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Efficacy and safety of different doses of ropivacaine for laparoscopy-assisted infiltration analgesia in patients undergoing laparoscopic cholecystectomy

A prospective randomized control trial

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Abstract

Background: Wound infiltration analgesia provides effective postoperative pain control in patients undergoing laparoscopic cholecystectomy (LC). However, the efficacy and safety of wound infiltration with different doses of ropivacaine is not well defined. This study investigated the analgesic effects and pharmacokinetic profile of varying concentrations of ropivacaine at port sites under laparoscopy assistance.

Methods: In this randomized, double-blinded study, 132 patients were assigned to 4 groups: Group H: in which patients were infiltrated with 0.75% ropivacaine; Group M: 0.5% ropivacaine; Group L: 0.2% ropivacaine; and Group C: 0.9% normal saline only. The primary outcome was pain intensity estimated using numeric rating scale (NRS) at discharging from PACU and at 4 hours, 6 hours, 8 hours, and 24 hours after infiltration. Secondary outcomes included plasma concentrations of ropivacaine at 30 minutes after wound infiltration, rescue analgesia requirements after surgery, perioperative vital signs changes, and side effects.

Results: The NRS in Group C was significantly higher at rest, and when coughing upon leaving PACU and at 4 hours, 6 hours, 8 hours, and 24 hours after infiltration ($P < .05$) and rescue analgesic consumption was significantly higher. Notably, these parameters were not significantly different between Groups H, Group M and Group L ($P > .05$). Intra-operative consumption of sevoflurane and remifentanil, HR at skin incision and MAP at skin incision, as well as 5 minutes after skin incision were significantly higher in Group C than in the other 3 groups ($P < .01$). In contrast, these parameters were not significantly different between Groups H, Group M and Group L ($P > .05$). The concentration of ropivacaine at 30 minutes after infiltration in Group H was significantly higher than that of Group L and Group M ($P < .05$). No significant differences were observed in the occurrence of side effects among the 4 groups ($P > .05$).

Conclusions: Laparoscopy-assisted wound infiltration with ropivacaine successfully decreases pain intensity in patients undergoing LC regardless of the doses used. Infiltration with higher doses results in higher plasma concentrations, but below the systematic toxicity threshold.

Abbreviations: ERAS = enhance recovery after surgery, HR = heart rate, LC = Laparoscopic cholecystectomy, MAP = mean arterial pressure, NRS = numerical rating scale, PONV = postoperative nausea and vomiting, TAP = transversus abdominis plane block.

Keywords: laparoscopic cholecystectomy, local infiltration, ropivacaine, systematic concentration

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The authors have no conflicts of interests to disclose.

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

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1. Introduction

Laparoscopic cholecystectomy (LC) is the mainstay approach for the treatment of cholelithiasis. This is because it is considered to be minimally invasive and accelerates recovery.[1] However, this approach is associated with high post-operative pain intensity, especially in the early period.[2,3] Effective pain control is crucial for enhancing recovery after surgery (ERAS).[4,5] Studies have shown that traditional pain management using opioids often lead to side effects, such as postoperative nausea, vomiting (PONV), and respiratory depression.[6]

Previous studies have shown that multimodal analgesic strategies with local infiltration not only provide strong analgesic effects but also reduce incidence of opioid-related side effects, resulting in faster recovery and shorter hospital stay.[7–9] Several clinical studies have shown that local infiltration with ropivacaine effectively control postoperative pain and thus has been widely adopted in recent years.

Ropivacaine at 0.75%, 0.5%, or 0.2% doses have been applied for postoperative pain management, but no study has compared the analgesic effects of different doses of ropivacaine in LC.[10–12] Until now, no pharmacokinetic data of wound infiltration with ropivacaine has been described in LC, using different concentrations. Although local anesthetics are associated with few toxic effects, the consequences of higher concentration of ropivacaine could be lethal.

This study investigated the analgesic effects of different concentrations of ropivacaine for laparoscopy-assisted infiltration at port sites in patients undergoing laparoscopic cholecystectomy. Furthermore, we analyzed the peak systemic plasma concentrations of ropivacaine to assess the safety profile of this drug.

