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ORIGINAL RESEARCH

Effects of Ultrasound-Guided Thoracic Paravertebral Nerve Block Combined with Perineural or IV Dexmedetomidine on Acute and Chronic Pain After Thoracoscopic Resection of Lung Lesions: A Double-Blind Randomized Trial

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Background: Thoracic paravertebral block (TPVB) analgesia can be prolonged by local anesthetic adjuvants such as dexmedetomidine. This study aimed to evaluate the two administration routes of dexmedetomidine on acute pain and chronic neuropathic pain (NeuP) prevention compared with no dexmedetomidine.

Methods: A total of 216 patients were randomized to receive TPVB using 0.4% ropivacaine alone (R Group), with perineural dexmedetomidine 0.5 $\mu g \cdot kg^{-1}$ ($RD_{0.5}$ Group) or 1.0 $\mu g \cdot kg^{-1}$ ($RD_{1.0}$ Group), or intravenous (IV) dexmedetomidine 0.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (RD_{iv} Group). The primary outcome was the incidence of chronic NeuP, defined as a Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) pain score > 12 points at 3-month after surgery.

Results: (1) For the primary outcome, $RD_{0.5}$ Group and $RD_{1.0}$ Group demonstrated a decreased incidence of chronic NeuP at 3-month after surgery; (2) Compared with R Group, RD_{iv} Group, $RD_{0.5}$ Group, and $RD_{1.0}$ Group can reduce VAS scores at rest and movement and Prince-Henry Pain scores at 12 and 24-h after surgery, the consumption of oral morphine equivalent (OME) and improve QOD-15 at POD1; (3) Compared with RD_{iv} Group, $RD_{0.5}$ Group and $RD_{1.0}$ Group can reduce VAS scores at rest and movement and Prince-Henry Pain scores at 12 and 24-h after surgery, the consumption of postoperative OME and improve QOD-15 at POD1; (4) Compared with $RD_{0.5}$ Group, $RD_{1.0}$ Group effectively reduced VAS scores at rest at 12 and 24-h after surgery, VAS scores in movement and Prince-Henry Pain scores at 12-h after surgery. However, $RD_{1.0}$ Group showed an increased incidence of drowsiness.

Conclusion: Perineural or IV dexmedetomidine are similarly effective in reducing acute pain, but only perineural dexmedetomidine reduced chronic NeuP. Moreover, considering postoperative complications such as drowsiness, perineural dexmedetomidine (0.5 $\mu g \cdot kg^{-1}$) may be a more appropriate choice.

Clinical Trial Registration: Chinese Clinical Trial Registry (ChiCTR2200058982).

Keywords: dexmedetomidine, thoracic paravertebral nerve block, neuropathic pain, thoracoscopic surgery

Introduction

Chronic postsurgical pain (CPSP) can sometimes last for a long period after surgery and has been identified as a disabling consequence that seriously impacts patient health and quality of life.[1] Its prevalence has been reported to range between 3% and 85%, depending on the type of operation.[2] CPSP is one of the more common complications following thoracic

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surgery, and a meta-analysis reported that chronic pain at 3 and 6-month after thoracic surgery was 57% and 47%, respectively.[2–4]

CPSP is composed of both nociceptive and neuropathic (also called "neurogenic") components.[5] A significant proportion of CPSP is neuropathic pain (NeuP). NeuP is results from a specific injury or illness that affects the somatosensory system.[6,7] Compared with non-neuropathic chronic pain, NeuP is generally more intense.[6,8] According to the updated classification of chronic pain in the International Statistical Classification of Diseases and Related Health Problems (ICD)-11, NeuP is first categorized into peripheral and central NeuP.[7] The proposal suggests that chronic NeuP can occur after peripheral nerve injury, with exacerbation observed post-surgery.[9–11] Previous research has demonstrated that intraoperative nerve impairment during thoracotomy can lead to the development of chronic NeuP.[11] Video-assisted thoracoscopic surgery (VATS) minimizes damage to the chest wall during lung resection, thus decreasing the pain associated with conventional thoracotomy. However, patients undergoing VATS may still endure considerable pain in the absence of adequate analgesia, which can be severe and long-lasting.[12]

