Analgesic Effect Comparison and Pharmacokinetic Study of Ropivacaine with Different Concentrations in Continuous Serratus Anterior Plane Block in Patients Undergoing Video-Assisted Thoracoscopic Surgery

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Abstract

Aims: The serratus anterior plane block (SAPB) has commonly been utilized as a regional anesthesia technique for pain management in various upper chest surgical procedures. The purpose of this study was to investigate the analgesic effect and pharmacokinetics of ropivacaine in continuous SAPB undergoing VATS. Methods: This prospective randomized study included patients scheduled for elective VATS. Patients first received a bolus of 20 ml of 0.2% (Group L) or 0.375% (Group H) ropivacaine that was administered beneath the serratus anterior muscle. The pump was connected to the catheter for continuous administration within 48 hours postoperatively, in which a background infusion at a rate of 7 ml·h-1 of low-dose at 0.2% (Group L) or high-dose at 0.375% (Group H) of ropivacaine was administered. The main results were to compare the analgesic effects and analyze the pharmacokinetics of different concentrations of ropivacaine. Results: Eighty-eight patients agreed to participate in the trial and were recruited. The VAS scores in Group H at 12, 24, and 48 hours postoperatively at rest and on coughing were significantly lower than those in Group L. The peak values of total ropivacaine plasma concentrations were observed at 48 hours (2.01 μg·mL-1 for Group L and 2.93 μg·mL-1 for Group H), which were far below the theoretical toxicity threshold. Postoperative rescue analgesia, complications, and other outcomes did not differ significantly. Conclusions: In VATS patients, the analgesic effect of 0.2% ropivacaine for continuous SAPB was not inferior to that of 0.375% ropivacaine, and the blood concentration of 0.2% ropivacaine was

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Keywords: Ropivacaine, Continuous serratus anterior plane block, Analgesia, Pharmacokinetics

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Aims: The serratus anterior plane block (SAPB) has commonly been utilized as a regional anesthesia technique for pain management in various upper chest surgical procedures. The purpose of this study was to investigate the analgesic effect and pharmacokinetics of ropivacaine in continuous SAPB undergoing video-assisted thoracoscopic surgery (VATS).

Methods: This prospective randomized study included patients scheduled for elective VATS. Patients first received a bolus of 20 ml of 0.2% (Group L) or 0.375% (Group H) ropivacaine that was administered beneath the serratus anterior muscle. The pump was connected to the catheter for continuous administration within 48 hours postoperatively, in which a background infusion at a rate of 7 $ml \cdot h^{-1}$of low-dose at 0.2% (Group L) or high-dose at 0.375% (Group H) of ropivacaine was administered. The main results were to compare the analgesic effects and analyze the pharmacokinetics of different concentrations of ropivacaine.

Results: Eighty-eight patients agreed to participate in the trial and were recruited. The VAS scores in Group H at 12, 24, and 48 hours postoperatively at rest and on coughing were significantly lower than those in Group L. The peak values of total ropivacaine plasma concentrations were observed at 48 hours (2.01 $\mu g \cdot mL^{-1}$ for Group L and 2.93 $\mu g \cdot mL^{-1}$ for Group H), which were far below the theoretical toxicity threshold. Postoperative rescue analgesia, complications, and other outcomes did not differ significantly.

Conclusions: In VATS patients, the analgesic effect of 0.2% ropivacaine for continuous SAPB was not inferior to that of 0.375% ropivacaine, and the blood concentration of 0.2% ropivacaine was lower.

The trial was registered in the Chinese Clinical Trial Registry (ChiCTR2100053517).

Abbreviations

SAPB: serratus anterior plane block, LAs: local anesthetics, VATS: video-assisted thoracoscopic surgery, TAP: transversus abdominis plane, BMI: body mass index, ASA: American Society of Anesthesiologists, ECG: electrocardiogram, HR: heart rate, MAP: mean arterial pressure, SpO_2: pulse oxygen saturation, EtCO2: end-tidal carbon dioxide pressure, BIS: bispectral index, VAS: visual analog scale

Bullet point summary:

1) The effectiveness and safety of local anesthetics used in continuous SAPB during VATS are still less understood.

2) When continuous SAPB was used for VATS, the analgesic effect of 0.2% ropivacaine was not inferior to that of 0.375% ropivacaine.

