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CLINICAL TRIAL REPORT

Thoracic Paravertebral Block with Liposomal Bupivacaine Versus Plain Bupivacaine in Patients Undergoing Thoracoscopic Lung Resection: A Randomized Controlled Study

Zhen Yang[1,2,*], Manman Liu[1,*], Chengyu Wang[3,*], Yuejiao Song[1], Junmei Wu[1], Dan Wu[1], Minmin Yao[3], Yan Yang[3], Changhong Miao[3], Chao Liang[3]

[1]Department of Anesthesiology, Xiamen Zhongshan Hospital, Fudan University, Xiamen, Fujian, People's Republic of China; [2]Department of Anesthesiology, Shanghai Geriatric Medical Center, Fudan University, Shanghai, People's Republic of China; [3]Department of Anesthesiology, Zhongshan Hospital, Fudan University, Shanghai, People's Republic of China

*These authors contributed equally to this work

Correspondence: Chao Liang; Changhong Miao, Department of Anesthesiology, Zhongshan Hospital, Fudan University, Shanghai, People's Republic of China, Tel/Fax +86-021-64041990, Email superwm226@126.com; miao.changhong@zs-hospital.sh.cn

Background: The effectiveness of a thoracic paravertebral blockade with liposomal bupivacaine for thoracic surgery pain management is not well examined. This study compared the effects of liposomal bupivacaine and plain bupivacaine on a thoracic paravertebral blockade in adult patients undergoing video-assisted thoracoscopic surgery (VATS).

Methods: Consenting participants (114) scheduled for VATS were randomly assigned to thoracic paravertebral blockade at T4–5 and T7-8 levels with 20 mL (266 mg) liposomal bupivacaine (LB) or 20 mL (37.5 mg) plain bupivacaine (PB) groups. The primary endpoint was opioid consumption at 48 hours postoperatively. Additional main outcomes included the opioid consumption 24 and 72 hours postoperatively; the pain score at rest and coughing 24, 48, and 72 hours postoperatively; Quality of Recovery-15 (QoR-15) scores 24 hours postoperatively, the time to the first analgesia request.

Results: Opioid consumption did not differ between the groups at 48 hours postoperatively. The QoR-15 scores 24 hours after surgery were higher in the LB group than in the PB group (mean [SD], 120.2 [7.1] vs 116.5 [7.8]; P = 0.009). The time to the first analgesia request was longer in the LB group than in the PB group (mean [SD], 585.8min [211.7] vs 315.3min [101.7]; P <0.001). The areas under the curve for the NRS score at rest were 21.2 and 35.8 for the LB and PB groups, respectively (P = 0.002). The NRS scores during coughing did not differ between the two groups, nor did the CPSP three months postoperatively.

Conclusion: Liposomal bupivacaine offers limited but measurable clinical benefits when used for thoracic paravertebral blockade in patients undergoing VATS.

Registration: Chinese Clinical Trial Registry; Registration number: ChiCTR2400081544, URL: https://www.chictr.org.cn/showproj.html?proj=221025.

Keywords: liposomal bupivacaine, paravertebral block, video-assisted thoracic surgery, chronic postsurgical pain

Introduction

Patients undergoing thoracic surgery often suffer from severe postoperative pain. Even less invasive surgeries, such as video-assisted thoracoscopic surgery (VATS), can cause moderate-to-severe acute postoperative pain and chronic postsurgical pain (CPSP), which occurs in 25 to 50% of patients.[1–3] Therefore, optimizing analgesia for thoracic surgery remains an important issue.

Regional anesthesia is a key component of multimodal analgesia in the perioperative period.[4,5] The thoracic paravertebral blockade, neuraxial analgesia, fascial plane block and intercostal nerve block have become the first line

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of regional anaesthesia for VATS, recommended by the Society of Cardiovascular Anesthesiologists and PROSPECT group.[6,7] However, when a single-dose approach is used for a thoracic paravertebral blockade, its effect is limited by the duration of the local anaesthetics.[8,9] In addition, for patients receiving a continuous thoracic paravertebral blockade, a percutaneously inserted catheter is inserted with its tip into the paravertebral space, which can be challenging and increases the risk of infection, leakage, and catheter dislodgement.[10]

Reports suggest that liposomal bupivacaine, which is used for infiltration and peripheral nerve blocks, can extend postoperative analgesia.[11–15] However, only one retrospective study assessed thoracic paravertebral blockades using liposomal bupivacaine in thoracotomy and VATS, reporting significantly improved pain scores for patients who received liposomal bupivacaine compared to those who received plain bupivacaine.[16] Given the limitations such as potential recall bias, unmeasured confounding factors, and restricted generalizability of retrospective studies, solid evidence of the effectiveness of a thoracic paravertebral blockade with liposomal bupivacaine for thoracic surgery pain management remains limited.