2. Materials and methods

2.1. Patients

We recruited a total of 132 patients pre-operatively from Jan 2018 to Feb 2019. This study was approved by the Institutional Ethics Board of Sir Run Run Shaw Hospital, and written informed consent was obtained from all patients. All patients scheduled for elective LC were included. The inclusion criteria were: the American Society of Anesthesiology physical status of I or II; patients aged 18 to 70 years; a body mass index (BMI) not exceeding 30. The exclusion criteria were: patients with known allergy to local anesthetics; patients with history of chronic pain following use of current opioids; patients with history of acute cholecystitis within 2 weeks prior to surgery; or those who converted to open abdomen cholecystectomy. Before surgery, all patients were trained to use a numerical rating scale (NRS), in which 0 denoted no pain, while 10 represented the worst imaginable pain. This trial was registered at chictr.org (ChiCTR-TRC-14004193).

2.2. Randomization and blinding

After obtaining informed written consent, a randomization table was generated by computer and was used to equally allocate the patients to 4 separate groups: (Group H, Group M, Group L, and Group C) in a 1:1:1:1 ratio by an independent anesthesiologist before surgery. Prior to surgery, a nurse blinded to the grouping prepared 20 ml of the experimental drug in the pre-anesthesia room as follows; 0.75% ropivacaine in Group H, 0.5% ropivacaine in Group M, 0.2% ropivacaine in Group L, and 0.9% normal saline in Group C. Results from the randomization were kept in a sealed envelope and relayed to 1 of the nurses who made preparations of the surgical procedure. The remaining members of the clinical team, including the chief anesthesiologist, were blinded to the group allocations.

2.3. Anesthesia protocol

A peripheral venous access was established prior to induction of anesthesia, and none of the patients received pre-medication before the induction. Standard monitoring included a five-lead electrocardiogram, non-invasive blood pressure, and pulse oxygen saturation using a multi-functional monitor (GE DATEX-OHMEDA S/5). All the patients who participated in the study were anesthetized with propofol (2.0–3.0 mg/kg), fentanyl (3 μg/kg), and cisatracurium (0.15 mg/kg) according to standardized general anesthesia guidelines set by the institute. General anesthesia was maintained using sevoflurane, inspired at 1.5% to 3.0%, and intravenous infusion of remifentanil, at a dose of 0.1 μg/kg/hour. An additional dose of cisatracurium (0.03 mg/kg) was administrated every hour from induction up to 1 hour before the end of the surgery. As anesthesia depth monitoring was not available, sevoflurane concentration was adjusted according to the anesthesiologists judgment for example, hemodynamic response to surgical stimulations, but narcotic doses were not adjusted to avoid impact on study results. After induction of general anesthesia, patients in Group H, M, and L received wound infiltration 20 ml of 0.75%, 0.5%, and 0.2% ropivacaine (Naropin; AstraZeneca, London, UK), respectively while patients in Group C received 20 ml of 0.9% normal saline. The four-port technique was then used to perform laparoscopic surgery. Briefly, the epigastric port site was infiltrated using the blind method before CO_2 pneumoperitoneum was established. The remaining port site infiltrations were implemented under the laparoscopy view to ensure good distribution of local anesthesia to the subcutis, fascia and peritoneum. The epigastric port and umbilical port toke 7 ml each, while the 2 smaller working ports toke 3 ml each. Blood samples were taken 30 minutes after infiltration to analyze ropivacaine concentration.

2.4. Surgery

All surgeries were performed by consultant surgeons proficient in LC. The standard 4-trocar technique was used for all procedures, with pneumoperitoneum pressure set to 12 mm Hg. After removal of the gallbladder and completion of the surgery, we carefully deflated the residual carbon dioxide.