3) The plasma concentrations of ropivacaine at both 0.2% and 0.375% were in the safe range in continuous SAPB undergoing VATS.

4) Continuous SAPB with 0.2% ropivacaine has a lower blood concentration within 48 hours.

Introduction

The serratus anterior plane block (SAPB) is a regional anesthesia method whereby local anesthetics (LAs) are injected into the serratus anterior space to block the lateral cutaneous branch of the intercostal nerve, long thoracic nerve, and dorsal thoracic nerve[1]. It has been increasingly acknowledged that SAPB can produce effective analgesia for the chest wall because it fully covers surgical incisions impacted by thoracoscopic surgery and the site of the chest tube, which are often located in the anterolateral chest wall[2]. Continuous techniques are highly recommended for prolonged analgesia duration [3, 4], and we and others have successfully implemented continuous SAPB for multiple surgical procedures [2, 4-7], including video-assisted thoracoscopic surgery (VATS).

The efficiency of regional analgesia is importantly dependent on the volume and concentration of the LA solution[8]. However, potentially toxic plasma concentrations of LAs have been reported after administration of transversus abdominus plane (TAP) block[9, 10], especially in patients with hepatic or renal insufficiency. It has been commonly seen that SAPB is performed clinically using different concentrations of ropivacaine, ranging from a minimum of 0.125% ropivacaine to a maximum of 0.75% ropivacaine[11-13]. At present, the safety of different concentrations of ropivacaine in SAPB has not been well studied, especially under the condition of continuous administration of LAs. The objective of this prospective randomized study was therefore to compare the analgesic efficacy and pharmacokinetics of ultrasound-guided continuous SAPB using 0.2% and 0.375% ropivacaine in patients undergoing VATS.

Methods

Trial Design

This is a prospective, randomized, double-blind, controlled, and noninferiority trial implemented in First Affiliated Hospital, University of Science and Technology of China (USTC) (Approval No. of the ethics committee: 20171219), and the trial was registered in the Chinese Clinical Trial Registry (ChiCTR2100053517). The trial compliance with ethics guidelines. From November 2021 to March 2022, 88 patients were recruited. Patients were given a detailed explanation of the study protocol and informed of the potential benefits and side effects of the technology's development. Informed consent was obtained from the patient or family. Figure 1 shows the flow diagram of participant recruitment.

Patients

Participants met the following inclusion criteria: age 18-70 years, body mass index (BMI) 18-30 kg/m^2, unlimited sex, American Society of Anesthesiologists (ASA) I-III, awareness, good communication, informed about the experiment, and voluntarily signed informed consent. The exclusion criteria were as follows: 1) severe coagulopathy; 2) systemic or puncture site infection; 3) allergy to the study drugs and contraindications; 4) severe impairment of liver, kidney, and heart function (New York Heart Association Classes III-IV); and 5) a history of chronic pain or persistent pain due to other diseases and analgesic treatment before surgery.

General Anesthesia

Electrocardiogram (ECG), heart rate (HR), mean arterial pressure (MAP), pulse oxygen saturation (SpO_2), end-tidal partial pressure of carbon dioxide ($ETCO_2$), body temperature, and bispectral index (BIS) were monitored before anesthesia, and peripheral venous access of the upper limbs was opened. All subjects received standard general anesthesia. Sevoflurane was mixed with oxygen/air to maintain anesthesia, and the circulatory system was ventilated with positive pressure. Propofol 4-6 mg/kg/h and remifentanil 0.1-0.3 μg/kg/min were given intraoperatively to maintain anesthesia. According to the operation needs, cisatracurium 0.05 mg/kg was injected intravenously. All procedures are performed by the same team of surgeons and do not require any additional local anesthesia by the surgeon. At the end of the surgery, before extubation and full consciousness, patients were randomly examined and treated by independent staff.