Thus, we designed this prospective, randomized controlled trial to compare the analgesic effectiveness of a thoracic paravertebral blockade using liposomal bupivacaine versus plain bupivacaine in patients undergoing VATS. We hypothesized that liposomal bupivacaine reduced postoperative opioid consumption 48 hours postoperatively compared to plain bupivacaine.

Methods

The Ethics Committee of the Xiamen Branch of Zhongshan Hospital, affiliated with Fudan University, approved this study on February 1, 2024 (Approval No.: B2023-145R). This single-center, randomized controlled trial was conducted at Xiamen Branch of Zhongshan Hospital, affiliated with Fudan University. The study was performed in the Departments of Anesthesiology and Thoracic Surgery between March 2024 and August 2024. All participants provided written informed consent. The trial was pre-registered in the Chinese Clinical Trial Registry on March 5, 2024 (ChiCTR2400081544) before enrolling the first patient (March 6, 2024). This study adhered to the ethical principles of medical research involving human participants, as outlined in the 1975 Declaration of Helsinki (revised in 2013).

Participants

The study was conducted between March 2024 and August 2024 in patients scheduled for VATS for lung tumors. The inclusion criteria were: (1) patients with a preoperative lung tumor diagnosis aged 18 to 80 years; (2) those with an American Society of Anesthesiologists physical status of 1 to 3; (3) patients who underwent pulmonary resection using the biportal minimally invasive video-assisted approach; and (4) those who signed an informed consent form agreeing to the research protocol. The exclusion criteria were: (1) patients with a known allergy to the local anesthetics used in this study; (2) those experiencing side effects from the analgesics used in this study; (3) patients with infected wounds or severe inflammation; (4) those with cirrhosis or renal impairment (glomerular filtration rate <30 mL m^{-1} 1.73 m^2[–1]); (5) those with serious intrathoracic adhesion based on preoperative imaging data, which affects the operation under VATS; (6) uncooperative patients who prevented the completion of a clinical evaluation; (7) pregnant women; and (8) those who had undergone chest surgery on the same side. Participants were also excluded if: (1) they withdrew their informed consent, (2) the surgery was converted to an open surgery, or (3) they experienced severe operation-related complications.

Randomization and Blinding

A total of 114 eligible patients were enrolled and were randomized at a 1:1 ratio to liposomal bupivacaine (LB) or plain bupivacaine (PB) groups. All group assignments in this trial were performed randomly, and the random number table was generated using SPSS version 21 (IBM Corp., Armonk, NY, USA); even and odd numbers designated the LB and PB groups, respectively. Given the visible difference in appearance between liposomal bupivacaine (milky white suspension) and plain bupivacaine (clear solution), the paravertebral blocks were performed by a dedicated anesthesiologist who was not involved in subsequent outcome assessment. Study syringes were prepared by a separate unblinded researcher and labeled only with patient identifiers. Patients, postoperative care providers, data collectors, and outcome assessors were

all blinded to group allocation. This approach ensured that while the proceduralist was aware of group assignment, blinding was strictly maintained for all other study personnel and participants.

Anesthetic Treatment

After entering the operating room, all participants underwent standard monitoring with electrocardiography, capnography, pulse oximetry, invasive arterial pressure, and a bispectral index (BIS) (Covidien) evaluation. General anesthesia was induced with propofol (Aspen Pharma Trading Limited, Dublin, Ireland) via a target-controlled infusion (effect site Marsh model) using a Diprifusor target-controlled infusion pump (B. Braun Melsungen AG, Melsungen, Germany). The initial target plasma propofol concentration was 4 μg mL-1 for both groups. Additionally, 0.5 μg kg^{-1} sufentanil (Yichang Renfu Pharmaceutical Industry, Yichang, China) and 0.9 mg kg^{-1} rocuronium (Merck Sharp & Dohme Corp., Rahway, NJ, USA) were administered for induction in both groups. Vasoactive agents (atropine and norepinephrine) were used based on the patient's hemodynamics. After anesthesia induction, a double-lumen endobronchial tube was intubated.

