Randomized Trial of Immediate Postoperative Pain Following Single-incision Versus Traditional Laparoscopic Cholecystectomy

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Abstract

Background: We undertook a randomized controlled trial to ascertain if single-incision laparoscopic cholecystectomy (SILC) was more beneficial for reducing postoperative pain than traditional laparoscopic cholecystectomy (TLC). Moreover, the influencing factors of SILC were analyzed.

Methods: A total of 552 patients with symptomatic gallstones or polyps were allocated randomly to undergo SILC ($n = 138$) or TLC ($n = 414$). Data on postoperative pain score, operative time, complications, procedure conversion, and hospital costs were collected. After a 6-month follow-up, all data were analyzed using the intention-to-treat principle.

Results: Among SILC group, 4 (2.9%) cases required conversion to TLC. Mean operative time of SILC was significantly longer than that of TLC (58.97 ± 21.56 vs. 43.38 ± 19.02 min, $P < 0.001$). The two groups showed no significant differences in analgesic dose, duration of hospital stay, or cost. Median pain scores were similar between the two groups 7 days after surgery, but SILC-treated patients had a significantly lower median pain score 6 h after surgery (10-point scale: 3 [2, 4] vs. 4 [3, 5], $P = 0.009$). Importantly, subgroup analyses of operative time for SILC showed that a longer operative time was associated with greater prevalence of pain score >5 (≥ 100 min: 5/7 patients vs. <40 min, 3/16 patients, $P = 0.015$).

Conclusions: The primary benefit of SILC appears to be slightly less pain immediately after surgery. Surgeon training seems to be important because the shorter operative time for SILC may elicit less pain immediately after surgery.

Key words: Laparoscopic Cholecystectomy; Postoperative Pain; Randomized Controlled Trial; Single-incision Laparoscopic Surgery

INTRODUCTION

Advances in natural orifice transluminal endoscopic surgery (NOTES), including improvements in the technology itself and its application by practiced surgeons, have allowed more complex procedures to be undertaken. However, the major barriers that limit its clinical application include access, closure, infection, suturing technology, and intra-abdominal orientation.[1] In recent years, single-incision laparoscopic surgery (SILS) has been considered a more feasible method compared with NOTES owing to its safety and acceptable cosmetic effects [Figure 1b and 1c] (especially for cholecystectomy).

However, the view that single-incision laparoscopic cholecystectomy (SILC) is superior to traditional laparoscopic cholecystectomy (TLC) has been controversial since the first report of SILC in 1997.[2] In theory, the less invasive nature of SILC should produce less incisional pain with lower requirements for analgesia after surgery, shorter stays in hospital, faster return to work and routine activity, improved cosmetic effects, and a higher prevalence of overall patient satisfaction. Recent studies have reflected a growing interest in the validation of these hypotheses. Indeed, results from case series,[3] a case–control study,[4]

and randomized controlled trials (RCTs)[5,6] have supported the proposed safety and practicality of SILC. Unfortunately, results from meta-analyses and systematic reviews[7,8] have not determined definitively the precise benefits of SILC over TLC, because of small study populations and inadequate follow-up data.[9]

This prospective RCT was designed to assess the perioperative features and short-term outcomes of SILC versus TLC using a large population and 6-month follow-up in a single-center setting to gain better understanding of the benefits of these procedures.

METHODS

Ethical approval of the study protocol

The Institutional Review Board of Beijing Friendship Hospital (Beijing, China) approved the study protocol in October 2011. The study had been registered at www. clinicaltrials.gov (NCT01383031). The decision to participate was voluntary, and each patient provided written informed consent before enrollment.

Patient recruitment

Patients (aged 18–75 years old) with symptomatic gallstones or polyps documented by imaging were enrolled. Patients were required to have a low degree of functional impairment (Karnofsky performance scale [KPS] of ≥ 70) and nonobese status (body mass index [BMI] of $< 30 \text{ kg/m}^2$).

Patients were excluded according to a diagnosis of acute cholecystitis, previous upper-abdominal surgery, current/anticipated pregnancy, current breast-feeding, preoperative indication for endoscopic retrograde cholangiopancreatography, or indication for intraoperative imaging of the biliary tract. In addition, discretion was given to the surgeon to exclude otherwise eligible patients according to their judgment of contraindications for laparoscopy. Enrollment or exclusion of all participants was judged by a senior surgeon who worked independently of this RCT.

