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ORIGINAL SCIENTIFIC REPORT

Effects of Intra-abdominally Instilled Isotonic Saline on Pain, Recovery, and Health-Related Quality-of-Life Following Laparoscopic Cholecystectomy: A Randomized Prospective Double-Blind Controlled Study

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Abstract

Introduction The postoperative installation of isotonic saline in the abdomen has been suggested as a method to reduce the effect of local toxins, thereby reducing postoperative pain in patients undergoing laparoscopic surgery. The aim of this randomized prospective double-blind trial was to assess whether installation of isotonic saline can reduce postoperative pain and nausea following laparoscopic cholecystectomy (LC).

Methods Altogether 71 LC patients were randomized to either intra-abdominal instillation of isotonic saline group (S) ($n = 36$) or no saline (NS) group ($n = 35$) at the end of surgery. Data were collected by means of questionnaires. The postoperative recovery profile questionnaire was answered prior to surgery and 1 week postoperatively, SF-36 prior to surgery and at 1 month postoperatively, and a pain diary recording a Visual Analogue Scale score each day during the first week.

Results The overall response rate was 94 %. No significant differences were seen between the groups regarding abdominal and shoulder pain. However, the NS group reported more pain (NS = 53 %, $S = 29$ %) and fatigue (NS = 50 %, $S = 35$ %) than the S group postoperative day 7. Moreover, the most frequently reported problem in both groups 7 days after surgery was getting back to normal life (60 %). Females reported a slower recovery profile than males and also more postoperative symptoms day 7. HRQoL results were similar between the groups.

Conclusion Instillation of isotonic saline does not improve recovery after laparoscopic cholecystectomy. Postoperative pain was more often reported in the NS group than in the S group, though the difference was not significant.

Registration—Ethics Committe Sthlm (2010/159-31/1)—KCTR (CT 20110066).

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Introduction

Laparoscopic cholecystectomy (LC) has been shown to significantly improve both gastrointestinal symptoms and health-related quality-of-life (HRQoL) among patients with symptomatic gallstone disease [1, 2]. Postoperative pain, nausea, and vomiting, however, are still problems in the recovery period and are the main factors preventing patients from resuming recreational activity and work during the early postoperative period [3, 4]. Since it is common practice to perform LC as a day-care procedure, it is crucial that postoperative pain is treated optimally.

Postoperative pain in most patients undergoing LC is predominantly located in the shoulders, abdomen, and back

[5]. The pain is usually reported to be most intense on the day of surgery and during the first two postoperative days, with a considerable variation between individuals [6]. One week following LC surgery, most patients report less pain and significant improvement is seen during the first postoperative month [7]. The degree of change in Quality-of-life (QoL) after surgery depends upon the preoperative situation. Patients without symptoms benefit less and may even perceive a decrease in QoL [8]. Studies intended to minimize pain through the instillation of isotonic saline in the abdomen at the end of surgery have been performed, showing effects on immediate postoperative pain [9–11]. In the longer perspective, however, there is no clear evidence that this regimen effectively decreases pain, time to recovery, or increases HRQoL. There is a lack of systematic data on patient-related outcomes. The aim of this study was to investigate the impact of isotonic saline instilled in the abdomen at the end of LC surgery on time to recovery and patientś self-reported HRQoL preoperatively, at 1 week and 1 month following LC.

Methods

Participants

The study was conducted at three surgical centers in Stockholm. From December 2010 to September 2013, 75 patients scheduled for elective LC were included in the study. The patients fulfilled the following inclusion criteria: ultrasonography documented cholelithiasis; symptomatic gallstone disease (pain attacks, a history of cholecystitis or a history of gallstone pancreatitis); planned elective laparoscopic cholecystectomy; American Society of Anesthesiologists (ASA) I–II; and age between 18 and 80 years. Indications for surgery were severe symptoms or complications of gallstone disease. In order to receive day-care surgery, patients were required to have access to support at home of an adult relative for the first night following LC. Exclusion criteria were immunodeficiency, HIV, previous upper gastrointestinal tract surgery, and confirmed malignancy. In cases where the procedure had to be converted to open cholecystectomy, the patients were maintained in the study for intention to treat analysis, but no saline was installed. Since the unit where the procedures were performed is a teaching hospital, the operations were often performed with an experienced surgeon teaching a resident with short experience in surgery. Informed consent, verbal and written information about the aim and procedure of the study were given to the patients. All patients had the right to withdraw their participation at any time. The Ethics Review Board at the Karolinska University Hospital, Huddinge, approved the study protocol.

