided technique of SAP block in the study because of decreased risk of complications such as pneumothorax and local anesthetic systemic toxicity.

We accomplished the US-guided SAP block after surgery, after the skin was closed. Skin closing time may vary from surgeon

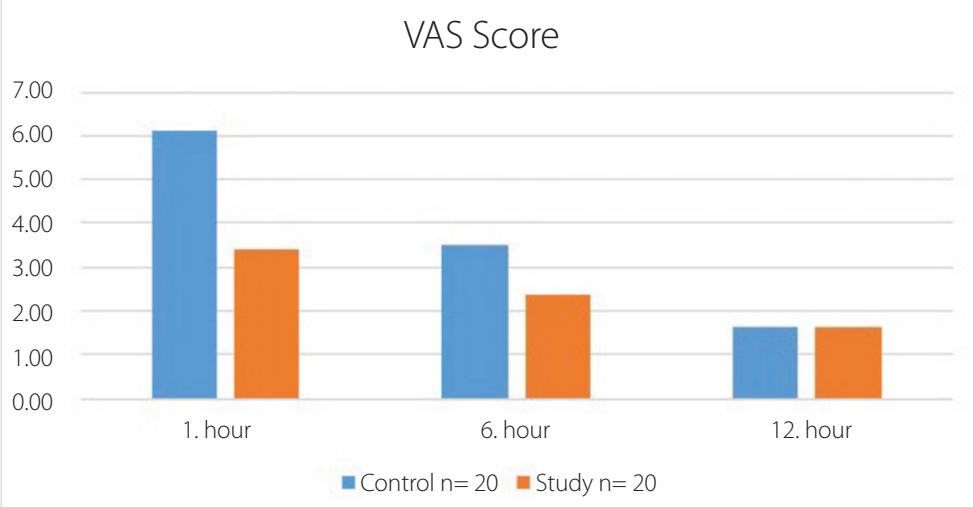

Figure 2. VAS values of the patients.

to surgeon. The standardization of the study could be disrupted because of the time between local anesthesia infiltration performed before the skin closure and the waking-up of the patient would vary. Regardless of how long the duration of the US-guided SAP block lasts after the surgical procedure is completed, the procedure after performing local anesthesia infiltration was the waking-up the patients. Thus, a standardization was achieved in the patients in terms of the time to start the local anesthetic effect and the patients to start feeling pain.

The popularity of the PECS block, described by Blanco et al. for the first time in 2011, has increased (2). This block provides analgesia on the anterior thoracic wall. The serratus anterior block, which Blanco et al. first described in 2013, can be used effectively in thoracotomies in addition to the PECS block. On MR images, it was thought that the drug was distributed both to the anterior and posterior walls and that it could provide analgesia in T-2 and T-9 dermatomes. Blanco and his friends found the average duration of paresthesia in the PECS block as 721 minutes, and the motor block time as 743 minutes in their study (2).

In a study conducted by Kunigo et al. in 2017, patients were divided into two groups. The first group was blocked with 20 ml of 0.375% ropivacaine and the second group with 40 ml of 0.375% ropivacaine. The second group (T2-T6) affected significantly more dermatomes than the first group (T1-T3) (p= 0.004). As a result, it was found to have a better drug distribution in a group of 40 ml (8). Our study was conducted with 40 ml of 0.25% bupivacaine and was found to be longer compared in terms of the first rescue analgesia. Although given at the same volume of drug, it showed effectiveness for a longer time in our study. It was thought that the local anesthetic was different, and the drug concentrations were also different in our research, and also blocking the patients postoperatively could have caused this condition. In addition, patients receiving morphine with PCA are likely to need analgesics over a longer period of time.

Abdallah et al. conducted a retrospective cohort study in 2017 (9). They divided the patients into 3 groups of PECS block group, SAP block group, and control group. US-guided PECS I block was applied to the PECS block group with 15-20 ml of 0.33% -0.5% ropivacaine. In the SAP block group, 20-25 ml of 0.33- 0.5% ropivacaine was applied by using US. There was no significant difference between PECS and SAP groups in terms of postoperative nausea and vomiting and oral morphine consumption in their study (9). In our study, parallel to this study, we achieved similar results in terms of postoperative morphine consumption, first analgesic and additional analgesic requirement, and postoperative complications.

The case series of Khemka et al. on oncological breast surgery was performed on 11 patients (10). Patients had SAP blockade with 25 ml of 0.25% levobupivacaine. Then, the PCA device was attached to all patients in the PACU unit and observed for 24 hours. All patients received 1 gram of paracetamol IV at 6-hour intervals. The average blockage time was 6 minutes and the average surgical time was 234.5 minutes. During follow-up, the first patient with a VAS score of more than 3 was found at the 9^{th} hour, two patients at the 10^{th} hour, and 4 patients at the 12^{th} hour. They demonstrated that the SAP block is effective in breast surgery and can be applied including the latissimus dorsi flap (10). In our study, we obtained similar results in terms of mean surgical time and block application time. VAS scores were lower than the ones in our study. We attributed this to the fact that Khemka et al. routinely gave analgesics. In addition, the amount of local anesthetic delivered remained at a lower volume than in our study. In the blocks we did, the need for secondary analgesics emerged in the later hours although the effect of the block ended.

In a randomized, double-blind, parallel-group, placebo-controlled study conducted by Yao et al. with 72 patients, patients received 25 ml of 0.5% ropivacaine or physiological saline as a placebo during SAP block. Compared to the control group, postoperative VAS pain scores were lower in the SAP group for up to 24 hours. It was found that preoperative SAP block with ropivacaine reduced the cumulative postoperative opioid consumption by 0.5% in the first postoperative 24 hours. Patients in the SAP block group had a lower risk of developing postoperative nausea and vomiting (PONV) compared to the control group. Based on the VAS scores of acute postoperative pain and cumulative opioid consumption, they found that the results show that the SAP block is a powerful part of multimodal pain management after mastectomy (11). Although our study had 12 hours of follow-up, it is similar to this study. Morphine consumption, VAS scores and PONV reduction significantly decreased in both studies. The difference in our study was that the SAP block was performed after the surgical procedure, and we obtained similar results. In our study, we think that it provides more effective analgesia due to the absence of side effects in the high volume of local anesthetic used.

In a meta-analysis including 19 randomized controlled studies (13 breast surgery, 6 thoracic surgery) involving 1260 patients in total, morphine consumption of the SAP block and control group were examined by Matthew et al (12). They found that SAP block significantly reduced morphine consumption at 0^{th}, 6^{th}, and 24^{th} hours postoperatively. When all studies were examined, it was found that the risk of PONV was decreased in patients who received SAP block (12). In our study, we found morphine consumption less than in the control group in the first 12 hours in the SAP block in accordance with the literature. Due to the decrease in morphine consumption, the number of PONV occurrences decreased in the SAP group in our study.

Ali et al. studied 40 patients in total, as 20 patients in the control group, 20 patients in the SAP block group (13). Thirty ml of 0.25% bupivacaine was used in the SAP block; and 2 ml saline was injected in the control group. Routine and standard analgesic treatments were started for the patients. 24-hour opioid consumption and PONV incidence of the SAP block group were found to be less. VAS scores were lower in the SAP group at all hours. A significant difference was found between the two groups in terms of the time of first analgesic need (13). Our study revealed similar results to this study; 12-hour observation results and 24-hour observation results were found to be compatible with the literature. The difference in our study was that the block was applied postoperatively as 40 ml and similar results were obtained.

In this study, postoperative SAP block provided effective analgesia in accordance with the literature. The blockage was preemptive in other studies; however, in our study, it was performed postoperatively and its effectiveness was shown. Postoperative opioid complications decreased and the SAP block provided effective analgesia. None of our patients developed complications related to block application.

CONCLUSION

In this randomized, controlled and prospective study, the effectiveness of postoperative SAP block, and its effects on opioid consumption and VAS scores were investigated. It was found that it reduced morphine consumption, caused significant decreases in VAS scores, and reduced side effects stemming from opioids. SAP block is an effective, easy-to-apply and safe method to reduce acute pain as part of multimodal analgesia in pain management in thoracic surgeries.

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ORİJİNAL ÇALIŞMA-ÖZET
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Meme cerrahisi geçiren hastalarda postoperatif serratus anterior plan bloğunun postoperatif analjezi üzerine etkisi

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ÖZET

Giriş ve Amaç: Bu çalışmada serratus anterior plan bloğunun postoperatif morfin tüketimi üzerine etkisini değerlendirdik. Hem benzer bloklarla hem de bu bloğun uygulanma metodlarında olan farklılıkların hastaların postoperatif ağrı skorlarına ve morfin tüketimlerine etkisini görmeyi ve en etkili yöntemi bulmayı amaçladık.

Gereç ve Yöntem: Bu çalışma elektif şartlarda meme cerrahisi planlanan, ASA I-III, 18-70 yaş aralığında olan gönüllü 40 hastada gerçekleştirilen tek merkezli, prospektif ve gözlemsel bir çalışmadır. Genel anestezi uygulanan toplam 40 hasta 20'şer hasta şeklinde iki gruba ayrıldı. Çalışma grubuna serratus anterior plan (SAP) bloğu uygulanırken kontrol grubuna herhangi bir blok uygulanmadı. İki kas planı arasına 2 ml serum fizyolojik ile test dozu yapıldıktan sonra toplam 40 ml %0,25'lik bupivakain enjekte edilerek serratus anterior plan bloğu yapıldı. Tüm hastalara PCA pompası takılarak postoperatif 12 saat izlendi. Hastaların postoperatif 1, 6 ve 12. saatlerdeki morfin tüketimleri, VAS skorları ve yan etkiler kayıt edildi.

Bulgular: Her iki grup arasında hemodinamik parametreler ve demografik veriler açısından anlamlı bir fark yoktu. Postoperatif morfin tüketimi ve postoperatif analjezik gereksinimi SAP blok grubunda anlamlı olarak daha düşüktü ($p< 0,001$). Yine postoperatif VAS skorları SAP blok grubunda anlamlı olarak daha düşüktü ($p< 0,001$). Blok ilişkili herhangi bir komplikasyon gözlemlenmedi.

Sonuç: Postoperatif uygulanan SAP bloğunun; morfin tüketimini azalttığını, VAS skorlarında anlamlı düşüşe neden olduğunu ve opioidlere bağlı yan etkileri azalttığını bulduk.

Anahtar Kelimeler: Serratus anterior plan bloğu, meme cerrahisi, postoperatif ağrı tedavisi

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ORIGINAL ARTICLE
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Hepatolithiasis: clinical series, review and current management strategy

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ABSTRACT

Objective: Hepatolithiasis (HL) continues to be a problem due to its local and systemic complications, insufficiency in treatment modalities and high risk of recurrence. There are various surgical options available, ranging from endoscopic interventions to a small segment resection and ultimately to transplantation. In this article, patients with the diagnosis of HL and our treatment strategies were evaluated in the light of literature.

Material and Methods: The patients diagnosed with HL in our clinic between 2014-2019 were evaluated retrospectively by examining the patient files. Demographic characteristics of the patients, causes of the disease, complications and treatment options were evaluated.

Results: 17 patients were included into the study. Mean age of the patients was 64.3 years (range 32-89 years). Seven patients had previous cholecystectomies. Stenosis was found to be developed in hepaticojejunostomy (HJ) site in three patients (two had HJ due to bile duct injury and one had HJ following the Whipple procedure), and in hepaticoduodenostomy site in one patient who had the history of biliary tract injury during cholecystectomy. Two patients with HL without previous cholecystectomies had no gallbladder stones. Nine patients underwent surgery. Left hepatectomy was performed in two patients and lateral sector resection was performed in 2 patients. Two patients with anastomotic stenosis underwent HJ revision and two patients with anastomotic stenosis and one patient with stent ingrowth underwent bifurcation resection and neo-hepaticojejunostomy. Eight patients were followed-up nonoperatively with medical and endoscopic approaches.

Conclusion: Hepatolithiasis is a serious condition that needs to be treated with a multimodal approach. Stenting and anastomotic stenosis facilitate the development of hepatolithiasis and increase the risk of its occurrence. In particular, by performing functional hepaticojejunostomy, the development of this complication will be decreased.

Keywords: Anastomosis, bile duct stricture, etiology, hepatolithiasis, treatment

INTRODUCTION

The term primary hepatolithiasis (HL) (also known as oriental cholangiohepatitis) refers to stones in the intrahepatic bile duct prior to the bifurcation of the common bile duct. It has been known since the 16th and 17th centuries. The incidence of HL varies by country. The rate is around 2-25% in far east countries. In Taiwan, HL accounts for about 25% of the patients with gallstones. This rate is 15% in Hong Kong and 4% in Japan. The incidence in Western countries is approximately 1% (1-3). In Europe and America, the incidence of HL increases due to migrations. The global incidence has increased from 0.32/100.000 to 0.85/100.000 in the last three decades (3,4). Interestingly, in eastern countries where westernized diet has become more common, the incidence has been decreasing.

Although the exact etiology of the disease is unknown, cholestasis, biliary strictures, infection, anatomical anomalies and disorders in bile metabolism are considered as the most important predisposing factors (4-6). In addition to these, genetic mutations and ethnic differences play a role in etiology. Lipopolysaccharides have been shown to induce endogenous β-glucuronidase and c-myc release from hepatocyte and intrahepatic biliary epithelium and contribute to the formation of pigment stones. In East Asian countries, ascaris infestations especially Clonorchis sinensis as a result of raw fish consumption are responsible for 30% of the cases (7,8).

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Japanese researchers have described patients with HL clinically in four different grades. According to this, patients with no clinical symptoms are classified as Grade 1, those with abdominal pain as Grade 2, patients with transient jaundice and cholangitis as Grade 3, and those with recurrent jaundice, sepsis and intrahepatic cholangiocarcinoma (ICCA) as Grade 4 (2). On the other hand, Liu et al. (9) have classified HL as follows; the primary type without a past surgical history as type 1, inflammatory type with previous surgery and episodes of cholangitis as type 2, complicated type that forms a mass in the liver as type 3 and terminal type with severe cirrhosis and portal hypertension as type 4. The Dong classification is based on the treatment approach. Type 1 is localized disease and type 2 contains multiple HL divided into three different subgroups. The presence of extra-liver stones in this classification is defined as type E with three subgroups (10-12). Suzuki et al. (13) have classified HL as Grade 1, 2 and 3 according to minor (over 65 years of age, jaundice > 1 week) and major (cirrhosis, HL-ICCA) factors contributing to the severity of the disease.