CPSP typically starts with acute postoperative pain and quickly transforms into long-term chronic postoperative pain when it is poorly controlled, which may be related to the inflammatory response and peripheral or central sensitization caused by secondary inflammation or injury of nerves.[13,14] Preoperative, intraoperative, and postoperative factors can all lead to trigger central sensitization (CS), which can result in hyperalgesia and chronic pain.[15] In order to reduce chronic pain, a concept called pre-emptive analgesia has been proposed as perhaps the best timing for regional anesthesia.[16] The use of thoracic paravertebral block (TPVB) for thoracic procedures is well accepted, providing effective analgesia and alleviating the inflammatory response as well as the incidence of chronic pain after surgery.[17,18]

Various analgesic adjuvants have been utilized in combination with local anesthetics to extend the duration of their effects, with varying degrees of success. Dexmedetomidine is a highly selective drug α_2-adrenergic receptor agonist that can prolong analgesia in a variety of routes, including neuraxial, perineural, and intravenous (IV) administration.[19] Among these routes, perineural dexmedetomidine was found to significantly prolong the duration of analgesia after single-injection peripheral nerve blocks (PNBs) by inhibiting the activation of I_h current (hyperpolarizing cation current).[20] Compared with perineural dexmedetomidine, IV dexmedetomidine can also prolong analgesia; however, to date, the results are inconsistent.[20,21]

We hypothesized that perineural dexmedetomidine in TPVB and IV dexmedetomidine would be helpful to decrease both acute pain and chronic NeuP at 3-month after surgery, compared to TPVB without dexmedetomidine.

Methods

Trial Design

This single-center, randomized controlled study was prospectively registered with the Chinese Clinical Trial Registry (https://www.chictr.org.cn, ChiCTR2200058982; principal investigator: Yanwu Jin; date of registration: April 21, 2022). This study was approved by the institutional ethics committee of the Second Hospital of Shandong University (No: KYLL-2022P254) and written informed consent was obtained from all patients before enrollment. The guidelines outlined in the Declaration of Helsinki were followed and this manuscript adhered to the applicable CONSORT guidelines.

Patient Recruitment

Between May 6, 2022, and February 4, 2023, a total of 224 adult patients who were undergoing thoracoscopic resection of lung lesions under general anesthesia (GA) were recruited at the second hospital of Shandong University, a tertiary care academic health sciences center fully affiliated with Shandong University.

Inclusion criteria were: (1) American Society of Anesthesiologists (ASA) physical status I–III; (2) Age 18–65 years, no limitation to gender; (3) Patients scheduled to undergo thoracoscopic unilateral pulmonary lesion resection (cuneiform/segmental/lobectomy); (4) Consenting to study participation;

Exclusion criteria were as follows: (1) Patient refusal; (2) Existing contraindications to TPVB such as coagulopathy and local and systemic infection. Coagulopathy was defined as a prothrombin time or activated partial prothrombin time

that exceeded standard values or an international normalized ratio (INR) ≥ 1.4, or a platelet count < 80×10^9 L^{-1}; (3) BMI > 28 kg/m^2 or < 18 kg/m^2; (4) Allergic to experimental drugs or general anesthetics; (5) Liver and kidney insufficiency; (6) History of chronic pain or opioid use; (7) History of surgery within the last 6 months; (8) Mental or nervous system diseases and language problems; (9) Pregnant or lactating patients; (10) Sick sinus syndrome (SSS), severe bradycardia (HR < 50/min) or atrioventricular block (AVB) II or above.

Randomization and Blinding

Patients were randomly assigned to one of the four groups (1:1:1:1) using a computer-generated randomization code and the sealed opaque envelope method. The assignment was carried out by a clinician who was not involved in the study. On the day of the surgery, the anesthesiologist (CLG) opened the opaque envelopes and each patient received the corresponding protocol. Prior to the surgery, TPVB was performed by the anesthesiologist (HZ) in the pre-anesthesia room, and GA was administered by another anesthesiologist (LZ) in the operating room. Postoperative follow-up was conducted by two certified nurses and an anesthesiologist (YCZ) who were also blinded to the patient group assignments. The TPVB injection mixture was identical in appearance and was prepared using an aseptic technique by one investigator (SSZ) who was informed of the group assignments but had no further involvement in patient care or data collection. Meanwhile, saline or dexmedetomidine infusion prepared by the investigator (SSZ) were all labeled "Intravenous Medication", to which the anesthesiologist (LZ) was blinded. In this way, the anesthesiologist and the surgical team were all blinded to group allocation.