Interventions

Patients were randomized to receive isotonic saline instilled in the abdomen or not. It was hypothesized that pain difference between the two groups, measured as mm on VAS, would be 10 mm or more.

Surgical procedure and anesthesia

An experienced surgeon was present at every procedure. Paracetamol, morphine, and diclofenac were given as preoperatively as prophylaxis against postoperative pain, and betamethasone and ondansetron against nausea. Anesthesia was maintained with remifentanil, sevorane, and the patient relaxed with rocuronium. LC was performed using a standard four-trocar technique with carbon dioxide insufflation. Intraoperative cholangiography was routinely performed. A standardized anesthetic protocol was followed. Thirty minutes from the end of anesthesia, morphine 0.1 mg/kg was administered intravenously. The trocar puncture sites were infiltrated with 20 cc of 0.5 % bupivacaine with adrenalin prior to completion of surgery.

Sample size

The sample size was based on the hypothesis that installation of isotonic saline in the abdomen at the end of LC surgery could reduce postoperative abdominal and shoulder pain. In a previous study, pain assessed with a VAS scale was found to be reduced from 3.76 to 2.32 with a standard deviation of 2.06 in the group receiving saline [9]. For a power of 80 % and a significance level of 95 %, 64 patients would be required to confirm a difference between the groups at that level. In order to compensate for included patients not being valid for efficacy analysis, our initial intention was to enroll 100 patients into the study.

Randomization

The study participants were allocated to one of the groups by opening a sealed envelope. The envelopes were opened preoperatively and the patient's group was only shared with the personnel present at surgery.

Sequence generation

The sequence was produced by a computerized random generator. No blocking was done.

Allocation

At the end of the procedure, the abdominal cavity was cleansed with saline-irrigation and suction followed by

instillation of 500 ml saline in the abdominal cavity in the study group (S).

Concealment mechanism

Only the surgeon and personnel present at the procedure were aware of the patient's allocation. The allocation was recorded in a separate file, but was not documented in the patient's notes. Neither the patient nor the surgeons and nursing staff responsible for postoperative care were aware of the allocation.

Blinding

The patient as well as the physician and research nurses responsible for evaluation of the outcome were blinded to the allocation.

Data collection

Background data

Data on medication, BMI, age, sex, marital status and work, and use of urine catheterization were obtained from patient records.

Pain diary

A pain diary was designed for this study, where patients rated their perceived level of pain each evening postoperative days 1 to 7, using a 10-cm visual analogue scale (VAS) [12]. The patients were requested to do the recording in the evening in order to recall the pain they had perceived during the day.

The postoperative recovery profile questionnaire, PRP

The PRP questionnaire was developed by Allvin et al. [13]. It is a discriminative and evaluative scale for self-assessment of general postoperative recovery after surgical procedures. It contains 19 items concerning the dimensions physical symptoms, physical functions, psychological, social and activity on a four-point scale. The verbal descriptive response grades "none," "mild," "moderate," and "severe" were used. Besides, the detailed individual four-grade response profiles, the PRP responses were used for an overall score of recovery by defining the patient's level of recovery as the number of 'None' responses to the 19 items. The more the "None" responses, the greater the recovery. A grade of "None" for all 19 items represented full recovery. Additionally, a classification of the indicator sums into recovery levels was done. The categories fully recovered (19 points), almost fully recovered (15–18 points), partly recovered (8–14 points), slightly recovered (7 points), and not recovered at all (<7 points) were used. The questionnaire was used before surgery, 1 week and 1 month following surgery. The PRP questionnaire has been shown to have construct validity [14].

The medical outcome survey, short form-36, SF-36

The SF-36 is a generic multipurpose, short-form health survey with 36 items, used to assess HRQoL [15]. The SF-36 Standard Swedish Version 1.0 was used to measure self-reported HRQoL previously tested for validity and reliability in the Swedish population [16, 17]. The questionnaire was answered before surgery and at 1 month following LC.

Ethics

All patients received verbal and written information about the aim of the study and how it was to be conducted, and that they could withdraw their participation in the study at any time.

Statistics

To describe the basic features, descriptive statistics were used. Student's t test was used to test differences between two independent group means. Mann–Whitney U test was used to test the difference in ranks of scores on two independent groups. Repeated measurements analysis was used to analyze time-dependent data. Significance was accepted at $p < 0.05$. Analyses were conducted using STATISTICA 7.0 (StatSoft Inc., Tulsa, OK).