The first choice in the diagnosis of HL is ultrasound (US) and computed tomography (CT). Ultrasound has the advantages such as being non-invasive, practical and accessible. It is also very useful in determining the location, size, echogenicity, and shadowing characteristics of the stones. Computed tomography is performed in the identification of dilated ducts, stricture regions, masses and calcified lesions (Figure 1). With these two methods, 66-87% of the cases can be diagnosed (7,14). More detailed information on stenosis may be available with intraoperative US, endoscopic US (EUS) and intraductal US (IDUS) (15,16). A comet tail sign on the endoscopy shows the location of the stones and stenosis (14). Magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP) are also beneficial in the differential diagnosis of intraductal lesions, in the detection and localization of the stones (Figure 2). PET-CT can be utilized for the diagnosis of HL-ICCA-induced mass lesions and distant metastases with a ring-shaped image. The strictures in the bile ducts can be best detected by cholangiography and cholangioscopy. As long as there is no risk of atrophy or HL-ICCA in the liver, US and MRI are recommended for follow-up. Most of the cases with HL (85%) are diagnosed with preoperative imaging methods while in some cases (15%), they are diagnosed during surgery and endoscopic procedures (14-16).

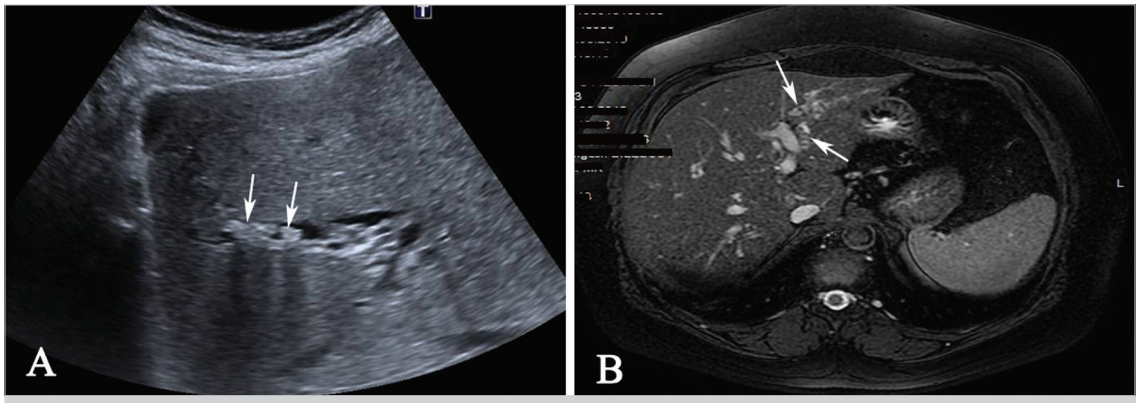

Figure 1. The ultrasonography of the liver shows **(A)** the stones in the left hepatic bile ducts and their reflections (acustic shadow). Axial tomography section **(B)** of the same patient shows multiple stones in the left lateral sector.

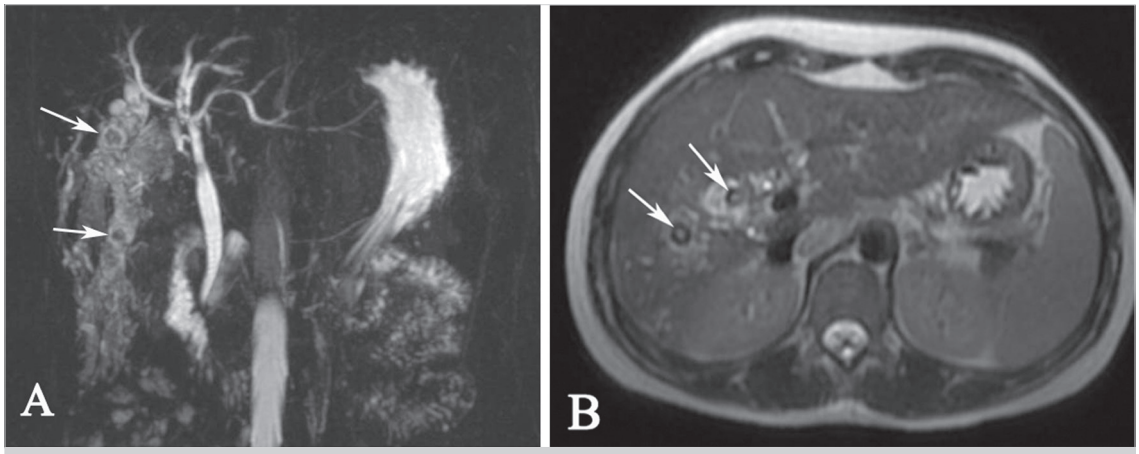

Figure 2. The axial **(A)** and coronal **(B)** sections of MRCP figures show multiple stones in the right bile ducts.

Interventional instruments (balloon, steerable catheters, forceps, lithotripsy instruments), endoscopic methods such as endoscopic retrograde cholangiopancreatography (ERCP) and percutan transhepatic cholangiography (PTC), and surgical procedures are used in the treatment. There is not adequate data on medical treatment, it has limited efficacy especially in primary patients (10,11). In cases of HL caused by parasitic infections, antihelmintic drugs are also added to the treatment (2,8). Endoscopic methods are used primarily in treatment-resistant cases. In cases where medical treatments and endoscopic interventions are insufficient, there are surgical options ranging from operative endoscopy, anastomosis revisions, a small segment resection to liver transplantation.

Here, our approach to HL cases in the last four years was examined in the light of the literature.

MATERIAL and METHODS

The retrospective study protocol was approved by the institutional Ethics Committee (Number: 260, Date: 30.05.2019). A written informed consent was obtained from each patient for both treatment modalities and publication. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patients

In this study, patients who were diagnosed with HL between 2014 and 2019 in our department of general surgery were included. Medical records of the patients were retrospectively evaluated, and the patients with unavailable follow-up data were excluded. The patients with choledochal stones were also not included into the study. Demographics, comorbidities, etiology of hepatolithiasis, presenting complaint, laboratory tests, imaging results, grade of the disease, treatment methods, surgical procedures, pathology results, complications and morbidity/mortality were assessed.

Diagnosis and Management of Hepatolithiasis

Patients were either admitted to our clinic or referred from gastroenterology clinic. Ultrasound, CT and EUS were the initial imaging methods. Diagnosis of HL was confirmed with MRCP, ERCP and/or PTC. Brush biopsy sampling was performed in required cases.

In terms of conservative treatment, parenteral antibiotics were administered and endoscopic interventions were performed in the presence of cholangitis. Ursodeoxycholic acid (UDCA) was prescribed to the patients who were candidates for nonoperative follow-up.

Failed endoscopic interventions, recurrent episodes of cholangitis despite endoscopic interventions and presence of the suspicion of malignancy constituted the indications for surgery. Hepatectomy and hepaticojejunostomy (HJ) were the performed surgical procedures. All HJs were carried out with Roux-en-Y technique. Patients were followed up with four months period of outpatient visits during the first year and then annually.

Statistical Analysis

Descriptive statistics (mean, standard deviation, n and percentile) for discrete and continuous variables were given. The assumption of normality was tested via the Shapiro-Wilk test. Descriptive analysis was conducted via SPPS 20 (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.).

RESULTS

Seventeen patients with HL were included into the study. Ten patients were females, and mean was 64.3 years (range: 32-89 years). The most common complaints were abdominal pain, intermittent jaundice and fever. Seven patients had previously undergone cholecystectomy.

Demographic data of the patients are shown in Table 1.

Majority of the cases had Grade III HL according to Japanese classification (n: 12, 70.5%). Stenosis was detected in four patients. It was found to be developed in HJ site in three patients (two had HJ due to bile duct injury and one had HJ following the Whipple procedure), and in hepaticoduodenostomy site in one patient who had the history of biliary tract injury during cholecystectomy. Two patients with HL and without previous cholecystectomies had no gallbladder stones. US, EUS, MRCP, CT, PTC and recurrent ERCP methods were used for diagnostic and therapeutic purposes.

Surgical treatment was required in nine patients. Left hepatectomy was performed in two patients and lateral sector resection was performed in two patients (Figure 3). Among the four patients with anastomotic stenosis, two underwent HJ revision and the remaining two underwent bifurcation resection and neo-hepaticojejunostomy (collector type portoenterostomy). Collector type portoenterostomy was also performed in one patient with metallic stent ingrowth. One patient underwent laparoscopic cholecystectomy and was followed-up. Most common postoperative complication was surgical site infection which occurred in four patients, and bile fistula accompanied one of them. Postoperative mortality did not occur in any patient.

Eight patients were followed-up nonoperatively with medical and endoscopic approaches. Three of these patients underwent stone extraction and stenting with ERCP and were followed-up with repeated ERCPs. One patient without any further symptoms and clinical problems, one patient who had been receiving medical treatment due to thymoma and one patient who did not consent to operation were followed up conservatively. An 89-year-old patient died due to cholangiohepatitis and sepsis. A patient who was scheduled for a left hepatectomy awaited the remission from the current systemic disease (Pemphigus vulgaris). Recurrent cholangitis was the most common complication among the patients who underwent nonoperative management (n: 5).

Table 1. Demographic data of the patients with Hepatolithiasis

	Age	Sex	Diagnosis/Grade (*)	Etiology/Comorbities	Intervention/Treatment	Complication	Follow up
1.	82	M	R&L HL (2015) (Grade III)	Vagotomy + Billroth 2 (1995) Cholecystectomy + BD Trauma (2013)	ERCP fail Neo-HJ + Permanent access (2016) (**)	Bile fistula Cholangitis SSI	Follow
2.	66	F	L HL (2013) (Grade III)	CL + CDL	ERCP fail, PTC + Stenting Cholecystectomy + Left hepatectomy (2015)	SSI	Health
3.	32	M	L HL (2013) (Grade III)	CL + Left portal vein thrombosis (?)	Cholecystectomy + Left hepatectomy (2015)	-	Health
4.	89	M	L HL (2011) (Grade IV)	Vagotomy + Billroth 2 (1998) CL	ERCP fail, PTC + Stenting + UDCA (2011, 2012, 2014)	Cholangitis + Sepsis + MODS	Excitus (2014)
5.	41	M	Segment 6 (2015) (Grade II)	Timoma + Lung metastasis (2011) CL + CDL	Follow	Cholangitis ?	Follow
6.	83	F	R&L HL (2014) (Grade III)	Cholecystectomy (2008) CDL	ERCP + Stenting + Baloon (2017)	Cholangitis	Follow
7.	75	M	Segment 2-3 (2015) (Grade II)	Pneumonia (2015) CL	Cholecystectomy (2015)	Left liver atrophy	Follow
8.	76	F	L HL (2011) (Grade III)	Cholecystectomy (2001)	ERCP (9) + EST + Baloon + Stenting (2014) Operation (Left hepatectomy) refused	Cholangitis	Follow
9.	43	F	R&L HL (2015) (Grade III)	Whipple procedure (2004) HJ stenosis (2015)	HJ revision (2017)	SSI	Health
10.	53	M	R HL (2015) (Grade III)	-	ERCP (3) + EST + Baloon + Stenting (2016) + UDCA	Cholangitis	Follow
11.	59	F	L HL (2015) (Grade III)	CL (2009)	ERCP (2)+EST + Baloon Cholecystectomy + Left sector resection (2016)	SSI	Health
12.	82	F	R&L HL (2013) (Grade II)	Cholecystectomy (2010)	-	Left liver atrophy	Follow
13.	34	F	Segment 6-7 (2016) (Grade I)	Cholecystectomy (2016)	ERCP (2)+ EST + Baloon + UDCA	-	Follow
14.	74	F	R&L HL (2014) (Grade III)	Cholecystectomy + BD Trauma + HJ (2007) HJ stenosis + PTC + Stent ingrowth	ERCP + Stenting followed by PTC + Stenting Neo-HJ (2017)	-	Health
15.	76	M	L HL (2015) (Grade III)	Bullous pemphigoid + Pemphigus vulgaris (Streoid treatment)	ERCP + EST + Baloon (2017) Operation (Left hepatectomy) suggested ?	-	Follow
16.	61	F	R&L HL (2009) (Grade III)	Cholecystectomy + BD Trauma (2008) HJ Stenosis (2009)	HJ revision 2009 and 2010 + UDCA	Fistula Cholangitis	Follow
17.	64	F	L HL (2017) (Grade III)	Cholecystectomy (2004) + HL (2019)	Lateral sector resection	-	Follow

*: Classification (Japan),
**: Hepatico-cutaneous jejunostomy.
BD: Main bile duct, CL: Cholelithiasis, CDL: Choledocholithiasis, ERCP: Endoscopic retrograde cholangiopancreatography, EST: Endoscopic sphincterotomy, HJ: Hepaticojejunostomy, HL: Hepatolithiasis, PTC: Percutan transhepatic cholangiography, R/L: Right/Left, SSI: Surgical site infection, UDCA: Ursodeoxycholic acid.

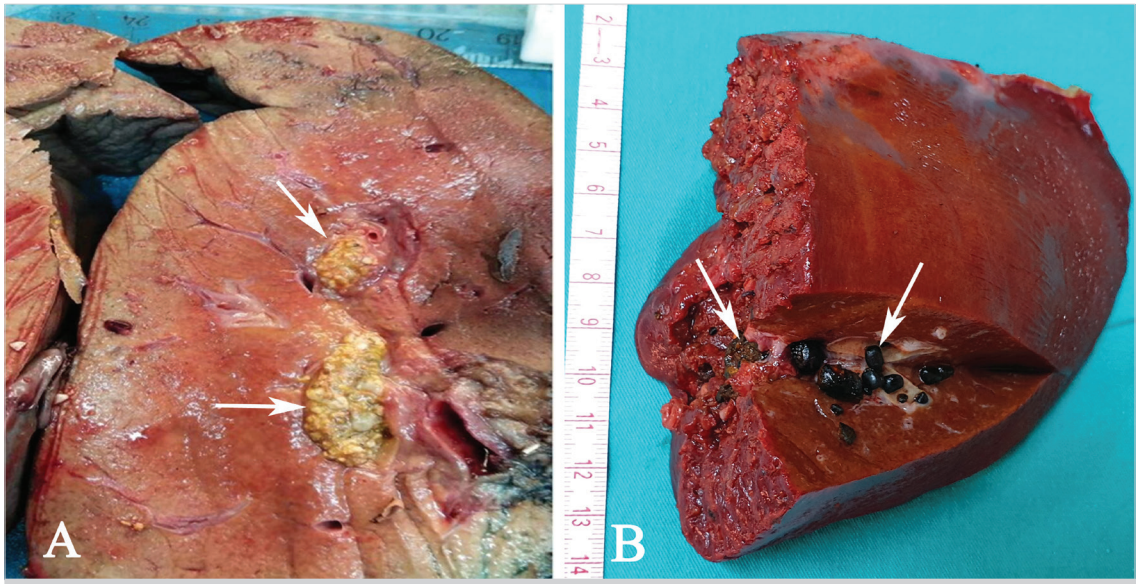

Figure 3. Left hepatectomy specimen **(A)** shows yellow-green multiple stones in the left hepatic main bile ducts and lateral sector specimen **(B)** shows multiple black stones in the bile ducts of segment 3.