Assigned Interventions

Patients providing informed consent who met all eligibility criteria were randomized (1:1:1:1) into the following four groups: R Group, RD_{iv} Group, $RD_{0.5}$ Group, and $RD_{1.0}$ Group.

R Group: TPVB injection mixture [ropivacaine 1% + 0.9% saline]; IV infusion 0.9% saline;

RD_{iv} Group: TPVB injection mixture [ropivacaine 1% + 0.9% saline]; IV infusion 0.5 $\mu g\cdot kg^{-1}\cdot h^{-1}$ dexmedetomidine;

$RD_{0.5}$ Group: TPVB injection mixture [ropivacaine 1% + dexmedetomidine 0.5 $\mu g\cdot kg^{-1}$ + 0.9% saline]; IV infusion 0.9% saline;

$RD_{1.0}$ Group: TPVB injection mixture [ropivacaine 1% + dexmedetomidine 1.0 $\mu g\cdot kg^{-1}$ + 0.9% saline]; IV infusion 0.9% saline;

The dosing regimen was individualized based on the patient's weight. The final ropivacaine concentration was 0.4%, and the total volume of TPVB injection in each group was calculated according to the weight of the patient (0.4% ropivacaine 0.3 $mL\cdot kg^{-1}$). To facilitate the comparison of the IV infusion of each group, dexmedetomidine IV infusion was administered at a concentration of 4 $\mu g\cdot mL^{-1}$ and a rate of 0.125 $mL\cdot kg^{-1}\cdot h^{-1}$ (0.5 $\mu g\cdot kg^{-1}\cdot h^{-1}$) in RD_{iv} Group, and the remaining three groups were given 0.9% saline at a rate of 0.125 $mL\cdot kg^{-1}\cdot h^{-1}$ for 1 hour. Furthermore, to account for dead space in the block needle tubing in each group, 2 mL of 0.9% saline was used before TPVB medications were administered at the paravertebral spaces in each group.

Presurgical and Surgical Procedures

At 1-h before surgery, subjects were admitted to the pre-anesthesia room. After establishing IV access and successful local anesthesia, radial artery puncture and catheterization were performed. Standard monitors (electrocardiogram, invasive arterial pressure, and continuous oxygen saturation) were applied and supplemental oxygen was delivered via nasal cannula. The patients were placed in a standard lateral position for TPVB before induction of anesthesia. Before performing the nerve block, all patients received IV midazolam 0.02 $mg\cdot kg^{-1}$ or sufentanil 0.08 $\mu g\cdot kg^{-1}$ for anxiolysis and analgesia, as needed. Under complete aseptic measures, a 5–2 MHz low-frequency probe (C5-1B convex transducer, Wisonic Navi, Shenzhen, China) was placed in the oblique parasagittal plane to distinguish the intended transverse process.

The highlighted pleura and superior costotransverse ligament were identified, and a 21-G×100 mm short bevel non-echogenic nerve block needle (PAJUNK Gmbh Medizintechnologie, Geisingen, Germany) was carefully advanced using an in-plane technique, moving from a lateral to medial direction. The needle was slowly inserted until its tip punctured the superior costotransverse ligament and entered the paravertebral space. The position of the needle tip was confirmed

by hydrodissection under direct ultrasound visualization via inject a small volume of saline (1mL). Following the verification of the anatomical location and absence of blood aspiration, medications for TPVB were administered at the paravertebral spaces between the fifth and sixth thoracic vertebrae. Ultrasound subsequently confirmed the presence of a faint echogenic shadow outside the pleura, accompanied by downward displacement of the pleura resulting from the administered mixtures. TPVB injection mixtures were identical in appearance and prepared by an investigator (SSZ) using an aseptic technique. In order to allow enough time for the TPVB to take effect, the sensory block level was tested 30 min before anesthesia induction, and patients with primary block failure were excluded (block level < T3~T8). The performance time of TPVB was defined as the sum of imaging and needling times.[22] US-guided TPVB was performed by the same experienced anesthesiologist (HZ) who was blinded to group allocation.

