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Preemptive visceral analgesic effect of thoracic paravertebral block on postoperative opioid consumption in patients undergoing laparoscopic cholecystectomy: a prospective, randomized, assessor-blind study

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Background: The preemptive visceral analgesic effect of regional nerve block has not been adequately investigated to date. We evaluated the preemptive visceral analgesic effect of thoracic paravertebral block (TPVB) in patients undergoing laparoscopic cholecystectomy (LC) in whom pre-incisional rectus sheath block (RSB) was used to minimize somatic surgical pain.

Methods: In this prospective, randomized, assessor-blind study, 70 patients scheduled for elective LC were randomly assigned to the pre-TPVB (n = 35) or the post-TPVB (n = 35) group. Both groups received pre-incisional RSB, and patients in the pre-TPVB group received TPVB before skin incision while those in the post-TPVB group received TPVB after skin closure. The primary outcome was the total rescue analgesic consumption (morphine equianalgesic dose) during the 24 h post-surgery. The secondary outcomes were the cumulative analgesic consumption and pain intensity for 24 h after surgery, and adverse events.

Results: Pre-TPVB significantly reduced total rescue analgesic consumption (estimated mean [95% CI]) during the 24 h after surgery than post-TPVB (16.9 [14.5, 19.3] vs. 25.3 [22.8, 27.7] mg, estimated difference: –8.3 [–11.8, –4.9], P < 0.001). The cumulative rescue analgesic consumption was significantly lower in the pre-TPVB group from 2–24 h after surgery (P < 0.001). The postoperative pain intensity was significantly lower in the pre-TPVB group as well at 0.5–6 h after surgery. There were no adverse events in both groups.

Conclusions: Pre-incisional TPVB conferred a significant preemptive visceral analgesic effect in patients undergoing LC, and significantly reduced the amount of postoperative opioid consumption.

Keywords: Analgesia; Nerve block; Opioid analgesics; Postoperative pain; Prospective studies; Visceral pain.

Introduction

Reducing the amount of postoperative opioid consumption is a critical issue considering the opioid crisis in high-income countries [1,2]. Preemptive analgesia that involves the application of analgesic drugs or procedures before surgical stimulation is effective in reducing postoperative opioid consumption and pain, and may reduce the incidence of postoperative hyperalgesia and allodynia by preventing the establishment of peripheral and central sensitization caused by surgical injuries [3–5]. Indeed, several randomized control trials showed the preemptive somatic analgesic effect of regional nerve block [6–10]; of those, our team compared the effect of preoperative rectus sheath block (RSB) with postoperative RSB on postoperative pain after laparoscopic cholecystectomy (LC) and showed that the cumulative rescue analgesic consumption was significantly lower in the preoperative RSB group [9]. A recent meta-analysis showed consistent results [11].

However, central sensitization occurs not only due to the surgical stimulation caused by skin incision, but also due to visceral tissue damage incurred during surgery [3,4,12]. Prolonged noxious stimulation of the viscera can lead to peripheral sensitization of visceral nociceptors and central sensitization that could cause uncontrolled pain [13]. Theoretically, preemptive analgesia for post-surgical visceral pain can be obtained by performing a preemptive nerve block that interrupts the visceral afferent pathway. In order to solely evaluate the preemptive visceral analgesic effect, the groups being compared should only differ in the timing of the administration of visceral analgesia; in other words, only the degree of visceral—not somatic—noxious stimulation should differ during surgery. However, it is difficult to satisfy this condition in a perioperative setting because both somatic pain and visceral pain are induced in surgery and there are no appropriate clinical models for studying surgery-related visceral pain [14]. Furthermore, a potent regional block before surgical incision theoretically alleviates both visceral pain and somatic pain at the same time. Because of this technical issue, the sole preemptive visceral analgesic effect of regional nerve block has not been adequately investigated to date.

In the present study, we designed a clinical model for solely investigating the preemptive visceral analgesic effect of regional nerve block. Thoracic paravertebral block (TPVB) is a regional nerve block that can prevent visceral nociceptive transmission by inducing a sympathetic block [15]. We evaluated the preemptive visceral analgesic effect of TPVB in patients undergoing LC, in whom the somatic pain caused during surgery could be readily minimized by pre-incisional RSB [9,11]. Therefore, after performing RSB, we performed TPVB either prior to skin incision or after skin closure to compare and determine the effects of preemptive visceral analgesia in terms of opioid consumption and postoperative pain intensity during the first 24 h after surgery.