Postoperative Pain Management

Under the condition that patients were still not awake after the operation, patients were placed in a lateral

position for SAPB. Between the anterior axillary line and posterior axillary line, the serratus anterior and latissimus dorsi muscles overlying the fourth to sixth ribs were easily identified by ultrasound (Navis, Wisonic, Shenzhen, China) with a linear transducer (4-15 Hz, L15-4B). The needle was placed on the fourth or sixth rib, not restricted to the fifth rib in the mid-axillary line, to avoid disturbing the surgical incision. After sterilization of the puncture site, the epidural needle (1.6 mm outer diameter, 80 mm length, Tuoren, China) was introduced in the caudal-cephalad direction using an in-plane approach. When the needle almost reached the surface of the rib, 3 ml of saline was injected to test the location of the needle tip and open the potential interfacial space between the rib and the serratus anterior muscle, and then an epidural catheter (0.5 mm inner diameter, 113 mm length, Tuoren, China) was threaded. Catheters were placed 4.5 cm inside the serratus anterior muscle plane beyond the end of the needle and confirmed with ultrasound guidance. After confirming negative aspiration, a bolus of 20 ml of 0.2% (Group L) or 0.375% (Group H) ropivacaine was administered beneath the serratus anterior muscle. The ultrasound scan confirmed that local anesthetic liquid was distributed adequately into the fascial plane between the serratus anterior muscle and the external intercostal muscle. The catheter was inserted and connected to a pump, in which a background infusion at a rate of 7 ml/h of 0.2% (Group L) or 0.375% (Group H) ropivacaine was used continuously until 48 hours postoperatively. Rescue analgesia with 50 mg tramadol if the VAS score was [?]4. The details have been previously reported elsewhere [5, 6].

Randomization and Blinding

Eligible patients were randomly allocated in a 1:1 ratio to either continuous SAPB Group L or Group H. Allocation sequence was created by a computer-generated list. Allocation concealment was implemented by using sequentially numbered, opaque, sealed envelopes. Block randomization was performed with a 1:1 allocation ratio by fixed block size. The drug concentration was assigned by specialized staff, and the user, follow-up personnel, and patients were not informed of the grouping. The data analysis was performed by independent research staff who did not inform the group assignment.

Blood Samples and Pharmacokinetic Analysis

Blood samples (2 mL) were then obtained at 0,2,6,12,24,48 and 56 hours after the block injection. The blood samples were centrifuged within 60 minutes after collection. The plasma samples were stored at –20 °C until the assays were performed. The total plasma concentration of ropivacaine was measured by ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS, Waters, American) after direct injection of diluted serum without further cleanup pretreatment. The method and validation characteristics have been described elsewhere [14].

Outcome measures

Patients were instructed to use a visual analog scale (VAS) from 0 cm (no pain) to 10 cm (most severe pain). VAS scores were measured at 2, 6, 12, 24, and 48 hours after continuous SAPB. The primary outcome was the VAS score of pain while coughing at 48 hours after surgery. The blood concentration of ropivacaine at different time points after continuous SAPB was used as the secondary outcome.

Statistical analysis

Despite the comparison of analgesic effects of different concentrations of ropivacaine under a single shot of SAPB[13]. However, no previous studies have tested the analgesic effect of different concentrations of ropivacaine in continuous SAPB. The sample size was determined according to the primary outcome using Power Analysis and Sample Size (PASS) 15. Following previous reports, we set the VAS non-inferiority margin at 1.3 as an acceptable difference in this study, and the standard deviation is anticipated to be 2.0 cm[15-17], assuming a one-sided type I primary error rate of 2.5% and 80% power. Group L: Group H=1:1, and a minimum sample size of 39 patients for each group was estimated. Considering a 10% rate of potential dropout, a total of 44 patients for each group were finally included.

Data were analyzed using Statistical Package for Social Sciences (SPSS) 26.0 for Windows (SPSS Inc., Chicago Illinois, USA). Descriptive data are shown as the mean (with standard deviation) depending on the

(normal or skewed) distribution of data, and categorical data are shown as percentages. Comparisons of categorical data were performed with the chi-square test, and an independent t test was used for numerical data comparisons. All statistical tests were two-sided tests, and p values <0.05 were considered significant.

Results

Baseline characteristics

Ninety-eight patients eligible for the trial were identified. Eighty-eight patients consented to participate in the trial and were recruited. The flow diagram is detailed in Figure 1. There was no difference in general characteristics between the two groups (Table 1).

Clinical Results

After continuous SAPB for 2, 6, 12, 24, and 48 hours, VAS scores were obtained and recorded during ward follow-up. From the comparison of VAS scores, the VAS scores at rest and on coughing were lower in Group H at 12, 24, and 48 hours than in Group L (Table 2). The number of rescue analgesia procedures was comparable between the two groups (10 patients in Group L and 8 patients in Group H, P =0.597). There were no significant differences in the incidence of postoperative nausea/vomiting, hypoxemia, or postoperative hospital stay between the two groups. No postoperative wound infections occurred in either group (Table 3).

