Effect of preoperative thoracic paravertebral nerve block using liposomal bupivacaine combined with drainage-tube patient-controlled analgesia on postoperative pain after thoracoscopic lobectomy: a prospective, multicentre, double-blind, randomized controlled study protocol

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Research Article

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Abstract

**Background:** Thoracic paravertebral nerve block (TPVB) with liposomal bupivacaine (LB) is increasingly used for postoperative pain control in patients undergoing thoracic surgery, but relevant data are scarce, and there are few data on LB-TPVB combined with drainage tube patient-controlled analgesia (PCA). The aim of this study was to explore the effect of LB-TPVB combined with drainage-tube PCA on postoperative pain after thoracoscopic lobectomy.

**Methods:** This is a prospective, multicentre, double-blind, randomized controlled study. Participants will be randomly assigned to the standard bupivacaine (SB) group, SB + drainage-tube PCA (DTA) group, LB group, or LB + DTA group. The primary outcome is the 72-h mean numerical rating scale (NRS) pain score at rest. The target sample size is 228 patients, with 57 patients in each group.

**Discussion:** Our study hypothesizes that preoperative ultrasound-guided thoracic nerve block combined with drainage tube self-controlled analgesia is more effective in reducing postoperative pain following thoracoscopic lobe resection compared to thoracic nerve block alone. Additionally, liposomal bupivacaine was found to be more effective than standard bupivacaine in this context. These results will have implications for improving postoperative analgesia protocols for patients undergoing thoracoscopic lung surgery.

**Trial registration:** ClinicalTrials.gov, NCT06165991. Registered 29 November 2023, https://clinicaltrials.gov/study/NCT06165991.

**Background**

In recent years, video-assisted thoracoscopic surgery (VATS) has become a popular thoracic surgical technique. Compared with thoracotomy, VATS is a less invasive and less painful surgery[1]. However, moderate to severe pain has been reported after thoracoscopic surgery[2–4], and this pain is mainly caused by surgical trauma, intercostal nerve stimulation, lung or pleural traction, and the use of an indwelling chest drainage tube. Thoracic epidural analgesia (TEA) is still the gold-standard treatment for postoperative pain after thoracic surgery[5–7]. Currently, thoracic paravertebral nerve block (TPVB) is the first-line nerve block method for post-thoracoscopic pain relief[8, 9]. Clinical studies of TPVB application have shown that TPVB can produce an analgesic effect similar to that of thoracic epidural block but with fewer adverse effects. TPVB can significantly reduce the incidence of post-thoracoscopic pulmonary atelectasis and lung infection, and TPVB has a lower incidence of nausea and vomiting, circulatory hypotension, urinary retention, and skin itching than thoracic epidural block [10].

For many patients, one of the main sources of pain after thoracic surgery is the presence of a pleural and mediastinal drainage tube, which is inserted by the surgeon at the end of the surgery and is maintained for 2 to 3 days. This pain is usually described as sharp, piercing pain that radiates to the back or shoulder and occurs with breathing, movement, or coughing. These symptoms are often not relieved despite taking medications[11].
At present, the greatest limitation of the use of local anaesthetics in TPVB for the treatment of pain is the limited duration of a single injection[12]. These agents can provide effective pain relief for only 7–16 h and may also cause severe pain[12]; therefore, it is difficult for these agents to meet the patient’s analgesic needs for the 48–72 h the tube must remain in place after surgery. Although continuous nerve block can maintain long-term pain relief, there are many catheter-related complications. Single administration of liposomal bupivacaine (LB; Jiangsu Hengrui Medicine Co., Ltd., Lianyungang, China) can achieve postoperative pain relief for 72 h, which is more in line with the clinical needs of multimodal analgesia under the enhanced recovery after surgery (ERAS) concept and has been included in the recommended pathway of several surgical ERAS guidelines in Europe and the United States [13, 14].

LB is a sustained-release formulation suitable for topical administration. LB allows slow drug diffusion for up to 72 h and provides adequate local analgesia after surgery[15]. On the other hand, the effect of bupivacaine, which contains epinephrine, lasts for only 8–12 h. Some studies (including two randomized trials) have compared the effects of intercostal injection of LB with those of standard bupivacaine (SB) after thoracic surgery [8, 16–18], but the results are mixed. At present, studies on the application of LB in thoracic surgery are mostly limited to intercostal nerve blocks[19–21] and local invasion block[22]. Currently, the evidence supporting the use of LB in TPVB is limited to retrospective studies[16]; however, prospective, randomized controlled trials with large samples are lacking.