2.5. Analgesia

Parecoxib 40 mg was administered at the end of the procedure and all patients spent a night in the hospital. Pain intensity was assessed using NRS. In cases where patients experienced significant post-operative pain (NRS $\geq$ 4), we administered rescue analgesics, either using intravenous 2.5 mg morphine for PACU patients, or tramadol 100 mg P.O. for those in the ward. Analgesics were administered repeatedly in cases where NRS remained higher than 4.

2.6. Analysis of primary outcomes

Pain intensity at rest and coughing were recorded upon leaving PACU and at 4 hours, 6 hours, 8 hours, and 24 hours after

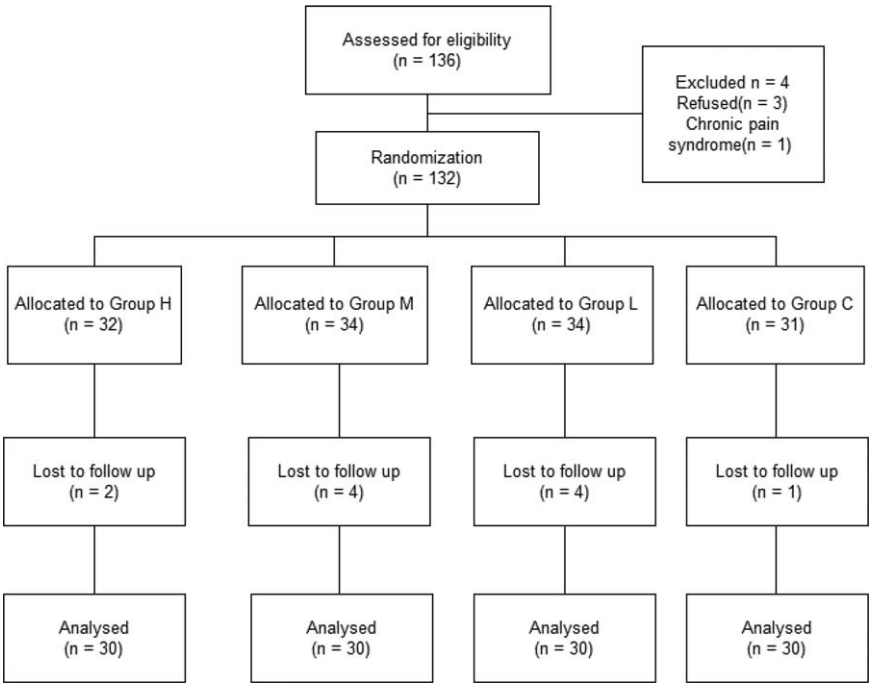

Figure 1. A flow chart showing patients inclusion and exclusion procedure.

infiltration. This information was considered the primary outcome and was conducted by a blinded investigator.

2.7. Analysis of secondary outcomes

Secondary outcomes comprised plasma concentration of ropivacaine at 30 minutes after wound infiltration and was determined via high performance liquid chromatography-mass spectrometry (HPLC-MS) performed at the Pharmacology Laboratory of the Second Affiliated Hospital of Zhejiang University School of Medicine. We recorded and compared heart beats (HR) and mean arterial pressure (MAP) before endotracheal intubation (T0), at endotracheal intubation (T1), at skin incision (T2), at 5 minutes after skin incision (T3), at 10 minutes after skin incision (T4), at 15 minutes after skin incision (T5) and 20 minutes after skin incision (T6). The frequency at which rescue analgesics were used in the PACU and ward were compared. In addition, we recorded and compared incidences of sufentanil-associated adverse effects, including PONV, pruritus, respiratory depression, and dizziness. Furthermore, any signs of local anesthetic toxicity such as prolonged Q-T interval, arrhythmia, muscle tremors, or convulsions were recorded.

2.8. Statistical analysis

Sample size was determined from a power calculation. The calculation showed that 26 subjects per group were required to achieve 80% power to detect a 20% difference in plasma concentration of ropivacaine, assuming a significance level of 0.05. Taking into consideration of a possible dropout rate of 20%, we enrolled 33 subjects for each group. This allowed a final data analysis to be performed. Therefore, 132 subjects were recruited to ensure adequate data collection.