Pharmacological Results

We studied the pharmacokinetics of ropivacaine after a continuous SAPB injection in 88 patients aged 18-70 years with BMI 18-30 kg/m^2 (44 patients in each group). All expected blood samples were collected. The peak total plasma concentrations of ropivacaine were 2.93 $\mu g \cdot mL^{-1}$ in Group H and 2.01 $\mu g \cdot mL^{-1}$ in Group L 48 hours after injection (Figure 2). The maximum total plasma level of ropivacaine was still well below the theoretical toxicity threshold of 3.40 $\mu g \cdot mL^{-1}$[18].

Discussion

There is an increasing appreciation of SAPB for pain management in the perioperative period, and SAPB has been reported to be widely used in rib fractures, thoracotomy, breast cancer surgery, and shoulder arthroplasty[19]. The success of SAPB is highly related to the volume and optimal concentration of LAs used[8]. In theory, a greater concentration of LAs may produce a better analgesic effect. However, LAs also have a certain toxic effect, and the safety of ropivacaine for SAPB is still not discussed, especially in the condition of continuous administration of LAs. Therefore, more studies are necessary to determine the optimal dosing regimen to achieve the desired analgesic effect while avoiding potentially toxic side effects. The purpose of this study was to compare the pharmacokinetic characteristics and analgesic efficacy of continuous SAPB by using high and low concentrations of ropivacaine in patients who received VATS.

In terms of postoperative pain control, the VAS scores in Group H at 12, 24, and 48 hours postoperatively were significantly lower than those in Group L, whether at rest or on coughing, and the results were statistically significant. However, the clinically important difference in VAS scores was defined as 1.0˜1.3 cm for a single measurement[15]. Therefore, in our trial, there were no clinically significant results for the difference in mean VAS scores between the two groups. In this study, rescue analgesia was administered with 50 mg tramadol if the patient had a VAS score [?]4. However, there was no significant difference in rescue analgesia between the two groups, probably because of the good analgesic effect already achieved with continuous SAPB. Collectively, the analgesic effect of Group L was not inferior to that of Group H.

The toxicity of LAs agents is commonly determined by studying the plasma concentration following intravenous infusions in healthy volunteers[18, 20, 21]. Ropivacaine is a local anesthetic commonly used for preoperative or postoperative nerve blocks[22]. Knudsen and colleagues evaluated the plasma toxicity concentrations of ropivacaine in healthy volunteers after intravenous infusion and found that plasma concentrations cause toxicity during intravenous infusion and thus might differ from plasma levels observed during extravascular infusion; symptoms attributable to toxicity commenced in the sampled range of 3.4-5.3 mg/L[18]. The

pharmacokinetics of LAs, however, vary depending on the site of injection, and plasma concentrations of ropivacaine have been reported to peak at 2.2μg·mL^{-1}at 30 minutes and remain high for approximately 6 hours after ultrasound-guided TAP[9, 10]. E. C. Hessian*et al* studied the safety of ropivacaine by continuous TAP[23]. Recent studies have shown that continuous SAPB analgesia is more effective and helps improve patient satisfaction and postoperative recovery [2, 5, 6]. There are no studies evaluating the plasma concentration of ropivacaine during continuous infusion of SAPB thus far. Our findings collectively revealed that the peak concentration of total plasma ropivacaine during continuous SAPB was 2.93 μg·mL^{-1} for Group H and 2.01 μg·mL^{-1} for Group L. The results showed that the maximum plasma in Group H remained far below the theoretical toxicity threshold of 3.4 μg·mL^{-1}, and the blood concentration was lower in Group L. By pharmacokinetic studies, the concentration of ropivacaine used was well below the concentration threshold for intoxication. No hypoxemia or incision infection occurred in either group in the postoperative period. At the same time, we also followed up the patients for postoperative nausea or vomiting, with no patients in Group L and one patient in Group H, which was consistent with the results of previous studies[5, 6]. This also indicates that the two groups of ropivacaine concentrations were safe in continuous SAPB. Therefore, continuous SAPB with 0.2% ropivacaine was both effective and safe.