Todd L et al. showed that intermittent or continuous injection of SB through a chest tube could effectively reduce the postoperative pain and 24-h opioid use in patients undergoing thoracoscopic surgery[23]. Several prospective randomized studies have also shown the benefits of intrathoracic anaesthesia[11, 24–29]. However, some investigators have found that intrapleural injection of SB alone cannot reduce the pain score to an acceptable level[30–32]. Evidence on the efficacy and safety of local anaesthetic injection through drainage tubes for postoperative analgesia in patients undergoing thoracoscopic lobectomy is still insufficient. The main objective of this study is to investigate the effect of LB-TPVB combined with drainage tube placement for patient-controlled analgesia (PCA) in patients undergoing thoracoscopic lobectomy.

**Methods and analysis**

**Trial objectives**

The main objective of this study is to investigate the effect of LB-TPVB combined with drainage-tube postoperative PCA after thoracoscopic lobectomy.

**Ethics and communication**

This study is approved by the Ethics Committee of the First Affiliated Hospital of Shandong First Medical University (ID YXLL-KY-2023 (156), December 22, 2023). All participants will provide written informed consent before participation in the study. The results of this study will be presented at national and international conferences and in peer-reviewed scientific journals.
Study design

This is a multicentre, randomized, controlled trial (Fig. 1). This study is approved by the Ethics Committee of the First Affiliated Hospital of Shandong First Medical University (ID YXLL-KY-2023 (156), December 22, 2023) and is registered in the Clinical Trial Registration Centre. This trial will be performed in 7 research centres in China. Written informed consent will be obtained from each patient before enrolment. Eligible patients will be recruited and randomly assigned to 4 study groups. The trial will comply with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) (Fig. 2). [33]

Participants

A total of 228 patients scheduled to undergo thoracoscopic lobectomy will be recruited for this study according to the inclusion and exclusion criteria. We plan to enrol the first patient on June 1, 2024, and to complete recruitment by December 31, 2025.

Inclusion criteria

1. Patients who will undergo unilateral primary thoracoscopic lobectomy under general anaesthesia (video-assisted or robotic-assisted);
2. Patients aged ≥ 18 years;
3. Patients classified as American Society of Anaesthesiologists (ASA) grades I-III;
4. Patients agree to voluntarily participate in this study and sign an informed consent form.

Exclusion criteria

1. Women who are pregnant or breastfeeding;
2. Patients who will undergo lung wedge resection;
3. Patients for whom ≥ 2 chest drainage tubes are necessary;
4. Patients with abnormal liver function: alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) > 2× the upper limit of normal (ULN) or total bilirubin (TBIL) ≥ 1.5×ULN;
5. Patients with renal impairment (serum creatinine > 176 µmol/L) or receiving dialysis treatment within 28 days before surgery;
6. Patients who have participated in another research trial involving investigational drugs within the previous 6 months;
7. Patients with a history of drug or alcohol abuse;
8. Patients with long-term use of opioid drugs (> 3 months or daily morphine equivalent > 5 mg/day for 1 month);
9. Patients with a history of allergy to local anaesthetics or one of the study drugs;
10. Patients with uncontrolled mental or neurological symptoms.

Dropout criteria
1. Patients lost to follow-up;
2. Patients withdraw their informed consent;
3. Patients with serious adverse events;
4. Patients who have no study records or incomplete records for other reasons;
5. Patients who are unable to complete the entire clinical trial for other reasons.

The detailed reasons for dropout patients will be recorded in the case report form (CRF).

**Study implementation**

All members of the research team will receive systematic training to master and use the Numerical Rating Scale (NRS), overall benefit of analgesic score (OBAS), cumulative opioid consumption, and 15-item Quality of Recovery (QoR15) before the study and may participate only after passing the examination (Supplemental Appendix 1).

