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Risk and benefit analysis of single-shot nerve block for postoperative analgesia for uniportal video-assisted thoracic surgery (uVATS): a randomized controlled trial

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Abstract

Background There is lack of the clinical evidence of optimized perioperative analgesic protocol for uniportal video-assisted thoracoscopic surgery (uVATS).

Methods We performed a RCT enrolling participants scheduled for uVATS (Trial registration: NCT06016777; registration date: Aug 28, 2023). Participants were randomized for thoracic paravertebral block combined with patient-controlled intravenous analgesia (*PVB + PCIA*), erector spinae block combined with PCIA (*ESPB + PCIA*), or *PCIA group*. Participants were followed-up till 6 months. Primary outcome was total opioid consumption. Secondary outcomes included postoperative rest and cough pain scores, ambulation time, chest tube duration, length of stay, anaesthesia expense and adverse events.

Results We enrolled 108 participants between October 16th, 2023 to April 14th, 2024. Neural block did not reduce opioid consumption. Postoperative rest and cough pain scores did not differ among the groups at all the follow-up time points. None of the participants experienced chronic pain. The ambulation time, duration of chest tube maintenance and length of stay did not differ among groups. Duration of anaesthesia procedure was significantly prolonged in both neural blockade groups compared to *PCIA group* ($p = 0.033$). Anaesthesia expenses were significantly higher in both nerve block groups than in the *PCIA group* ($p < 0.001$). Adverse events related to neural blockade occurred in 17.9% in *PVB + PCIA group* and 2.9% in *ESPB + PCIA group* ($p = 0.010$), including local haemorrhage and block failure. Adverse events related to opioid use did not differ among groups.

Conclusions Both PVB and ESPB did not exhibit analgesic advantage for uVATS. Neural block may carry the risk of haemorrhage and block failure, prolonged the anaesthesia procedure and increased the anaesthesia expenses.

Trial registration Clinical Trial Number was NCT06016777, trial registration date was Aug 28th, 2023.

Keywords Postoperative pain, Thoracic surgery, Uniportal, Nerve block, Single-shot

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Introduction

Reduction of postoperative pain after thoracic surgery has always been challenging. Current studies on perioperative analgesia protocols for video-assisted thoracoscopic surgery (VATS) are flourishing. The guidelines in 2022 [1] recognized that thoracoscopic surgery could greatly reduce postoperative pain. The guidelines have recommended single-shot paravertebral block (PVB) or erector spinae block (ESPB) combined with systemic analgesia as the first-line perioperative analgesic protocol. Latest studies have shown that uniportal thoracoscopy (uVATS) is an improved surgical plan to further reduce postoperative pain [2–4]. However, there seemed to be no evidence-based perioperative pain management for uVATS. We assume that uVATS may significantly alter the optimal analgesic regimen.

On the basis of optimizing the surgical incision and the chest tube management, we compared the analgesic effect of single-shot PVB or ESPB with ropivacaine, in addition to patient-controlled intravenous analgesia (PCIA), to investigate the risks and benefits of these analgesic regimens for uVATS.

Methods

Study design

We performed a single-centre, three-arm, single-blind RCT, conducted in China-Japan Friendship Hospital between October 16, 2023 to April 14, 2024. The trial was registered prior to patient enrolment at https://www.clinicaltrials.gov/, Clinical Trial Number was NCT06016777, the registration date was Aug 28, 2023. This study was approved by the Ethics Committee of China-Japan Hospital (2022-KY-127–1, approved on Jun 16, 2023). Human Ethics and Consent to Participate was obtained before enrollment**.** Written informed consent was obtained from all subjects participating in the trial. The protocol of this trial has been published [5]. No protocol modification was performed throughout the study. This report was written in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines (Supplementary File 1).

Participants were eligible for this study if they were scheduled for wedge resection, segmentectomy, or lobectomy under uVATS. Patients with history of intrathoracic or chest wall surgery, previous multiportal VATS, history of chronic pain, current analgesic treatment or with contraindications to analgesics or nerve blocks were excluded from the study (Table 1).

Grouping and blinding

After enrolment, participants were randomly assigned to one of the three groups with the allocation ratio 1:1:1. (a) The *PVB + PCIA group*: participants received ultrasound-guided paravertebral nerve block in combination with PCIA. (b) The *ESPB + PCIA group*: participants received ultrasound-guided erector spinae block in combination with PCIA. (c) The *PCIA group*: participants received PCIA without regional block.

Block randomization method was performed. A researcher (T Bu) stratified the participants based on sequential ID numbers with a permuted block of six. Random sequences of six numbers between 0 and 1 were

Table 1 Inclusion and exclusion criteria

Inclusion criteria
1. ≥ 18 years
2. ASA I-III[a]
3. Early-stage lung cancer or intrathoracic tissue biopsy, suitable for elective uVATS[b]
4. Written informed consent obtained
Exclusion criteria
1. ASA > III
2. History of intrathoracic or chest wall surgery
3. Chronic pain
4. Pre-operative analgesic medication use
5. NSAIDs[c] contraindications: aspirin asthma, allergic to NSAIDs, peptic ulcer, liver and kidney insufficiency, high risk of thrombotic events
6. Active autoimmune disease
7. Allergic to local anesthetics
8. Severe coagulation dysfunction, contraindicated for nerve block
9. Soft tissue infections of the chest wall