Randomization

Enrolled patients were assigned to receive SILC or TLC using a 1:3 ratio randomization scheme. The complete randomization sequence was generated by a statistician who had no other role in this RCT. The allocation sequence was delivered in sealed opaque envelopes to a nurse within the operating room (who was not otherwise engaged in the study) immediately before surgery. Only the operating surgeon and accompanying staff in the operating room were aware of the procedure selected.

Surgical procedures

All surgical procedures were carried out by surgeons with extensive experience in TLC and who had undertaken >50 SILC procedures.
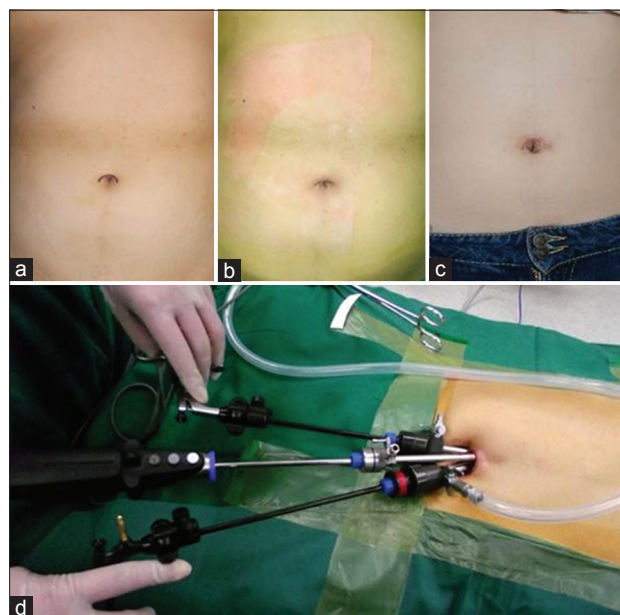
Traditional laparoscopic cholecystectomy

All TLC-treated patients were placed in the reverse Trendelenburg position with their legs placed together.

With the operating surgeon located on the patient's left side, a 10-mm subumbilical incision was made. Then, 12-mmHg insufflation of the abdominal cavity was performed. A 10-mm trocar was inserted to introduce a 30° laparoscope. Then, under direct vision, one 10-mm trocar and one (three-port) or two (four-port) 5-mm trocars were placed in the subxiphoid region and the right subcostal region along the midclavicular (third port) or anterior axillary line (fourth port). One or two graspers were used to retract the gallbladder and expose Calot's triangle. After dissection of the cystic duct and cystic artery, endoclips were applied, and the duct and artery were transected. The gallbladder was dissected from the gallbladder bed, placed in the retrieval bag, and removed through the subumbilical port. Finally, port openings were sutured, and all patients were dressed with four bandages to simulate four-port TLC.

Single-incision laparoscopic cholecystectomy

All SILC-treated patients were placed in the reverse Trendelenburg position with the legs well-separated to accommodate positioning of the operating surgeon. With the patient under general anesthesia, a 2.5-cm semicircular incision was made in the upper half of the umbilicus [Figure 1a]. After a pneumoperitoneum was generated in the abdominal cavity by adding 12 mmHg of insufflation pressure, two 5-mm trocars and one 10-mm trocar were inserted through the umbilical incision at different fascial levels and in a triangular fashion [Figure 1d]. Then, a 5-mm, rigid, 30° laparoscope was introduced through the upper trocar; the remaining two trocars were used to introduce the various other instruments required for the

Figure 1: Incision and placement of instruments in single-incision laparoscopic cholecystectomy (a) shows the mark of the incision site (b and c) that show a curved scar present 7 days and 30 days after surgery, respectively (d) shows the triangular placement of three conventional trocars in a semicircular incision (≤ 2.5 cm in all patients) on the slope of the umbilicus.

laparoscopic procedure. All of the instruments used in the SILC procedure were the same as those used for TLC (see above) except that the grasper used to expose Calot's triangle was 10 cm longer to prevent external crowding. After dissection of the cystic artery and cystic duct, endoclips were applied to facilitate transection of both. Next, the gallbladder was resected completely from the gallbladder bed and retrieved through the 10-mm trocar. Finally, peritoneal and subcutaneous tissues were closed with a 4/0 absorbable suture. The skin was closed with an intradermal suture, and four bandages were left to simulate four-port TLC.