a. **Evaluation of postoperative analgesia.** Postoperative pain will be evaluated using the NRS. With the NRS, pain is scored between 0 and 10, with higher points indicating greater pain. The following criteria are often used: 0, no pain; 1–3, mild pain that can be tolerated; 4–6 points, pain that also affects sleep but can still be tolerated; and 7–10 points, relatively severe pain, which is unbearable and affects appetite and sleep. The occurrence of two different types of pain will be recorded: pain at rest and pain when coughing. At 72 h after surgery, PCIA will be discontinued. The cumulative consumption of sufentanil, the dosage of rescue analgesics and the incidence of nausea and vomiting will be recorded. During hospitalization, if the NRS score is ≥ 4 points after 3 consecutive PCA doses, the intravenous injection of 10 mg oxycodone will be used for rescue analgesia. A NRS score ≥ 7 for more than 24 h will be defined as an adverse event. All the detailed information will be recorded in the CRF.

b. **OBAS.** The OBAS is a multidimensional quality assessment tool that is used to measure the benefit of postoperative pain treatment for patients. To calculate the OBAS, the sum of the scores for Items 1–6 is calculated and added to the sum of the score for Item 7 + 2. For example, a patient with minimal pain (NRS = 0), severe vomiting (NRS = 4), and no itching, sweating, or freezing who is slightly dizzy (NRS = 1) and is not very satisfied with his postoperative pain treatment (NRS = 1) has an OBAS of 8. Note that a low score indicates a high benefit.[34]

c. **Cumulative opioid consumption (morphine milligram equivalent, MME),** morphine (iv) 1 mg = morphine (oral) 3 mg = oxycodone (oral) 1.5 mg; morphine (iv) 1 mg = fentanyl (iv) 10 µg = remifentanil (iv) 10 µg = sufentanil (iv) 1 µg = tramadol (iv) 10 mg = pethidine (iv) 10 mg; morphine (iv) 1 mg = sufentanil (epidural) 1 µg; each opioid analgesic drug has a conversion factor; for example, the conversion factor of oxycodone (oral) is 1.5, that of oxycodone (intravenous injection) is 3, and that of tramadol (oral) is 0.2.

d. **QoR-15.** The QoR-15 is a patient-reported outcome measurement validated to measure the QoR after surgery and general anaesthesia. The OoR score ranges from 0 to 150, with a higher score indicating better recovery.28 The QoR-15 is a smaller version of the 40-time QoR (QoR-40). The psychometric properties of the two versions are comparable, but the QoR-15 is more practical to use
because it is shorter and takes less time to complete.\textsuperscript{28,29} Scoring criteria: excellent (QoR-15 score > 135), good (122 ≤ QoR-15 score ≤ 135), moderate (90 ≤ QoR-15 score ≤ 121), and poor (QoR-15 score < 90).

e. **Drainage-tube PCA.** This is the innovation in this study. We improve the traditional drainage tube by adding a drug injection channel, and we connect the drainage tube to an electronic PCA pump for continuous analgesia, which is defined as drainage-tube PCA (Fig. 3).

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<td><strong>The OBAS.</strong></td>
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<tr>
<td>1. Please rate your current pain at rest on a scale between 0 = minimal</td>
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<tr>
<td>pain and 4 = maximum imaginable pain</td>
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<tr>
<td>2. Please grade any distress and bother from vomiting in the past 24 h</td>
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<td>(0 = not at all to 4 = very much)</td>
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<tr>
<td>3. Please grade any distress and bother from itching in the past 24 h</td>
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<td>(0 = not at all to 4 = very much)</td>
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<tr>
<td>4. Please grade any distress and bother from sweating in the past 24 h</td>
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<td>(0 = not at all to 4 = very much)</td>
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<tr>
<td>5. Please grade any distress and bother from freezing in the past 24 h</td>
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<td>(0 = not at all to 4 = very much)</td>
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<tr>
<td>6. Please grade any distress and bother from dizziness in the past 24 h</td>
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<td>(0 = not at all to 4 = very much)</td>
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<tr>
<td>7. How satisfied are you with your pain treatment during the past 24 h?</td>
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<td>(0 = not at all to 4 = very much)</td>
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**Randomization and blinding**

We will use a stratified blocked randomization method, with a block length of 4, and participants will be randomly divided into 4 groups at a 1:1:1:1 ratio. The patients and researchers will be blinded to the group allocation in this study. It should be noted that LB is a white or almost white suspension, whereas SB is a colourless, clear liquid; therefore, we will use a 20 mL opaque syringe and infusion tube to ensure investigator blinding. A blinded independent researcher will be responsible for the preoperative visit and obtaining informed consent from the participants. The outcome will be evaluated by an independent researcher to minimize the bias associated with data collection. The statisticians will also be blinded to the allocation.