A senior anaesthesiologist performed the thoracic paravertebral blockade under ultrasound guidance with the patients in a lateral position. After confirming the correct position of the needle tip (USG TYPE CCR, 22G, 70 mm, Hakko Co., Ltd., Osaka, Japan), the thoracic paravertebral blockade was performed at the T4–5, and T7-8 levels following the standardized technique. Under real-time ultrasound visualization, the T4–5 and T7-8 levels were respectively injected with 10 mL (133 mg) of liposomal bupivacaine (Jiangsu Hengrui Medicine Co, Ltd., Jiangsu, China) or with 10mL (18.75mg) of plain bupivacaine (Shanghai Hefeng Pharmaceutical Co., Ltd., Shanghai, China). Although both groups received equal injection volumes (10 mL at T4–5 and T7–8 levels), the total bupivacaine content differed: the liposomal bupivacaine group received 133 mg of bupivacaine, whereas the plain bupivacaine group received 37.5 mg in total (0.1875% solution). This reflects current commercial formulations and prior studies using fixed clinical doses rather than dose-equivalent pharmacokinetic matching.

All patients received total intravenous anaesthesia during surgery. The target plasma propofol concentration was 3.0 to 4.0 μg mL^{-1} to maintain a BIS value range from 40 to 60. A bolus of 10mg rocuronium was given intermittently to maintain muscle relaxation during surgery. If needed, an additional 0.1 μg kg^{-1} of sufentanil was given each time. The double-lung ventilation parameters were: tidal volume: 8 mL kg^{-1}; respiratory rate: 10 to 12 breaths per min; positive end-expiratory pressure (PEEP): 5 cmH_2O; end-tidal carbon dioxide ($ETCo_2$): maintained between 35 and 45 mmHg; and peak airway pressure <20 mmHg. The single-lung ventilation parameters were: tidal volume: 6 mL kg^{-1}; respiratory rate: 10 to 12 breaths/min; PEEP: 5 cmH_2O; $ETCo_2$: maintained <60 mmHg; and peak airway pressure, <30 cmH_2O. Before the end of the surgery, parecoxib was administered as a fixed dose based on body weight: 40 mg for patients weighing ≥50 kg and 20 mg for those <50 kg (Pfizer Pharmaceuticals, New York, NY, USA). This weight-based dosing regimen was applied uniformly to all patients, and 0.6 mg of ramosetron (Chongqing Changhui Pharmaceutical Co, Ltd., Chongqing, China) were administered. Additionally, 2 mg kg^{-1} of sugammadex (Merck Sharp & Dohme Corp) was given to reverse the residual effect of rocuronium.

All procedures were performed via a biportal, minimally invasive video-assisted approach. An 8-mm incision was made at the seventh or eighth intercostal space of the posterior axillary line for the camera, and a 4-cm incision was made at the fourth or fifth intercostal space of the anterior axillary line for the surgeon performs the operation.

In the post anaesthesia care unit (PACU), when the numeric rating scale (NRS; 0, no pain; 1–3, mild pain; 4–6, moderate pain; and 7–10, severe pain) score was ≥4; both groups received 5 μg of sufentanil. The drugs used for postoperative patient-controlled intravenous analgesia (PCIA) were sufentanil (250μg) and ramosetron (0.6 mg), which were diluted in 0.9% normal saline to a final volume of 250 mL. The analgesia pump settings were as follows: background dose, 0 mL/h; self-controlled additional dose, 4 mL/time; and lockout time, 10 min. The patients were sent to the ward after the observation period if they had a NRS score <4 and a Steward score ≥4 for one hour. In the post-surgery ward, the patient determined the NRS score, and a surgical departmental nurse blinded to the group assignments gave instructions for the PCIA pump.

Study Outcomes

The primary outcome parameter was the amount of sufentanil delivered by the patient-controlled intravenous analgesia pump 48 hours postoperatively. The secondary outcomes were the amount of sufentanil delivered by patient-controlled intravenous analgesia pump 24 and 72 hours postoperatively; the NRS score at rest and coughing 24, 48, and 72 hours postoperatively; perioperative opioid consumption; CPSP three months after surgery (a NRS of ≥1 at three months postoperatively was considered CPSP); chest tube removal time and length of stay.