Blinding

Identical opaque dressings were used on all patients regardless of the surgical procedure. The dressings remained in place and unopened until pain scoring was completed during the first postdischarge visit (postoperative day [POD] 7). Thus, the randomization allocation was concealed from participants and investigators until the first postdischarge visit.

Outcome measures

Patients received analgesics as required. Six hours after surgery, patients were encouraged to begin oral intake and mobilize. Duration of hospitalization and date of discharge from hospital were set according to routine practice of the hospital and discretion of the treating surgeon. The first follow-up examination (6 h after surgery) was undertaken in the surgical ward. All subsequent follow-ups were conducted in the outpatient department.

Primary endpoint of our RCT was postoperative pain, which was evaluated by a visual analog scale (VAS) and assessed at 6 h, 24 h, and 7 days, as well as 1, 3, and 6 months after surgery. Secondary endpoints were the KPS, wound-related complications, operative time, duration of hospital stay, and cost.

Sample size

The study was designed and initiated without calculation of sample size because of the lack of confirmative pain-score data in PubMed for dates earlier than October 2011. Therefore, we determined the mean VAS score for the first 10 patients in the SILC group and the first 30 patients in the TLC group. Using the mean VAS score (SILC: 3.9 ± 1.5; TLC: 5.2 ± 1.7), we calculated the sample size required to detect a significant difference between the experimental (i.e., SILC) group and control (i.e., TLC) group using a two-tailed test with a type-I error of 5% and statistical power of 80%, and allowed for a 10% dropout rate. The target number of SILC patients was 138, which is three-fold than number for TLC patients.

Statistical analysis

Collection of prospective data was carried out from enrollment through to follow-up. Data were recorded in a password-protected computerized database. Categorical variables were summarized using frequencies. Continuous variables were summarized as the mean $\pm$ standard deviation (SD) or as the median with the 25th and the 75th percentiles (P25, P75). Categorical variables were compared using the chi-squared test. Continuous variables

were compared using the Student's t-test or Mann–Whitney U-test according to the distribution. The relationship between VAS score and operative time was examined using scatter plots and Kendall's tau correlation coefficients. Statistical significance was determined by two-sided P values, with a $P < 0.05$ set as the threshold for significance. Data were analyzed using the intention-to-treat principle. Statistical analyses were carried out using SAS version 8.2 (SAS Institute, Cary, NC, USA).

RESULTS

Characteristics of enrolled patients

A total of 710 consecutive patients were recruited from 1 November 2011 to 12 August 2012. However, 121 of these patients were excluded, and 37 persons refused to provide written informed consent. Therefore, the final study comprised 552 patients (415 women and 137 men; 19–75 [median, 43] years old). Follow-up was completed on 17 February 2013.

Randomization of patients provided 138 patients in the SILC group and 414 in the TLC group. Of those, 516 (93%) of the patients completed the 6-month follow-up as 127 (92%) in the SILC group and 389 (94%) in the TLC group [Figure 2]. Loss of patients (11/138 in the SILC group, and 25/414 in the TLC group) occurred because of relocation and/or changes in contact information (telephone number). Patient characteristics are presented in Table 1. There were no significant differences between the SILC group and TLC group with regard to age, sex ratio, BMI, preoperative KPS, and indication for surgery.

Intraoperative features

Intraoperative outcomes are presented in Table 2. None of the patients required conversion to open surgery. However, owing to massive adhesions around the gallbladder, four patients in the SILC group required conversion to TLC. Operative time in the SILC group was significantly longer than that in the TLC group (58.97 ± 21.56 vs. 43.38 ± 19.02 min, $P < 0.001$). Within the SILC group, patients who required conversion to TLC had a significantly longer operative time than patients who did not require conversion (125.25 ± 34.20 vs. 56.99 ± 17.79 min, $P < 0.001$). When "converted" cases were excluded, the

Table 1: Characteristics of patients enrolled in the two groups

Characteristics	SILC (n = 138)	TLC (n = 414)	χ^2 or t	P
Age (years), mean ± SD	42.65 ± 11.86	44.44 ± 12.20	1.505	0.133
Sex, male:female	33:105	104:310	0.081	0.776
BMI (kg/m²), mean ± SD	24.68 ± 2.20	25.13 ± 2.96	1.865	0.063
Stone:polyps ratio	110:28	336:78	0.140	0.708
Preoperative KPS, mean ± SD	96.81 ± 4.68	97.10 ± 4.54	0.644	0.520