[a] American society of Anesthesiologists (ASA) physical status classification system

[b] uniportal video-assisted thoracoscopic surgery

[c] NSAIDs: non-steroidal anti-inflammatory drugs

generated using EXCEL (Office V.2021, Microsoft). A group code (A, B or C) was defined as the remainder of the sequence number divided by three. T Bu was unaware of the analgesic protocols referred to by each group code. He placed the group code in a light-proof envelope and into record folder. Participants were unaware of their group assignments throughout the study. After induction, the anaesthesiologists (MT Zheng or WX Li) opened the light proof envelope and obtained the group code and performed the perioperative analgesia protocol corresponding to the group. The identifiable personal information was hidden in the case report form. Only the principal investigator (ZR Zhang) and anaesthesiologists were privy to the intervention indicated by each group code. All the anaesthesiologists and the surgeons were not involved in the postoperative follow-up or data collection. All the physicians and nurses in charge of postoperative follow-ups (YH Shi, Y Li and Fei Q) were unaware of the perioperative protocols regarding each group code.

Baseline information

Baseline information including the age, sex, height, weight, primary disease, comorbidity, surgical and anaesthesia history, medication use, the proposed operation, and American Society of Anaesthesia (ASA) classification were recorded.

Surgical management

To maintain optimal surgical position for uVATS, all the enrolled participants were placed in lateral position with a 5 cm cotton chest pad below the shoulder and above the waist, to help make the intercostal space at the surgical incision be the widest (Fig. 1A). Depending on the widest intercostal space palpated after positioning, a 5 cm incision for uVATS was made in the 4th or 5th intercostal space at the anterior to mid-axillary line. The distance from the upper rib's lower edge to the lower rib's upper edge, parallel to the pleural line, was measured by ultrasound as the width of the intercostal space (Fig. 1B). A wound protector was used after thoracotomy. Surgeons tried as much as possible to avoid cutting or continuously compressing the intercostal nerve or stretching the intercostal space. A 24F chest tube was placed at the incision, with a depth of approximately 5 cm, which was confirmed via thoracoscopy that the tube did not compress the pleura.

At the end of the surgery, bilateral lungs were reinflated and the chest was closed. The chest tube was connected to a water-sealed bottle. The chest tube would be removed when the patients met the following conditions: (a)daily drainage volume of pleural fluid less than 30 ml, (b)normal respiratory function, (c)no sign of air leakage or bleeding in the drainage bottle. To confirm no sign of gas leakage, patients were asked to cough before chest tube removal, and the reserved sutures were ligated immediately after removal of the chest tube.

Anaesthesia protocol

There was no preoperative medication. Anaesthesia was induced by propofol or combined with etomidate, and cis-atracurium or rocuronium were used as muscle relaxants. Sufentanil was used as the intraoperative long-acting analgesic at a dose of 0.3–0.6 $\mu g \cdot kg^{-1}$ for induction, and additional dosage would be added as needed during intubation, skin cutting or to prevent postoperative flare-ups ($\leq 1\ \mu g \cdot kg^{-1}$ during the whole procedure). Propofol, remifentanil (0.2–0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and sevoflurane were used to maintain anaesthesia. Before the end of the surgery, local anaesthesia was performed with 3–5 ml of 0.5% ropivacaine at the surgical incision.

According to group allocation, the participant would receive one of the three interventions corresponding to the group code: (a)the *PVB+PCIA group*, ultrasound-guided paravertebral nerve block with ropivacaine

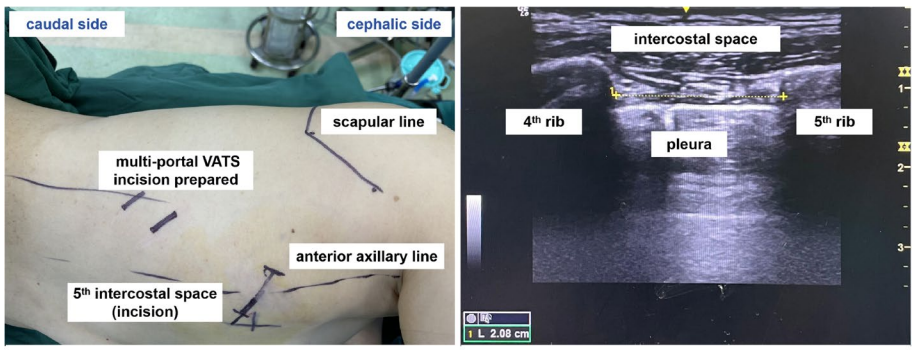

Fig. 1 (**A**) Surgical incision for uVATS (**B**) Intercostal space at the surgical incision

(0.33%) and 5 mg of dexamethasone in a total of 30 ml of saline at the T4 or T5 level on the operative side, combined with PCIA; (b)the *ESPB + PCIA group*: ultrasound-guided erector spinae block with ropivacaine (0.25%) and 5 mg of dexamethasone in a total of 40 ml of saline at the T4 or T5 level combined with PCIA; (c)the *PCIA group*: PCIA was used for postoperative analgesia, the participant would not receive a regional block. The ultrasound image of PVB and ESPB and the local anaesthetic injection are shown in Fig. 2. PCIA with sufentanil (1.8–3.2 $\mu g \cdot h^{-1}$) with preset bolus injection (0.8–1 μg) was administered to all participants immediately after surgery, with minimal bolus injection interval of 15–20 min. Education of postoperative analgesia was given to all participants before surgery. Bolus dose of sufentanil was recommended to be administered prophylactically before ambulation, when coughing or pain aggravated, or during chest tube removal.