Distribution of variables was assessed using the Kolmogorov-Smirnov test, while homogeneity of variance was evaluated using Levenes tests. Quantitative data were expressed as mean ± standard deviations, or medians and inter-quartile ranges. We employed analysis of variance (ANOVA) to compare consistent data, while SNK and LSD methods were used to compare groups. A nonparametric test was used to compare inconsistent data, Kruskal–Wallis H method for overall comparison, and Mann–Whitney *U* method to compare groups. Categorical data were expressed as frequencies and percentages, and were analyzed by Chi-Squared or Fishers exact tests where appropriate. Value with $P < .05$ were considered statistically significant. All statistical analyses were carried out using SPSS for Windows version 17.0 (SPSS Inc. Chicago, IL, USA).

3. Results

3.1. Baseline characteristics

A summary of patient characteristics is shown in Figure 1. A total of 132 subjects were recruited, 12 of which did not complete the study due to either change of surgery method or surgical cancelation. Consequently, only data from the remaining 120 subjects were analyzed in this study. There was no significant difference in the demographic parameters among the 4 groups (Table 1).

3.2. Port infiltration reduced pain intensity

NRS values for subjects in Group C were significantly higher at rest ($P = .000$) and when coughing ($P = .000$) upon leaving PACU and at 4 hours, 6 hours, 8 hours, and 24 hours after infiltration compared to those in Group H, M, and L (Fig. 2). However, these parameters were not significantly different among Groups H, M,

Table 1

Demographic and perioperative data.

Variable	Group H (n=30)	Group M (n=30)	Group L (n=30)	Group C (n=30)	*P* value
Age, yr	49.5±12.1	50.0±13.0	47.2±13.9	51.5±12.8	.638
Sex, (male/female)	10/20	13/17	12/18	8/22	.544
BMI, kg/m^2	23.6±2.7	23.4±3.0	22.6±2.8	23.5±2.8	.505
ASA, (I/II)	14/16	12/18	17/13	15/15	.629
Blood loss, ml	20.3±5.0	23.2±7.3	21.1±6.3	23.5±5.3	.122
Length of surgery, min	33.2±9.3	32.5±8.5	33.5±8.2	33.4±6.4	.969
Fluid infusion, ml	371.7±118.7	360.0±96.8	355.0±120.6	385.0±115.3	.741
Urine, ml	183.3±86.4	161.3±78.8	176.7±83.6	141.3±77.8	.202

Data are presented as mean±standard deviation or number of patients (%).
ASA = American Society of Anesthesiology, BMI = body mass index.

and L at rest or when coughing upon leaving PACU ($P=.685$, $P=.382$) and at 4 hours ($P=.152$, $P=.957$), 6 hours ($P=.924$, $P=.822$), 8 hours ($P=.150$, $P=.314$), and 24 hours ($P=1.171$, $P=.245$) after infiltration (Fig. 2).

3.3. Anesthetic agents and intraoperative medications

Consumption of sevoflurane and remifentanil in Group C were significantly higher ($P=.002$, $P=.000$) than in the other 3 groups, but no significant difference was observed among Groups H, M and L ($P=.634$, $P=.245$). Similarly, no significant differences were recorded in intra-operative medication among the 4 groups (Table 2).