Intraoperative Management

Once in the operating room, all patients were continuously monitored for oxygen saturation, electrocardiogram, heart rate, non-invasive blood pressure, invasive blood pressure, temperature, and entropy using multichannel monitors (Datex-Ohmeda S/5 Avance). GA was induced with IV midazolam (0.02 $mg \cdot kg^{-1}$) for anxiolysis, IV sufentanil (0.4 $\mu g \cdot kg^{-1}$), IV propofol (1.5–2.0 $mg \cdot kg^{-1}$) and the neuromuscular block was achieved with cisatracurium (0.2 $mg \cdot kg^{-1}$). After induction, the trachea was intubated and mechanical ventilation was initiated. Intraoperatively, anesthesia was maintained by 1%~3% sevoflurane, propofol (3–10 $mg \cdot kg^{-1} \cdot h^{-1}$), and remifentanil (0.1–0.3 $\mu g \cdot kg^{-1} \cdot h^{-1}$) to maintain a suitable depth of anesthesia (Entropy index, EI 40–60). IV Sufentanil boluses (5 μg) were administered every 30 min as needed to maintain invasive blood pressure and heart rate within 10% of the patient's baseline upon arrival at the hospital. Bradycardia (HR < 40 $beats \cdot min^{-1}$) was treated with atropine 0.6 mg IV. Muscle relaxation was reversed using glycopyrrolate (0.3 $mg \cdot kg^{-1}$) and neostigmine (0.04 $mg \cdot kg^{-1}$). About 30 min before emergence from anesthesia, all patients were administered ketorolac 30 mg IV to prevent acute pain and standard anti-emetic prophylaxis with the serotonin antagonist ondansetron 8 mg IV.

Surgery

The same surgical team performed unilateral thoracoscopic pulmonary lesion resection (cuneiform/segmental/lobectomy) on all subjects, who were placed in the lateral recumbent position. One or two ports were set up at different intercostal space levels according to the location of the tumor and lung nodule. All procedures were performed under minimally invasive thoracoscopic techniques, and none used rib expansion or any of the mechanical retractors used in conventional thoracotomy. At the end of surgery, a chest tube drain was placed at the surgical incision site. No postoperative administration of local anesthetic infiltration was performed on the wound.

Postoperative Management

All patients were admitted to the Thoracic Surgery Postoperative Observational Unit, which consists of a post-anesthesia care unit (PACU) and a level two surgical step-down unit. They were observed for the initial 48 hours following surgery before being transferred to a regular hospital floor.

The postoperative analgesic regimen consisted of routine intravenous administration of 50 mg of flurbiprofen every 12 h and patient-controlled intravenous analgesia (PCIA). The PCIA pump was set up with sufentanil 2 $\mu g \cdot kg^{-1}$ + ondansetron 8 mg + 0.9% saline = 100 mL; 2 $mL \cdot h^{-1}$ as basal infusion, control single dose 0.5 mL, lock-on time 15 min. The PCIA pump was started immediately after the operation upon arrival in the Thoracic Surgery Postoperative Observational Unit.

Postoperative pain in the PACU was defined as a visual analog scale (VAS; 10 cm-scale where 0 = no pain and 10 = worst pain) pain severity score > 4 after two boluses of PCIA and was treated with rescue analgesia as needed [oral combination acetaminophen (325 mg) oxycodone (5 mg) tablet or intramuscular pethidine 50 mg]. The rescue antiemetic ondansetron 0.1 $mg \cdot kg^{-1}$ was given intravenously if patients showed nausea or vomiting.

Patients were discharged at the discretion of the surgical team and in accordance with standard discharge guidelines. After patient recruitment, the nursing staff trained the patients and their families on how to conduct LANSS assessments. The LANSS pain scores were collected through a combination of telephone interviews and outpatient follow-ups at two time points, specifically 3-month and 6-month after surgery. The patients were followed up until 6-month after surgery.