Materials and Methods

This was a single-center, prospective, randomized, assessor-blind study performed at Asan Medical Center in Seoul, Republic of Korea. The study protocol was approved by our Institutional Review Board (IRB no. 2019-0334). The trial was registered before patient enrolment at the Clinical Research Information Service (http://cris.nih.go.kr; KCT0003810). Written informed consent was obtained from all participants. We conducted this study in accordance with the Declaration of Helsinki, 2013 and followed the Consolidated Standards of Reporting Trials guidelines for study reporting.

To examine whether preoperative TPVB confers a preemptive visceral analgesic effect in patients undergoing LC, we randomly divided the study participants into the pre-TPVB group (TPVB before skin incision) and the post-TPVB group (TPVB after skin closure). Adult patients scheduled for elective LC between August 12 and October 16, 2019, at our institution were considered eligible for the study. Inclusion criteria were age between 20 and 80 years and American Society of Anesthesiologists Physical Status class of ≤ 2. Exclusion criteria were as follows: contraindications for regional anesthesia (e.g., history of allergy to local anesthetic); use of anticoagulants; pregnancy or breastfeeding; history of abdominal surgery; pre-existing anatomical abnormalities in the vertebrae, chest wall, or abdomen; and refusal to participate. We also excluded patients with severe intraperitoneal inflammation or adhesions resulting from cholecystitis (Parkland grade > 3), those with a single-port insertion, those with intraoperative bile duct injury, and those in whom percutaneous drainage was maintained before and after surgery.

For random allocation of participants, a web-based randomization (http://randomization.com) was performed with random block sizes of 4 and a 1 : 1 allocation ratio. The enrolled patients were randomly assigned to either the pre-TPVB group or the post-TPVB group. Group allocation was blinded to the assessor, anesthetist, surgeons, research coordinator, investigator, medical staff in the post-anesthesia care unit (PACU) and wards, and the participants, except for the interventionist.

RSB and TPVB were performed by the expert interventionist with more than 10 years of experience in regional anesthesia and more than 1,000 experiences each for RSB and TPVB. In the pre-TPVB group, RSB and TPVB were both performed before skin incision. In the post-TPVB group, RSB was performed before skin

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incision, and TPVB was performed after the end of surgery. RSB and TPVB were performed using a 12-MHz linear transducer (GE Healthcare, USA) and a 23-gauge Quincke needle (TaeChang, Korea). RSB was performed just below the umbilicus at each side. TPVB was performed by transversal technique at the right 6th and 8th transverse processes, lateral to medial, in-plane approach (Supplementary Fig. 1). For RSB and TPVB, 30 ml of 0.25% ropivacaine was injected each. If 30 ml of 0.25% ropivacaine exceeds 1.5 mg/kg, ropivacaine was injected up to 1.5 mg/kg. In maximum, 60 ml or 3 mg/kg of 0.25% ropivacaine was injected for RSB and TPVB.

Blinding of the group allocation for anesthetists was carried out as follows. After the induction of general anesthesia, the anesthetist went out of the operating room (OR) and remotely monitored the vital sign and ventilation parameters. RSB was performed in all participants by the interventionist before skin incision; at this time, TPVB was additionally performed in patients in the pre-TPVB group. After the block, the anesthetist entered the OR, maintained the general anesthesia, and recorded the data during surgery. After the end of surgery (i.e., skin closure before emergence from general anesthesia), the anesthetist went out of the OR and monitored remotely again; then, the interventionist performed TPVB in the post-TPVB group. The interventionist remained in the OR in both groups during each block procedure. The blinded assessor examined the analgesics administered in the PACU and general ward during 24 h after surgery and assessed the postoperative outcomes.

All operations were performed by a team of laparoscopic surgeons with experience in more than 300 LCs. LC was performed according to standard procedures in all patients. Briefly, three trocars were inserted below the xiphoid process (5 mm), right costal arch (5 mm), and umbilicus (10 mm). A camera port was inserted via the umbilical port, and the gallbladder (GB) was retracted. Pneumoperitoneum was created and maintained by carbon dioxide insufflation with an intraperitoneal pressure of 12 mmHg.