Mean duration of follow-up was 43 months (range: 24-70). None of the patients who underwent surgical treatment developed any late postoperative complication or recurrence.

DISCUSSION

The main principle in the treatment of HL is the removal of stones, correction of related strictures and prevention of recurrent cholangitis. Stenosis of the biliary tract is the main cause of stone formation, recurrence, and failure of treatment (8,17,18). In patients with untreated HL, lethal complications, which may vary from cholestasis and cholangitis to sepsis, cirrhosis, and ICCA may develop. Depending on the duration of follow-up, it is reported that 3.7% -14.1% of HL cases develop biliary cirrhosis and 3.3-21.2% develop HL-related intrahepatic cholangiocellular carcinoma (HL-ICCA) (4,13,19-21).

As a result of recurrent cholestasis and cholangitis episodes, biliary cirrhosis develops due to stenosis that occurs in the ducts as a result of fibrosis. Chen et al. (22) have found that a precancerous lesion of biliary tract, which is called intraductal papillary neoplasia, is encountered in 30% of HL cases (23,24). Presence of HL is considered as a precancerous lesion for ICCA (4). Biliary intraepithelial neoplasia, a precancerous lesion in the areas close to the lesion, is also frequently detected in the specimens of patients undergoing resection for HL-ICCA. It has been shown that c-erbB2, epidermal growth factor (EGFR), COX-2 and nuclear factor-κB (NF-κB) which are markers of prolonged inflammation are higher in cases developing HL-ICCA (23, 25). p16 and DPC4/Smad4 genes which are tumor suppressor genes are frequently inactivated in patients with HL-ICCA (26). It should be kept in mind that the risk of ICCA is higher in patients with biliary stricture, liver atrophy, high levels of CA 19-9, in cases of HL especially located on the left side, in the presence of microabscess and in patients with choledochoenterostomies (4,13,21,27). The risk of tumor increases in bilateral HL cases (28,29).

There is very little clinical data on the medical treatment of HL. There is not yet a suitable drug for HL which is rich in pigment in the majority. However, there are limited clinical studies on the effect of UDCA and kenodeoxycholic acid (CDCA) for cholesterol stones which present in 15% of HL cases (30-34). In their series of 3 cases of Caroli syndrome, Ros et al. (32) achieved partial cure in 9 patients and full recovery in 3 patients with extracorporeal shock-wave lithotripsy (ESWL) and UDCA therapy. There are many cases reported to benefit from ESWL+UDCA, and with only UDCA in the series of 53 patients by Guma et al. (35). Regarding this subject, in their evidence-based clinical practice study from Japan, Tazuma et al. (30) have pointed out that medical treatment cannot be recommended (Strength of recommendation degree is 2 -%100) (31). However, algorithms related to UDCA and CDCA use have been determined especially in cholesterol-rich stones and in some special clinical situations. Accordingly, it has been reported that the stones disappear in 25% of HL cases with Caroli syndrome with 6-12 months of UDCA treatment, and it diminishes 75% of the stones. In addition, UDCA administration has been reported to prevent relapse in HL patients with MDR3 deficiency (a genetic disorder causing intrahepatic cholestasis). UDCA has also been reported to be used in HL cases with cholesterol oversaturation and negative X-rays (30, 31). There are studies reporting that the use of UDCA in patients with HL prevents the development of HL-ICCA (35,36). De Vries and Beuers (33) stated that UDCA is the standard treatment for cholestasis due to primary biliary cholangitis (PBC) and primary

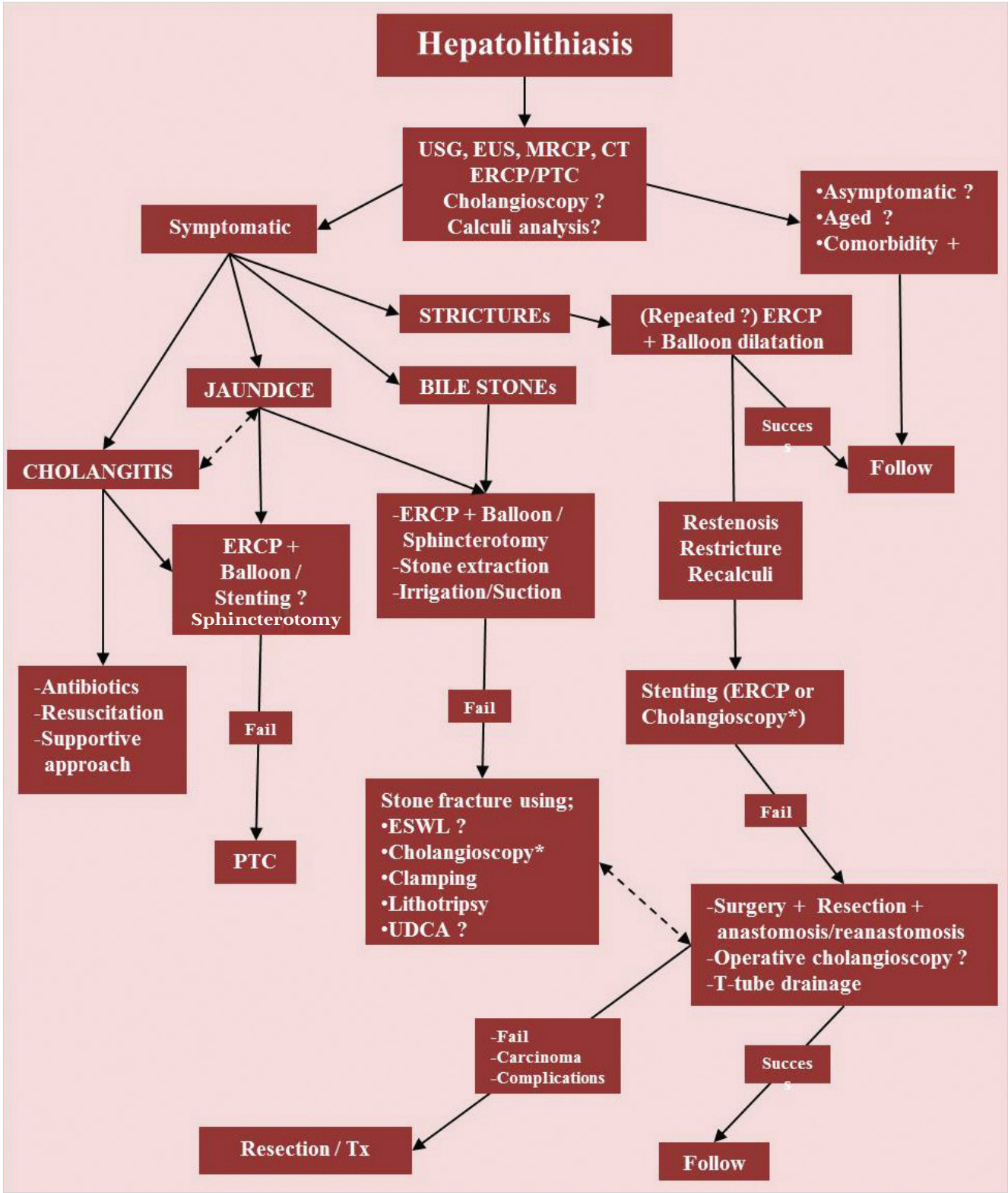

Figure 4. Management strategy for hepatolithiasis symptoms including bile stones, jaundice, cholangitis and also stricture as a reason. *Oral, percutaneous or T-tube line cholangioscopy (optional) and interventive procedures including balloon dilatation, stenting and stone extractions. Tx: Transplantation. UDCA: Ursodeoxycholic acid.

sclerosing cholangitis (PSC). UDCA was used in 4 patients (1 revised HJ and 3 medical follow-ups) in our series.

Until the 1970s, HL treatment consisted of cholecystectomy, extraction of stones in the main bile ducts and T-tube application. A significant improvement has been achieved in treatment when Nakamura used choledochoscopy to remove residual biliary calculi (37). Surgical treatment was the first choice until 2000, but with the increase of the use of choledochoscope and ERCP, the need for surgical treatment started to decrease. Irrigation of the biliary tract, removal of the stones by endoscopic instruments and steerable catheters and percutaneous lithotripsy are used for treatment. In the last decade, surgical treatment is required in 33-77% of HL cases depending on the centers and technological resources (7,28,37). Surgical procedures were required in half of the cases in our series. Lorio et al., in 2020, offered endoscopic or combined interventional radiology/endoscopy management as a first line treatment in HL since these interventions had relatively lower complication rates (38). Surgery was proposed as a secondary choice in this study when minimally invasive interventions failed. In our study, all cases initially underwent ERCP and PTC when possible.

Strictures are tried to be treated primarily by endoscopic methods (Figure 4). For this purpose, first, balloon dilatation, bougie dilatation, and needle-knife electrocautery can be used. Extraction of the stones behind the stenosis by using a basket can expand the area of the stenosis. It may also be necessary to place a stent in the stubborn stenosis areas of the main bile duct (39). In the four cases from our series (25%), HL developed as a result of the stenosis after a bile duct operation. In all of these patients, recurrent ERCP or PTC procedures were not sufficient due to recurrent stones and cholangitis so, a corrective surgery was performed.

Nowadays, removal of the stones by sphincterotomy, choledochoscopy and basket with ERCP and by lithotripsy (pneumatic, hyperacoustic, electrohydrolic or laser) are the most commonly used methods (Figure 4). Although there are very few studies, it has been reported that stones may disintegrate with ESWL in 60-90% of the cases that have no bile duct stenosis (31). The removal of the disintegrated stones by saline irrigation facilitates the procedure. Choledochoscopy can be performed from the normal gastrointestinal tract (per-oral) and as well as from the T tube tract. For the cholangioscopy performed from the T tube tract, the T tube should be kept for at least 4 weeks in normal patients and for 12 weeks in cachectic or diabetic patients (14). Endoscopic approaches may be preferred due to the risk of insufficient liver residue after hepatectomy or the fact that HL is bilateral. ERCP should be preferred in cases with stones in the main bile duct (Figure 4). In their series with 42 permanent access (hepatico-cutaneous jejunostomy) cases, Kassem et al. (40) have reported that they successfully treated remnant stones and recurrent stones (40). Choi et al. (1) have reported that the addition of permanent access (hepatico-cutaneous jejunostomy) to the treatment, especially in patients with previous HJs, would be very useful in the treatment of stenoses that will occur in later stages and the removal of Stones. They stated that repeating the choledochoscopy procedure with an interval of 5-7 days and cleaning off the mud and small particles with continuous saline irrigation is much more effective. Recurrent ERCP procedures were performed for diagnosis and treatment in 7 of our patients. The most common complaints after cholangioscopy and stone extraction are pain and fever, and antibiotics and transamines are recommended in the treatment because of the risk of cholangitis and bleeding (1,8,14). In Japanese surveys, 22% of the patients (range from 5 to 54) have been reported to develop recurrence, cholangitis, abscess, and ultimately HL-ICCA cancer after cholangioscopy (31). In a series of 396 patients followed by an average of 308 months by Suzuki et al., 118 patients died and the most common cause of death was HL-ICCA in 25 (21.2%) patients. This was followed by deaths due to liver cirrhosis (11 patients, 9.3%), lung diseases (10 patients, 8.5%) and cholangitis + liver abscesses (9 patients, 7.6%) (36).

On the other hand, it is known that reflux caused by laxation in the Oddi sphincter after sphincterotomy with ERCP increases the risk of development of cholangitis and HL. For this reason, it is recommended to perform balloon dilatation first and then sphincterotomy in cases when necessary (20). In cases where the biliary tract is enlarged, percutaneous transhepatic biliary drainage (PTBD) which was first described by Mondet in 1962, may be preferred in opening of the strictures and extraction of the stones (14,40,41). Shin et al. (42) stated that there were some disadvantages of sphincterotomy with ERCP and developed the PTBD method (balloon sphincterotomy and flushing technique) and published a large series. In their large series with 916 cases, they reported that they entered the canal with the PTBD technique, they performed sphincterotomy with a balloon and completely cleaned the stones by using the flushing technique in 92.3% of the cases.

In the treatment of primary HL, even though there are many technological procedures, there is still a condition of being insufficient. Despite all technological interventions, residual stones or recurrent stones occur in 15-59% of the cases (43). The presence of biliary stricture, impacted calculi, and unreached peripheral calculi are the main reasons for the failure of the procedure (1,14). Many alternative methods have been tried and continue to be tried as a result of the deficiencies in treatment.

In HL surgery, interventions targeting the etiology should be firstly performed. These etiologies can be biliary strictures and anastomosis strictures secondary to past operations (14). The use of an operative cholangioscope in patients undergoing surgery to remove stones will facilitate the clearance of the bile

ducts. The rate of residual HL after hepatectomy is 15.6% (14). In patients with postoperative stones, stones can be removed in 60-90% of the cases by postoperative choledochoscopy and endoscopic lithotomy (14,17,18). After all treatment modalities, the bile ducts can be cleared from stones in 95% of cases. (29,44). Eight cases in our series were treated with endoscopic methods, and their follow-up and treatment continue.

Partial resections, cholecystectomy, choledocholithotomy, choledochojejunostomy or T-tube placement have been preferred for many years when the location of the stones cannot be detected. Hepatectomy seems to be the most effective treatment since the stenotic area causing the stones is removed. Hepatectomy should be preferred in patients who cannot undergo stone extraction, who have abscess resistant to treatment, especially in patients with left lobe localization and in patients with atrophy and fibrosis (6,10,14,45,46). Liver resection (two left lobe and two lateral sector) was performed in four of nine patients who underwent surgery in our series (Table 1). Two of the four patients who had previously undergone HJ underwent anastomosis revision, and a patient who developed stent ingrowth and another patient with anastomotic stenosis underwent aggressive resection and portoenterostomy. In another patient with HJ and bilateral HL due to biliary tract trauma, anastomotic revision, permanent access and stone extractions were performed, and the patient was observed without any complications for three years.