**Intraoperative monitoring and anaesthesia management**

Standard intraoperative monitoring will include pulse oximetry, noninvasive monitoring of arterial blood pressure, electrocardiography (ECG), and end-tidal carbon dioxide (EtCO\textsubscript{2}) monitoring. Blood pressure and central venous pressure will be monitored invasively when necessary. A bispectral index (BIS) monitor (Medtronic, USA) will be used to monitor the depth of anaesthesia, and a neuromuscular monitor (JS-100, Beijing SLGO Medical Technology Co., Ltd., China) will be used to confirm neuromuscular block (NMB).
Before induction of anaesthesia, the patient will wear a face mask and will be preadministered h 100% oxygen for 5 min. Anaesthesia will be induced using 0.04 mg/kg midazolam, 1.5–2.5 mg/kg propofol, 0.3–0.5 µg/kg sufentanil, and 0.6 mg/kg rocuronium bromide. When the train-of-four ratio (TOFR) reaches 0, a dual-lumen endotracheal tube will be inserted. After the patient is placed in the lateral position according to surgical needs, the location of the surgical incision will be selected based on the corresponding thoracic segment for ultrasound-guided TPVB.

During the maintenance period of anaesthesia, mechanical ventilation will be performed at a tidal volume of 6–8 mL/kg (ideal body weight (IBW): male IBW = actual height (cm)-100, female IBW = actual height (cm)-105). The respiratory rate will be adjusted as needed to maintain the EtCO$_2$ between 35 and 45 mmHg, and the inspiratory-to-expiratory ratio will be 1:2. Propofol will be administered at a rate of 4–10 mg/kg/h, and remifentanil will be administered at a rate of 0.1–0.3 µg/kg/min to maintain anaesthesia. Rocuronium bromide will be administered and adjusted to achieve deep NMB (defined as a train-of-four count (TOFC) = 0 and a post-tetanic count = 1–2). After surgery, patients will be transferred to the post-anaesthesia care unit (PACU) or intensive care unit (ICU) for further monitoring. NMB will be reversed with sugammadex (2–4) mg/kg according to the manufacturer’s instructions.[35]

**Intervention**

Participants will be randomly assigned to the SB group, SB + DTA group, LB group and LB + DTA group at a ratio of 1:1:1:1. The specific medication regimens of the four groups are as follows:

1. **SB group**: 0.5% SB for TPVB combined with postoperative PCIA with equivalent normal saline;
2. **SB + DTA group**: 0.5% SB for TPVB combined with drainage-tube PCIA;
3. **LB group**: 1.33% LB for TPVB combined with postoperative PCIA with equivalent normal saline;
4. **LB + DTA group**: 1.33% LB for TPVB combined with drainage-tube PCIA.

After induction of anaesthesia, under ultrasound guidance, an independently trained anaesthesiologist will perform a three-point TPVB with the patient in the lateral position (with the corresponding intervertebral space at the surgical centre as the midpoint and other two points being two spaces above and below). An electronic PCIA pump (100 mL, Jiangsu Apon Medical Technology Co., Ltd., China) consisting of sufentanil at 2 µg/kg in a total volume of 100 mL will be used for postoperative pain control without a background dose. The single dose will be 1 mL, with a lockout interval of 10 minutes, and the number of compressions and dose used will be recorded using the postoperative analgesia management system. Drainage-tube PCA will be performed using the drainage tube along with a lateral tube. After the surgery, a single bolus injection of 0.25% SB (10 mL) will be administered. The analgesia drainage tube will be fixed (Fig. 3), and an external electronic PCA pump will be connected, with the following parameters: a background dose of 5 mL/h and no PCA dose.

**Termination criterion**

The study will be automatically terminated at the end of the follow-up period. Follow-up after the end of the trial will be performed with the consent of the participants. Other termination criteria are as follows:
(1) voluntary withdrawal, the participant can withdraw from the study at any time without any explanation or any impact on his future medical care; (2) the surgery is cancelled for various reasons; (3) drug use during observation in violation of protocol requirements; (4) conditions that increases the risk of adverse events in patients; and (5) serious complications during the observation period. Any trial deviations from the experimental protocol will be approved by the Ethics Committee before implementation.

Primary outcome indicators

The 72-h mean NRS pain score at rest and at 24, 48, and 72 h.