Outcomes

The primary outcome was the incidence of chronic NeuP defined as a LANSS score > 12 points at 3-month after surgery.[23,24]

Secondary outcomes included: (1) LANSS score at 6-month after surgery; (2) Prince-Henry Pain Score at 1, 12, 24, 48-h after surgery; (3) VAS pain scores at rest and during movement at 1, 3, 6, 12, 24 and 48-h after surgery; (4) Quality of Recovery-15 (QoR-15) with a maximum score of 150 points at preoperative,[25] postoperative day 1 (POD1) and day 2 (POD2); (5) Intraoperative and postoperative oral morphine equivalent (OME);[26,27] (6) Number of rescue analgesia and PCIA attempts; (7) Incidence of adverse effects at 24-h after surgery.

The additional indicators were recorded (eg concentrations of sevoflurane, number and location of thoracoscopic incisions, surgical, anesthesia, hospital, and postoperative chest tube drainage time). Surgical incisions, either single or double port, were performed at distinct intercostal space levels and denoted by "T". Furthermore, the pre-operative Hospital Anxiety and Depression Scale score was recorded. Sleep quality in the last month was assessed by the Pittsburgh Sleep Quality Index before surgery and the adverse effects were monitored 24 hours following surgery (eg, nausea; vomiting; and drowsiness).[28,29]

Sample Size Calculation

The Power Exploration and Sample Size (PASS) 15.0 program (NCSS, LLC., Kaysville, UT, United States) was employed to calculate the sample size of this research. A LANSS score > 12 points was considered neuropathic, causing the patient's pain.[23] According to our pilot study of 45 patients, the incidence of LANSS score exceeding 12 points at 3-month after surgery in R Group, RD_{iv} Group, $RD_{0.5}$ Group, and $RD_{1.0}$ Group were 46.7%, 26.7%, 20%, and 13.3%, respectively. Assuming a two-tailed α error = 0.05 and β error = 0.1 with a power of 0.90, the sample size required per group was at least 45 participants. Accounting for a dropout rate of 20% to accommodate for incomplete data or loss to follow-up and increasing the sample scale, the research finally included 56 patients in every group.

Statistical Analysis

The SPSS for Windows statistical package (version 19.0; SPSS Inc., IBM, Chicago, IL, USA) was used in our calculations. The normality of continuous variables, expressed as mean (standard deviation, SD) or median (interquartile range, IQR), was assessed using the Kolmogorov–Smirnov test. A one-way ANOVA was used for data conforming to a normal distribution. For cardinal variables with non-normal distribution, differences were assessed using the Kruskal–Wallis *H*-test. Categorical variables were presented as numbers (n/%) and assessed using $\chi 2$ or Fisher's exact test where appropriate. The threshold of statistical significance of the two-tailed *P* value for the one-way ANOVA and $\chi 2$ test comparison among groups was set at 0.0083 according to the Bonferroni correction. A repeated-measures analysis of variance was used to test the difference in continuous variables over time (eg, VAS score, Prince-Henry Pain, and QoR-15). For repeated outcome measurements, the *P* values were corrected using the Bonferroni–Holm step-down adjustment.

Results

The study recruited 224 patients at this tertiary hospital who were scheduled for thoracoscopic unilateral pulmonary lesion resection under general anesthesia between May 2022 and February 2023. Eight patients were excluded, including 5 who did not meet inclusion criteria, 2 who declined, and 1 who had their surgery canceled. A total of 216 patients were included in the study and then randomized into the 4 groups; among them, 205 patients completed the study, as shown in the Consolidated Standards of Reporting Trials (CONSORT) flowchart (Figure 1). No significant differences in demographic and operative data were observed among the four groups (Table 1).

The follow-up of the chronic NeuP incidence is shown in Figure 2. At 3-month after surgery, $RD_{0.5}$ Group and $RD_{1.0}$ Group showed a significantly lower incidence of LANSS pain score >12 in comparison to R Group and RD_{iV} Group (Figure 2A). However, no significant difference was found between groups at 6-month after surgery (Figure 2B).