The Quality of Recovery-15 Score (QoR-15) 24 hours postoperatively (comprised of a 15-item questionnaire scored on a 10-point scale, total scores range from 0 [poor recovery] to 150 [excellent recovery]), the time to the first analgesia request and perioperative adverse events (such as nausea, vomiting, and pruritus) were also collected.

Sample Size Calculation

The sample size was calculated using G power software 3.1.[17,18] Our primary outcome was opioid consumption at 48 hours postoperatively. Preliminary research indicates that the amount of morphine equivalents consumed within 48 hours in the bupivacaine group was mean 75 and standard deviation 26 μg sufentanil. Opioid consumption in the LB group was 20% lower than that in the PB group, indicating a significant difference between the two groups. Thus, with an α-value of 0.05 and a 1-β-value of 0.8, the required sample size per group was 48 cases. Accounting for a 20% loss to follow-up, the required sample size per group was 58.

Statistical Analyses

The SPSS version 21 (IBM Corp) and R version 4.0.0 (R Core Team, Vienna, Austria) were used to performed Statistical analyses. Descriptive statistics of continuous variables are expressed as means (SDs) or medians (interquartile spacing), depending on the data distribution. Dichotomous variables are presented as counts and percentages (%). Dichotomous data were compared using the two-tailed chi-squared test with the Yates correction. The Shapiro–Wilk test was used to evaluate the normality of continuous variables. T-tests and ANOVAs were used to compare normally distributed variables, and the two-sample Wilcoxon rank-sum, chi-squared, or Fisher's exact tests were used for classification or rank variables. Two-sided significance tests were performed; P-values <0.05 were considered significant.

Results

From March 2024 to August 2024, 120 patients were screened, 114 underwent randomization, and 113 were included in the analyses (56 and 57 patients in the LB and PB groups, respectively) (Figure 1). Table 1 presents the demographic and clinical characteristics of both groups.

Table 2 compares the perioperative variables between the two groups. The surgery duration, amount of bleeding, amount of urine and time to extubation did not differ between the groups. All patients received parecoxib in a fixed weight-based dose (either 20 mg or 40 mg), with comparable distributions across the two groups; therefore, no formal statistical comparison was performed. However, the amount of fluid infused significantly differed between them (P = 0.049).

Opioid consumption in the PACU and 24, 48, and 72 hours postoperatively did not differ between the groups (Table 3). However, the QoR-15 score 24 hours after surgery was higher in the LB group than in the PB group (mean [SD], 120.2 [7.1] vs 116.5 [7.8]; mean difference [95% CI], –3.7 [–6.4, –1.0]; P = 0.009) (Table 3). Additionally, the time to the first analgesia request was longer in the LB group than in the PB group (mean [SD], 585.8 min [211.6] vs 315.3 min [101.7]; mean difference [95% CI], –270.5 [–331.6, –209.4]; P <0.001) (Table 3). The chest tube removal time and length of hospital stay did not differ between the groups. The incidence of CPSP also did not differ between the LB and PB groups (17.9% [10/56] vs 19.3% [11/57]).

The area under the pain-time curve (AUPC) for NRS score at rest was significantly lower in the LB group (21.2 vs 35.8, P = 0.002), but the AUPC for the NRS score for coughing has no statistically significant difference between the two groups (126.0 vs 135.0) (Figure 2). The postoperative dizziness, postoperative nausea and vomiting, pruritus, hypotension, and bradycardia incidence rates did not differ between the two groups (Table 4). In addition, no other liposome bupivacaine related adverse events were found.