In the OR, all patients were routinely monitored by electrocardiography, non-invasive blood pressure measurement, and pulse oximetry. Anesthesia was induced by propofol, rocuronium, and remifentanil. Anesthesia was maintained with desflurane in 50% oxygen/air and a continuous infusion of remifentanil using a target-controlled infusion pump (Orchestra®, Fresenius Vial, France) to maintain the blood pressure within 20% of baseline values. After emergence from general anesthesia, patients were transferred to the PACU.

In the PACU, intravenous fentanyl 0.4 μg/kg was administered for rescue analgesia when the numerical rating scale (NRS) score of pain intensity was ≥ 4 or when the patient requested pain relief, and repeated until the NRS score was < 4 or the patient did not request further pain relief. In the general ward, intravenous ketorolac 30 mg was first administered when the NRS was ≥ 4 or when the patient requested pain relief. When intravenous ketorolac was insufficient, intravenous pethidine 25 mg was administered. The total and cumulated doses of rescue analgesics administered during 24 h post-surgery in the PACU and general ward were recorded.

Cumulative rescue analgesic consumption and postoperative pain scores were measured at 0, 0.5, 1, 2, 6, 12, 18, and 24 h after surgery. We defined '0 h after surgery' as the time point at which the patient arrives at the PACU after full arousal enough to communicate in the OR. Total and cumulated rescue analgesic consumptions were converted to equianalgesic doses of intravenous morphine based on previously published conversion factors (intravenous morphine 10 mg = fentanyl 0.1 mg = pethidine 75 mg = ketorolac 30 mg) [16,17], and expressed in intravenous morphine equianalgesic dose (MED, mg). The worst postoperative pain scores were assessed using an 11-point NRS (0 = no pain and 10 = the worst pain imaginable) at 0, 0.5, 1, 2, 6, 12, 18, and 24 h after surgery. The adverse effects of analgesics (e.g., dizziness, sedation, respiratory depression, nausea, and vomiting) and complications associated with RSB or TPVB such as hematoma or pneumothorax were evaluated.

The primary outcome was the total amount of rescue analgesic consumption during the 24 h after surgery. The secondary outcomes were the cumulative rescue analgesic consumption and worst postoperative pain scores at 0, 0.5, 1, 2, 6, 12, 18, and 24 h after surgery, and adverse events associated with analgesics and RSB or TPVB. Previous studies had shown that in patients with acute pain after surgery, the minimal clinically important difference for pain was 9.9 (rounded to 10) in terms of the 100 mm visual analogue scale score [18]; therefore, we chose a 1-point difference in the NRS pain score as the margin of significance between the compared groups.

Additional factors associated with visceral pain, such as the severity of adhesion and cholecystitis inflammation status, were graded according to the Parkland grading scale (range 0–5) [19]. Surgical procedure characteristics related to visceral pain, such as the duration of surgery, severity of GB bed injury during surgery, and rate of intraoperative bile leakage, were also compared between the groups. The severity of GB bed injury was reported by the surgeon as follows: 1 = insignificant injury to the liver; 2 = mild injury to the liver; 3 = moderate injury to the liver. Vital signs including blood pressure and heart rate were measured before the incision and their maximum values were measured after the incision and before the induction of pneumoperitoneum. In-

traoperative remifentanil consumption was also recorded.

In the PACU, the blinded assessor evaluated the appropriate somatic block by RSB. An algometer (Baseline® algometer, Fabrication Enterprises Inc., USA) was used to induce experimental pressure pain on the umbilicus. The pressure was applied for 5 s to exclude patients with insufficient RSB that was determined by a threshold of pressure pain lower than 2 kg/cm^2 pressure [20,21].

Sample size and statistical analysis

Based on the previous studies [9,22] and considering the additional effect of TPVB, we determined the expected effect size as 8 mg MED (the difference of total rescue analgesic consumption between groups during the 24 h post-surgery converted to equianalgesic doses of intravenous morphine). According to previous studies, the expected standard deviation (SD) for the sample size calculation of the present study was 10.9 [9,22]. With a two-sided level of significance of 0.05 and a power of 80%, a sample size of 30 patients in each study group was required. Assuming a dropout rate of 15% during the study period, 35 patients were recruited for each group. The PS power and sample size calculations (version 3.1.2; 2014) developed by the Department of Biostatistics, Vanderbilt University, Nashville, Tennessee, were used to calculate the sample size.