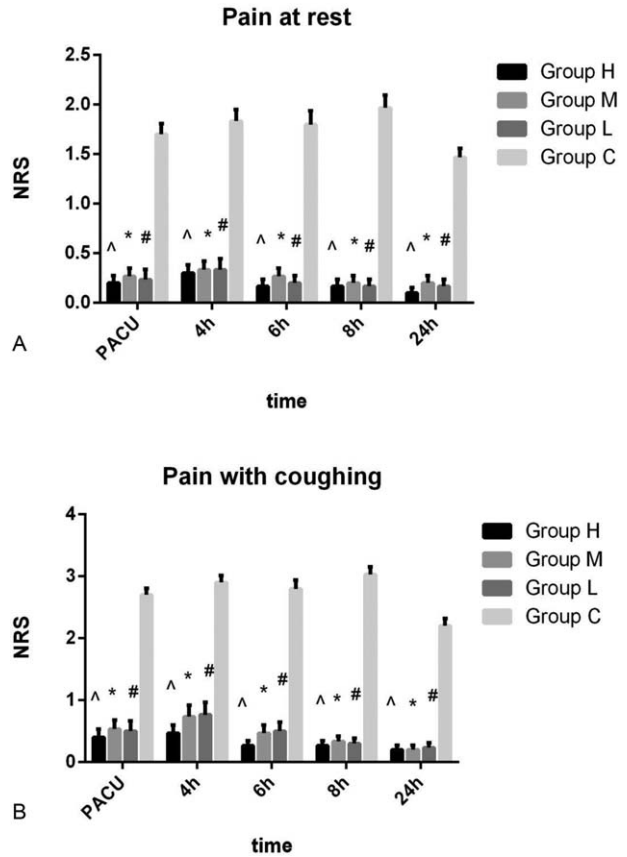

Figure 2. Pain score (NRS) at rest (A), and accompanied with coughing (B) upon leaving PACU and at 4 hours, 6 hours, 8 hours, and 24 hours after infiltration in the 4 groups. ^$P<.05$ vs Group C, $^{*}P<.05$ vs Group C, $^{\#}P<.05$ vs Group C.

3.4. HR and MAP at T0 to T6

The HR at T2 in Group C was significantly higher ($P=.000$) than in the other 3 groups (Fig. 3), while HR at T2 was not significantly different among Groups H, M, and L ($P=.61$) (Fig. 3). In addition, we found significantly higher ($P=.000$, $P=.000$) MAP at T2 and T3 in Group C compared to the other 3 groups (Fig. 3), but no significant differences were obtained in MAP at T2 and T3 among Groups H, M, and L ($P=.376$, $P=.766$) (Fig. 3).

3.5. Plasma concentration of ropivacaine

The plasma concentration of ropivacaine at 30 minutes after wound infiltration in Group H and M were significantly higher ($P<.05$) than that in Group L (Fig. 4). On the other hand, the difference in plasma concentrations of ropivacaine between Groups H and M were not significant ($P=.100$) (Fig. 4).

3.6. Rescue analgesic requirements and side-effects

The frequency of analgesic use in Group C was significantly higher ($P=.016$, $P=.005$) than the other 3 groups, while no significant difference was recorded among Groups H, M, and L ($P=.866$, $P=.749$) (Table 3). With regard to side-effects, there was no significant difference in the incidence of post-operative nausea and vomiting ($P=.180$, $P=.644$) (Table 4) at 24 hours among the 4 groups. A similar trend was observed for pruritus ($P=.288$) (Table 4). In addition, none of the subjects experienced respiratory depression or convulsions (Table 4), and there were no signs of local anesthetic toxicity such as prolonged Q-T interval, arrhythmia, muscle tremors, or convulsions.

4. Discussion

This study compared the analgesic effect, as well as the safety profile of laparoscopy-assisted wound infiltration with different concentrations of ropivacaine in patients undergoing LC. A key finding of this trial is that infiltration with 0.75%, 0.5%, and 0.2% ropivacaine provides equally strong analgesic effects. This is the first clinical study revealed that high concentration of ropivacaine is not necessary for infiltration and dilution is preferred when larger volume is needed.

Pain after LC emerge from:

Table 2

Anesthetic agents and intraoperative medication.