There were routine daily follow-ups by the anaesthesiologists till 3 days after surgery. Acute pain greater than 3 points in VAS/NRS (visual analgesic scale or numeric rating scale, 1–10 points), which makes the patient unable to rest or sleep, was treated immediately. VAS and NRS are known to be in good agreement, while NRS is less susceptible to the influence of other clinical factors [6, 7]. Therefore, patients who could properly express themselves were given priority to be scored according to NRS before discharge. If the patients were unable to express themselves, they were scored according to VAS. If the two scores were inconsistent, the NRS shall prevail. If the patient had been discharged, they were scored according to NRS during telephone follow-up. If the pain assessment could not be given via NRS, it was treated as missing data.

Rescue opioid analgesics included intramuscular injections of pethidine hydrochloride (25–100 mg) as needed (up to 3 times per day) or dihydrocodeine tartrate (500 mg of acetaminophen and 10 mg of dihydrocodeine tartrate per tablet). Non-opioid analgesics included flurbiprofen, loxoprofen, acetaminophen, ketorolac, and indomethacin. Overlapping use of nonopioids was prohibited. Other analgesics, sedatives or hypnotic drugs were not allowed to use in this study.

Data collection

Baseline data included demographic data, comorbidities and ASA classification. Intraoperative data included dose of opioids and vasoactive agents, duration of anaesthesia and surgery, intake and output volume, and intercostal space at the incision.

Participants were followed-up at 1, 4, 12, 18 h, 1, 2, 3, 4, 7 days, and 1, 2, 3, 4, 6 months after surgery. Postoperative follow-ups included total opioid use, rescue analgesics, dosage of nonopioids, rest and cough pain scores, sensory perception on bilateral chest wall. The doses of opioids were converted to morphine milligram equivalents as referred in the literature or indicated in the drug label. Tactical and cold sensations were measured using an alcohol-stained cotton swab. Four points on bilateral chest wall were tested: < 3 cm near the incision, on the

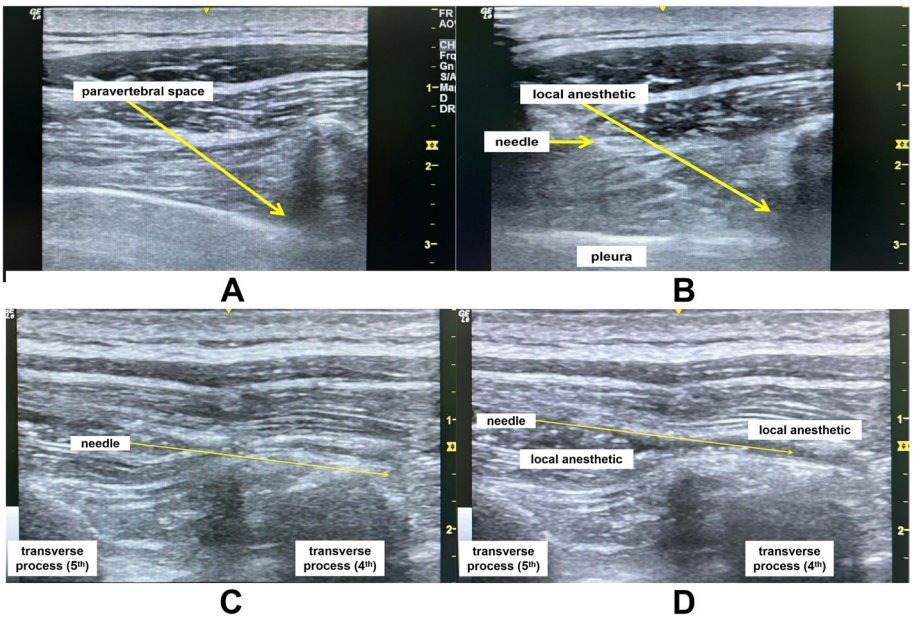

Fig. 2 Ultrasound-guided nerve block (**A**) Ultrasound-guided PVB (**B**) Successful injection of PVB (**C**) Ultrasound-guided ESPB (para-median sagittal plane, in-plane approach) (**D**) Successful injection of ESPB (short axis, in-plane approach)

symmetrical point on the chest wall, bilateral mid-clavicular-costal arch, to determine the effect and duration of the nerve block. Time of chest tube removal, time of ambulation, the hospital stays and anaesthesia expenses were also recorded.

Adverse events included neural blockade failure or haemorrhage, local anaesthetic intoxication, hypotension (blood pressure 30% below baseline), dizziness, postoperative nausea and vomiting, skin itching, and prolonged hospitalization due to complications. Severe adverse events included anaphylactic shock, total spinal anaesthesia, severe nerve injury, extensive intrathoracic bleeding, tension pneumothorax, severe infection, peptic ulcer, respiratory inhibition, thrombotic events, postoperative delirium, and severe liver and kidney injury.