Continuous variables of baseline and intraoperative data are presented as mean with SD, or median with interquartile range, while categorical variables are presented as frequency (percentage). Between-group comparisons of baseline and intraoperative characteristics were evaluated with Student's t-test or the Mann–Whitney *U* test for continuous variables and with the Chi-squared test or Fisher's exact test for categorical variables, appropriately. All statistical analyses were conducted in the modified intention-to-treat population that consisted of all the patients who received the allocated intervention. Primary and secondary outcomes between the two groups were compared using a linear mixed-effect model with group, time, and group-by-time interaction as fixed effects and patient indicator as a random effect, because of repeated measurements of outcomes and the possibility of missing data from loss to follow-up. These linear mixed model analyses were followed by post hoc test. Statistical significance was set at $P < 0.05$. Data manipulation and analyses were performed using R software, version 4.1.0 (R Foundation for Statistical Computing, Austria) and Stata version 13.1 (StataCorp LP, USA).

Results

Of the 73 patients screened for eligibility from August 12 to October 16, 2019, three patients were excluded from the study and the remaining 70 patients were randomized into the pre-TPVB (n = 35) and post-TPVB (n = 35) groups (Fig. 1). Among the 35 eligible patients in the pre-TPVB group, two patients did not receive the allocated intervention due to anatomical abnormality (left-sided GB) and protocol violation. Among the 35 eligible patients in the post-TPVB group, four patients did not receive the allocated intervention due to a Parkland grade of 4 and percutaneous drainage after surgery. Consequently, a total of 64 patients (33 in the pre-TPVB group and 31 in the post-TPVB group) were included in the modified intention-to-treat analysis.

As shown in Tables 1 and 2, there were no significant differences in the baseline characteristics and intraoperative characteristics between the two groups. When the experimental pressure pain was examined on the umbilicus by using the algometer in the PACU, there were no patients who experienced pain under the threshold of pressure pain that indicated that pre-incisional RSB was effective.

The estimated means of total rescue analgesic consumption during the 24 h after surgery were 16.9 (95% CI [14.5, 19.3]) mg in the pre-TPVB group and 25.3 (95% CI [22.8, 27.7]) mg in the post-TPVB group (estimated difference: –8.3 mg, 95% CI [–11.8, –4.9], $P < 0.001$). Moreover, there was a significant group-by-time interaction for the cumulative rescue analgesic consumption between the pre-TPVB group and the post-TPVB group ($P < 0.001$). At 0, 0.5, and 1 h after surgery, the cumulative rescue analgesic consumption between the two groups was not significantly different. However, the cumulative rescue analgesic consumption was significantly lower in the pre-TPVB group than in the post-TPVB group from 2 to 24 h after surgery (Table 3, Fig. 2).

For postoperative pain intensity, there were no significant group-by-time interactions between the two groups over time ($P = 0.087$). However, postoperative pain intensity was significantly lower in the pre-TPVB group than in the post-TPVB group at 0.5, 1, 2, and 6 h after surgery, and the absolute estimated mean difference was larger than the margin of significance (Table 4), although there were no significant differences after 12 h of surgery. There were no adverse events associated with analgesics and RSB or TPVB.

Discussion

In this prospective, assessor-blind, randomized study, the total amount of analgesic consumption during the 24 h after LC was