From 12 to 24h postoperatively, the VAS scores at rest and movement and Prince-Henry Pain scores in RD_{iV} Group, $RD_{0.5}$ Group, and $RD_{1.0}$ Group were significantly lower compared with those in R Group (Table 2). Compared with RD_{iv} Group, $RD_{0.5}$ Group and $RD_{1.0}$ Group can reduce VAS scores at rest and movement and Prince-Henry Pain scores at 12

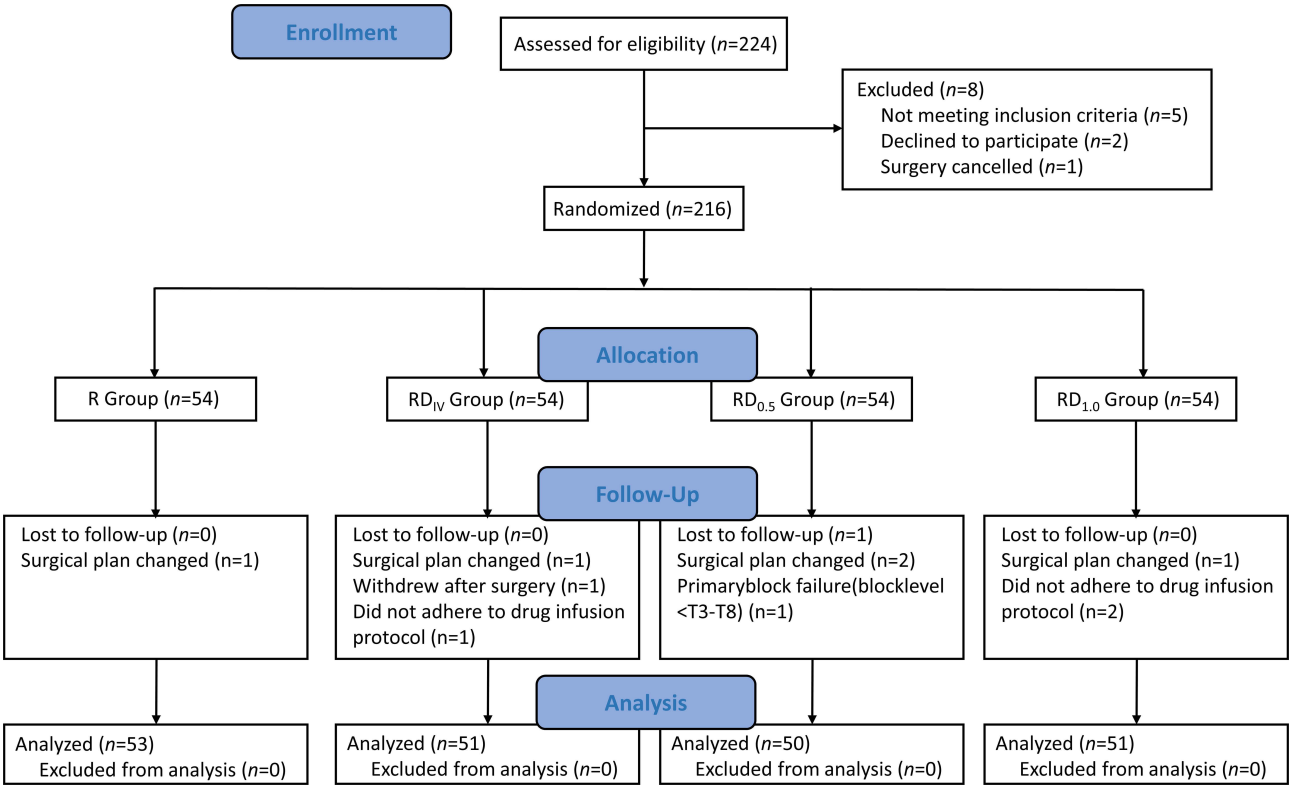

Figure 1 Flow diagram in CONSORT format.

and 24-h after surgery (Table 2). Compared with $RD_{0.5}$ Group, $RD_{1.0}$ Group effectively reduced VAS scores at rest at 12 and 24-h after surgery, VAS scores in movement and Prince-Henry Pain scores at 12-h after surgery. No differences were detected between groups at the other time points.