On the other hand, there are different approaches regarding liver resection. Feng et al. (10) have stated that Dong type 1 and type 2b patients were good candidates for hepatectomy and they recommended HJ for patients with extrahepatic stones (type E). Kim et al. (4) have recommended lobectomy for patients suffering from HL for more than 10 years, due to the difficulties in the differential diagnosis and the risk of ICCA. However, there is not enough information about whether the operation has a protective effect on the risk of HL-ICCA development in those who undergo lobectomy. If there is no liver reserve problem in HL-ICCA cases, hepatectomy and regional lymph node dissection are the initial treatment option (Figure 4). In patients undergoing resection for HL-ICCA, 1-year survival rate is 58% and in the 5^{th}-year, this rate decreases to 10.6% (7). Surgical margin negativity (> 1 cm) is one of the most important factors affecting survival positively (47,48). In Zhu et al.'s (49) series of 38 patients with curative resection (R0), 1st and 5th year survival rates have been confirmed as 71% and 50%, respectively. As 40% of patients with HL-ICCA developed satellite lesions, there are also centers that prefer to have a larger hepatectomy (47, 48). Since survival is much higher in lymph node-negative patients than positive ones, regional lymph node dissection is recommended (50). The effect of adjuvant chemotherapy on survival is insufficient (4,7,47).

Hepatectomies can be performed by laparotomy, laparoscopy and robotic methods. Laparoscopic hepatectomy is a technique that can be used safely in both lobes, and it is the most preferred and recommended method especially for the cases localized in the left lobe or lateral sector (51). With the help of three-divisional visualization system (3DVS), the anatomy of the liver is revealed and it is possible to clearly reveal the location of the stenosis, stone, anomaly, and dilatation. In hepatectomies performed using 3DVS, it has been reported that more stones can be cleaned by using the rigid choledochoscope during the procedure (43,52). It has been also reported that palliative resection procedures in the treatment of HL have a positive effect on survival (53,54). The mortality rate of surgical treatment varies between 4-10% (1).

According to the Dong classification, patients with Type IIc HL are candidates for liver transplantation. Transplantation is the only choice in patients with HL resulting in liver failure (10,55). In patients who are resistant to treatment or in patients who cannot be operated, chemical hepatectomy may be tried by chemical bile duct embolization (CBDE) with experimentally proven chemical substances. However, there is a very limited number of clinical trials on this subject (56-58).

In conclusion, prevention of cholangitis attacks, prevention of strictures and development of ICCA should be prioritized in the treatment of HL patients. Endoscopy, radiology and surgical modalities should be applied with a multidisciplinary approach in the diagnosis and treatment of the disease. Treatment with endoscopic procedures and technological hand tools should be recommended first. Surgical resection should be the first choice in cases that develop atrophy, abscess, and ICCA. Efforts should be made to avoid HL due to its serious morbidity and serious adverse effects on life comfort. For this purpose, in addition to the prevention of biliary tract trauma, reconstruction and monitoring in experienced centers should be recommended. In patients with a high risk of stenosis, permanent access may be added to the procedure to facilitate recurrent endoscopic interventions. In order to prevent reflux to the biliary tract, it is more appropriate to perform hepaticojejunostomies in Roux-en-Y style.

Ethics Committee Approval: The approval for this study was obtained from İzmir Katip Çelebi University Non-Interventional Clinical Research Ethics Committee (Decision No: 260, Date: 30.05.2019).

Peer-review: Externally peer-reviewed.

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ORİJİNAL ÇALIŞMA-ÖZET
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Hepatolityazis: klinik seri, değerlendirme ve güncel tedavi stratejisi

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ÖZET

Giriş ve Amaç: Hepatolityazis (HL), lokal ve sistemik komplikasyonları, tedavi konusunda yetersizlikler ve nüks riskinin yüksekliği gibi nedenlerle problem olmaya devam etmektedir. Endoskopik girişimlerden, küçük bir segment rezeksiyonuna ve nihayetinde karaciğer transplantasyonuna kadar değişebilen cerrahi seçenekler mevcuttur. Bu makalemizde hepatolityazis tanısı almış hastalar ve uyguladığımız tedavi stratejileri literatür verileri ışığında değerlendirilmiştir.

Gereç ve Yöntem: Çalışmada kliniğimizde 2014-2019 yılları arasında hepatolityazis tanısı almış hastalarımız ve uyguladığımız tedavi yöntemleri ,hasta dosyaları retrospektif olarak incelenerek değerlendirilmiştir. Hastaların demografik özellikleri, hastalık sebepleri, komplikasyonlar ve uygulanan tedavi seçenekleri irdelenmiştir.

Bulgular: Çalışmaya 17 hasta alınmıştır. Hastaların yaş ortalaması 64,3 (yaş aralığı 32-89 yıl) tür. Yedi hastaya daha önceden kolesistektomi yapılmış olduğu saptandı. Kolesistektomi sırasında safra yolu travması gelişen üç hastadan ikisine hepatikojejunostomi, birine hepatikoduodenostomi yapıldığı ve darlık geliştiği saptandı. Bir hastada Whipple prosedürü sonrasında HJ yerinde darlık sonrasında HL gelişmişti. Kolesistektomi yapılmamış HL'li iki hastanın safra kesesinde taş yoktu. 9 hasta ameliyat edildi. İki hastaya sol hepatektomi, iki hastaya lateral sektör rezeksiyonu yapıldı. Anastomoz darlığı olan iki hastada HJ revizyonu, birinde stent *ingrowth*'u olan iki hastada anastomoz ve bifurkasyon rezeksiyonu ve neo-hepatikojejunostomi yapıldı. 8 hasta ise nonoperatif olarak medikal ve endoskopik yaklaşımlarla izleme alındı.

Sonuç: Hepatolityazis multimodal yaklaşımla tedavi edilmesi gereken ciddi bir durumdur. Stent uygulaması ve anastomoz darlığı hepatolityazis gelişimini kolaylaştırmakta ve görülme riskini artırmaktadır. Özellikle fonksiyonel hepatikojejunostomilerin yapılması bu komplikasyonun gelişimini azaltacaktır.

Anahtar Kelimeler: Anastomoz, etyoloji, hepatolityazis, safra yolu darlığı, tedavi

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REVIEW
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Lymph node mapping in gastric cancer surgery: current status and new horizons

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ABSTRACT

Gastric cancer (GC) remains one of the most important malignant diseases with significant geographical, ethnic, and socioeconomic differences in distribution. Sentinel lymph node (SLN) mapping is an accepted way to assess lymphatic spread in several solid tumors; however, the complexity of gastric lymphatic drainage may discourage use of this procedure, and the estimated accuracy rate is, in general, reasonably good. This study aimed at reviewing the current status of SLN mapping and navigation surgery in GC. SLN mapping should be limited to tumors clinically T1 and less than 4 cm in diameter. Combination SLN mapping with radioactive colloid and blue dye is used as the standard. Despite its notable limitations, SLN mapping and SLN navigation surgery present a novelty individualizing the extent of lymphadenectomy.

Keywords: Lymph node mapping, gastric cancer, surgery

INTRODUCTION

Gastric cancer (GC) remains one of the most important malignant diseases with significant geographical, ethnic, and socioeconomic differences in distribution (1). Gastric cancer is the second leading cause of death from malignant diseases worldwide, with especially high mortality rates in East, South, and Central Asia; Central and Eastern Europe; and South America. Gastric cancers are most frequently discovered in advanced stages, except in East Asia, where screening programs have been established. The prognosis of advanced GC remains poor, and curative surgery is regarded as the only option for cure. Early detection of resectable GC is extremely important for good patient outcomes; therefore, technologically sophisticated screening programs are needed. In the near future, however, improving the prognosis of advanced GC is necessary, which includes multimodality treatment using chemotherapy, radiotherapy, and surgery (2).

Sentinel lymph node (SLN) mapping is an accepted way to assess lymphatic spread in several solid tumors (i.e. breast cancer, vulvar cancer and melanoma). In an ideal world, SLN mapping should be as good as systematic lymphadenectomy in the identification of patients with lymph node dissemination, while reducing the morbidity associated with an extensive surgical procedure. In breast cancer and melanoma surgery, SLN biopsy has proven to be a valuable tool in lymph node mapping with a sensitivity of more than 95%. When SLN biopsy is negative, lymphadenectomy can safely be omitted. Hence, SLN biopsy is now routinely practiced in these cancer types (3).

Although the complexity of gastric lymphatic drainage may discourage the use of this procedure, the estimated accuracy rate is, in general, reasonably good (4).

Current Status of GC Surgery

Gastric carcinoma shows a high tendency to lymph node metastasis. The risk of regional nodal involvement increases with deep penetration through the gastric wall, and the nodal extension of the cancer takes place gradually, radiating from

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primary location via the lymphatic system (4). Nodal metastases are observed in 3%-5% of the gastric carcinomas which are limited to the mucosa, 11%-25% of which extend to the submucosa, 50% of which reach the muscularis propria (T2), and 83% of which extend to the serosa (T3) (4). After curative radical resection, local recurrence is represented in 87.5% of cases by nodal metastases to local or regional lymph node stations (4).

The Japanese Classification of Gastric Carcinoma (Japanese Gastric Cancer Association, JGCA, 1998) (5) has defined 16 different lymph node stations (n) which drain the stomach (Figure 1).

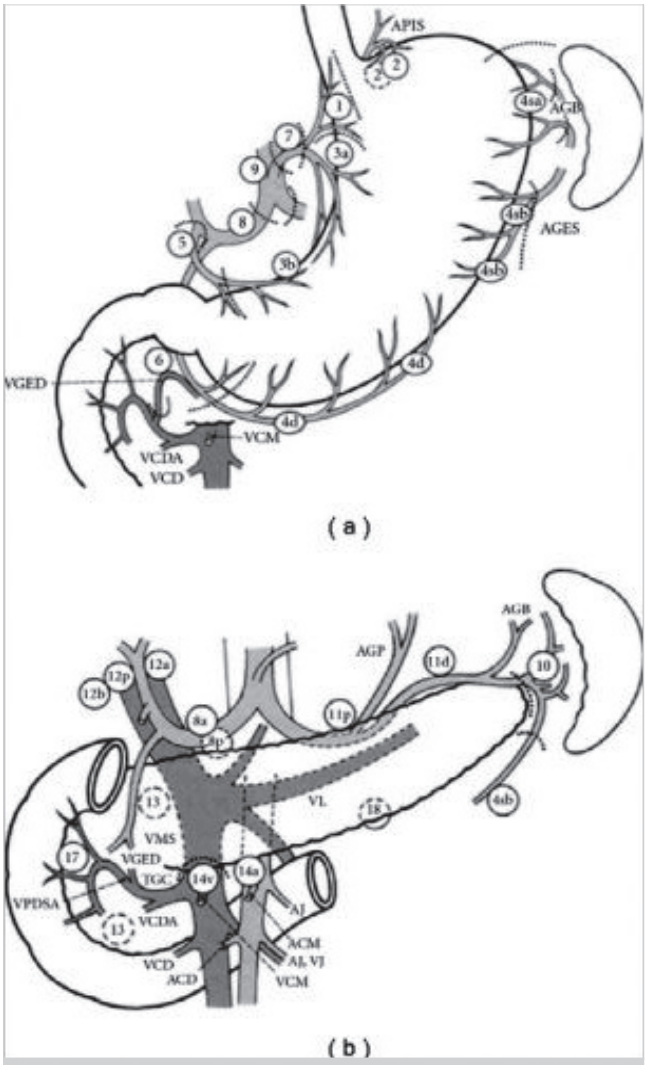

Figure 1. Lymph nodes that can be affected by dissemination of gastric carcinomas according to "Japanese Classification of Gastric Carcinoma. 2nd English Edition".

ACD: *A. colica* dexira, ACM: *A. colica* media, AGB: *A. gastricae* breves, AGES: *A. gstroepiploica* sinistra, AGP: *A. gastrica* posterior, AJ: *A. jejunalis*, APIS: *A. phrenica* inferior sinistra, TGC: *Truncus gastrocolicus*, VCD: *V. colica* dextra, VCDA: *V. colica* dextra accessoris, VCM: *V. colica* media, VGED: *V. gastroepiploica* dextra, VJ: *V. jejunalis*, VMS: *V. mesenterica* superior, VPDSA: *V. pancreaticoduodenalis* superior anterior.

These are subdivided into three levels according to their distance from the tumor, thus entailing three types of lymph node dissection (D) that can be associated to total or partial gastrectomy: D1, in which perigastric lymph nodes from n1 to n6 are removed (N1 level); D2, in which perigastric lymph nodes are removed as well as those located along the main arterial vessels from n7 to n12 (N2 level); D3, in which stations n13 to n16 are removed, as well as those mentioned before (N3 level). During the 1960s, the Japanese authors first introduced D2 lymphadenectomy in patients with potentially curable advanced gastric carcinoma. Short- (6) and long-term (7) results of a comparative randomized controlled trial (RCT) between D1 and D3 (the D3 definition reported in did not include para-aortic lymph nodes) conducted on 221 patients who received curative surgery in a single institution were reported in 2004 and 2006. The authors concluded that D3 dissection improves survival rates, and suggested that it should be performed in specialized centers in order to limit the chance of postoperative complications. A RCT conducted by the East Asia Surgical Oncology Group in 2008 (8) compared the data of 135 patients treated with D2 gastrectomy, with 134 patients receiving D4 gastrectomy (in D4 dissection inter-, pre-, and latero-aortic lymph nodes of abdominal aorta as far as bifurcation are removed). The authors stated that D4 dissection is not the best treatment option for patients with gastric carcinoma, whereas D2 dissection is recommended if performed by experienced surgeons. The Dutch Gastric Cancer Group Trial (9), published in 2004, updated data on the survival of 711 patients previously enrolled in published RCTs. The authors concluded that D2 lymph node dissection can be recommended only if operative morbidity and mortality can be reduced. A further update of these data was published in 2010 (10), with a median follow-up of 15.2 years. The overall 15-year survival was 21% after D1 resection and 29% after D2 resection (P= 0.34). Gastric cancer-related mortality rates resulted significantly higher in D1 than in D2 (41% vs 37%; P= 0.01). The incidence of local recurrence (D1= 22% vs D2= 12%) and distant recurrence (D1= 19% vs D2= 13%) were different, albeit not significantly. Patients who received splenectomy and pancreatectomy had significantly lower overall survival rates in both D2 and D1 groups. On the other hand, patients who received D2 resection without pancreatico-splenectomy had a significantly higher overall 15-year survival compared to patients receiving D1 resection (35% vs 22%, P= 0.006). The authors concluded that D2 resection should be considered the standard procedure to treat resectable gastric carcinoma. The Italian Gastric Cancer Study Group (11) published a multicentric RCT on 267 patients in 2010, comparing the short-term results of D1 and D2 gastrectomy for curable GC. Pancreaticosplenectomy was not considered a routine part of D2 gastrectomy, and the spleen and pancreas were removed only when indicated by the surgeon. The study did not show significant differences in terms of operative mortality, morbidity and duration of postoperative

hospital stay. The authors concluded that D2 gastrectomy is a safe option to treat gastric carcinoma of Western patients as well, if it is performed in specialized centers (11).