BMI: Body mass index; KPS: Karnofsky performance scale; SILC: Single-incision laparoscopic cholecystectomy; TLC: Traditional laparoscopic cholecystectomy; SD: Standard deviation.
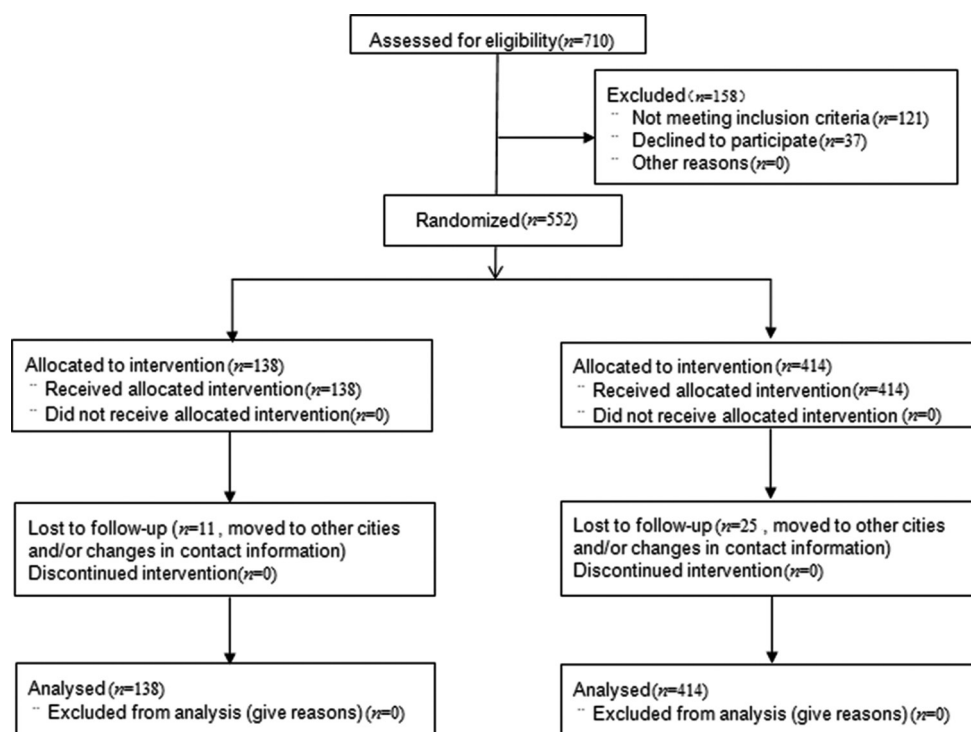
Figure 2: Patient selection and procedure allocation.

Table 2: Intraoperative outcomes associated with SILC and TLC

Outcomes	SILC (n = 138)	TLC (n = 414)	χ^2 or t	P
Operative time (min), mean ± SD	58.97 ± 21.56	43.38 ± 19.02	8.056	<0.001*
Complications				
Yes	22	48	1.767	0.184
No	116	366		
Rupture of gallbladder	17	41	0.642	0.423
Rupture of gallbladder artery	3	7	0.136	0.712
Stones left in the abdomen	12	31	0.210	0.647
Bile duct injury	0	0	NA	NA
Bowel injury	1	2	0.112	0.738
Vascular injury	0	0	NA	NA
Hepatic injury	2	2	1.343	0.246

*P<0.05: The difference is statistically significant. SILC: Single-incision laparoscopic cholecystectomy; TLC: Traditional laparoscopic cholecystectomy; NA: No answer; SD: Standard deviation.

significant difference in operative time between two groups remained (56.99 ± 17.79 vs. 43.81 ± 19.40 min, $P < 0.001$).

The SILC group did not have a significantly higher prevalence of intraoperative complications than the TLC group (22/138 vs. 48/414, $P = 0.184$). Fortunately, severe bleeding did not occur in cases in which the gallbladder artery was ruptured accidentally by improper retraction. In both groups, the hepatic lesions caused by dissection hooks, clip applicators, or trocars were small and repaired

successfully by electrocautery. All procedure-induced bowel injuries were recognized and repaired intraoperatively. No injuries to major vessels were recorded.