Secondary outcome indicators

Resting and exercise NRS scores at 1 h, 3 h, 6 h, 12 h, 18 h, 24 h, 36 h, 48 h, 60 h, and 72 h after surgery will be recorded. The area under the receiver operating characteristic curve (AUC) of the NRS score at rest and during exercise within 72 h after surgery will be calculated, and the 72-h mean NRS pain score during exercise; time of first use of rescue analgesic within 72 h; cumulative opioid consumption (MME) during the 72 h after surgery; participant OBAS; QoR-15 scores at 24, 48, and 72 h after surgery; incidence of postoperative complications; incidence of nausea and vomiting; and incidence of adverse events will be recorded.

Adverse events

1. Local anaesthetic toxicity: Mild local anaesthetic toxicity: if a patient develops hypotension, he/she will be treated symptomatically. A paravertebral operation will be performed after general anaesthesia and tracheal intubation so that breathing can be ensured. For particular patients, LB will be used as soon as possible. If the patient suffers from cardiac arrest, cardiopulmonary resuscitation will be performed as soon as possible.
2. Local haematoma: A mild haematoma can be slowly absorbed. Severe bleeding will be treated surgically when necessary.
3. For nerve injury, patients will receive treatments such as nerve support.
4. Infection will be treated with anti-infection treatment.
5. When the pleura and lung are punctured, a chest drainage tube will be placed during thoracic surgery.
6. For total spinal anaesthesia, symptomatic treatment of blood pressure and heart rate will be used.
7. Tachycardia: When the heart rate is > 100 beats/min or increases by > 20% from baseline if the baseline value is > 83 beats/min, 10 mg esmolol will be given, and/or the dose of anaesthetics will be adjusted.
8. Hypertension: Patients with a systolic blood pressure > 160 mmHg or an increase from baseline of ≥ 20% if the baseline value is > 133 mmHg will be given 10 mg urapidil and/or the dose of anaesthetics will be adjusted.
9. Bradycardia: Patients with a heart rate < 55 beats/min or a heart rate reduction of > 20% from baseline or a baseline heart rate < 69 beats/min will be given 0.3 mg atropine and/or 2 µg isoproterenol or the anaesthetic dose will be adjusted.
10. Hypotension: Patients with a systolic blood pressure < 95 mmHg or a decrease in systolic blood pressure > 20% if the baseline value is < 119 mmHg will be given a liquid infusion of 6 mg ephedrine or 4 µg norepinephrine and/or the anaesthetic dose will be adjusted.

Data collection

Resting and exercise NRS scores at 1 h, 3 h, 6 h, 12 h, 18 h, 24 h, 36 h, 48 h, 60 h, and 72 h after surgery will be recorded; the AUC of the resting and exercise NRS scores within 72 h after surgery will be calculated; and the QoR15 scores at 24, 48, and 72 h after surgery, the OBAS, the incidence of postoperative complications, the cumulative opioid consumption (MME) within 72 h after surgery, the time of the first opioid rescue within 72 h after surgery, unexpected hospitalizations after surgery, and adverse events will be recorded.

Data and safety monitoring board

We will form a data and safety monitoring board (DsMB) to ensure the integrity and authenticity of the randomized controlled trial and to protect the privacy of the participants. The DsMB will periodically review the scientific and ethical standards of the trial and review the validity of the data analysis. Although members of the DsMB will not participate in this study, they will review the interim results and make the final decision on whether to terminate the trial. The DsMB will be formed in accordance with the World Health Organization (WHO) guidelines for the establishment and operation of a DsMB, and the DsMB will be responsible for the data evaluation during the study period.

Data management

Validation of the test systems and clinical research equipment will be performed regularly. All investigators will strictly follow the standard operating procedures (SOPs) and the research protocol. The data will be recorded in a timely, direct, accurate, clear, signed, and dated manner. The accuracy and completeness of the data records will be evaluated, and errors will be corrected according to the prescribed methods. Patient inclusion and personnel training will be performed in strict accordance with the inclusion and exclusion criteria. Validated and reliable statistical software will be used for the statistical processing of the data. Effective quality control measures, such as double personnel and double entry (missing-missing method and double-entry method), will be used for data entry.