Results

Number analyzed

The sample assembly flow for the study is presented in Fig. 1. A total of 75 patients with verified gallstones were included in the study. Of these, 71 patients, 45 women (63 %) and 26 men (37 %), completed the study. They were allocated to the saline group (S, $n = 36$) and no saline group (NS, $n = 35$). A total of four patients were excluded from the study because of drain left postoperatively ($n = 2$), colonic fistula at the time of operation ($n = 1$), or suspect tuberculosis following preoperative findings ($n = 1$). There were no conversions to open surgery.

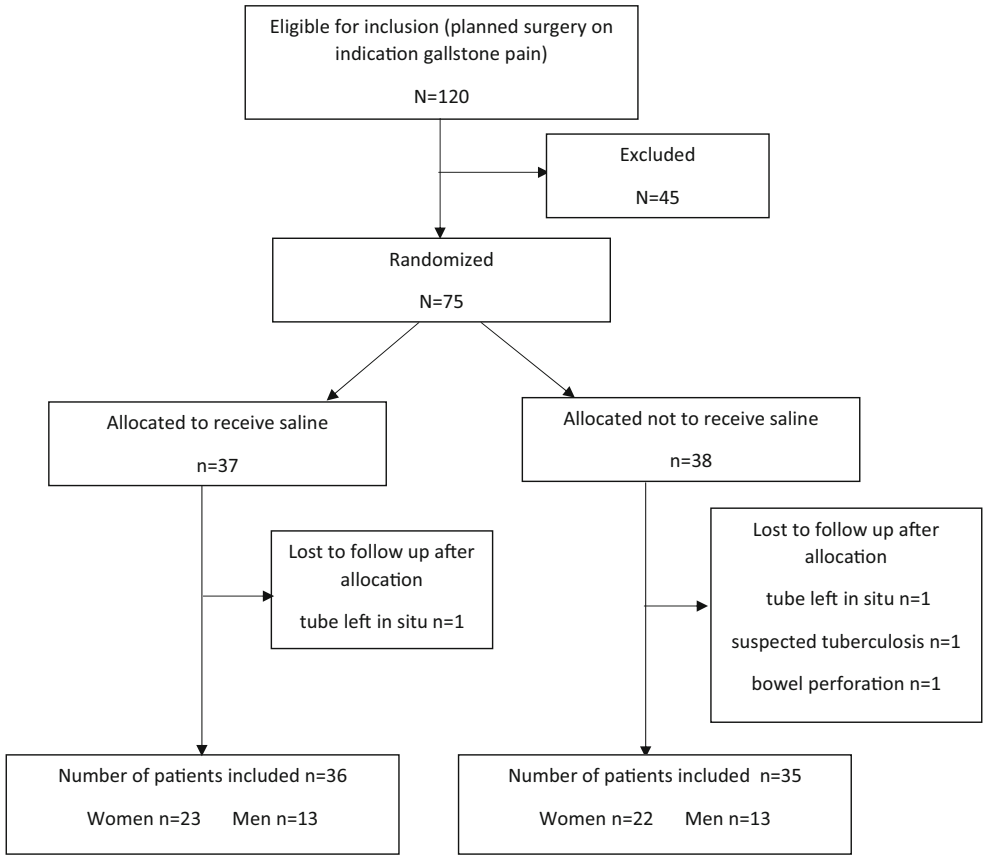

Fig. 1 Participant flow chart of the study

Recruitment

Participants were recruited from December 2010 to October 2013 at the Department of Surgery, Karolinska University Hospital Huddinge. Table 1 shows the baseline data. Mean ages were 52 years, (range 19–80 years) in the S group and 50 years, (range 18–76 years) in the NS group. There were no significant differences between the groups as regards age, sex, marital, status, occupation, body mass index, BMI, or indication for surgery. Due to a long operation time, 52 patients (74 %) received a urinary catheter on the day of surgery, and 3 patients visited a doctor because of a urinary tract infection postoperatively. The study was interrupted prior to inclusion of the intended 100 patients due to organizational changes at the three units.

Outcomes and estimation

Pain

There were no statistically significant differences concerning the intensity of shoulder pain and abdominal pain (VAS) between the groups measured at 1 and 4 h, postoperative day 1 and at 1 week (Table 2). Pain intensity decreased significantly in the NS group between postoperative days 1 and 3 (Fig. 2, $p = 0.03$). Furthermore, at postoperative day 1, VAS > 3 was reported by 44 % in the NS group and 36 % in the S group. When comparing the intensity of pain between females and males, no significant differences were found between the groups at any of the measurement time points.