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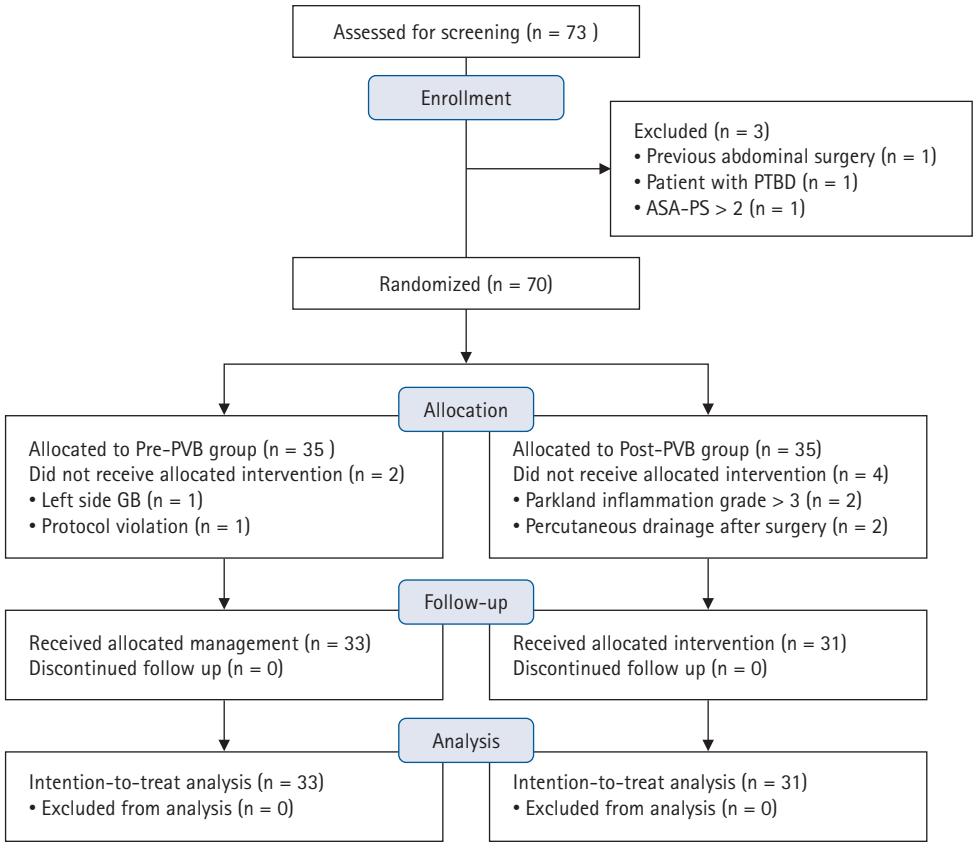

Fig. 1. Flowchart of the study population. PTBD: percutaneous transhepatic biliary drainage, ASA-PS: American Society of Anesthesiologists Physical Status, Pre-TPVB: pre-incisional thoracic paravertebral block combined with rectus sheath block, Post-TPVB: pre-incisional rectus sheath block and thoracic paravertebral block after skin closure, GB: gallbladder.

Table 1. Baseline Characteristics of the Study Participants

Variables	Pre-TPVB group (n = 33)	Post-TPVB group (n = 31)	P value
Age (yr)	50.5 ± 11.2	48.1 ± 11.2	0.399
Sex (M/F)	17 (51.5)/16 (48.5)	10 (32.3)/21(67.7)	0.192
Weight (kg)	67.1 ± 12.0	65.9 ± 10.4	0.682
Height (cm)	166.0 ± 9.3	163.8 ± 9.7	0.357
Body mass index (kg/m^2)	24.2 ± 2.9	24.6 ± 3.3	0.635
ASA-PS class (1/2)	20 (60.6)/13 (39.4)	22 (71.0)/9 (29.0)	0.543
Hypertension	8 (24.2)	5 (16.1)	0.620
Diabetes	4 (12.1)	5 (16.1)	0.729
Diagnosis			0.236
Acute cholecystitis	6 (18.2)	10 (32.3)	
Chronic cholecystitis	18 (54.5)	17 (54.8)	
GB polyp	9 (27.3)	4 (12.9)	
Pre-operative drain			> 0.999
None/ENBD	31 (93.9)/2 (6.1)	29 (93.5)/2 (6.5)	

Values are presented as mean ± SD or number (%). Pre-TPVB: pre-incisional thoracic paravertebral block combined with rectus sheath block, Post-TPVB: pre-incisional rectus sheath block and thoracic paravertebral block after skin closure, ASA-PS: American Society of Anesthesiologists Physical Status, GB: gallbladder, ENBD: endoscopic nasobiliary drainage.