Outcome measurements

The primary outcome was total opioid consumption. The secondary outcomes included trajectory of postoperative rest and cough pain, ambulation time, chest tube duration, length of stay, anaesthesia expense and adverse events.

Sample size and statistical analysis

For sample size estimation, we referred to the mean morphine milligram equivalents in participants after VATS who received PVB with PCIA, ESPB with PCIA, or sufentanil PCIA only[6–8]. The PASS V.2021 software was used for sample size estimation. The morphine equivalent in each group was subjected to *one-way analysis of variance (ANOVA) and F tests* via *an effect size* model. With a two-sided hypothesis, power = 0.8, α = 0.05, and G(group) = 3, considering that the drop-out rate was no higher than 20%, the total sample size was 102 (n = 34 in each group) (Supplementary File 2).

Normal distributed data were presented by mean ± SD, and nonnormal data were presented as median (IQR). Categorical data were presented as percentages. One-way ANOVA was used to compare the differences among the three groups. For nonnormal distributed data and nonparametric data (pain scoring), Kruskal–Wallis test was used to compare the differences among the groups. To test categorical variables among groups, when the expected frequency greater than five, multiple χ^2 test would be used; when the expected frequency less than five, Fisher exact method would be used. $P < 0.05$ was considered statistically significant.

Results

Basic information in participants

Three hundred and thirty-seven participants were screened for this trial. The last participant follow-up was completed on October 15th, 2024. Thirty-six participants were randomized to each group. Ninety-seven participants reached the outcomes. Three participants dropped-out due to intraoperative change into multiportal VATS, 7 participants were lost to follow up. There was failure in ultrasound guided localization in one case in the *PVB + PCIA group*. As a result, the per-protocol set included 28 participants in *PVB + PCIA group*, 35 participants in *ESPB + PCIA group*, and 34 participants in *PCIA group* (Fig. 3).

As shown in Table 2, there were no significant differences in preoperative conditions or type of surgical procedures among the three groups. According to the primary outcome of this study, the power of this trial was 0.83 (Supplementary File 3).

Outcome measurements

Total opioid consumption in morphine milligram equivalents was 109.8 ± 35.7 mg. Cumulative opioid consumption (morphine equivalent) was 124.5 ± 35.1 mg *PVB + PCIA group*, 103.8 ± 36.1 mg in *ESPB + PCIA group* and 103.9 ± 33.1 mg in *PCIA group*. Compared to *PCIA group*, the nerve block groups did *not* reduce opioid consumption (Table 3). There was no significant difference in cumulative opioid consumption among the three groups at each follow-up time point. Detailed opioid consumption by the end of each follow-up time point was shown in Supplementary File 4, Table S2.

The mean duration of surgery was 91.6 ± 37.9 min, which was similar among the three groups. However, duration of anaesthesia was significantly shorter in *PCIA group*. The anaesthesia time was defined as the beginning of induction to the time of extubation. To exclude the effect of the surgical procedure, we defined the duration of anaesthesia procedure as the anaesthesia time minus the operation time. Duration of anaesthesia procedure was significantly prolonged in neural blockade group (40.2 ± 13.9 min in *PVB + PCIA group*, 38.0 ± 13.2 min in *ESPB + PCIA group*) compared to *PCIA group* (31.2 ± 15.0 min).

Total dose of intraoperative sufentanil was 29.4 ± 5.9 μg, which was comparable among the three groups. Determined by the sensory perception on chest wall, the analgesic effect of PVB could maintain 28.1 (95%CI 23.3–32.8) hours, and the effect of ESPB could maintain 25.2 (95%CI 21.0–29.4) hours. Participants ambulation time was 27.6 ± 11.1 h, duration of chest tube maintenance was 53.7 ± 17.8 h after surgery, and length of stay was 3.6 ± 0.83 days, which did not differ among the three groups. Anaesthesia expenses were significantly higher in both nerve block groups (5321.7RMB, 95%CI 4864.4–5778.9 in *PVB + PCIA group*, 5505.0RMB, 95%CI 5075.7–5934.3 in *ESPB + PCIA group*), than in the *PCIA group* (4566.8RMB, 95%CI 4221.5–4912.1).