In conclusion, in Western countries the prognostic value of D2 lymphadenectomy is still controversial, while in Eastern countries it is considered a standard procedure, likely to be further extended. Japanese authors do not even conduct RCT comparing D1 and D2 lymphadenectomies on the grounds that they consider D1 dissection unethical. Data indicate that D2 dissection is an adequate and potentially beneficial staging and treatment approach if operative mortality is avoided. Dissections extended to para-aortic lymph nodes do not show significant advantages in terms of survival. Splenectomy and distal pancreatectomy increase operative morbidity and mortality. D2 dissection is considered a difficult procedure and should be performed by experienced surgeons in specialized centers. Authors suggest that a surgeon should perform at least 200 gastrectomies under the supervision of an experienced surgeon before he can perform D2 lymph node dissections with acceptable morbidity and mortality rates (4). In Western countries, due to the lower incidence of gastric carcinoma, a surgeon is very unlikely to achieve such an experience (4).

Rationale of SLN Mapping and Biopsy

In GC, lymph node status is one of the most important prognostic factors. The extent of gastrectomy and lymphadenectomy is largely based on the likelihood of lymph node metastases to first- (N1) and second-tier (N2) lymph node stations. The applicability of SLN biopsy in GC has been studied in recent years in an effort to accurately predict metastasis to non-regional lymph nodes. The ultimate goal is to identify patients who truly need lymphadenectomy and to identify patients in whom lymphadenectomy can be omitted. Obviously, patients with suspicious or proven lymph node metastases are not eligible for SLN biopsy, and a routine D2 lymphadenectomy is deployed. Additionally, in patients with advanced tumors (T3 and more), SLN biopsy does not seem appropriate. These patients already have a high probability of having first- or second-tier lymph node metastases. Moreover, in advanced tumors, original lymphatic drainage routes might be obstructed or altered, resulting a lower accuracy of the SLN biopsy (1).

Surgical procedures for gastric cancer have been changing, for instance endoscopic mucosal or sub-mucosal resection, minimally invasive surgery and individualized management have become popular. For lymph node dissection, D2 lymph node dissection has been accepted standard procedure (5, 12). Since the early stage of GC has increased and SLN status is one of the most important prognostic factors, the extend of lymph node dissection is crucial during minimal invasive surgery. For this reason, the method to evaluate lymph node metastasis becomes more important. Behind the lymph node navigation method, complicated lymphatic drainage of the gastrointestinal system, possibility of micro and/or skip metastases are other issues in SLN evaluation.

Tracers

Selection of optimal radioactive tracers for SLN mapping is an important issue. Although most studies focus on a single tracer, using a dual-tracer method (dye plus radioactive) would be more accurate in routine practice. Moreover, several controversies have remained such as the injection way or timing and volume of the tracer. Kitagawa et al. have shared their experience and reported that tin colloid particles migrates to SLN within 2 hour and remains about 20 minutes. They have also recommended endoscopic or laparoscopic injection (13) and (14) suggested that technetium-99m tin colloid is recommended as an optimal tracer for SLN mapping for gastric cancer.

Peparini (15) has suggested that advances in imaging technologies could allow a more accurate preoperative detection of SLN than the current dye- or radio-guided methods. Moreover, new dye-guided intraoperative technologies might revolutionize the SLN mapping procedure in gastrointestinal cancers. Indocyanine green (ICG) infrared or fluorescence imaging may identify a higher number of SLN than radio-guided methods because the particle size of the dyes is smaller than that of radioactive colloids. In GC, ICG infrared imaging is a useful tool in the laparoscopic detection of SLN. ICG fluorescence imaging is feasible even by preoperative ICG injection at, for instance, 1 or 3 d before surgery; it is also feasible in laparoscopy-assisted gastrectomy via a small laparotomy (15).

Injection Route of Tracers

Submucosal injection of the tracer using an endoscope is a standard procedure in the trial conducted by the Japan Society of Sentinel Node Navigation Surgery (16).

Nevertheless, several researchers have reported that there is no difference in the detection rate, mean number of SLN, and sensitivity of the SLN biopsies between submucosal and subserosal injection (17,18).

Operative Technique to Retrieve SLN

Two techniques to retrieve SLN have been reported: the pick-up method and lymphatic basin dissection (LBD). The pick-up method is a very popular method for breast cancer and melanoma, but it is not applicable to GC (19). In the pick-up method, hot node or nodes are dissected, but in LBD, not only hot node also cold nodes are dissected. Kelder et al. have demonstrated that intra-operative accuracy for detecting SLN metastasis is 50% with node picking versus 92.3% with LBD (20).

Clinical Results

Radioguided SLN mapping is an accurate diagnostic procedure for detecting lymph node metastasis in patients with clinical T1-2N0 GC. Since the main purpose of introducing this technology

Table 1. Summary of the clinical results of the studies

Reference	Year	N	Detection rate (%)	Sensitivity (%)	Result
Niihara M et al. (28)	2016	385	96.6	98.9	Functional
Jalaly NY et al. (29)	2014	30	100	91.7	Functional
Toth D et al. (30)	2013	40	97.4	95.7	Functional
Stojanovic D et al. (31)	2013	137	98.2	100	Functional
Kitagawa Y et al. (25)	2013	397	97.5	93	Functional
Dong LF et al. (32)	2012	23	100	100	Functional
Park DJ et al. (33)	2011	68	91.2	100	Functional
Kelder W et al. (20)	2010	212	99.5	97	Functional
Ohdaira H et al. (34)	2009	60	100	100	Functional
Yanagita S et al. (35)	2008	160	98.8	96.7	Functional
Ichikura T et al. (36)	2006	80	100	93	Functional
Arigami T et al. (37)	2006	61	100	95.5	Functional
Nimura H et al. (38)	2004	84	99	100	Functional
Zulfikaroglu B et al. (39)	2005	32	97	100	Functional

into GC surgery is to extend the indication of minimally invasive surgery for pathologically node negative cases, there is no advantage to include advanced cases for which modified less-invasive surgical approaches are not applicable. The size of the primary lesion is also an important factor to consider regarding this technique. It is difficult to cover a whole lymphatic drainage route from a larger tumor exceeding 4 cm (21).

Nakajo et al. (22) have suggested that T1N0 patients are possible candidates for SLN scintigraphy. They have reported high micrometastases rate even in patients that do not have suspected lymph nodes during preoperative evaluation. Similarly, Kitagawa et al. (13) have found the detection rate as 95% and the accuracy as 98%. Saikawa et al. (23) have evaluated the accuracy of SLN scintigraphy in 35 T1No GC patients. They have reported a 94.3% detection rate and 97% accuracy. The only patient with false negative result had advanced GC with invasion into the proper muscular layer and vascular vessel invasion, causing destruction of normal lymphatic flow. At another view of aspect, Nakahara et al. (24) have reported the relation of body mass index (BMI) and success of preoperative lymphoscintigraphy, and they have found a significant difference between BMIs of successful and unsuccessful groups. Kitagawa et al. (25) have calculated the detection rate of sentinel node with dual tracer method (Tc-99m Tin Colloid and blue dye) as 97.5% in their large cT1 and cT2 gastric carcinoma group. Their 3 out of 4 false negative sentinel lymph node biopsies were pT2 tumors. They suggested that sentinel lymph node biopsy would be more successful in T1 tumors because false negative rate is higher in T2 tumors. Table 1 summarizes the clinical success of the studies.

Meta analyses results suggest that further studies are needed to confirm the best procedure and standard criteria for the clinical application of SLN mapping in GC (26,27).

CONCLUSION

Gastric cancer is now one of the most suitable targets of an individualized less-invasive surgery based on the SLN concept although there are several unresolved issues. In our opinion, SLN mapping and SLN navigation surgery present a novelty individualizing the extent of lymphadenectomy for GC.

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

Peer-review: Externally peer-reviewed.

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DERLEME-ÖZET
Turk J Surg 2020; 36 (4): 393-398

Mide kanseri cerrahisinde lenf bezi haritalaması: güncel durum ve yeni ufuklar

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ÖZET

Gastrik kanser (GC), dağılımda önemli coğrafi, etnik ve sosyoekonomik farklılıklara sahip en önemli malign hastalıklardan biri olmaya devam etmektedir. Sentinel lenf nodu (SLN) haritalaması, bazı solid tümörlerde lenfatik yayılımı değerlendirmenin kabul edilen bir yoludur, gastrik lenfatik drenajın karmaşıklığı bu prosedürün kullanımını engelleyebilir, tahmini doğruluk oranı genel olarak makul derecede iyidir. GC'de SLN haritalama ve navigasyon cerrahisinin mevcut durumu gözden geçirilmektedir. SLN haritalaması klinik T1 ve çapı 4 cm'den küçük tümörler ile sınırlı olmalıdır. Radyoaktif kolloid ve mavi boya ile kombinasyon SLN haritalaması standart olarak kullanılır. Kayda değer sınırlamalarına rağmen, SLN haritalaması ve SLN navigasyon cerrahisi lenfadenektomiyi kişiselleştiren bir yenilik sunmaktadır.

Anahtar Kelimeler: Lenf nodu haritası, mide kanseri, cerrahi

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CASE SERIES
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Mirizzi syndrome from type I to Vb: a single center experience

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ABSTRACT

Objective: The present study describes a cohort of patients diagnosed with Mirizzi syndrome from type I to Vb, over a period of four years. It aimed to identify diagnostic and management pitfalls of Mirizzi syndrome, as well as their concomitant cholecystobiliary or cholecystoenteric fistulas.

Material and Methods: We retrospectively reviewed all electronic medical records of patients who underwent surgery for Mirizzi syndrome at a single institution.

Results: Twenty-two patients (0.6%) were diagnosed with Mirizzi syndrome. Most of the patients were females (n=19, 86.3%). Mean age was 43.8 years (range: 21-71 years). Ultrasound was performed in all (100%) patients. Six (27.2%) patients had a CT scan and six (27.2%) patients had endoscopic retrograde cholangiopancreatography. Overall preoperative diagnosis was achieved on 36.6% (n=8) of the patients. There were the same total and partial cholecystectomies, accounting for ten (45.5%) cases each, one hepaticojejunostomy with cholecystectomy (4.5%), and one enterolithotomy (4.5%). Laparoscopic cholecystectomy was attempted in 15 (68.1%) patients, with conversion to open surgery in 93.3% (n=14) of the patients. An open approach was made in five (22.7%) cases. Four (18.1%) patients were reported as MS type I, both types II and III each account for 22.7% (n=5) of the cases, there was only one (4.5%) patient with type IV, and seven (31.8%) patients with type V.

Conclusion: There are limited studies of patients with Mirizzi syndrome, including type V classification, and when this syndrome is suspected, a preoperative diagnosis should be made to avoid bile duct injuries or lesions to adjacent organs.

Keywords: Biliary disease, cholecystectomy, cholecystobiliary fistula, cholecystoenteric fistula, gallstone disease, mirizzi syndrome

INTRODUCTION

Gallstone disease is a common digestive disease with an estimated prevalence of 10-20% in adults in developed countries (1,2). This disorder occurs when there is an imbalance in the composition of the bile, resulting in precipitation of one or more of its components (3). Mirizzi syndrome (MS) is an uncommon phenomenon, with an incidence of 0.7-2.9% of all cholecystectomies (2,4,5). Pablo Luis Mirizzi first described this entity in 1948, defining it as an obstruction of the common hepatic duct (CHD) or common bile duct (CBD) by the compression of an impacted stone in the neck of the gallbladder or cystic duct, causing obstructive jaundice, and leading occasionally to fistulization to the bile duct or surrounding organs (6,7).

The treatment of MS is either by laparoscopy or by open approach, with high conversion rates with the former, consisting of partial or complete cholecystectomy with or without common bile duct exploration, and sometimes bilioenteric anastomosis may be performed (8).

MS is a severe disease, and preoperative detection or intraoperative recognition of MS is essential for the surgeon to reduce the risk of operative complications, being the most common bile duct injury and residual stones (1).

The present study reviewed the experience of a single center with Mirizzi syndrome over a period of 4 years. It aimed to identify diagnostic and management pitfalls of Mirizzi syndrome, as well as their concomitant cholecystobiliary or cholecystoenteric fistulas.

This study was approved by IRB, Tecnologico de Monterrey, under the number 098.

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MATERIAL and METHODS

From 2014 to 2018, 22 consecutive patients underwent surgery for MS at a single teaching institution. We searched the surgical database for all patients diagnosed postoperatively with MS, and retrospectively reviewed all electronic medical records. Patient demographics, clinical characteristics, diagnostic method, surgical procedures, outcomes, and follow-up were all documented and organized. All patients underwent physical examination, laboratory testing, and ultrasonographic (US) or computed tomography (CT) evaluation of the gallbladder. All the cases diagnosed were based on preoperative investigations or intraoperative findings. Beltran and Csendes modified classification (9). was followed to categorize patients as the diagnostic criteria. Laparoscopic cholecystectomy under general anesthesia with a standard four-port technique was attempted in most patients. Conversion to open surgery was left to the discretion of the surgeon. When dense adhesions to adjacent organs and impacted stones in Hartmann's pouch rendered access to Calot's triangle difficult, a fundus-first dissection technique was applied, and subtotal cholecystectomy was performed. All patients were seen in the outpatient clinic within the first month of the initial surgery, and all patients had a follow-up of up of at least six months after surgery. Patients were examined clinically, and liver function tests were evaluated for each follow-up visit.

This manuscript was approved by Tecnologico de Monterrey ethics committee and institutional review board (IRB) number 098, and was therefore performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All patients provided informed consent to participate in the surveillance protocols.