Table 2. Intraoperative Data

Variables	Pre-TPVB group (n = 33)	Post-TPVB group (n = 31)	P value
Duration of surgery (min)	30.0 (25.0, 38.0)	33.0 (25.0, 40.0)	0.404
Duration of anesthesia (min)	65.0 (58.0, 80.0)	65.0 (60.0, 74.0)	0.877
TPVB to incision time (min)	11.2 ± 4.3	N/A	
Ropivacaine dose (mg/kg)	2.3 ± 0.4	2.3 ± 0.4	0.823
MBP change (%)*	0.0 (0.0, 4.0)	0.0 (−1.5, 2.5)	0.259
HR change (%)*	0.0 (−2.0, 2.0)	−2.0 (−3.5, 0.0)	0.088
Parkland grade			0.582
1	23 (69.7)	22 (71.0)	
2	7 (21.2)	4 (12.9)	
3	3 (9.1)	5 (16.1)	
Bile leakage (No/yes)	32 (97.0)/1 (3.0)	30 (96.8)/1 (3.2)	> 0.999
Severity of GB bed injury			0.849
1	29 (87.9)	27 (87.1)	
2	3 (9.1)	4 (12.9)	
3	1 (3.0)	0 (0.0)	
Remifentanil (μg)	292.0 (244.0, 355.0)	304.0 (254.5, 336.0)	0.638
Remifentanil (μg/kg/min)	0.066 ± 0.017	0.070 ± 0.014	0.328

Values are presented as mean ± SD, median (Q1, Q3), or number (%). *The largest vital sign change (%) from baseline within 5 min after incision. Pre-TPVB: pre-incisional thoracic paravertebral block combined with rectus sheath block, Post-TPVB: pre-incisional rectus sheath block and thoracic paravertebral block after skin closure, TPVB: thoracic paravertebral block, N/A: not applicable, MBP: mean blood pressure, HR: heart rate, GB: gallbladder.

Table 3. Postoperative Cumulative Rescue Analgesic Consumption

Variables	Time	Estimated mean (95% CI)		Estimated mean difference (95% CI)	P value
		Pre-TPVB group (n = 33)	Post-TPVB group (n = 31)		
Cumulative MED (mg)	0 h	0.7 (−1.7, 3.1)	1.1 (−1.4, 3.6)	−0.4 (−3.9, 3.0)	0.807
	0.5 h	2.8 (0.3, 5.2)	4.2 (1.7, 6.6)	−1.4 (−4.9, 2.1)	0.427
	1 h	3.7 (1.3, 6.1)	6.1 (3.6, 8.6)	−2.4 (−5.8, 1.1)	0.180
	2 h	9.0 (6.6, 11.4)	15.2 (12.7, 17.7)	−6.3 (−9.7, −2.8)	< 0.001
	6 h	11.1 (8.7, 13.5)	18.1 (15.6, 20.6)	−7 (−10.4, −3.5)	< 0.001
	12 h	15.9 (13.5, 18.3)	23.7 (21.2, 26.1)	−7.8 (−11.2, −4.3)	< 0.001
	18 h	16.7 (14.3, 19.1)	24.9 (22.4, 27.4)	−8.2 (−11.7, −4.7)	< 0.001
	24 h	16.9 (14.5, 19.3)	25.3 (22.8, 27.7)	−8.3 (−11.8, −4.9)	< 0.001

Values are presented as estimated mean (95% CI) or estimated mean difference (95% CI). Pre-TPVB: pre-incisional thoracic paravertebral block combined with rectus sheath block, Post-TPVB: pre-incisional rectus sheath block and thoracic paravertebral block after skin closure, MED: intravenous morphine equianalgesic dose. A linear mixed model was used for the statistical analysis. The group and time differences were statistically significant (both $P < 0.001$). The group-by-time interaction between the groups over time was also statistically significant ($P < 0.001$). Cumulated rescue analgesic consumptions were converted to equianalgesic doses of intravenous morphine and expressed in MED (mg).

significantly lower in those who received TPVB before skin incision than in those who received TPVB after skin closure. Postoperative pain intensity was also significantly lower in the pre-TPVB group than in the post-TPVB group.

In the present study, we designed the analgesia during surgery in two stages to adequately examine the effect of preemptive visceral analgesia on post-surgical pain. First, RSB was performed before skin incision in both groups. Pre-incisional RSB could effectively alleviate the pain in the umbilical port that was the site of maximal somatic pain in LC because the GB was extracted through the umbilical port at our institution. There were no patients in both groups who suffered pain under the threshold of pressure pain on the umbilicus when measured by an algometer in the PACU. Consequently, by the first stage of analgesia with

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pre-incisional RSB, somatic pain was sufficiently suppressed in both groups and both groups would have had minimal somatic noxious stimulation during surgery.