Variable	Group H (n = 30)	Group M (n = 30)	Group L (n = 30)	Group C (n = 30)	*P* value
Propofol, mg	127.2 ± 20.8	124.2 ± 20.5	119.0 ± 19.4	124.2 ± 21.3	.486
Fentanyl, mg	0.2 ± 0.04	0.2 ± 0.04	0.2 ± 0.04	0.2 ± 0.05	.978
Cisatracurium, mg	11.9 ± 1.7	11.8 ± 1.8	11.4 ± 2.1	11.8 ± 2.0	.762
Sevoflurane, n(%)	2.0 ± 0.5$^{\wedge\wedge}$	2.1 ± 0.5**	2.2 ± 0.6$^{\#\#}$	2.5 ± 0.3	.002
Remifentanil, mg	0.18 ± 0.04$^{\wedge\wedge}$	0.18 ± 0.03**	0.20 ± 0.02$^{\#\#}$	0.22 ± 0.03	.000
Atropine, n(%)	6 (20%)	5 (16.7%)	6 (20%)	7 (23.3%)	.937
Ephedrine, n(%)	2 (6.7%)	4 (13.3%)	3 (10%)	6 (20%)	.446

Data are presented as mean ± standard deviation or number of patients (%).

1. incision sites;
2. referred pain attributed to pneumoperitoneum; and
3. wounds intrinsic to the liver after gallbladder removal.[13,14]

The largest component (ranging between 50% and 70%) of this pain is attributed to incision sites.[15,16] Mild to moderate incisional pain exacerbates during episodes of coughing and movement, although this gradually fades over time. However, acute pain without effective control is likely to become chronic, and negatively influence a patients quality of life.[17]

Currently, given the recent advances in ultrasound, transversus abdominis plane block (TAP) has been extensively applied in pain management following LC.[18–20] However, only a handful of studies have demonstrated that TAP provides comparable analgesia effect with local anesthetic infiltration.[21,22] Wound infiltration with local anesthetics, is a simple, feasible, and financially considerate option, and is performed in multiple types of surgery, generating satisfactory analgesia without major side effects. Some studies have reported that local infiltration using 0.75%, 0.5%, or 0.25% ropivacaine effectively alleviates postoperative pain.[7,23–28] Our findings are consistent with these reports. Thierry et al demonstrated that 100 mg of intraperitoneal ropivacaine (0.25%) provided similar analgesia with 300 mg of ropivacaine (0.75%).[28] However, the surgical wound in this study had not been infiltrated with ropivacaine, and the recommended does (100 mg of ropivacaine) in this study is significantly higher than in our study. Meanwhile, other studies have demonstrated that higher doses of ropivacaine yield better and longer lasting analgesic effects compared to lower concentrations.[29,30] Explanations for these contradictory results include: First, The pain intensity after LC is mild to moderate, and the analgesic effect mainly depends on volume of local anesthetics rather than the concentration since it is to block the thin nerve endings. Second, traditional wound infiltration approaches with blind methods may lead to incomplete infiltration and thus suboptimal analgesia.[24] To ensure complete infiltration, we used laparoscopy-assisted wound infiltration with a large volume of ropivacaine. Third, our observation period was 24 hours, which may not be adequate to fully reveal differences between analgesic durations of ropivacaine with different concentrations. Finally, local infiltration, prior to incision, adopted in our study could have reduced central sensitization