Table 1 Patient Demographic and Operative Characteristics

Characteristic	R Group (n=53)	RD_{iv} Group (n=51)	$RD_{0.5}$ Group (n=50)	$RD_{1.0}$ Group (n=51)
Sex				
Male, (%)	19 (35.8)	20 (39.2)	27 (54.0)	21 (41.2)
Female, (%)	34 (64.2)	31 (60.8)	23 (46.0)	30 (58.8)
Patient specifications				
Age, yr	55.0 (47.5–58.5)	56.0 (51.0–60.0)	55.0 (48.0–63.3)	55.0 (51.0–59.0)
Height, cm	164.0 (160.0–170.0)	165.0 (160.0–170.0)	167.5 (160.0–170.0)	165.0 (160.0–170.0)
Weight, kg	68.0 (60.0–72.5)	66.0 (61.0–71.0)	65.0 (60.0–72.0)	65.0 (60.0–70.0)
BMI, kg/m^2	25.0 (23.6–27.3)	24.0 (22.4–26.0)	24.0 (22.3–25.8)	23.9 (22.5–26.4)
ASA status 1/2/3	8/42/3	7/35/9	3/37/10	4/41/6
NYHA Status Norm/I/II	17/34/2	13/31/7	9/37/4	12/34/5
Previous history				
Drinking history, (%)	6 (11.3)	5 (9.8)	5 (10.0)	3 (5.9)
Smoking history, (%)	10 (18.9)	9 (17.6)	10 (20.0)	11 (21.6)
Hypertension, (%)	14 (26.4)	9 (17.6)	8 (16.0)	9 (17.6)
Coronary disease, (%)	4 (7.5)	5 (9.8)	7 (14.0)	4 (7.8)
Diabetes, (%)	4 (7.5)	5 (9.8)	4 (8.0)	5 (9.8)
Allergy, (%)	4 (7.5)	2 (3.9)	1 (2.0)	1 (2.0)
Opioid use, (%)	0	0	0	0

(*Continued*)

Table 1 (Continued).

Characteristic	R Group (n=53)	RD_{iv} Group (n=51)	$RD_{0.5}$ Group (n=50)	$RD_{1.0}$ Group (n=51)
Anesthesia duration, min	150.0 (120.0–185.0)	140.0 (115.0–160.0)	150.0 (120.0–180.0)	130.0 (110.0–170.0)
Surgical Duration, min	125.0 (92.5–162.5)	110.0 (85.0–130.0)	125.0 (93.8–141.3)	105.0 (85.0–135.0)
Performance time of TPVB, min	9.0 (8.0–10.0)	9.0 (8.0–10.0)	9.0 (8.0–10.0)	9.0 (8.0–9.0)
Sevoflurane Concentration	2.0 (1.8–2.3)	2.0 (1.8–2.2)	2.0 (1.7–2.2)	2.0 (1.8–2.2)
Incisions*				
T4, (%)	3 (5.7)	2 (3.9)	3 (6.0)	7 (13.7)
T5, (%)	21 (39.6)	17 (33.3)	17 (34.0)	19 (37.3)
T4/T7, (%)	27 (50.9)	30 (58.8)	27 (54.0)	24 (47.1)
T5/T8, (%)	2 (3.8)	2 (3.9)	3 (6.0)	1 (2.0)
Hospital time, hour	124.0 (97.0–172.5)	125.0 (101.0–173.0)	124.0 (100.0–167.0)	125.0 (100.0–168.0)
Pre-operative evaluation				
Pain intensity	1.0 (0–1.0)	1.0 (0–1.0)	1.0 (0–1.0)	1.0 (0–2.0)
Anxiety	2.0 (1.0–3.0)	2.0 (1.0–3.0)	2.0 (1.0–3.0)	2.0 (1.0–3.0)
Depression	1.0 (1.0–2.0)	1.0 (1.0–2.0)	1.0 (0–2.0)	1.0 (1.0–2.0)
Sleep quality	6.0 (4.0–7.0)	6.0 (4.0–7.0)	6.0 (3.0–7.0)	4.0 (3.0–7.0)
Duration of postoperative chest tube drainage, hour	23.0 (18.0–48.5)	28.0 (17.0–63.0)	39.0 (21.75–46.0)	39.0 (21.0–47.0)

Notes: *The surgical incision was made at the intercostal space levels of T4, T5, T4/T7, and T5/T8, respectively. Values are means (SD), median (IQR) or number of patients.
Abbreviations: ASA, American Society of Anesthesiologists; TPVB, Thoracic paravertebral nerve block; NYHA, New York Heart Association; BMI, Body Mass Index.