Nausea

Patients rated their experience of nausea. At 1 h postoperatively, 16 patients (42 %) in the S group and 9 patients (26 %) in the NS group reported nausea $p = 0.04$. There were no statistically significant differences between the groups at any of the other measurement time points.

Postoperative recovery profile

The most frequently reported problem day 7 following LC was getting back to normal life ($S = 59$ %), NS $= 60$ %). Pain was more often reported in the NS group (53 %) than

Table 1 Sociodemographic data of the patients receiving isotonic saline, S installed in the abdomen and patients not receiving isotonic saline NS, and the total sample undergoing laparoscopic cholecystectomy

	Patients S group $n = 36$	Patients NS group $n = 35$	Total %
Women:men	23:13	22:13	45:26
Age (years)	52 ± 17	50 ± 14	–
BMI (body mass index) (kg m^{-2})	27.5±	28.9 ± 4.7	–
Marital status married/cohabiting:single	24:12	23:11	47:23
Occupation working/studying:sick leave/pension	24:12	29:4	53:16
Inpatients/outpatients	19:17	14:20	

Values are presented as mean or median (range) as appropriate. No statistically significant differences were seen between the groups regarding sociodemographic data

Table 2 Comparison between the saline (S) and no saline (NS) groups regarding postoperative shoulder pain, abdominal pain, and nausea at 1 and 4 h and day 1 and day 7 postoperatively

VAS	S $N = 35$	NS $N = 34$	p value
Shoulder pain			
1 h	1.21	0.90	ns
4 h	1.26	1.01	ns
Day 1	1.27	2.20	ns
Day 7	0.44	0.34	ns
Abdominal pain			
1 h	3.64	3.24	ns
4 h	2.31	1.83	ns
Day 1	2.50	3.01	ns
Day 7	1.17	2.13	ns
Nausea			
1 h	1.78	0.72	0.039
4 h	1.22	0.91	ns
Day 1	0.66	0.18	ns
Day 7	0.41	0.22	ns

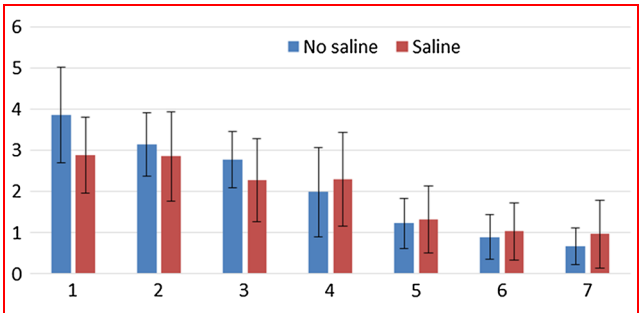

Fig. 2 Mean scores for pain intensity measured by visual analogue scale postoperative day 1 to 7 following laparoscopic cholecystectomy in the Saline and No saline groups. No statistically significant differences were found between the groups

in the S group (29 %), as well as fatigue ($S = 35$ %, NS = 50 %). Mobilization was reportedly similar in the two groups ($S = 32$ %, NS = 37 %) (Table 3).

Table 4 shows recovery stages at 1 week and 1 month. Postoperative Day 7, six patients (18 %) in the *S* group and two patients (6 %) in the NS group reported that they were "Fully recovered." Moreover, 15 patients (44 %) in the S group and 14 patients (47 %) reported that they were "Almost fully recovered."

At 1 month, 13 patients (38 %) in the S group and 9 patients (35 %) in the NS group were "Fully recovered" and 15 patients (44 %) in the S group and 12 patients (46 %) in the NS group were "Almost fully recovered." No statistical significant differences were seen between the groups (Table 4).

Preoperatively, patients in the *S* group reported a mean of 7.8 current symptoms and the NS group 6.1 current symptoms. One week after LC, symptoms had decreased in the *S* group to 6.7 and in the NS group to 7.6 reported symptoms. After 1 month, both groups reported 2.9 symptoms. No statistically significant differences were found between the groups. When comparing the postoperative recovery profile between females and males, females recovered more slowly than males and reported more symptoms on day 7 ($p = 0.04$). There were no significant differences between the groups regarding time to discharge.

HRQoL

There were no significant differences in any of the SF-36 subscales between the S and NS groups measured at baseline and 1 month after surgery.