Postoperative outcomes

None of the patients experienced severe complications such as injury to the bile duct, postoperative intra-abdominal bleeding, abdominal abscess, postoperative pancreatitis, bowel fistulae, or incision hernia. However, the median VAS score of the SILC group 6 h after surgery was slightly lower than that of the TLC group [Figure 3a]. The difference was only 1-point on a 10-point scale between two groups, which was significant. Differences in median VAS scores for all other time points (24 h, 7 days, as well as 1, 3, and 6 months after surgery) were not significant [Table 3].

When looking specifically at interdependency, there was no correlation between VAS score and operative time (Kendall's tau coefficient, 0.086; $P = 0.176$). However, subgroup analyses of the two parameters revealed some significant associations. When SILC-treated patients were stratified by operative time, operative time >100 min was associated with a significantly higher prevalence of pain score >5 than an operative time < 40 min (5/7 vs. 3/16, $P = 0.015$) [Figure 3b].

A total of 29 SILC-treated and 62 TLC-treated patients received the nonnarcotic analgesic loxoprofen sodium (60 mg, *per os*, <12 h after surgery). Four TLC-treated patients received pethidine (50 mg, intramuscular injection, <12 h after surgery). There was no significant difference between the two groups.

Prevalence of wound-related complications showed no significant differences between the two types of
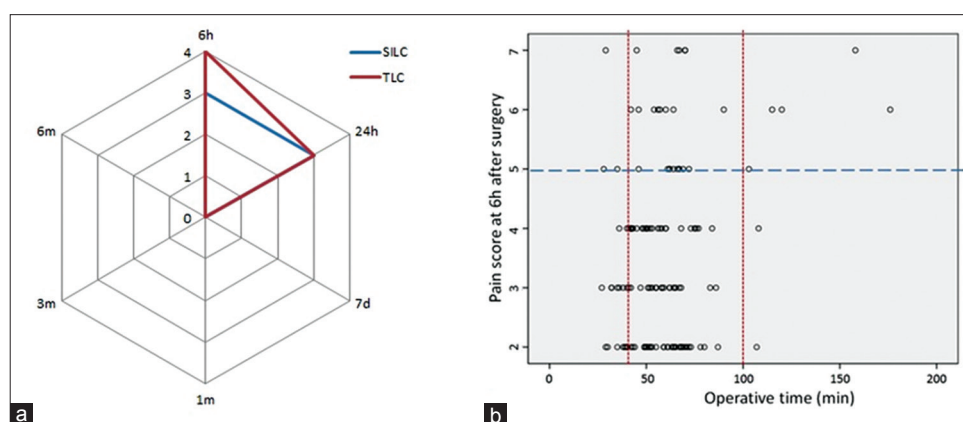
Figure 3: Postoperative pain associated with single-incision laparoscopic cholecystectomy and traditional laparoscopic cholecystectomy. (a) "Radar" chart of postoperative visual analgesia scores. A significant inter-group difference was seen only at the earliest postoperative time recorded (6 h after surgery). (b) "Dot plot" of subgroup analyses to compare operative time of single-incision laparoscopic cholecystectomy with earliest recorded postoperative pain (6 h after surgery).

Table 3: Postoperative outcomes associated with SILC and TLC

Outcomes	Postoperative time point	SILC ($n = 138$)	TLC ($n = 414$)	U or χ^2 or t	P
VAS, median (P25, P75)	6 h	3 (2, 4)	4 (3, 5)	32,748.0	0.009*
	24 h	3 (2, 4)	3 (2, 4)	27,389.0	0.455
	7 days	0 (0, 0)	0 (0, 0)	29,136.5	0.579
	1 month	0 (0, 0)	0 (0, 0)	28,846.5	0.760
	3 months	0 (0, 0)	0 (0, 0)	28,846.5	0.760
	6 months	0 (0, 0)	0 (0, 0)	28,428.5	0.892
KPS, median (P25, P75)	24 h	70 (70, 70)	70 (70, 70)	29,602.0	0.345
	7 days	90 (90, 92.5)	90 (90, 100)	30,952.5	0.105
	1 month	100 (100, 100)	100 (100, 100)	28,638.0	0.945
	3 months	100 (100, 100)	100 (100, 100)	28,124.5	0.668
	6 months	100 (100, 100)	100 (100, 100)	28,839.5	0.786
Wound-related infection		4	6	1.222	0.269
Wound-related hernia		0	0	NA	NA
Analgesic		29	66	1.869	0.172
Hospital stay (days)		3 (3, 5)	3 (3, 5)	29,425.5	0.554
Hospital cost ($), mean ± SD		1353.47 ± 124.87	1367.12 ± 116.31	1.126	0.222