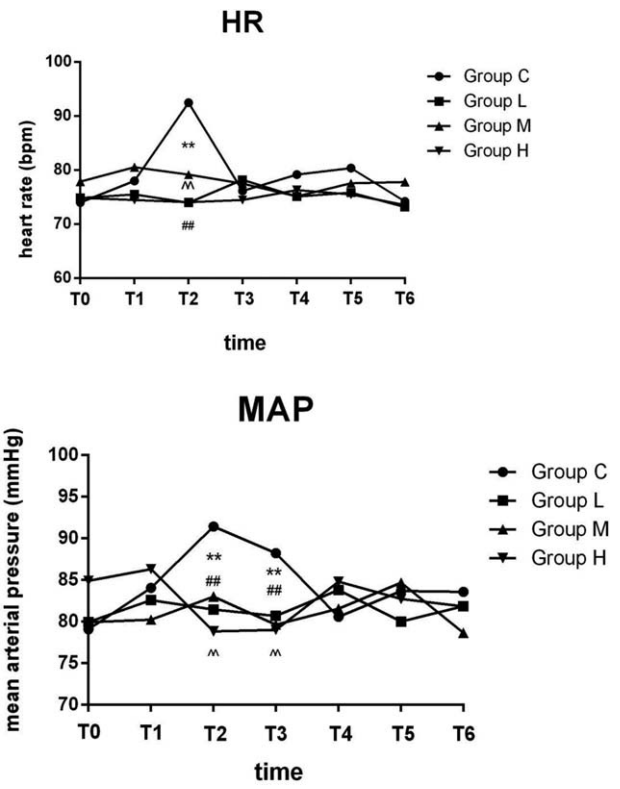

Figure 3. Heart rate (A), and mean arterial pressure (B) before endotracheal intubation (T0), at endotracheal intubation (T1), at skin incision (T2), at 5 minutes after skin incision (T3), at 10 minutes after skin incison (T4), at 15 minutes after skin incision (T5) and 20 minutes after skin incision (T6) in the 4 groups. $^{**}P < .01$ vs Group C, $^{\wedge\wedge}P < .01$ vs Group C, $^{\#\#}P < .01$ vs Group C.

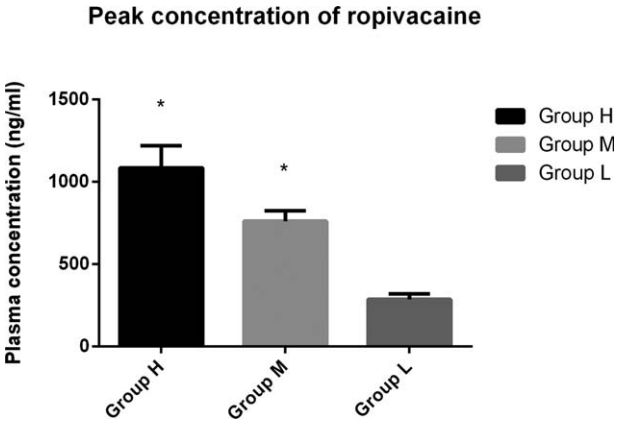

Figure 4. Plasma concentration of ropivacaine at 30 minutes after wound infiltration with different concentrations of ropivacaine in the 3 groups. $^{*}P < .05$ vs Group L.

Table 3

Rescue analgesia.

Variable	Group H (n = 30)	Group M (n = 30)	Group L (n = 30)	Group C (n = 30)	*P* value
PACU, n(%)	11 (36.7%)*	12 (40%)†	10 (33.3%)‡	21 (70%)	.016
WARD, n(%)	4 (13.3%)*	3 (10%)†	5 (16.7%)‡	13 (43.3%)	.005

Data are presented as mean ± standard deviation or number of patients (%).
* $P < .05$ vs Group C.
† $P < .05$ vs Group C.
‡ $P < .05$ vs Group C.

and pain intensity accordingly. Thus, the analgesic differences in ropivacaine action, between different concentrations, might be reduced. The reason why NRS remain different between Group C and the other 3 groups at 24 hours was beyond the study.

The consumption of sevoflurane and remifentanil in Group C were significantly more than in other 3 groups, while differences among Groups H, M, and L were not significant. Meanwhile, the HR at skin incision in Group C was significantly higher than in the other 3 groups, while MAP at skin incision as well as 5 minutes after skin incision were significantly higher than in the other 3 groups. In contrast, differences among the Groups H, M, and L were not significant, confirming our conclusion that laparoscopy-assisted wound infiltration with 0.2%, 0.5%, or 0.75% of ropivacaine decreased pain intensity to the same extent.