Postoperative Pain-Medicine

At discharge, patients were provided with a three-day supply of pain medications: diclofenac 50 mg three times a day, paracetamol 1 g four times a day, and morphine 5 mg (6 tablets) to be taken as prescribed if severe pain was experienced. Twenty-three patients in the S group and 18 patients in the NS group consumed opioids the first

Table 3 Comparisons between the saline (S) and the no saline (NS) groups regarding postoperative recovery profile postoperative day 7 following laparoscopic cholecystectomy

Postoperative symptoms 1 week			
Symptoms	S	NS	
	$n = 34$ (%)	$n = 30$ (%)	p value
Pain	10 (29)	16 (53)	ns
Nausea	6 (18)	5 (17)	ns
Gastrointestinal function	10 (29)	8 (27)	ns
Fatigue	12 (35)	15 (50)	ns
Muscle weakness	11 (32)	7 (23)	ns
Appetite changes	9 (26)	12 (40)	ns
Sleeping difficulties	11 (32)	13 (43)	ns
Anxiety and worry	5 (15)	5 (17)	ns
Feeling down	6 (18)	3 (10)	ns
Re-establishing everyday life	20 (59)	18 (60)	ns
Sexual activity	6 (18)	10 (33)	ns
Social activities	11 (32)	9 (30)	ns
Personal hygiene	3 (9)	3 (10)	ns
Interest in surroundings	3 (9)	0 (0)	–
Bladder function	6 (18)	7 (23)	ns
Mobilization	11 (32)	11 (37)	ns
Feeling lonely/abandoned	1 (3)	2 (6)	ns
Dependence on others	14 (41)	9 (30)	ns
Difficulty in concentration	5 (15)	5 (17)	ns

Numbers and percentages are given. Statistics used: Chi-square test and Fisher's exact test when appropriate

postoperative day, and 19 patients in the *S* group and 14 patients in the NS group were admitted for the first postoperative night (Table 5).

Harms

One patient in the control group had a transient increase of creatinine, but no signs of persisting kidney failure. No adverse events directly related to the intervention were seen.

Discussion

In the present study, no significant differences were seen between the groups in terms of abdominal and shoulder pain. However, approximately 40 % in both groups reported VAS > 3 the first postoperative day. VAS > 3 is usually considered as exceeding the acceptable level of pain in the normal postoperative course [18]. Pain [4] and PONV (postoperative nausea and vomiting) during the first postoperative days are probably underestimated after LC.

In day-care surgery, it is important to beware of the fact that not all of the postoperative adverse events and symptoms after discharge come to the knowledge of the healthcare provider. A more structured follow-up and contact during the early postoperative period may be a way of reducing unnecessary PONV that may be easily controlled if treated proactively. In a study by Tamhankar et al. [19], pain not controlled by prescribed analgesia after hospital discharge was reported by 11.7 % of the patients. Nausea and vomiting was present in 22.5 % but only 2.9 % lasted ≥ 2 days. The hypothesis of the present study was that installation of isotonic saline in the abdomen at the end of LC surgery reduces postoperative abdominal and shoulder pain, PONV and improves the postoperative HRQoL. However, no such effects were seen and the hypothesis refuted.

Previous studies have shown that LC may effectively reduce gallstone-related pain when performed based on adequate indication [20–22]. A positive effect of intra-abdominally instilled isotonic saline on postoperative abdominal and shoulder pain has been reported [9–11, 23, 24], especially during the first 24 h [9]. In a study by Szem et al. [11], patients randomized to receive bupivacaine had significantly better pain control than the saline group. However, the bupivacaine group had less pain in the first 6 h only. No reduction in PONV or shoulder pain was seen in bupivacaine group. Moreover, their study was small, with only 55 patients included in the analysis.

The study was initiated with the goal of including 100 patients. It was, however, interrupted prior to the intended

Table 4 Comparison between patients receiving saline (S) and no saline (NS) in different recovery stages at 1 week and 1 month following laparoscopic cholecystectomy

Postoperative recovery profile	1 Week		1 Month		
Indicator sum	Saline $n = 34$	No saline $n = 30$	Saline $n = 34$	No saline $n = 26$	p
Fully recovered (19)	6	2	13	9	ns
Almost fully recovered (1–18)	15	14	15	12	ns
Partly recovered (8–14)	9	10	6	3	ns
Slightly recovered (7)	2	2	–	–	ns
Not recovered at all (<7)	2	2	–	2	ns

Table 5 Analgesic consumption, postoperative day 1 before discharge in the saline (S) and the no saline (NS) groups

Incidence by groups	Saline $N = 36$	No saline $N = 34$	P value
Paracetamol	19	19	ns
Opioids	23	18	ns
NSAID's	15	4	0.03

Statistics: Fishers exact test

sample size. Nevertheless, the number of included was sufficient according to the power analysis, which stipulated a pain reduction from 3.76 to 2.32 with a standard deviation of 2.06 on the VAS scale.