At each subcentre, the investigators will review and approve all the data. Researchers at the participating centres will submit the CRFs and supporting documents directly to the data management system (coordinating centre: The First Affiliated Hospital of Shandong First Medical University). The data monitoring of this multicentre study will include central data consistency checks, statistical monitoring, and on-site monitoring of all centres.

Sample size calculation

This study is a randomized controlled study that will evaluate the efficacy and safety of four methods of administering postoperative analgesia after thoracoscopic lobectomy, with the primary study outcome
being the 72-h mean NRS pain score at rest. According to a previous study,[36] the 72-h mean NRS pain scores at rest for 0.5% SB with 4 mg dexamethasone and 1.33% LB with 0.5% SB were 3.4 and 2.4, respectively, and we hypothesise that, after combined with the drainage-tube PCA, both NRS pain scores will improve by 20% to 2.7 and 1.9, respectively. The means of the four groups are 3.4, 2.7, 2.4, and 1.9, and the predicted overall standard deviation is 1.9. For a two-sided test $\alpha$ of 0.05 and 90% power, the sample size, calculated using the “One-Way Analysis of Variance F Tests” in PASS15.0 software, is $N = 180$, with $N = 45$ in each group. If the rate of loss to follow-up and refusal to participate in follow-up is 20%, then 57 patients in each group of this study will be needed, and the total sample size needed is at least 228.

**Statistical analysis**

All the data will be analysed using SPSS (25.0) software, and a two-sided $P< 0.05$ will be considered to indicate statistical significance.

Continuous variables will be presented as the mean $\pm$ standard deviation if they obey a normal distribution; if they do not follow a normal distribution, they will be presented as the median (upper and lower quartiles); categorical variables will be presented as the frequency and rate (or composition ratio).

The main indicators evaluated in this study will include the mean resting-state NRS pain scores at 24, 48 and 72 h; the AUC of the NRS scores at rest and during exercise within 72 h after surgery; the cumulative opioid consumption used within 72 h after surgery (MME); and the time of the first opioid rescue within 72 h after surgery. For the comparisons among the four groups, if the data are normally distributed, a general analysis of variance (ANOVA) will be used; otherwise, the Kruskal-Wallis H rank-sum test will be used.

Repeated-measures ANOVA will be performed to evaluate the QoR15 score and OBAS at 24, 48, and 72 h after surgery.

The count data (opioid-free percentage, postoperative complication rate, incidence of postoperative unexpected hospitalization and adverse events) will be analysed using the chi-square test or Fisher’s exact probability test.

**Discussion**

This study protocol describes a multicentre, double-blind, randomized controlled trial to determine the effect of LB-TPVB combined with drainage-tube PCA on postoperative analgesia after thoracoscopic lobectomy. Although patients who undergo minimally invasive thoracic surgery exhibit less postoperative acute pain,[37] the incidence of conversion from acute to chronic pain is still as high as 47%[38], which is no different from the 50% commonly cited for thoracotomy[39]. These observations might be because the degree of trauma to the intercostal nerves is similar between thoracotomy and minimally invasive thoracic surgery even though the incision used in the minimally invasive surgery is smaller. In a retrospective study[40], Rachel E reported that the application of LB for TPVB significantly reduced
postoperative pain in patients who underwent thoracoscopic surgery and provided effective analgesia for patients who underwent thoracotomy. Multiple studies have shown\cite{37,41-48} that LB can help reduce the use of perioperative opioids, improve postoperative pain management, and accelerate the recovery of patients. The applications include ultrasound-guided transversus abdominis plane (TAP) block, erector spinae plane block, brachial plexus block, adductor canal block and local infiltration anaesthesia.

In addition, one of the leading causes of pain after thoracic surgery is the drainage tube inserted into the pleura and mediastinum, and the pain can persist for 2–3 days. This pain is usually described as sharp, piercing pain that radiates to the back or shoulder and occurs with breathing, movement, or coughing. These symptoms are often not relieved despite taking medications\cite{11}. In 1986, Reiestad et al., for the first time, described the administration of bupivacaine through the thoracic cavity and the thoracic catheter (including infusion and bolus injection) and used bupivacaine in many situations.\cite{49} Bupivacaine has been used in various conditions, such as after thoracoscopic examination,\cite{23} after thoracotomy,\cite{24,50,51} after hepatectomy,\cite{52} and for upper abdominal surgery,\cite{53} and it has also been used as an analgesic during pneumothorax drainage.\cite{23} Todd L et al.\cite{23} showed that for approximately two-thirds of VATS patients, chest pain was significantly reduced after chest tube removal. Todd L et al.\cite{23} also showed that intermittent or continuous intrapleural infusion of SB through a chest tube was associated with less postoperative pain and less 24-h opioid use in patients who underwent VATS. In this study, the injection of SB through a drainage tube may reduce the pain caused by the chest tube, reduce the use of opioids, and accelerate the recovery of patients. In this trial, LB-TPVB combined with drainage-tube PCA may prolong the analgesic duration, reduce the pain score, improve patient satisfaction, and accelerate recovery.