*$P<0.05$: The difference is statistically significant; median (P25, P75): Median with the 25th and 75th percentiles. VAS: Visual analgesia scores; KPS: Karnofsky performance scale; SILC: Single-incision laparoscopic cholecystectomy; TLC: Traditional laparoscopic cholecystectomy; $: United States dollar; NA: No answer.

procedure [Table 3]. Most (7/10 for both groups) infections presented 10 days after surgery with only three cases of infection presenting on POD 7. All cases were resolved by open packing, and no patient needed oral antibiotics. No incisional hernia was detected by physical examination in either group during the 6-month follow-up. The two groups had similar durations of hospital stay and cost of the procedure [Table 3].

Discussion

Since the first report on NOTES,[10] most NOTES-related studies have been limited to preliminary clinical trials owing to a shortage of instrumentation. Thus, SILS has been proposed as an alternative "conduit" procedure that may facilitate widespread transition from traditional laparoscopy to NOTES.[11]

As a new and rapidly developing method, SILS has been carried out on several complex procedures such as bariatric surgery,[12] radical mastectomy,[13] colorectomy,[14] hepatic lobotomy,[15] splenectomy,[16] and distal pancreatectomy.[17] Safety and feasibility of SILC have been validated, but a clinical trial with a large sample size is necessary to evaluate better the differences between SILC and TLC, particularly in terms of postoperative pain, KPS, wound-related complications, hospital stay, and cost. Our prospective RCT of SILC versus TLC was designed to evaluate a larger case series with longer follow-up than those documented previously.

Reports of SILC have provided inconsistent data regarding the presence and extent of postoperative pain and requirement for analgesics. For example, a prospective study suggested a trend in SILC-treated patients of less pain 3 h and 24 h after surgery.[18] However, another study demonstrated that VAS scores differed only on POD 7, and that the SILC group had significantly worse pain than the TLC group.[19]

Two meta-analyses of published RCTs have suggested that SILC might result in less postoperative pain,[8,20] but robust data showing definitively that a single-incision reduces the risk of postoperative pain are lacking.

Several factors can affect postoperative pain such as sex, age, wound size, and recovery time of gastrointestinal function. VAS is the most objective evaluation criterion, which is why we chose it to evaluate the postoperative pain. Our results were not in complete agreement with previous studies on postoperative pain. Patients treated with SILC or TLC showed no significant differences in VAS score 24 h, 7 days, or 1, 3, or 6 months after surgery. Only at 6 h after surgery did the SILC-treated group showed a significantly lower pain score than that of the TLC-treated group. However, when putting this 1-point difference on a 10-point scale, there seemed to be no dramatic change in clinical practice.

Interpretation of the findings from several studies in publicly available literature is difficult because of the heterogeneous design of such studies. Several variables are known to influence a patient's experience of the postoperative pain. Some authors have suggested that the higher VAS score associated with SILC may be explained by the larger incision wound.

However, our RCT suggested that operative time may contribute (at least in part) to higher pain scores because a significant relationship was found for long operative times (≥ 100 min) and the shortest operative time (< 40 min) when the potential correlation between postoperative pain and mean operative time was examined. Therefore, we postulated that single-incision-related pain might be more closely related to the multiple instruments "squeezed" into a single wound site than the wound size itself.

Unfortunately, our RCT did not address whether SILC-related postoperative pain was correlated with umbilical access methods such as direct-puncture or porous-channel puncture devices (e.g., TriPort [Olympus, Tokyo, Japan] or SILS Port [Covidien, Dublin, Ireland]). These commercial products not only protect the wound better during the procedure but can also shorten the operative time by reducing the risk of instrument collision within the wound site. Hospital cost would be increased considerably using these commercial products, and this has been considered a complicating factor that should be considered in future meta-analyses of RCTs of SILC.[21] As such, the expense of such procedures must be considered when interpreting our data.

Although our study had limitations, it provided evidence that the immediate postoperative pain associated with SILC is only slightly lower than that associated with TLC. In addition, the pain score was shown to be strongly affected by the operative time. If surgeons who carry out SILC are well-trained and operative time is shortened as a result, SILC might be more beneficial to patients than TLC.

Acknowledgments

Conflicts of interest

There are no conflicts of interest.

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