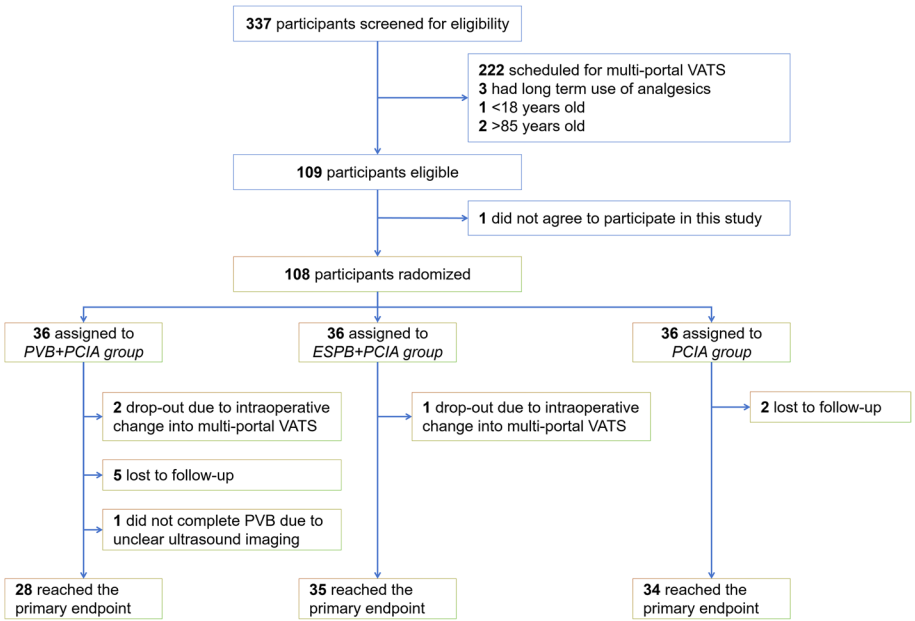

Fig. 3 Study diagram

Table 2 Clinical characteristics of participants

	PVB + PCIA group ($n = 28$)	ESPB + PCIA group ($n = 35$)	PCIA group ($n = 34$)	*p* value[a]
Age (year)	54.7 ± 13.4	60.4 ± 19.8	55.0 ± 12.2	0.512
Gender (male, %)	12 (42.9)	12 (34.3)	14 (41.2)	0.753
Somatotype measurement				
Height (cm)	167.0 ± 6.6	164.0 ± 9.3	165.5 ± 9.5	0.185
Body weight (kg)	66.1 ± 9.8	65.7 ± 11.9	64.6 ± 10.9	0.888
BMI ($kg \cdot m^{-2}$)	24.0 ± 2.9	24.3 ± 3.3	23.5 ± 3.2	0.596
Intercostal space (cm)	1.76 ± 0.38	1.93 ± 0.44	1.95 ± 0.39	0.251
Procedure[b]				
Left (%)	13 (46.4)	15 (42.9)	10 (29.4)	0.337
Wedge resection (%)	12 (42.8)	4 (11.4)	9 (36.0)	0.162
Segmentectomy (%)	7 (24.1)	13 (44.8)	9 (31.0)	
Lobectomy (%)	5 (20.8)	8 (30.8)	7 (28.0)	
Comorbidity (%)[c]				
Cardiovascular diseases	8 (28.6)	13 (37.1)	13 (39.4)	0.655
Pulmonary diseases[d]	1 (3.6)	3 (8.6)	3 (8.8)	0.701
Endocrine system diseases	5 (17.8)	3 (8.6)	3 (8.8)	0.558
Nervous system diseases	1 (3.6)	3 (8.6)	1 (2.9)	0.620

[a] $*p < 0.05$

[b] the "pneumonectomy" in the medical record, which possibly contained all the three procedures, were removed

[c] the other patients had no known preoperative comorbidities

[d] pulmonary diseases other than surgically resected lesions in the lung, e.g. COPD, bronchiectasis, bronchial asthma, etc.

There were no significant differences among the three groups in the scores of rest pain and cough pain at each follow-up time point (Fig. 4). Only 2 participants had transient sever cough pain within 12 h and 24 h after surgery, and were immediately treated with rescue opioids. None of the participants developed chronic pain.

Table 3 Outcome measurements

	PVB + PCIA group (*n* = 28)	ESPB + PCIA group (*n* = 35)	PCIA group (*n* = 34)	*p* value[a]
Total opioid consumption	124.5 ± 35.1	103.8 ± 36.1	103.9 ± 33.1	0.034*
Ambulation time (hour)	25.7 ± 10.1	28.1 ± 10.8	30.1 ± 11.3	0.588
Chest tube duration (hour)	52.3 ± 18.9	58.0 ± 19.6	48.9 ± 17.0	0.551
Length of stay (day)	3.7 ± 1.1	3.5 ± 0.8	3.9 ± 0.8	0.237
Anesthesia expense (RMB)	5210.2 (1650.0)	5341.3 (1200.0)	4345.1 (1099.0)	< 0.001*
Adverse events (%)				
Related to neural blockade	5 (17.9)	1 (2.9)	0	0.010*
Related to opioids	14 (50.0)	20 (57.1)	15 (44.1)	0.556
Duration of anesthesia (min)	146.4 ± 42.2	144.0 ± 33.6	122.7 ± 40.6	0.013*
Duration of surgery (min)	94.4 ± 46.0	100.8 ± 28.5	79.3 ± 36.4	0.058
Duration of anesthesia procedure (min)[b]	40.2 ± 13.9	38.0 ± 13.2	31.2 ± 15.0	0.033*
Intraoperative sufentanil (μg)	30.0 ± 6.37	29.8 ± 5.7	27.1 ± 5.6	0.781
Intraoperative norepinephrine (μg, 95%CI)	123.5 (41.9–205.2)	145.8 (58.3–233.3)	58.1 (2.8–113.5)	0.106
Input and output volume (mL, 95%CI)	542.7 (315.3–770.0)	568.0 (403.0–733.0)	589.1 (440.3–737.8)	0.924
Postoperative use of non-opioids for more than 3 days (%)[c]				
Small dose	11 (39.3)	14 (40.0)	9 (26.5)	0.432
Medium dose	1 (3.6)	4 (11.4)	3 (8.8)	0.528
Incidence of postoperative pain (%)[d]				
Mild pain within 1 week after surgery	27 (96.4)	35 (100.0)	34 (100.0)	0.289
Moderate to severe acute rest pain	6 (21.4)	8 (22.9)	6 (17.6)	0.860
Moderate to severe acute cough pain	12 (42.9)	11 (31.4)	12 (35.3)	0.639
Rest pain persisted for 1–3 months after surgery	12 (42.9)	10 (28.6)	10 (29.4)	0.419
Cough pain persisted for 1–3 months after surgery	15 (53.6)	15 (42.9)	14 (41.2)	0.580