Second, after pre-incisional RSB, TPVB was performed either before incision or after skin closure to comparatively examine the preemptive visceral analgesic effects. Visceral afferent neuron accompanies sympathetic neuron through the prevertebral and paravertebral ganglia [13,23], the latter of which is contained within the paravertebral space [24]. In addition, the GB is innervated from the coeliac plexus [25] that receives greater and lesser splanchnic nerve fibers derived from the fifth to eleventh thoracic paravertebral ganglia [26]. Therefore, considering the vertical spread of the injectates in TPVB [24], TPVB at the right 6th and 8th transverse processes used in the present study would have conferred visceral analgesic effect in patients undergoing LC. Because somatic pain was already minimized in the first stage of analgesia using pre-incisional RSB, TPVB would have affected visceral pain only in both groups. Therefore, through these two stages of analgesia, somatic noxious stimulation would have been similarly minimal in both study groups and only the timing of visceral analgesia would have differed that satisfies the condition needed for adequately evaluating the preemptive visceral analgesic effect.

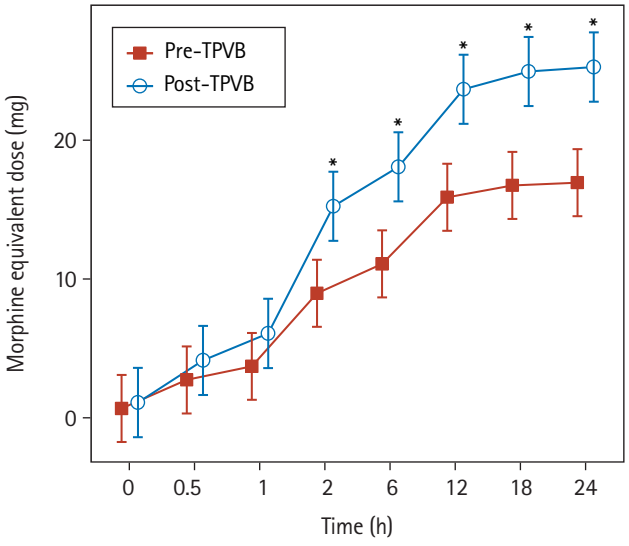

Fig. 2. Cumulative rescue opioid consumption during the 24 h after surgery. Values are presented as estimated means with 95% CIs. A linear mixed model was used for the statistical analysis. Rescue analgesic consumption was measured by calculating the total rescue analgesic consumption converted to the total intravascular morphine-equivalent dose (mg) up to each hour. Pre-TPVB: pre-incisional thoracic paravertebral block combined with rectus sheath block, Post-TPVB: pre-incisional rectus sheath block and thoracic paravertebral block after skin closure. *P < 0.05 between groups.

In our study, the post-TPVB group required more analgesics than the pre-TPVB group during the postoperative 24 h. Especially, the post-TPVB group consumed more analgesics from 2 h after surgery, and this difference between the two groups lasted up to 24 h after surgery. These results collectively suggest that preoperative TPVB was effective in preemptively inducing visceral analgesia and reducing the amount of analgesics needed postoperatively. While TPVB was shown to be effective for controlling postoperative pain and reducing opioid consumption in both open cholecystectomy and LC [27–30], there have been only two studies that compared the effects of preoperative TPVB and postoperative TPVB [31,32]. Naja et al. [31] found that bilateral TPVB performed prior to general anesthesia for LC could lead to early discharge and better postoperative pain management than TPVB performed immediately after surgery. Aydin and Aydin [32]