Conclusion

By using a comparison of VAS scores and blood concentrations, those findings from this study indicated that in continuous SAPB, 0.2% ropivacaine had a similar analgesic effect as 0.375% ropivacaine and was safer. However, the safety of drug concentration still needs further study to be confirmed in larger study samples and using different concentrations. In conclusion, ropivacaine with continuous SAPB provides durable management of pain after thoracoscopic surgery as an alternative for multimodal analgesic strategies.

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Authorship and author contribution

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published. Conception and design of the study: DW, FX and XQC. Literature search and collection and compiled pictures and videos: JRC, JQC. Acquisition, analysis and interpretation of data: WG, HG, JCH, and XLY. Drafting the article and revising it critically for important intellectual content: JRC, JQC, DW and FX. Final approval of the article: JRC, JQC, WG, HG, XQC, XNW, FX and DW. JRC and JQC should be considered joint first author.

Disclosure

The authors report no conflicts of interest in this work.

Compliance with Ethics Guidelines

The trial complied with ethics guidelines. The trial was implemented in the First Affiliated Hospital, University of Science and Technology of China (USTC) (Approval No. of the ethics committee: 20171219). All patients were participated in this trial signed an informed consent form.

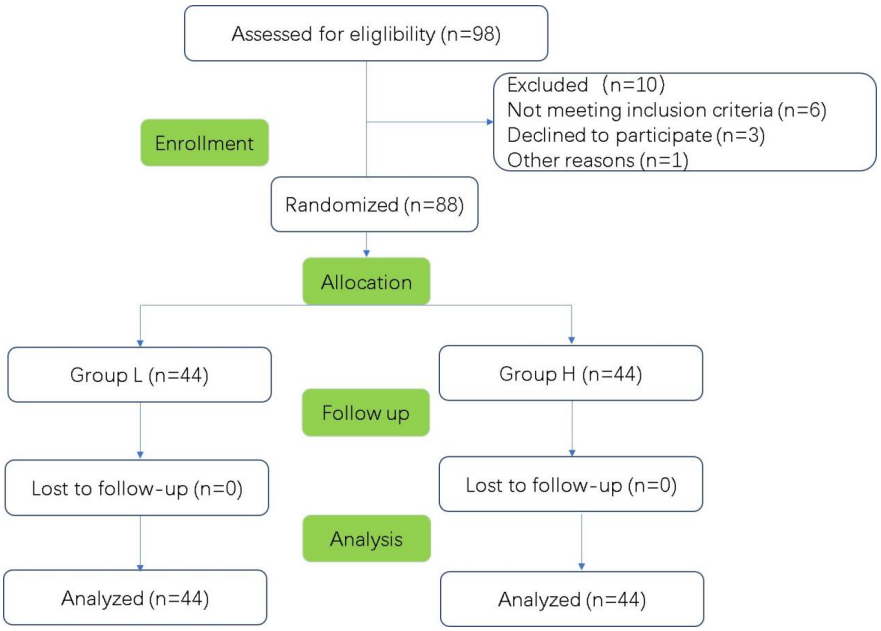

Figure 1. Flow chart of the study

Table 1. General characteristics of patients in both groups(n=88)

Variables	**Group L(n=44)**	**Group H(n=44)**	**P Value**
Age(years)	54.89±8.64	55.09±9.31	0.915
Sex, n (%)			0.829
Male	18(41)	19(43)	
Female	26(59)	25(57)	
Weight(kg)	63.02±8.70	62.70±9.53	0.982
Height(cm)	162.39±6.53	162.80±7.72	0.789
BMI (kg/m^2)	23.85±2.44	23.70±2.46	0.779
Duration of surgery(min)	107.09±30.60	109.52±23.55	0.677

Note: All continuous data are shown as the mean±SD. Differences between groups were tested by an independent t test. Categorical data are presented as frequencies and analyzed using the chi-square test. P values are not adjusted for multiple testing.