[a] *$p < 0.05$

[b] Duration of anesthesia procedure = Duration of anesthesia-Duration of surgery

[c] Determined according to the drug label

[d] Moderate to severe pain (NRS or VAS 4–10) occurred in the first week after surgery

[e] Pain that persisted up to 6 months after surgery

Ninety-one (93.8%) participants used non-opioids for analgesia (intravenous flurbiprofen, intravenous ketorolac or oral paracetamol), 89 (91.7%) in small dose, 12 (12.3%) in medium dose, 1 (1.0%) in large dose. More than 3 days of continuous nonopioid use occurred in 42 (43.2%) participants. There were no differences in nonopioid dosage among three groups.

Safety outcomes

There was local haemorrhage in 4 participants in *PVB + PCIA group,* 1 in *ESPB + PCIA group*, one neural block failure in *PVB + PCIA group*. As shown in Supplementary File 5, as confirmed by intraoperative thoracoscopy, the bleeding site located at the extension of the intercostal vessels. No postoperative treatment was required and no participant developed haemothorax.

Analgesics-related adverse events included dizziness, nausea and vomiting, all related to opioid use, which occurred in 49 (50.5%) participants, and did not differ among the groups. There were no non-opioid related adverse events including gastrointestinal discomfort, peptic ulcer or gastrointestinal bleeding. Local signs of would infection occurred in one participant in *PVB + PCIA group,* one in *ESPB + PCIA group*, and one in *PCIA group*. Fatigue and decrease of exercise capacity occurred in one participant in *ESPB + PCIA group*.

The total dose of intraoperative norepinephrine required was 108.1(95%CI 76.1–140.1) μg, the intraoperative intake and output volume was 576.9(95%CI 486.7–578.3) ml. There was no significant difference of fluid infusion among groups, with I/O of 542.7(315.3–770.0) ml in *PVB + PCIA group,* 568.0(403.0–733.0) ml in *ESPB + PCIA group*, and 589.1(440.3–737.8) ml in *PCIA group.* There was no significant difference of intraoperative norepinephrine among groups, with 123.5 (41.9–205.2) μg in *PVB + PCIA group,* 145.8 (58.3–233.3) μg in *ESPB + PCIA group*, and 58.1 (2.8–113.5) μg in *PCIA group.*