Table 4. Postoperative Pain Intensity

Variables	Time	Estimated mean (95% CI)		Estimated mean difference (95% CI)	P value
		Pre-TPVB group (n = 33)	Post-TPVB group (n = 31)		
NRS score	0 h	2.5 (2.0, 3.1)	3.0 (2.4, 3.6)	−0.5 (−1.2, 0.3)	0.245
	0.5 h	3.2 (2.7, 3.7)	4.4 (3.9, 5.0)	−1.2 (−2.0, −0.4)	0.002
	1 h	1.8 (1.3, 2.4)	2.8 (2.3, 3.4)	−1.0 (−1.8, −0.2)	0.011
	2 h	3.5 (3.0, 4.1)	5.2 (4.7, 5.8)	−1.7 (−2.4, −0.9)	< 0.001
	6 h	3.2 (2.7, 3.8)	4.3 (3.7, 4.8)	−1.0 (−1.8, −0.3)	0.007
	12 h	3.8 (3.3, 4.4)	4.1 (3.6, 4.7)	−0.3 (−1.0, 0.5)	0.473
	18 h	2.8 (2.3, 3.4)	3.5 (2.9, 4.0)	−0.6 (−1.4, 0.1)	0.104
	24 h	2.2 (1.7, 2.7)	2.7 (2.2, 3.3)	−0.5 (−1.3, 0.2)	0.175

Values are presented as estimated mean (95% CI) or estimated mean difference (95% CI). Pre-TPVB: pre-incisional thoracic paravertebral block combined with rectus sheath block, Post-TPVB: pre-incisional rectus sheath block and thoracic paravertebral block after skin closure, NRS: numerical rating scale of pain intensity. A linear mixed model was used for the statistical analysis. The group and time differences were statistically significant (both P < 0.001). The group-by-time interaction between the groups over time was not statistically significant (P = 0.087).

found that preoperative unilateral TPVB was superior to postoperative unilateral PVB in reducing postoperative pain. Although these results suggest that preoperative TPVB does provide preemptive analgesia, the preemptive analgesic effect of TPVB could not be differentiated between somatic pain and visceral pain. In contrast, the present study evaluated only the preemptive visceral analgesic effect of TPVB and our results clearly showed that preemptive visceral analgesia may be achieved by pre-incisional TPVB in patients undergoing LC.

The current study had several limitations. First, TPVB was performed in a unilateral manner, and the use of bilateral TPVB may have led to better results in terms of postoperative pain. Nevertheless, we believe that unilateral TPVB was sufficient to achieve the study aim that was to evaluate the preemptive visceral analgesic effect of TPVB rather than to induce a complete blockage of visceral pain after cholecystectomy. Second, we could not distinguish visceral pain from somatic pain while evaluating the preemptive visceral analgesic effect of TPVB. However, somatic pain was minimized in both groups through pre-incisional RSB. Thus, it can be assumed that the degree of somatic pain was subdued to a similar degree between the two groups and that the differences in the postoperative pain would largely stem from the timing of the visceral analgesia. Therefore, the degree of postoperative pain and the amount of analgesic consumption in our study could indirectly reflect the preemptive visceral analgesic effect of TPVB. Third, of the three criteria for evaluating the preemptive analgesic effect, we only evaluated the reductions in total analgesic consumption and decreases in postoperative pain, and not the delays in the time to first rescue analgesic [33], which should be addressed in future studies. Finally, the combination of RSB and TPVB may lengthen the duration of anesthesia. In the present study, the difference between the duration of surgery and anesthesia was 30 min that consisted of RSB, TPVB, and induction and emergence of general anesthesia. Therefore, the time taken for RSB and TPVB was less than 30 min that may not be expected to have significantly affected cost-effectiveness considering the usefulness of postoperative pain control.

In conclusion, this prospective, randomized, assessor-blind study in patients undergoing LC showed that pre-incisional TPVB was effective in reducing postoperative 24-h analgesic consumption and controlling postoperative pain, thus suggesting the effectiveness of preemptive visceral analgesia. The preemptive visceral analgesic effect of pre-incisional TPVB in surgeries other than LC should be explored in future studies.

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Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

Jong-Hyuk Lee (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing – original draft)
Chan-Sik Kim (Data curation; Formal analysis; Visualization; Writing – original draft)
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Supplementary Material

Supplementary Fig. 1. Ultrasound-guided thoracic paravertebral block. (A) Transverse ultrasound image of the thoracic paravertebral space (TPVS). The echogenic needle (white empty arrow) is approaching the paravertebral space between the internal intercostal membrane and pleura (white arrow), using an in-plane technique. The black empty arrow indicates the transverse process of the thoracic spine. (B) Transverse ultrasound image of the TPVS after local anesthetic (LA) injection. The widening of the paravertebral space and anterior displacement of the pleura (white arrow) due to spread of LA (black arrow) can be seen.

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