Data were reported as mean, range, or percentages for continuous variables and frequencies and percentages for categorical variables. Data analysis was performed, with a combination of Excel 16.0 (Microsoft Corporation, United States) and R software 3.4 (R Core Team, New Zealand).

RESULTS

A total of 3556 cholecystectomies were performed during the study period. Twenty-two patients (0.6%) were diagnosed with Mirizzi syndrome. Most of the patients were females (n= 19, 86.3%), with only three (13.6%) male patients. Mean age was 43.8 years (range: 21-71 years), four (18.1%) patients had diabetes mellitus (DM) concomitantly with systemic arterial hypertension (SAH), two (9%) patients had only DM, and one (4.5%) patient had only SAH. One (4.5%) patient had hypothyroidism, and one (4.5%) patient was asthmatic. All patients had a history of abdominal pain of 10.9 months on average (range 1-76 months), with a mean time of exacerbation of abdominal pain before their surgical treatment of 6 days (range: 1-21 days). Thirteen (59%) patients were jaundiced at presentation. Liver function tests were altered in almost all patients (n= 18, 81.8%) (Table 1).

Table 1. Laboratories values at initial presentation

Laboratories values	Mean (Range)
WBC X 10^9/L	12 (7-15.6)
Total Bilirubin (mg/dL)	5.41 (0.51-14.29)
Direct Bilirubin (mg/dL)	4.03 (0.23-11.88)
Indirect Bilirubin (mg/dL)	1.36 (0.2-3.6)
AST (U/l)	145.71 (11-500)
ALT (U/l)	196.28 (8-479)
AP (U/l)	400 (75-1236)
GGT (U/l)	521 (23-1297)

WBC: White blood count, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, AP: Alkaline phosphatase, GGT: Gamma glutamil transpeptidasa.

US was the initial imaging study performed in all patients. It revealed gallstones and features of acute cholecystitis in every case (100%), plus a single (4.6%) patient had choledocholithiasis. Mean size of gallbladder wall thickening was 4.86 mm (range: 1.2-10 mm), and mean diameter size of CBD was 8.21 mm (range: 3.17-14 mm). Ten (45.4%) had an impacted stone on the Hartman pouch or cystic duct, and in only six (27.2%) patients, a CT scan was ordered for suspicious of cholecystoenteric fistula, finding on 66% (n= 4) of the patients neumobilia and a sigmoid gallstone ileus on one (16.6%) patient. Endoscopic retrograde cholangiopancreatography (ERCP) was performed in six (27.2%) cases, performing sphincterotomy for bile duct decompression, placing bile duct stents at the end of the procedure. The diagnosis of MS was made in 50% of these patients by direct identification of a fistula.

Postoperatively, four (18.1%) patients were reported as type I, both types II and III each account for 22.7% (n= 5) of the cases, there was only one (4.5%) patient with type IV, treated with an open cholecystectomy and Roux-en-Y hepaticojejunostomy, and the remaining seven (31.8%) patients were found to have various types of cholecystoenteric fistulas (type V). We had the same number of patients with cholecystoduodenal and cholecystocolonic fistulas, accounting for three patients with each type of fistula. Of the three patients with cholecystoduodenal fistula, two were treated with a graham patch on the duodenum and primary closure of the CBD, and one was treated with choledochoplasty with a gallbladder flap and primary closure of the duodenum. Of the patients who presented with a cholecystocolonic fistula, a colostomy at the site of the fistula was performed on one patient, with primary closure of the CBD, another was treated with primary closure of the transverse colon and T tube insertion on the CBD, and the third patient was treated with enterolithotomy alone, for an intestinal obstruction due to a sigmoid gallstone ileus. The remaining patient with MS type V presented a gastrobiliary fistula on the lesser curvature,

Figure 1. MS type V treatment.

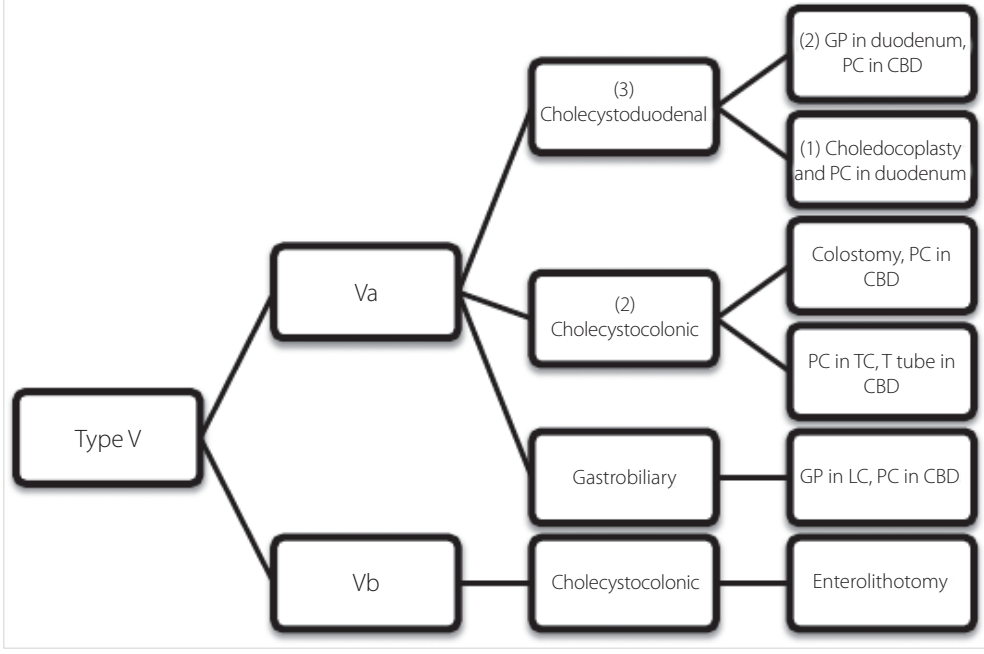

Table 2. Type of surgical treatment

Total (n= 22)	Type I (n= 4)	Type II (n= 5)	Type III (n= 5)	Type IV (n= 1)	Type Va (n= 6)	Type Vb (n= 1)
Open (n= 5)	-	2+	2	-	1	-
Laparoscopic + Conversion (n= 14)	3	3 (2*+, 1*)	3*+	-	5 (2*, 3+)	-
Laparoscopic (n= 1)	1	-	-	-		-
Hepaticojejunostomy (n= 1)	-	-	-	1	-	-
Enterolitotomy (n= 1)	-	-	-	-	-	1

*, T-tube; +: partial cholecystectomy.

treated with primary closure, and an omental patch on the site of the fistula in the stomach, a T tube was placed with a reconstruction of the CBD (Figure 1).

Overall, there were equal number of total and partial cholecystectomies, accounting for ten (45.5%) cases each, one hepaticojejunostomy with cholecystectomy (4.5%), and one enterolithotomy (4.5%). Laparoscopic cholecystectomy was attempted in 15 (68.1%) patients, and because of difficult dissection and misleading anatomy in Calot's triangle, conversion to open surgery was achieved in 93.3% (n= 14) of the patients. An open technique was used as the initial procedure in five (22.7%) cases. A trans-operative cholangiogram (TOC) was attempted in 76.1% (n= 16) of the cases where a cholecystectomy was performed (n= 21), being conclusive in 13 (81.25%) patients with evidence of either cholecystobiliary or cholecystoenteric fistula. In eight (38%) patients, a T-tube was placed on the common bile duct, and all patients had a tube drain left in the subhepatic space, which was removed within a mean of 5 days (range: 3-10 days) (Table 2).

Overall procedure-related morbidity was 13.6% (n= 3). Two patients developed bile leak, and one patient had a remaining stone. All were treated with ERCP and placement of biliary stents, removing them on postoperative week six, with an outstanding outcome. Mortality was accounted for 9% (n= 2) of the patients. In the remaining patients, mean length of hospital stay (LOS) was 8 days (range: 2-30 days). Final histopathology revealed chronic cholecystitis in all (100%) patients, except one 51-year-old patient, who presented associated adenocarcinoma of the gallbladder and treated with adjuvant therapy. All patients were followed up in the ambulatory clinic for at least 12 months, with a mean period of 23 months (range: 12-36 months), all symptoms free with normal liver function tests, except the patient treated with hepaticojejunostomy anastomosis, who had a persistent elevation of serum alkaline phosphatase and developed a mild episode of cholangitis treated successfully with antibiotics, with no further complications. The patient with gallbladder adenocarcinoma stage I did not need

any further surgery, and 12 months after his initial surgery, he is currently alive with oncology follow up.

DISCUSSION

The MS incidence of 0.6% in the present series correlates with the 0.7%-2.53% stated in the literature (10-12). This syndrome develops in patients with longstanding gallstone disease, with a female predominance, with this series supporting this majority. We had a mean age of 43.8 years, making it inferior to the ones reported in the literature that ranges from 48 to 61 years (9). The main confront in the management of MS is in accomplishing a precise preoperative diagnosis, with rates ranging from 8% to 62% of obtaining an accurate image identification of this condition, if this is not accomplished, the incidence of bile duct injuries could be as high as 17% (13,14). Several image studies can be used for achieving this; US is the most common modality used for the diagnosis of gallstones; however, it has limited sensitivity (48%). CT may show dilation of the biliary tree and the CBD, with low sensitivity for identifying stones at these sites, but it may exclude a malignancy in the porta hepatis area or the liver. Magnetic resonance cholangiopancreatography (MRCP), is a non- invasive imaging technique with a 50% diagnostic accuracy rate, having the advantage of avoiding the complications associated with ERCP, which is considered the gold standard for diagnosing this disorder with a mean sensitivity rate of 76.2%, with technical limitations in 5% to 10% of the cases, including inaccessibility to the bile ducts and incomplete filling of the ducts because of tight strictures, additionally it is not exempt from complications such as pancreatitis, cholangitis, and residual stones (4,14-16). Since, we lack MRCP in our institution, a preoperative diagnosis was challenging to attain, and even though almost half of our patients had a US with an impacted stone, a direct compression to the hepatic or common bile duct was difficult to visualize, therefore in patients with high suspicious of MS, a ERCP or a CT scan was ordered, visualizing a fistula in three patients with the former study, and neumobilia in four patients with the latter. We achieved an overall preoperative diagnosis of 36.6% in our patients, with nearly the same rate as the series of Greiasov et al. (17) who accomplished a preoperative diagnosis rate of 27% in a large cohort of 284 patients.

An often-absent sign of identification of this disease and almost pathognomonic is neumobilia (18). This sign was seen in 66% of our patients who had CT (n= 6), higher than the series from Li et al. (19) where this sign was seen in 33% of the CTs. We opted to treat our three patients with cholecystoduodenal fistula with primary closure and choledochoplasty in the CBD, performing primary closure of the duodenum with or without over sewing an omental patch, with satisfactory results. We had the same number of patients with cholecystoduodenal and cholecystocolonic fistulas, similar to the study of Pradeep et al. (20), who identified the duodenum and the colon, as their two most common organs involved. On the patients where the colon was involved, we performed on partial cholecystectomies. On one patient, we performed primary closure of the transverse colon and T tube insertion on the CBD, on a second patient, a colostomy was achieved with intestinal reconnection auspiciously implemented 20 weeks later, and on a third patient, a gallstone ileus on the sigmoid colon along with a cholecystocolonic fistula was faced, opting for a conservative management because of a low functional reserve, achieving only an enterolithotomy and antibiotic therapy with positive outcomes. This unusual site of impaction of the stone is exceptionally infrequent, occurring only in 8% of all patients with gallstone ileus (20-21).

There are two popular classifications well accepted for this condition. The first one is the one proposed in 1982 by McSherry and colleagues (22), categorizing MS into two types: type I, characterized by external compression of the adjacent common hepatic duct; and, type II, where a pressure necrosis of the common bile duct results in a cholecystocholedochal fistula. The second classification was developed seven years later by Csendes et al. (10) reclassifying MS in IV types, being type I lesions with external compression of the common bile duct, type II lesions where a cholecystocholedochal fistula is present with erosion of less than one-third of the circumference of the bile duct, distinguishing it from type III lesions where the fistula involves up to two-thirds of the duct circumference and finally type IV lesions where there is complete destruction of the bile duct. Almost two decades later, Csendes added an additional type to this classification, validated by Beltran (9), supplementing a type Va and Vb, corresponding with an MS with a cholecystoenteric fistula without and with a gallstone ileus respectively. Our most common type of MS was the type V, following equally by type II and III, and because MS type I does not involve a fistula, we think numerous MS type I passed undiagnosed, categorizing them as hydropic gallbladder or acute cholecystitis.

Beltran et al. (9) have supported that conventional surgery for patients with suspected MS is safer in most institutions of developing countries where access to diagnostic equipment, such as MRCP, ERCP, intraoperative ultrasonography, or choledoscopy are not available. Laparoscopic management can be performed especially in MS type I with a visualized cystic duct, and only cholecystectomy either total or partial is needed. However, patients with the other four types of MS always require bile duct exploration with intraoperative cholangiogram and common bile duct reconstruction through simple closure of the fistula or T-tube insertion, leaving bilioenteric anastomosis for patients with type IV (15). Of all surgeries performed at our hospital, only one patient with MS type I was completed by a laparoscopic approach; hence, we had a conversion rate of almost 100%. In patients with MS type II and III; a T tube was placed on 60% of them, with the remaining patients treated with primary closure or choledochoplasty. Almost all of these patients had adequate results, except for

our two fatalities, being two elderly and diabetic patients, treated with T-tube placement and without T tube placement, MS type II and MS type III respectively, presenting bile leakage treated at first with ERCP and biliary stent placement, reintervening both cases with abdominal washout and drainage placement with no favorable evolution. The patients died 45 days and 80 days after the initial surgery due to abdominal sepsis. Moreover, a bilioenteric anastomosis was achieved for our patient with MS type IV with worthy results.

The clinical diagnosis of MS is challenging to attain since there are no pathognomonic symptoms for presentation (4). Thus, obtaining a preoperative diagnosis is defiant, because signs like jaundice, acholia, or choluria may be lacking, adding that 20% to 40% of the patients have normal serum bilirubin levels (23). In our series, 18.1% of our patient's laboratory values were with standard parameters, and 59% of the patients presented with jaundice, differently from the series of Kwon et at. (23) where only 33% presented with this sign.