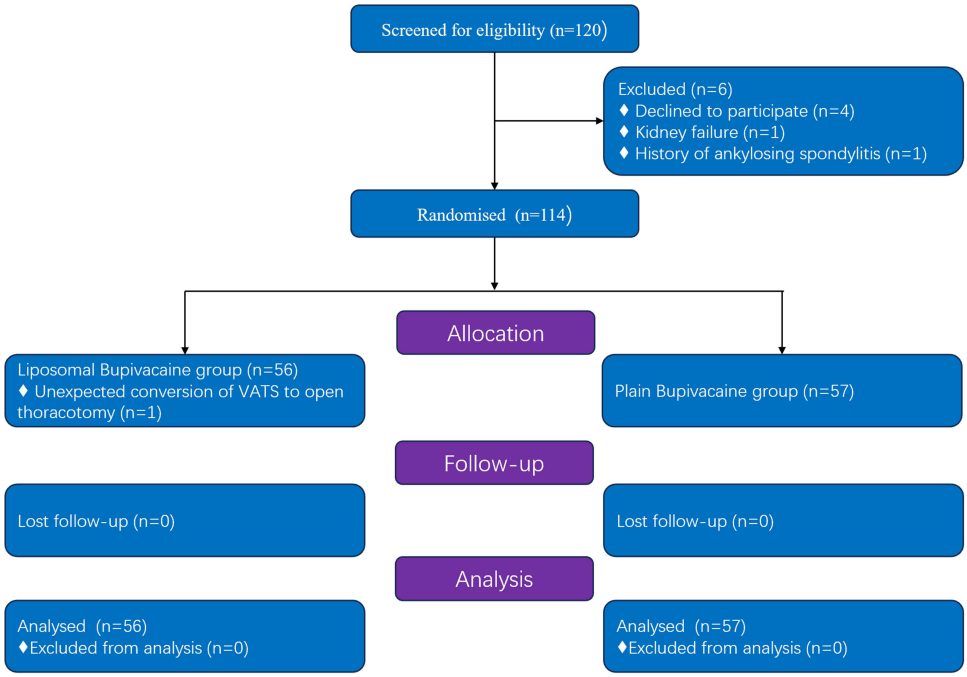

Figure 1 Flowchart of the study.

Discussion

The aim of this study was to investigate the effectiveness of liposomal bupivacaine for thoracic paravertebral blockade during VATS with chronic bupivacaine release. Our main results demonstrated that compared with plain bupivacaine, liposomal bupivacaine prolongs the time to the first request for analgesia after surgery and improves the NRS scores at rest, however, it does not reduce postoperative opioid consumption and affect pain while coughing.

Some recent review and meta-analysis studies suggested that the postoperative pain relief benefits of liposomal bupivacaine are not different from those of plain bupivacaine when used for periarticular infiltration in joint arthroplasty,

Table 1 Characteristics of the Patients

	Group LB (n = 56)	Group PB (n = 57)	p-Value
Age; y (mean, SD)	60 ± 11	56 ± 10	0.145
BMI; kg.m^2(mean, SD)	23.13 ± 2.68	23.38 ± 2.98	0.640
Sex			0.167
Female	31(55.45%)	41(71.9%)	
Male	25(44.6%)	16(28.1%)	
ASA physical status			0.071
1	19(33.9%)	33(57.9%)	
2	37(66.1%)	24(42.1%)	
Surgery type			0.213
1	23(41.1%)	15(26.3%)	
2	9(16.1%)	9(15.8%)	
3	24(42.9%)	33(57.9%)	
Hypertension	12(21.4%)	11(19.3%)	0.799
Diabetes	8(14.3%)	6(10.5%)	0.542
Prior opioid use	6(10.7%)	6(10.5%)	0.976

Notes: Values are presented as mean ± SD, or counts and percentage (%); Surgery type (1=lobectomy; 2=segmentectomy; 3=wedge resection).
Abbreviations: ASA, American Society of Anesthesiologists physiological status; BMI, body mass index; LB, liposomal bupivacaine; PB, plain bupivacaine; SD, standard deviation.

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Table 2 Perioperative Variables

	Group LB (n = 56)	Group PB (n = 57)	Median Difference (95% CI)	p Value
Amount of Bleeding; mL	30.5(21.76)	31.8(40.54)	1.31(−10.72,13.33)	0.832
Parecoxib; mg				0.683
20mg	4(7.1%)	3(5.3%)		
40mg	52 (92.9%)	54(94.7%)		
Amount of urine; mL	191.8(138.17)	165.6(139.32)	−26.17(−77.34,25.00)	0.318
Amount of fluid infusion; mL	900.0(224.01)	810.5(252.44)	−89.47(−177.53, −1.42)	0.049
Duration of operation, min	98.4(45.53)	94.4(44.74)	−3.99(−20.64,12.66)	0.639
Time to extubation, min	8.1(5.70)	8.0(5.69)	−0.11(−2.21,1.99)	0.921

Notes: Values are presented as mean ± SD or number (percentage); Parecoxib was administered in a fixed dose of 40 mg for patients ≥50 kg and 20 mg for those <50 kg.
Abbreviations: LB, liposomal bupivacaine; PB, plain bupivacaine.