In summary, this randomized clinical trial aims to determine the effect of LB vs. SB as the preoperative ultrasound-guided TPVB on postoperative pain after thoracoscopic lobectomy. We expect that LB can be safely used for TPVB and the application of LB as the preoperative ultrasound-guided TPVB will be more effective than SB in reducing 72-h mean NRS pain scores at rest after surgery.

**Abbreviations**

TPVB, Thoracic paravertebral nerve block; LB, liposomal bupivacaine; PCA, patient-controlled analgesia; SB, standard bupivacaine; DTA, drainage-tube PCA; NRS, numerical rating scale; VATS, video-assisted thoracoscopic surgery; TEA, thoracic epidural analgesia; PCA, patient-controlled analgesia; SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials; ASA, American Society of Anaesthesiologists; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal; TBIL, total bilirubin; CRF, case report form; OBAS, overall benefit of analgesic score; QoR15, 15-item Quality of Recovery; MME, morphine milligram equivalent; QoR-40, 40-time QoR; ECG, electrocardiography; EtCO\(_2\), end-tidal carbon dioxide; BIS, bispectral index; NMB, neuromuscular block; TOFR, train-of-four ratio; IBW, ideal body weight; TOFC, train-of-four count; PACU, post-anaesthesia care...
unit; ICU, intensive care unit; DsMB, data and safety monitoring board; WHO, World health Organization; SOPs, standard operating procedures; TAP, transversus abdominis plane.

Declarations

Acknowledgements

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Author contributions

JW, YS, KL, DS, ZL, YC, ZL, LY, BL, ZY, NF, PY, and WZ are in charge of the study conception and the overall design of the project. YS and NG are also the primary contributor to writing the manuscript. JW, YS, NG, MZ, and YZ designed the statistical approach for the study, conducted the a priori sample size estimates, and drafted the statistical portions of the manuscript. DS, ML, NG, HF, ML, LG, YR, and ML are participating in the execution, acquisition of data, quality control, analysis, and clinical interpretation. YS is the overall principal investigator of the study and has been involved in all aspects of project development and manuscript writing. All the authors have contributed to this article and approve the submitted version.

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Availability of data and materials: Not applicable.

Ethics approval and consent to participate

Our research is being conducted in accordance with the principles of the Declaration of Helsinki (64th WMA General Assembly, October 2013) and has been approved by the Ethics Committee of the First Affiliated Hospital of Shandong First Medical University (YXLL-KY-2023 (156), December 22, 2023). Written informed consent will be obtained from all participants and/or their legal representatives. The results will be disseminated through a peer-reviewed publication and at conferences or congresses.

Consent for publication

Not applicable.

competing interests
The authors declare they have no competing interests.

References


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Figures

Figure 1

Study flow chart.

SB group: 0.5% SB for TPVB combined with postoperative patient-controlled intravenous analgesia (PCIA) with equivalent normal saline; SB+ DTA group: 0.5% SB for TPVB combined with drainage-tube PCIA; LB group: 1.33% LB for TPVB combined with postoperative PCIA with equivalent normal saline; LB+ DTA group: 1.33% LB for TPVB combined with drainage-tube PCIA.
The study timeline and schedule of enrolment, allocation, interventions, and assessment.

SB group: 0.5% SB for TPVB combined with postoperative patient-controlled intravenous analgesia (PCIA) with equivalent normal saline; SB+DTA group: 0.5% SB for TPVB combined with drainage-tube PCIA; LB group: 1.33% LB for TPVB combined with the postoperative PCIA with equivalent normal saline; LB+DTA group: 1.33% LB for TPVB combined with drainage-tube PCIA. NRS, Numerical Rating Scale; OBAS, overall benefit of analgesic score; QoR15, quality of recovery-15.
Figure 3

Drainage-tube PCA.