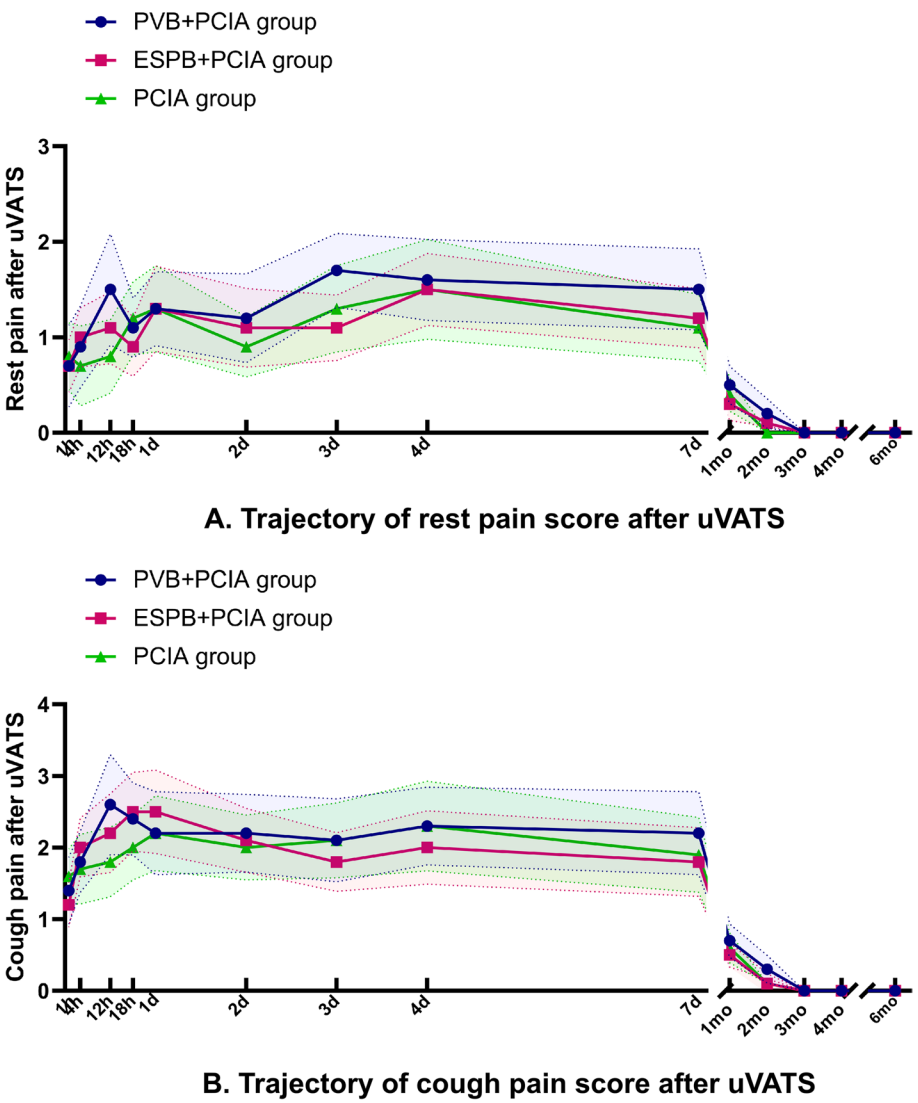

Fig. 4 Trajectory of pain after uVATS. (**A**) Trajectory of rest pain. (**B**) Trajectory of cough pain. Pain scores were shown with 95% CI

No serious adverse reactions occurred during the whole study. Detailed perioperative data in three groups were shown in Supplementary File 4.

Discussion

The focus of this study on the optimization of multimodal analgesia of uVATS included the single incision at the widest intercostal space, the fine drainage tube dwelling, the local anesthesia of the wound and the postoperative analgesia of PCIA. In regard to the quantitative analysis of pain scores and opioid consumption up to 6 months after surgery, single-shot nerve block did not increase the analgesic effect of compared with PCIA. The multimodal analgesia regimen exhibited good safety profile in this study. There were problems with nerve block related injuries, increased anesthesia duration, and increased anesthesia costs in nerve blocks.

Why single-shot nerve block exhibited no absolute advantage for uVATS? In terms of the surgery type, uVATS is the least traumatic subtype of thoracic surgery. The greatest advantage of uVATS is to minimize the trauma, and to place the chest tube in the widest intercostal space at the same incision to reduce postoperative pain. A systemic review including 4635 patients comparing uVATS with multiportal VATS reported that uVATS exhibited significantly less postoperative pain regardless of pain management strategies [8]. Therefore, uVATS may allow the analgesic regimen to be reformulated. Local anaesthesia of the incision blocked the signal in the nociceptive afferent pathway, which may have overlapped

the effect of the single-shot nerve block. Therefore, this study did not exhibit the advantage of single-shot nerve block for postoperative analgesia after uVATS.

In terms of the characteristics of the onset of pain after uVATS, single-shot nerve block may not cover the most painful period after uVATS, which was before the drainage tube removed. Both the opioid consumption and pain scores significantly reduced after removal of the chest drainage tube (at 49 to 58 h after uVATS, Figure S1, Supplementary File 1). However, the duration of the nerve block lasted for approximately 25 to 28 h. It seemed that single-shot PVB or ESPB with ropivacaine 100 mg did not effectively control the pain caused by ambulation or the removal of chest tube. Possible further optimization strategies include other nerve block strategies or continuous nerve block. A systemic review [9] compared epidural analgesia (EA), ESBP, PVB and intercostal nerve block for VATS using ropivacaine and concluded the rank order of the effect of analgesia was EA > ESPB≈PVB > placebo. However, this study only covered 6 h and 24 h after surgery. Actually, we found that the pain score did not decrease within 2–4 days after surgery, which cannot fully prove that nerve block presented ideal analgesic effect. Meanwhile, there were not enough studies to determine whether continuous or single nerve block more suitable for uVATS. A case series [10] reported that continuous ESPB was effective after thoracotomy in 48 h. A controlled trial [11] reported that continuous PVB for VATS could achieve satisfactory analgesia for 36 h, which was comparable with EA, but with higher risks of catheter heterotopia and hypotension. These studies suggested that continuous nerve block seemed to achieve longer postoperative analgesia, but with higher incidence of adverse events.

In terms of opioid use, the Canadian Association of Thoracic Surgeons guidelines recommended less than 90 mg morphine after VATS [12]. The amount of morphine consumed in our study did not successfully decrease to that level. However, the opioids consumption in this trial was not greater than that in any other similar study [13–15]. A cohort study comparing Asian *and* Caucasian populations after VATS suggested that, owing to the lower BMI in Asians, postoperative pain scores were also lower, as was the need for opioids [16]. In our study, nerve block did not have significant advantages over systemic analgesics at this level of opioid use, and future research should focus on reducing opioid use after uVATS. A meta-analysis concluded that PVB could reduce more opioid consumption than ESPB only at 24 h after VATS [17]. Another meta-analysis enrolling 1284 participants receiving VATS indicated that comparing PVB, ESPB and other neural blockade methods, regardless of the dose and volume of local anaesthetics, the opioid consumption and pain scores had no statistical difference [18]. A meta-analysis that included 3973 participants also concluded that regardless of surgery type, there were no reduction of pain intensity in PVB or ESPB compared with placebo group [19]. Our study supported that single-shot PVB or ESPB may not be the major way to reduce the use of opioids for uVATS.