Table 3 Patient Outcomes

	Group LB (n = 56)	Group PB (n = 57)	Median Difference (95% CI)	p Value
PACU opioid; μg	0.5(1.29)	0.7(1.50)	0.21(−0.32,0.74)	0.443
24h total opioid consumption; μg	11.8(15.20)	13.6(14.26)	1.85(−3.59,7.28)	0.507
48h total opioid consumption; μg	22.4(24.67)	29.0(27.05)	6.57(−2.98,16.12)	0.180
72h total opioid consumption; μg	27.3(28.54)	33.6(36.67)	6.31(−5.82,18.44)	0.310
24h QoR-15	120.2(7.05)	116.5(7.75)	−3.70(−6.43, −0.97)	0.009
Time to first request for analgesia; min	585.8(211.65)	315.3(101.72)	−270.49(−331.55, −209.43)	<0.001
Chest tube removal time, d	3.1(1.9)	3.3(1.8)	−0.2(−0.9, 0.5)	0.575
Lengths of hospital stay, d	8.2(3.09)	7.8(3.73)	0.39(−1.65,0.88)	0.548
CPSP (3 months after surgery), n (%)	10(17.9)	11(19.3)		0.844

Notes: Values are presented as mean ± SD or number of patients (percentage).
Abbreviations: CPSP, chronic postsurgical pain; LB, liposomal bupivacaine; PB, plain bupivacaine; PACU, post-anesthesia care unit; QoR, quality of recovery.

perineural applications in peripheral nerve blocks, and abdominal fascial plane blocks, with no clinically differences in opioid consumption up to 72 hours postoperatively; they also reported no differences in the time to the first request for analgesia, the lengths of hospital stay, and the incidence of opioid-related adverse events.[11,19–21] Similarly, although we found that the average opioid consumption in the PACU and at 24, 48, and 72 hours postoperatively were lower in the liposomal bupivacaine group than in the plain bupivacaine group, these differences were statistically insignificant. Moreover, we only found improvements in the NRS scores at rest, but not during coughing. The prolonged time to first request for analgesia in the liposomal bupivacaine group can be attributed to differences in pharmacokinetics between the two formulations. Plain bupivacaine is a conventional local anesthetic with a relatively short half-life (approximately 2.7 hours) and rapid systemic absorption, typically providing analgesia for 6–8 hours. In contrast,

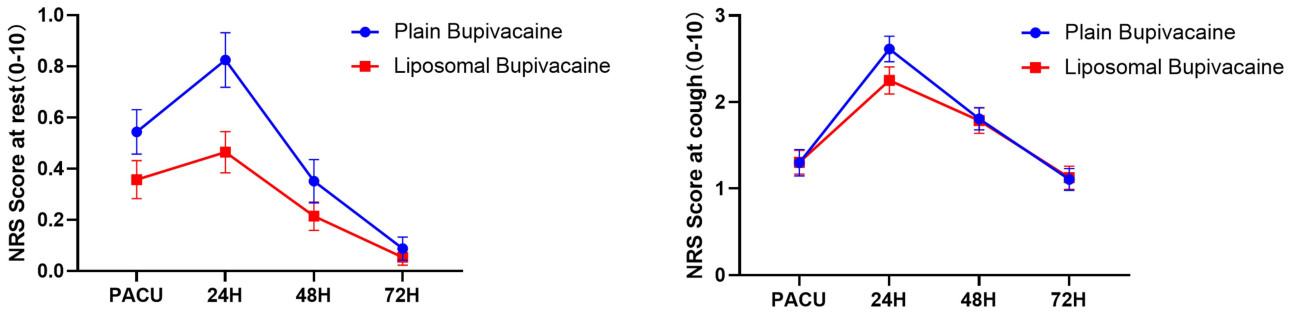

Figure 2 Time course of pain intensity at rest (left) and during coughing (right) following video-assisted thoracoscopic surgery in patients receiving liposomal bupivacaine (blue) or plain bupivacaine (red) for paravertebral blockade. Data are presented as mean ± standard deviation. The area under the pain-time curve (AUPC) for NRS at rest was significantly lower in the liposomal bupivacaine group (P = 0.002), while no significant difference was observed for cough pain.