Although there was a tendency toward a non-significant difference in pain between the groups that may have turned significant if more patients had been included, this difference was still too small to reach the level of minimal clinical important difference.

Many of the patients in the present study had a history of complications from gallstone disease, and they were operated by an experienced surgeon and a resident in the learning situation and hence, the operation time was relatively long. It cannot be excluded that the onset of the inflammatory and stress response was already initiated and manifested and that the addition of saline at the end of the operation had no effect on this response.

One week after surgery 39 % in the (*S* group) and 54 % (NS-group) reported pain, but the intensity of pain had decreased to VAS 1.5. This is in line with the results of Gupta et al. [10] who reported that postoperative pain was minimal after 1 week. Nevertheless, one third of their patients in the *S* group and half of the NS group still reported pain.

At 1 h, patients in the S group reported higher frequency of nausea compared to the NS group. On the contrary, Tsimoyiannis et al. [23] and Ahmed et al. [9] found that nausea was reduced by saline installation, whereas Szem et al. [11] reported that nausea was perceived equally between their patients. Although the nausea perceived by patients in the saline group in the present study may have been due to distention of the peritoneum and that a larger volume was used than earlier reported, these results should be interpreted with some caution. Furthermore, the clinical relevance was limited as the effect ceased very quickly.

The length of hospital stay was the same in both groups in our study. Similar results have been seen in other studies [11, 23]. The opposite has also been demonstrated [9]. No serious side effects were seen from saline installation.

The consumption of analgesics postoperatively was similar in the two groups. This is an agreement with many previous studies [10, 11]. However, in the study by Ahmed et al. analgesic consumption was lower in their saline group [9].

Recovery

We lack adequate tools for the measurement of postoperative recovery. Recovery profiles after LC assessed from the patients' own experience up to 1 month after surgery have not previously been reported. The PRP questionnaire for self-assessment of postoperative recovery following surgery [14] has not been tested on LC patients. Furthermore, no publications regarding time to recovery have been published. We used the PRP questionnaire before surgery to obtain baseline data and at 1 week and 1 month following LC surgery. The patients recovered equally well, no significant differences were seen between the groups. This finding may depend on the fact that 1 week after LC, most symptoms have resolved. If the PRP questionnaire had been completed earlier in the recovery period, e.g., on postoperative days 1 and 3, more valuable results might have been provided.

In the present study, return to normal life was a problem for approximately 60 % of our patients in both groups. Gupta et al. [10] reported in their study that patients felt normal after 1 week, and that 93 % of their patients could continue with ADL. This discrepancy may depend on the fact that we used the PRP questionnaire and return to normal life does not mean the same as feeling normal and the ability to continue with daily life.

That females recover slower than males and report more symptoms 1 week following LC surgery has been seen in previous studies [7, 25]. However, the small sample in this study may limit generalization of our results, and the small proportion of the females and males did not allow comparison between sexes.

Health-related quality-of-life

Some studies have investigated HRQoL outcome following LC surgery [2, 8, 26]. A QoL change may reflect factors other than the effects of the procedure itself, e.g., preoperative functional status, the general state prior to surgery, and demographic characteristics [8, 22, 27]. However, no previous research has focused on the impact of intra-abdominally instilled saline on HRQoL. In our study, this had no impact on HRQoL and no significant differences were seen between our groups of patients.

Generalizability

The long time taken for some of the procedures may be explained by the fact that many patients were operated after a previous history of cholecystitis. Patients included

in the study represent a normal mix of patients scheduled for elective cholecystectomy at centers where gallstone surgery is performed routinely. We do not see any reason to believe that there was any selection mechanism. Further bias may exist because of the small sample size in each group.

Interpretation

Although no significant difference was seen between our groups, the present study shows the importance of being aware of pain and recovery, the first days after discharge after LC. Even if the study sample was large enough to reach stipulated statistical power, there may still be a type II error. Slight differences with regard to postoperative nausea and a gender difference with regard to recovery were noted. The present study could, however, serve as a reference for power-calculation in future studies. Whether saline installation has a greater effect during emergency surgery than in planned cholecystectomy remains an open question.

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