Abbreviations: BMI, body mass index; ASA, American Society of Anesthesiologists

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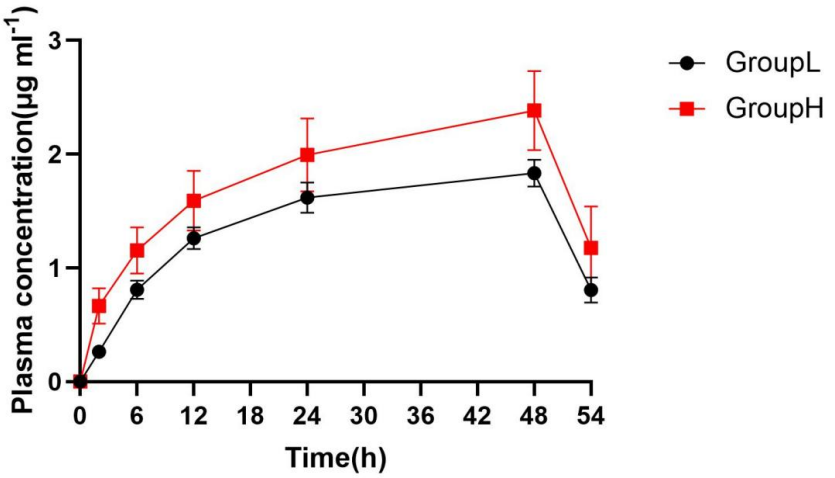

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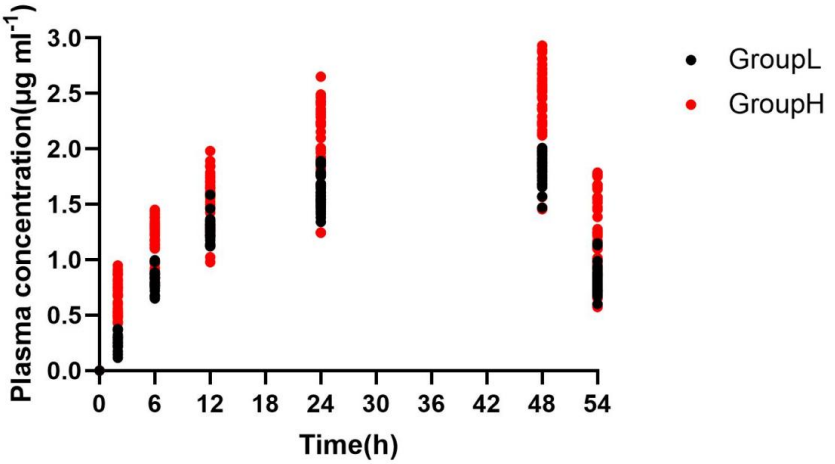

Figure 2. Total plasma concentrations of ropivacaine at different concentrations were continuously SAPB infusion. (A) Line chart of total plasma ropivacaine; (B) Scatter plot of total plasma ropivacaine.

Table 2. Postoperative pain intensity was assessed by VAS during rest or coughing.

	Group L(n=44)	**Group H(n=44)**	**Δ**	**P Value**
VAS at rest, cm				
2 h	2.25±0.78	2.07±0.79	0.18	0.281
6 h	2.50±0.70	2.30±0.73	0.20	0.184
12 h	3.00±0.86	2.39±0.78	0.61	0.001*
24 h	2.45±0.82	1.93±0.66	0.52	0.001*
48 h	2.50±0.82	1.77±0.80	0.73	¡0.001*
VAS on coughing, cm				
2 h	3.07±0.90	2.91±0.83	0.16	0.391

	Group L(n=44)	Group H(n=44)	Δ	P Value
6 h	3.43±0.97	3.18±0.58	0.25	0.147
12 h	3.91±1.10	3.45±0.79	0.46	0.028*
24 h	3.16±0.81	2.77±0.71	0.39	0.019*
48 h	3.07±0.66	2.39±0.62	0.68	¡0.001*

Note: All continuous data are presented as the mean±SD and compared using the independent t test. Categorical data are presented as frequencies and were analyzed using the chi-square test. P values are not adjusted for multiple testing.

Abbreviations: VAS, visual analog scale

Table 3. Other outcomes of patients(n=88)

	Group L(n=44)	Group H(n=44)	P Value
Rescue analgesia, n (%)	10(23)	8(18)	0.597
Nausea/Vomiting, n (%)	5(11)	4(9)	0.725
Hypoxemia, n (%)	0	0	-
Incision infection, n (%)	0	0	-
Hospital stay duration (d)	5.91±0.74	6.11±0.66	0.174

Note: All continuous data are presented as the mean±SD and were compared using the independent t test. Categorical data are presented as frequencies and were analyzed using the chi-square test. P values are not adjusted for multiple testing.

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