Table 4 Perioperative Adverse Events

	Group LB (n = 56)	Group PB (n = 57)	p Value
Postoperative dizziness			0.357
No	52(92.9%)	50(87.7%)	
Mild	4(7.1%)	7(12.3%)	
PONV			>0.999
No	53(94.6%)	54(94.7%)	
Mild	1(1.8%)	1(1.8%)	
Moderate	1(1.8%)	2(3.5%)	
Severe	1(1.8%)	0(0.0%)	
Pruritus			0.496
No	56(100.0%)	55(96.5%)	
Mild	0(0.0%)	2(3.5%)	
Hypotension			0.323
No	49(87.5%)	55(96.5%)	
Mild	7(12.5%)	11(19.3%)	
Bradycardia			0.427
No	50(89.3%)	48(84.2%)	
Mild	6(10.7%)	9(15.8%)	

Notes: Values are presented as counts and percentage (%).
Abbreviations: LB, liposomal bupivacaine; PB, plain bupivacaine; PONV, postoperative nausea and vomiting.

liposomal bupivacaine consists of multivesicular lipid-based structures that encapsulate bupivacaine and allow for slow, sustained release of the drug over up to 72 hours. This extended-release profile maintains effective local concentrations for a longer period, which may account for the delayed onset of breakthrough pain and hence the prolonged time to the first patient-controlled analgesia demand observed in our trial.

Although liposomal bupivacaine significantly prolonged the time to first analgesia request, this did not translate into a reduction in total opioid consumption over 24–72 hours. Several factors may account for this apparent discrepancy: Transient benefit: The analgesic advantage of liposomal bupivacaine may be most pronounced in the early postoperative phase (first 6–12 hours). Once its concentration drops below the effective threshold, patients may require similar amounts of opioids as the control group, thereby nullifying cumulative differences. Breakthrough pain from other sources: After the initial effect of the block wears off, patients may experience visceral pain, coughing-induced chest pain, or drain-related discomfort—pain types that may be less responsive to paravertebral blockade and require systemic opioids in both groups. PCIA usage patterns: The patient-controlled analgesia system delivers fixed bolus doses on demand, which may lead to similar cumulative opioid doses once patients begin requesting analgesia, regardless of initial timing. Analgesic ceiling effect: Since baseline pain scores were relatively low in both groups (mean NRS <3 at rest), the room for further opioid reduction may have been limited, attenuating measurable differences in opioid use. These factors suggest that while liposomal bupivacaine can delay the onset of moderate pain, it may not substantially reduce overall opioid needs unless combined with multimodal strategies targeting different pain components.

In this study, we find liposomal bupivacaine for thoracic paravertebral blockade liposomal bupivacaine may have failed to reduce opioid use. From a pharmacokinetic perspective, the lack of opioid-sparing effect observed in our study may relate to the drug release profile of liposomal bupivacaine in the paravertebral space. Although the formulation is designed for slow and sustained release over 72 hours, several factors may limit its effectiveness in this anatomical region: Limited spread in the paravertebral space: The multivesicular liposomes may remain localized near the injection site due to their particle size and viscosity, resulting in restricted cranio-caudal spread and incomplete coverage of the targeted dermatomes. Physiological clearance and vascular uptake: The paravertebral space is highly vascularized, potentially leading to faster systemic absorption and clearance of the released drug, especially compared to other fascial planes. Altered pH or enzymatic microenvironment: The local environment may affect liposomal stability or membrane degradation kinetics, thus altering the intended release profile. Non-linear dose-response curve: While liposomal

bupivacaine provides prolonged duration, it may not achieve a high enough local concentration to continuously block nerve conduction over the entire analgesic window. These pharmacokinetic challenges highlight that the efficacy of liposomal formulations is not solely dependent on drug content, but also on site-specific release behavior and tissue pharmacodynamics.