From the safety considerations, nerve block-related adverse events in our study included local bleeding and failure to localization. PVB has been considered as the first-line or "gold standard" analgesic strategy for VATS [17]. ESPB is the best alternative, which can reduce complications such as hypotension, bleeding and pneumothorax. A single-centre retrospective study in France [20] found that combined with intravenous opioids and non-opioids, single-shot PVB with ropivacaine achieved lower pain score than ESPB after VATS, despite higher dose of ropivacaine in ESPB group. However, there was no difference in pain score and morphine consumption between the two groups at 24 h after surgery, and the dose of systemic analgesics were similar to our experiment. The nerve block-related complications were higher than in our experiment. This experiment concluded that the analgesic efficacy of ESPB and PVB might be comparable, but remains controversial.

Considering the safety of systemic analgesics, in our study, 50.5% participants suffered from opioid related adverse events, including dizziness and PONV, which were comparable with other studies[19]. A single-centre, double blind RCT in China verified the analgesic effect of combined oral oxycontin and continuous infusion of flurbiprofen in VATS compared with 0.4% ropivacaine 30 mL PVB and ESPB at T4 and T6, and ESPB was non-inferior in analgesic quality compared with PVB [21]. The study also suggested that the analgesic effect of single-shot nerve block was no more than 12–16 h after surgery. However, no one developed nausea and vomiting in this study. Therefore, it is worth implementing opioid-free anaesthesia protocol for uVATS in the future.

In terms of medical cost, the total cost of hospitalization was between 50,000–80,000RMB for uVATS. Therefore, the additional cost of 200-400RMB for nerve block did not affect the medical cost. The cost-effectiveness was not formally assessed in this trial. However, considering the time, safety, and long-term prognosis, single-shot nerve block did not show significant advantages for uVATS.

We unexpectedly found that in *PVB + PCIA group*, there were higher rest and cough pain scores from 12 h to 4 days after surgery, coincided with higher opioid consumption than the other 2 groups. The width of intercostal space in *PVB + PCIA group* was tended to be narrower but without statistical significance. In the exploratory

study (Supplementary File 6), all enrolled patients were regrouped according to whether they had moderate or severe postoperative pain (pain score ≥ 5). There were 28.9% patients who experienced onset of moderate to severe pain and seemed to have exceptionally thin intercostal spaces that were out of proportion to height and weight. Limited to the study design, we cannot draw conclusions from explorative study. Future studies are needed to quantitatively investigate the relationship between pain after uVATS and anthropometric measures.

Limitations and potential bias

As this was a single-centre study with small sample size, the elements of multi-modal analgesia for uVATS, including (a)selection of intercostal incision at the widest intercostal space; (b)local anesthetic drug infiltration; (c) indwelling of thin drainage tube; (d) PCIA-based postoperative analgesia, were only testified suitable in our medical centre. The main conclusions of this study still need to be verified in uVATS surgery in multi-centre studies in the future.

The surgeons and anaesthesiologists must be aware of the grouping to administer the analgesic regimen; therefore, the design was single-blinded. To decrease reporting bias, the bedside and telephone follow-up personnel (YH Shi, Y LI and F Qi) were unaware of the patient group assignment. Future studies can validate the results of this trial with a double-blind design.

To minimize selection bias, we consecutively screened all eligible patients, and the principle of randomization and blinding were maintained throughout the study. To minimize performance bias, uVATS was performed by two individual surgical groups (HX Feng and ZR Zhang), anaesthesia procedure was performed by two attending anaesthesiologists (WX Li and MT Zheng). To minimize attrition bias, the cases lost to follow-up did not exceed the predicted drop-out rate, and there was no difference of the baseline data of drop-out cases compared with those of other participants. To minimize detection bias, pain scores were measured using both NRS and VAS and sensations on chest wall were examined in standardized method.

Conclusion

For uVATS, there may be no additional analgesic effect of single-shot PVB or ESPB in addition to PCIA. Potential costs of nerve block for uVATS included local haemorrhage, block failure, extra anaesthesia time and expenses.

Declaration

Abbreviations

ANOVA	One-way analysis of variance
ASA	American Society of Anaesthesia
CI	Confidence interval
CRF	Case report form
ESPB	Erector spinae block
H	Hour
IQR	Interquartile range
Kg	Kilogram
Mg	Microgram
Min	Minute
NRS	Numeric rating scale
PCIA	Patient-controlled intravenous analgesia
PVB	Paravertebral block
RMB	Renminbi
uVATS	Uniportal video-assisted thoracic surgery
VAS	Visual analgesic scale

Supplementary Information

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Supplementary Material 1. CONSORT2010 checklist.

Supplementary Material 2. Sample Size Estimation.

Supplementary Material 3. Power Analysis.

Supplementary Material 4. Integrated Data and Other Detailed Perioperative Data

Supplementary Material 5. Local Hemorrhage After Neural Block.

Supplementary Material 6. Exploratory Study.

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Authors' contributions

Author contributions: Li Fang Wang: original manuscript preparation; Fei Qi: follow-ups; Hong Xiang Feng: surgical performance; Yu Hui Shi: follow-ups; Yan Li: follow-ups; Meng Tao Zheng: provision of nerve blocks; Tegeleqi Bu: randomization; Wei Xia Li: quality control; Zhen Rong Zhang: surgical performance and experimental design.

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Data availability

Data is provided within the manuscript or supplementary information files.

Declarations

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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