Local anesthetics used at the incision site trigger analgesia by blocking peripheral afferents thereby inhibiting transmission of noxious impulses to the spinal dorsal horn neurons.[31,32] Moreover, local anesthetics inhibit local inflammatory reaction as well as hyperalgesia at the incision site.[33] Ropivacaine and bupivacaine are long-acting local anesthetics that are widely used worldwide as local anesthesia for postoperative pain management. Ropivacaine has equal analgesic effects to bupivacaine but results in fewer side effects, such as motor block, toxicity to central nervous and cardiovascular system.[34,35]Thus, ropivacaine appears to be the most preferred local and postoperative analgesic drug. Previously, ropivacaine at a concentration of 0.75% was found to be safe for infiltration, and its peak plasma concentration was reported to be within safety limits. However, the side effects of using high ropivacaine concentrations remain unknown.[36]

When compared to bupivacaine, ropivacaine is safer and has higher systemic toxicity threshold. However, it is not risk-free. For this reason, a single infiltration dose, not exceeding 200 mg is recommended. Studies have found that blood concentration of ropivacaine peaked 30 to 45 minutes after infiltration, and the threshold was 3.4 μg/ml when central toxic reactions occurred.[36,37] Under general anesthesia, symptoms of systemic toxicity of the central nervous system, such as dizziness, muscle tremors, and convulsions may be concealed. However, higher blood concentrations of ropivacaine may trigger cardiovascular toxicity, causing circulatory collapse and even cardiac arrest.

In this study, plasma concentration of ropivacaine at 30 minutes after wound infiltration was significantly lower in Group L compared to H and M. However, the difference between Group H and Group M was not significant. The highest concentration of ropivacaine (2.49 μg/ml) was detected in Group H, which may have been caused by excessive absorption of ropivacaine. Although none of the patients showed symptoms toxicity due to local anesthesia, the necessity to use high concentration of ropivacaine was not required. To ensure safety, we recommend dilution of ropivacaine when a large volume is needed.

Nausea and vomiting are common complaints in patients under anesthesia, which come from several factors.[38] Previous studies show that wound infiltration can reduce consumption of opioids as well as the associated side effects in traditional opioid-based analgesia strategy. Notably, incidence of PONV, pruritus and respiratory depression was not significantly different among the 4 groups, although more morphine and tramadol were consumed in Group C relative to other groups. This can be attributed to the small sample size in the study.

The current study contains some limitations. First, the observation period was too short to reveal potential differences between analgesic durations under different ropivacaine doses. Second, frequent blood samples collection after surgery will make patients feel bored and increase complaints. Therefore, we only observed the systematic blood concentration of ropivacaine at 1 time point, and could not assess the relationship between dosage and blood concentration. Third, the depth of anesthesia monitoring was not used in this study, which may affect the results of the study. Finally, we did not consider other factors affecting pain intensity, such as age, gender, and education status.

In conclusion, laparoscopy-assisted wound infiltration with 0.2%, 0.5%, or 0.75% ropivacaine provide equally effective pain control in patients undergoing LC. Furthermore, higher peak plasma concentration was recorded when ropivacaine was infiltrated at high dose, and the peak levels did not exceed the threshold of central toxicity. Future studies should explore the optimal duration for different doses of ropivacaine wound

Table 4

Side effects.

Variable	Group H (n = 30)	Group M (n = 30)	Group L (n = 30)	Group C (n = 30)	*P* value
Nausea, n(%)	4 (13.3%)	9 (30%)	7 (23.3%)	3 (10%)	.180
Vomiting, n(%)	1 (3.3%)	3 (10%)	1 (3.3%)	2 (6.7%)	.644
Pruritus, n(%)	0 (0)	1 (3.3%)	0 (0)	2 (6.7%)	.288
Respiratory depression, n(%)	0 (0)	0 (0)	0 (0)	0 (0)	1.000

Data are presented as number of patients (%).

infiltration in LC, as well as the relationship between dosage and plasma concentration.

Author contributions

Min Liang, Dachun Zhou conceived and designed the trail. Yijiao Chen, Wenchao Zhu collected the data. Min Liang analyzed the data. Min Liang, Yijiao Chen and Wenchao Zhu wrote this paper.
Conceptualization: Min Liang, Dachun Zhou.
Data curation: Min Liang, Yijiao Chen and Wenchao Zhu.
Methodology: Min Liang, Dachun Zhou.
Project administration: Dachun Zhou.
Software: Min Liang, Wenchao Zhu.
Writing – original draft: Min Liang, Yijiao Chen.
Writing – review & editing: Min Liang, Dachun Zhou.

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