Although pain relief and reduced opioid consumption are common signs of a successful block, they are limited indicators for assessing the overall quality of patient recovery. The QoR-15 questionnaire, is an validated and widely accepted patient-centered approach for assessing the overall "quality of recovery" after various surgeries.[22] In the present study, the liposomal bupivacaine group had higher QoR-15 scores 24 hours after surgery, indicating that the patients were satisfied with the postoperative pain control using liposomal bupivacaine. We speculated that the longer time to the first request for analgesia in the liposomal bupivacaine (about 4.5h longer than that of plain bupivacaine group) may have partially contributed to the higher QoR-15 scores. However, the statistically significant difference in QoR-15 scores we observed in present study (3.7 points) may not be considered clinically significant, since a minimal clinically difference is 6 points.[23] Therefore, while the result suggests a possible trend toward improved early recovery with liposomal bupivacaine, it should be interpreted with caution and may not represent a clinically perceptible benefit to patients. Moreover, future study needs a large sample size to investigate this patient-centered outcome in thoracic paravertebral blockade using liposomal bupivacaine, since it was not the primary outcome of present study.

In the present study, postoperative pain at rest in both groups was mild, with an average NRS score of less than 3, likely due to the use of the biportal VATS and a multimodal analgesia protocol during the perioperative period. These results are similar to those previously reported.[24,25] Studies have also reported incidence rates of 12 to 42% for CPSP at three months when using a thoracic paravertebral blockade after minimally invasive thoracic surgery.[26–28] Similarly, our results showed that the overall incidence of CPSP in both groups was 18.6% (21/113) at three months, and the incidence rates did not differ between the groups. We also found comparable postoperative adverse reactions between the two groups, and no adverse reactions associated with liposomal bupivacaine were observed. The incidence of nausea and vomiting after surgery was around 5% in both groups, which is significantly lower than those previously reported for minimally invasive thoracic surgery (22.0 to 34.0%),[24,29] which is likely related to less perioperative opioid use and total intravenous anaesthesia.

This study has some limitations. First, we only analyzed biportal VATS with indwelling thoracic drainage tubes in the seventh or eighth intercostal space of the posterior axillary line. The chest tube is one of the main causes of pain after video-assisted thoracoscopic surgery;[30] thus, our conclusions may not directly apply to uniportal and triportal VATS. Second, it is important to remind clinicians that the use of liposomal bupivacaine for thoracic paravertebral blockades remains an off-label application and that the liposomal bupivacaine dosage for thoracic paravertebral blockade requires further optimization. Furthermore, although liposomal bupivacaine offers theoretical pharmacologic advantages and has demonstrated partial clinical benefit in our study, its cost-effectiveness remains uncertain. The drug is substantially more expensive than plain bupivacaine—often by a factor of 10 or more—and is not universally available due to pricing and regulatory constraints. In settings where healthcare resources are limited, such cost may not be justified given the absence of opioid-sparing effects and only modest improvements in early recovery. Future studies should include health-economic evaluations and comparative cost-utility analyses before recommending routine adoption of liposomal bupivacaine in thoracic regional anesthesia. Third, an important methodological limitation is the unequal total dose of bupivacaine between groups. While both groups received equal volumes, the liposomal bupivacaine formulation delivered a higher total drug content. This was intended to replicate clinically available concentrations and mirrors the approach of previous studies. However, we acknowledge that this may introduce bias in interpreting efficacy comparisons, as the pharmacodynamic effects of the two formulations are not directly dose-equivalent. Another limitation of our study is the definition of chronic postsurgical pain (CPSP) as an NRS score ≥1 at 3 months postoperatively. While this criterion is commonly used for sensitivity, it may capture trivial pain that is not clinically meaningful. Future studies should consider stricter thresholds (eg, NRS ≥3) or incorporate validated tools assessing pain interference or functional impact to better reflect patient-relevant chronic pain outcomes. Finally, the addition of liposomal bupivacaine to plain bupivacaine versus plain bupivacaine alone has been investigated in other regional anaesthesia, such as in brachial plexus block and periarticular injection,[31,32] and this comparison is the aim of our future study in paravertebral blockade.

Conclusion

In conclusion, this trial demonstrated that compared to plain bupivacaine, although using liposomal bupivacaine for a thoracic paravertebral blockade in VATS prolongs the time to the first analgesia request and improves the NRS scores at rest, however, it does not reduce the amount of postoperative opioid consumption and affect pain while coughing. These findings suggest that liposomal bupivacaine offers limited but measurable clinical benefits, and further studies are needed to clarify its role in thoracic regional anesthesia.

Data Sharing Statement

For reasonable data requests, contact the corresponding author by email.

Disclosure

The authors disclose no conflicts of interest with respect to this work.

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