In their systematic review, Antoniou et al. (8) have stated that the outcome of laparoscopic treatment of MS is not inferior to that of open surgery; however, it carries a meaningful conversion rate of 41%, with complications rates of 20% and a mean hospital stay of 8 days. In another study of 27 MS, Chowbey et al. (24) have reported a 22% conversion rate. This contrasts with our experience, where we had a much higher conversion rate corresponding for 93.3% of all laparoscopic approaches, with a similar complication rate of 22.7% and the same mean hospital LOS of 8 days. We believe it is essential for surgeons to prevent CBD injury and manage the fistula and CBD obstruction adequately. Thus, if an obliterated Calot's triangle and surrounding adhesions are encountered trans operatively, it is obligatory to obtain a cholangiogram, and if a cholecystobiliary or cholecystoenteric fistula is visualized, conversion to open cholecystectomy may be preferred, nonetheless, in inexperienced laparoscopic hands, an endoscopic approach may be feasible and secure.

All our patients' final histopathology results were benign for malignancy except for one male mid-age patient, who presented a final diagnosis of adenocarcinoma. Redaelli et al. (25) have stated an association of MS with gallbladder cancer in 28% of their cases, in contrast with an Indian study by Kumar et al. (26) where only 5% of the patients with MS presented concomitantly gallbladder cancer, making it similar to our series.

In summary, we believe stronger importance should be given to the preoperative diagnosis of this syndrome, and when doubting after ultrasonography is performed, an MRCP or ERCP should be achieved to prevent severe complications during surgery. Nowadays, there is no consensus for the right treatment for each type of MS, and outstanding long-term outcomes can be anticipated by using a variety of operative techniques to address Calot´s triangle, the cystic duct stump, and the biliary or enteric fistula. Although signs and symptoms are not precise, the primary clinical manifestation is jaundice with a predominantly obstructive laboratory pattern, along with right upper quadrant pain, making it difficult to distinguish it from cholangitis. This is one of the few case series describing MS, including the type V classification, contributing with our experience to the existing literature regarding this unusual and controversial syndrome.

Ethics Committee Approval: The approval for this study was obtained from Hospital Zembrano Hellion Ethics Committee (Decision No: 098, Date: 18.11.2019).

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - M.G.U.; Design - G.G.G.; Supervision - M.G.U.; Materials - M.G.U.; Data Collection and/or Processing - M.G.U.; Analysis and/or Interpretation - M.G.U.; Literature Search - M.G.U.; Writing Manuscript - M.G.U.; Critical Reviews - G.G.G., M.R.S.

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OLGU SERİSİ-ÖZET
Turk J Surg 2020; 36 (4): 399-404

Tip I'den Vb'ye Mirizzi Sendromu: tek merkez deneyimi

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ÖZET

Giriş ve Amaç: Bu çalışma, dört yıllık bir süre boyunca tip I'den Vb'ye Mirizzi sendromu (MS) tanısı konan bir hasta grubunu içermektedir. Mirizzi sendromunun tanı ve yönetim güçlüklerinin yanı sıra eşlik eden kolesistobiliyer ve kolesistoenterik fistülleri tanımlamayı amaçlamaktadır.

Gereç ve Yöntem: Tek bir kurumda Mirizzi sendromu nedeniyle ameliyat edilen hastaların tüm elektronik tıbbi kayıtlarını retrospektif olarak inceledik.

Bulgular: Yirmi iki hastaya (%0,6) Mirizzi sendromu tanısı kondu. Hastaların çoğu kadındı (n= 19, %86,3). Ortalama yaş 43,8 idi (aralık: 21-71 yaş). Tüm hastalara (%100) ultrason yapıldı. Altı hastada (%27,2) BT taraması, altı hastada (%27,2) endoskopik retrograd kolanjiyopankreatografi uygulandı. Preoperatif tanı hastaların %36,6'sında (n= 8) sağlandı. Her birinde onar olgunun (%45,5) olduğu total ve parsiyel kolesistektomi, bir (%4,5) kolesistektomi ile hepatikojejunostomi ve bir de (%4,5) enterolitotomi uygulandı. On beş (%68,1) hastada laparoskopik kolesistektomi ile başlandı ve hastaların %93,3'ünde (n= 14) açık cerrahiye dönüşüm yapıldı. Beş (%22,7) olguda doğrudan açık cerrahi bir yaklaşım uygulandı. Dört (%18,1) hasta MS tip I idi. Tip II ve III, olguların %22,7'sini (n= 5) oluştururken, tip IV olan sadece bir (%4,5) ve Tip V'li ise yedi hasta (%31,8) vardı.

Sonuç: Mirizzi sendromlu hastaların tip V sınıflandırması dahil sınırlı sayıda çalışmaları vardır ve bu sendromdan şüphelenildiğinde, safra kanalı yaralanmalarını veya komşu organlara lezyonları önlemek için ameliyat öncesi tanı konulmalıdır.

Anahtar Kelimeler: Safra hastalığı, kolesistektomi, kolesistobiliyer fistül, kolesistoenterik fistül, safra taşı hastalığı, Mirizzi sendromu

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CASE REPORT
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Gossypiboma mistaken for a hydatid cyst: case report

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ABSTRACT

Although considered a rare complication, gossypiboma continues to be a clinically important and probably more frequently encountered than reported situation. This study aimed to report a case of gossypiboma that was mistaken for a hydatid cyst in the preoperative evaluation. A 34-year-old male patient with a history of Nissen Fundoplication presented with a large mass palpable in the epigastrium and both the left upper and lower quadrants of the abdomen. Computerized tomography was reported to show a 20x18 cm cystic mass with a collapsed germinative membrane inside it. Laparotomy, which was performed with a suggested diagnosis of type 3 hydatid cyst, revealed that the mass was caused by a 30x30 cm surgical abdominal compress. We believe gossypiboma should be kept in mind in the differential diagnosis of abdominal hydatid cysts in the presence of a former abdominal operation, especially when the result of indirect hemagglutination test is negative.

Keywords: Gossypiboma, retained foreign body, hydatid cyst

INTRODUCTION

Gossypiboma is the term that is used to describe a mass of cotton matrix or surgical sponge accidentally retained in the body after surgery (1). Although considered a rare complication, it continues to be a clinically important and probably more frequently encountered than reported situation (2,3). Due to its nonspecific symptomatology and the fact that it can stay asymptomatic for years, its diagnosis is difficult (4). It may mimic an abdominal or pelvic soft tissue tumor and on abdominal computerized tomography (CT) it may be indistinguishable from an abdominal abscess (5). Thoracic gossypibomas can even be mistaken for ecchinococcal lesions (6).

This study aimed to present an abdominal case of gossypiboma that was mistaken for a hydatid cyst in the preoperative evaluation.

CASE REPORT

A 34-year-old male patient was admitted to our clinic for complaints of nausea and vomiting after meals and abdominal distention that was apparent for the last 5 months. He had a history of Nissen fundoplication performed with open approach 10 years ago. On physical examination there was a median laparotomy incision from the tip of the xiphoid to the umbilicus. A large mass was palpable in the epigastrium and both the left upper and lower quadrants of the abdomen. Laboratory tests, including indirect hemagglutination test, were in normal range. Abdominal computerized tomography (CT) revealed a 20x18 cm calcified cystic mass with a collapsed germinative membrane inside it. The lesion was in close proximity with the left lobe of the liver, the stomach and the spleen; pushing the stomach to the superior right and the spleen to the superior left (Figure 1). Esophagogastroduodenoscopy showed an unexpanding stomach with a hyperemic mucosa.

Although indirect hemagglutination test was negative, the patient was operated with a suggested diagnosis of type 3 hydatid cyst. Laparotomy revealed a large mass, filling the epigastrium and expanding into both left upper and lower quad-

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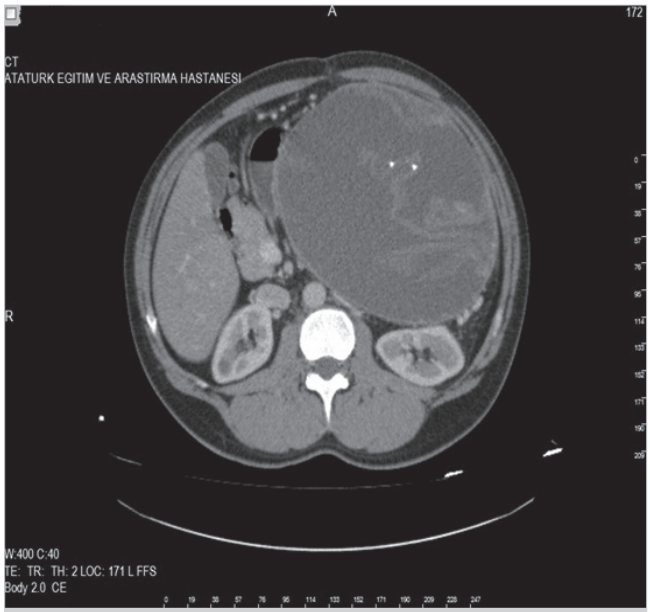

Figure 1. CT view of the calcified cystic mass.

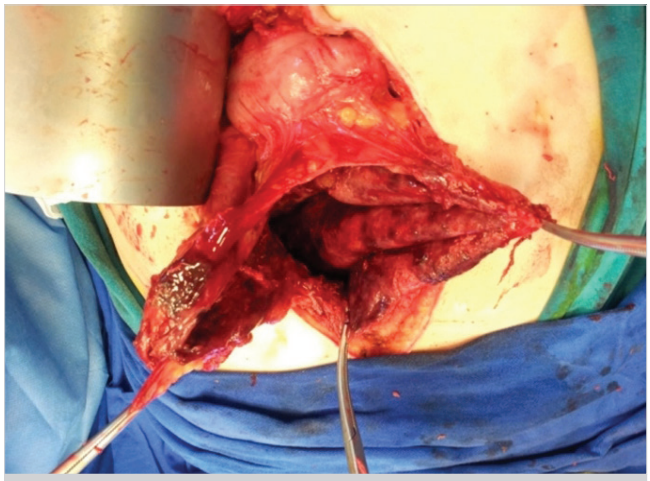

Figure 2. Cavity of the pseudocyst.

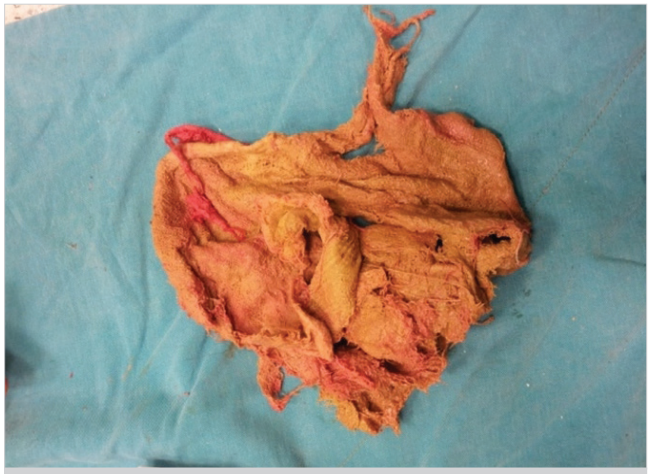

Figure 3. The extracted sponge.

rants of the abdomen. The pseudocapsule of the mass was impossible to dissect from the adjacent structures. When the pseudocapsule was opened, 3 liters of brown-black, non-smelly liquid discharged. In the cystic cavity there was a 30x30 cm surgical abdominal compress near the esophageal hiatus (Figure 2,3). The compress was extracted, and the cavity was washed with saline. After the insertion of a drain into the cavity, the abdomen was closed.

The patient was discharged from the hospital on the second postoperative day without any problems and he was well in his outpatient control at the end of his fifth postoperative year.

The patient gave informed consent allowing his medical information to be used in medical research and scientific papers.

DISCUSSION

The estimated incidence of gossypibomas is highly variable, reports ranging from one in 100 to one in 19000 cases; and since many cases go unreported due to medico-legal problems, the incidence is quite difficult to predict (3,7,8).

There are two sorts of foreign body reactions caused by retained sponges. The first is an aseptic fibrous reaction resulting in adhesions, encapsulation and granuloma formation. These patients may remain asymptomatic or present with a pseudotumor syndrome. The other sort of reaction involves exudative inflammatory reaction with abscess formation or chronic external or internal fistula formation (7).

Clinical presentation may vary according to the location of the foreign body (7). Symptoms and clinical findings are usually nonspecific and may include nonspecific abdominal pain, nausea, vomiting, and a palpable mass or intestinal obstruction (5). The symptoms may appear early in the postoperative period or the situation may remain asymptomatic for years and some cases may even never be discovered (7). The median time for the cases to be discovered is reported to be 7 years and there are reports of foreign bodies remaining undetected for 40 years (2,9). In our case the patient had stayed asymptomatic for 10 years.

Radiographs are the most commonly used method to detect retained sponges (5). Generally surgical sponges have radiopaque markers that facilitate detection with standard radiography; however, sponges without these markers are still being used in some institutions, decreasing the chance of detection of gossypibomas by direct radiography and even by abdominal CT (10). The absence of such a marker in our case contributed to the confusion in radiologic diagnosis.

On CT the spongiform pattern with gas bubbles is the most characteristic sign for gossypibomas (5). As a result, the differential diagnosis includes hematoma and abscess early in the postoperative period. However, in time, the air trapped in the foreign material is absorbed and in the absence of a radiopaque marker

as in our case, lesions appear with or without whirl-like high density stripes (6). Differentiation from neoplasms or degenerated hydatid cysts may be difficult at this stage (6). Hydatid cysts are highlighted in the differential diagnosis of thoracic gossypibomas (6). However, to our knowledge, there are only six cases of gossypiboma in the literature together with the present case to be mistaken for an abdominal hydatid cyst during the preoperative evaluation (7,11-14). All of these cases have been reported from countries in which echinococcosis is endemic.

Indirect hemagglutination test, which is frequently used in combination with radiologic tests in the diagnosis of hydatid cysts, has a sensitivity varying between 60-100% (15) Therefore, when deciding for a surgical operation with a suggested diagnosis of a hydatid cyst, we rely on the radiologic tests more than the indirect hemagglutination test.

CONCLUSION

We believe gossypiboma should be kept in mind in the differential diagnosis of abdominal hydatid cysts in the presence of a former abdominal operation. A negative indirect hemagglutination test may urge the surgeon to suspect the condition even if the abdominal CT suggests an echinococcal lesion. This is especially important in countries with a high incidence of hydatid cysts as these will be the countries in which the lesion is most likely to be mistaken for an echinococcal lesion.

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

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - B.O.B., P.E.E., M.O.; Design - All of authors; Supervision - R.H.G., S.A.; Materials - All of authors; Data Collection and/or Processing - B.O.B., S.A., M.O.; Analysis and/or Interpretation - B.O.B., R.H.G., P.E.E.; Literature Search - All of authors; Writing Manuscript - B.O.B.; M.O.; Critical Reviews - R.H.G., P.E.E., S.A.

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OLGU SUNUMU-ÖZET
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Kist hidatik öntanısıyla ameliyat edilen hastada saptanan gosipiboma: olgu sunumu

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ÖZET

Ender bir komplikasyon olarak kabul edilen gosipiboma, klinik olarak önemli ve muhtemelen de bildirildiğinden daha sık rastlanan bir durumdur. Burada ameliyat öncesi değerlendirmede kist hidatik tanısı alan bir gosipiboma olgusu sunulacaktır. Nissen Fundoplikasyon öyküsü bulunan 34 yaşında bir erkek hasta, epigastrik bölgede ve sol üst ve sol alt kadranlarda ele gelen kitle ile bölümümüze başvurdu. Bilgisayarlı tomografide 20x18 cm boyutlarında, içinde çökmüş germinatif membran bulunan kistik kitle görüldüğü rapor edildi. Tip 3 kist hidatik öntanısı ile yapılan laparotomide kitlenin nedeninin 30x30 cm boyutlarında bir karın kompresi olduğu görüldü. Önceden geçirilmiş bir karın ameliyatı varlığında gosipibomanın kist hidatiğin ayırıcı tanısında, özellikle de kist hidatik hemaglütinasyon testi negatif ise akılda bulundurulması gerektiğini düşünüyoruz.

Anahtar Kelimeler: Gosipiboma, unutulmuş yabancı cisim, kist hidatik

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CASE REPORT
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Endometriosis of the rectosigmoid colon mimicking gastrointestinal stromal tumor

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ABSTRACT

Endometriosis is defined as the growth of functional endometriotic gland and stroma outside the uterine cavity. Although it is common in women of reproductive age, extragenital endometriosis is considerably rare. Due to its frequent localization at the rectosigmoid junction in the gastrointestinal system, endometriosis may manifest with abdominal pain, constipation, and rectal bleeding. Gastrointestinal stromal tumor is the most common mesenchymal tumor of the gastrointestinal system and develops from the muscularis propria. Its extraluminal component is prominent. This study aimed to report a rare case of a 37-year-old patient who was operated with laparoscopic colon resection for a malignant-appearing submucosal mass with indistinct borders at the rectosigmoid junction that received the final diagnosis in histopathological examination. Endometriosis should be considered in the differential diagnosis of non-specific gastrointestinal symptoms in female subjects of reproductive age as the one reported here.

Keywords: Endometriosis, rectosigmoid, malignancy, laparoscopic resection

INTRODUCTION

Endometriosis is defined as the presence of endometrial glands and stroma outside the uterine cavity (1). Its prevalence among women of reproductive age is 15% and 50% among infertile women. The diagnosis of extrapelvic endometriosis is challenging, and clinicians usually fail to consider it in differential diagnosis owing to variable symptoms depending on the site of localization. Despite its characteristic pathological appearance independent of its localization, it may be radiologically confused with tumors originating from tissues it is located (2). This study aimed to report a case of endometriosis that mimicked a gastrointestinal stromal tumor (GIST) in the rectosigmoid region.

CASE REPORT

A 37-year-old nulliparous woman presented to the obstetrics and gynecology outpatient clinic with pelvic pain and abdominal bloating for 2 days. Her history was not remarkable for any chronic disorder, regular use of medications, or previous surgery. On physical examination, she had tenderness upon palpation, guarding, and rebound in the left lower quadrant and suprapubic region. Rectal examination revealed no palpable mass. Laboratory findings indicated leukocytosis, and elevated CRP and CA-125 levels; other laboratory results were normal. She underwent a transvaginal ultrasonography for an initially suspected ovarian cyst rupture or pelvic abscess, which showed a hypoechoic lesion located adjacent to the left ovary that had a diameter of 3 cm with a dense content. In order to rule out a hemorrhagic cyst or abscess formation, a multislice computed tomography (CT) was obtained, which demonstrated a mass lesion with a size of 4x3.5 cm in the rectosigmoid region. The mass was indiscernible from the intestinal wall; it was mildly enhanced by I.V. contrast agent; and it caused no obstruction (Figure 1). The lesion was initially considered to be a GIST or an endometriotic lesion. A subsequent rectosigmoidoscopic examination showed a submucosal mass in the rectosigmoid region. With these findings, the patient was taken to the operating theater to be operated jointly with the Obstetrics and Gynecology department. Upon exploration, a firm mass

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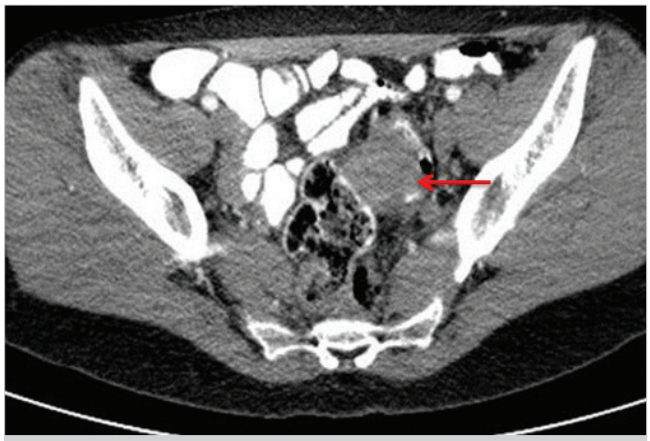

Figure 1. Axial contrast-enhanced CT shows a mass lesion in the rectosigmoid region. The mass is indiscernible from intestinal wall, it is mildly enhanced by I.V. contrast agent, and it causes no obstruction.

with irregular borders was spotted in the rectosigmoid junction, which was suspected for a malignancy, and frozen examination was done and the diagnosis of endometriosis was confirmed. Laparoscopic anterior resection + end-to-end anastomosis using staplers were performed. No postoperative complication was observed, and the patient was discharged with full recovery on the postoperative seventh day. The definitive histopathological diagnosis of the patient was reported to be foci of endometriosis interspersed in-between the submucosa and muscularis propria muscle fibers in the rectosigmoid colon (Figure 2A, B).

DISCUSSION

The most accepted theory about the development of endometriosis is the retrograde extension theory put forth by Sampson, which theorizes the migration of endometrial cells into the peritoneal cavity and various other sites via Fallopian tubes during menstrual cycles (3). Endometriosis typically involves genital organs and pelvic peritoneum, but it also rarely affects the gastrointestinal system (GIS), lungs, mesentery, urinary bladder, greater omentum, surgical scars, skin, kidneys, and nasal cavity. In the GIS, it usually involves the rectosigmoid junction (74%) followed by the ileum and appendix (4). Intestinal endometriosis is usually asymptomatic but may lead to gastrointestinal bleeding, abdominal cramps, nausea, vomiting, diarrhea, constipation, and intussusception. Symptoms alone are not diagnostic (5). Our patient had severe abdominal pain and bloating.

GIST is the most common mesenchymal tumor of the GIS. It originates from Cajal interstitial cells found in the myenteric plexus and smooth muscle cells of the GIS. It usually affects people older than 40 years of age. It may appear anywhere in the GIS, although it frequently involves the stomach (39-70%) and small intestine (20-32%) but also, albeit rarely, the colon, rectum (5%), esophagus (2%), and appendix. GIST is usually asymptomatic in its early stages. In advanced cases, it most commonly gives rise to abdominal pain (50-70%), gastrointestinal bleeding (20-30%), and a palpable abdominal mass. Its diagnosis is usually achieved by CT and magnetic resonance imaging (MRI). In addition, a submucosal mass may be revealed by GIST endoscopy or colonoscopy, a regular-border filling defect by double contrast colonic X-Ray, or a hypoechoic lesion originating from muscularis propria by endoscopic ultrasonography (6).

Endometriosis usually involves serosa or subserosa although it may involve all layers of the colon simultaneously. It may rarely appear as a nodular mass infiltrating the intestinal wall. In the presence of a deep invasion by lesions, it may falsely be interpreted as colon cancer, Crohn's disease, or carcinoid tumor. Furthermore, it may incite inflammation and fibrosis within the intestines, leading to luminal narrowing and obstruction in time. As a result, intestinal obstruction and perforation may occur (7).

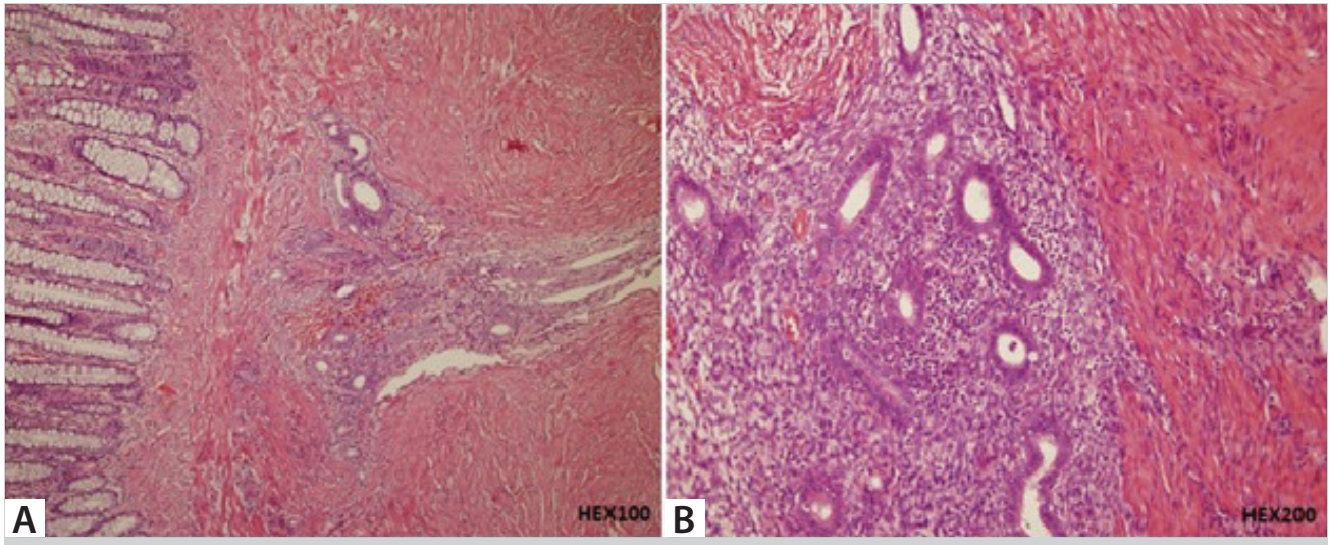

Figure 2. A.B Endometrial stroma and endometrial glands between submucosa and muscle fibers of muscularis propria (HEX100, HEX200).

As for GIST, diagnosis can be achieved by ultrasonography, CT, MRI, and colonoscopy, depending on the localization of the lesion. Although radiological imaging techniques cannot always provide a definitive diagnosis, they can still inform about the lesion's size, localization, and depth. Submucosal mass lesions protruding into the lumen and covered by normal mucosa seen in colonoscopy may be of intramural or extramural origin. Lipoma, lymphangioma, carcinoid tumor, GIST, and leiomyoma are examples of intramural lesions while peritoneal carcinomatosis, extracolonic tumor invasions are examples of extramural neoplasms. Non-neoplastic intramural lesions include lymphoid hyperplasia, hematoma, vascular lesions, pneumatosis cystoides coli, while extramural lesions include endometriosis (8). Since the clinical presentation of patients with intestinal endometriosis may be confused with many disorders including malignant conditions, diagnosis may be delayed and difficult. Fine needle biopsy is helpful for making the diagnosis although surgery and histopathological examination of the surgical excision material are usually required for a definitive diagnosis and to rule out a malignancy. Most intestinal endometriosis cases are diagnosed at laparoscopy or laparotomy (9). Our case could similarly not be diagnosed in the preoperative phase. Despite the lesion's resemblance to a GIST for its rectosigmoid involvement pattern, tomographic findings, and rectosigmoidoscopic appearance, it received a definitive diagnosis after the pathological examination of the laparoscopically excised lesion from the rectosigmoid junction.

Various hormone suppression therapies previously applied for intestinal endometriosis usually proved unhelpful. Patients who cannot be operated for any reason can be medically managed by non-steroidal anti-inflammatory drugs, danazol, gonadotropin-releasing hormone and oral contraceptives. The majority of patients with this condition display significant improvement although recurrences are common when therapy is stopped. Hence, surgery should particularly be the first option in younger patients and those with severe symptoms. Resection of the affected intestinal segment and re-anastomosis of the intact parts is the best accepted approach for intestinal endometriosis. Recurrence rates remain low after total excision (10).

CONCLUSION

In women of reproductive age, intestinal endometriosis, even if asymptomatic, should be included in the differential diagnosis of submucosal lesions of the rectosigmoid colon in addition to GISTs and carcinoid tumors. This rare condition may mimic many other disorders. Definitive diagnosis is only possible through surgical resection and histopathological examination of the lesions.

Informed Consent: Informed consent was obtained from patient who participated in this case.

Peer-review: Externally peer-reviewed.

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Gastrointestinal stromal tümörü taklit eden rektosigmoid kolon endometriyozis

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ÖZET

Endometriyozis, fonksiyonel endometriyotik gland ve stromanın uterin kavite dışında büyümesi olarak tanımlanır. Ekstragenital endometriyozis oldukça nadir görülen bir hastalık olmakla birlikte, doğurganlık çağındaki kadınlarda daha yaygın görülür. Gastrointestinal sistemde en sık rektosigmoid bileşkede görülen endometriyozis; karın ağrısı, konstipasyon, rektal kanama gibi semptomlara neden olabilir. Gastrointestinal stromal tümör, gastrointestinal sistemin en sık görülen mezenkimal tümörüdür ve muskularis propriadan gelişir. Ekstraluminal komponenti belirgindir. Bu yazıda, rektosigmoid bileşkede sınırları net ayırt edilemeyen, malign görünümlü submukozal kitle nedeniyle laparoskopik kolon rezeksiyonu yapılan ve histopatolojik inceleme ile kesin tanı alan 37 yaşında, nadir bir olgu sunuldu. Olgumuzda olduğu gibi nonspesifik gastrointestinal semptomları olan üreme çağındaki kadın hastalarda, ayırıcı tanıda endometriyozis de düşünülmelidir.

Anahtar Kelimeler: Endometriyozis, rektosigmoid, malignite, laparoskopik rezeksiyon

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