At POD1, the QoR-15 score in RD_{iV} Group, $RD_{0.5}$ Group, and $RD_{1.0}$ Group were significantly higher compared with those in R Group. Compared with RD_{iV} Group, the QoR-15 in $RD_{0.5}$ Group and $RD_{1.0}$ Group both demonstrated higher scores. However, no significant difference in QoR-15 was observed between groups preoperatively and at POD2 (Table 2). The intraoperative OME and postoperative OME within the 0–24 hour period, as well as the overall postoperative OME, exhibited significantly lower levels in RD_{iV} Group, $RD_{0.5}$ Group, and $RD_{1.0}$ Group compared to R Group (Table 2). Furthermore, the postoperative OME in $RD_{0.5}$ Group and $RD_{1.0}$ Group were lower compared with RD_{iV} Group from 0 to 24-h and totally postoperatively (Table 2). The number of PCIA attempts, rescue analgesia received, and anti-emetics required were similar among the four groups (Table 2). In addition, the overall cumulative incidence of drowsiness was highest in $RD_{1.0}$ Group, while no significant difference was observed in other postoperative adverse reactions at 24-h after surgery (Table 3).

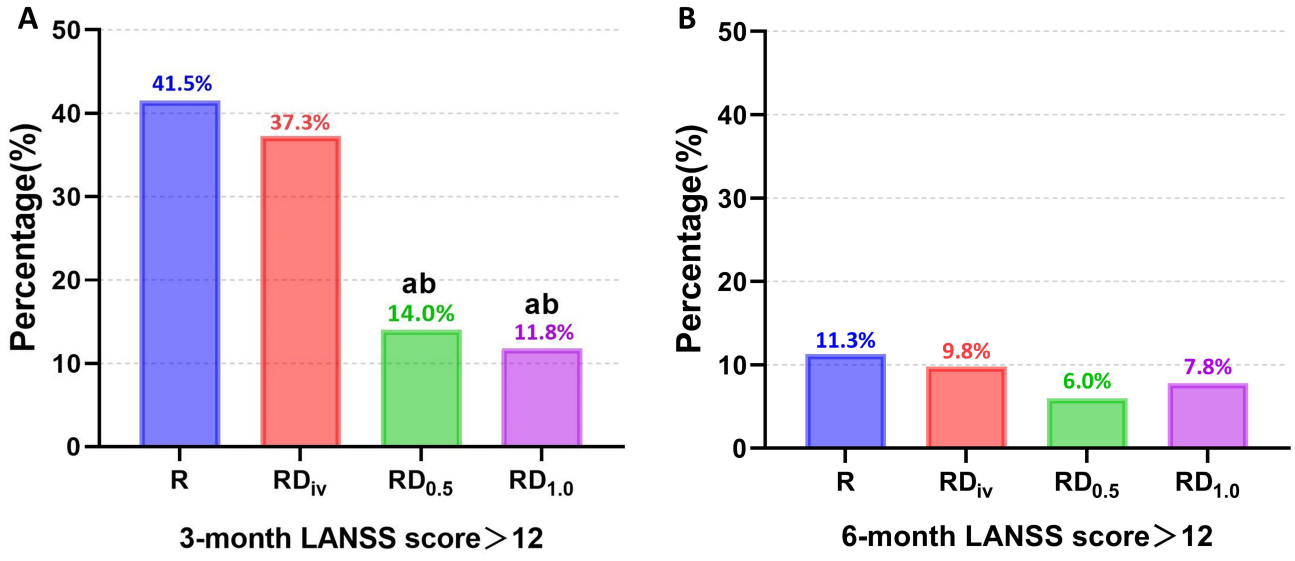

Figure 2 Incidence of LANSS pain score >12. (**A**) 3-month after surgery; (**B**) 6-month after surgery.
Notes: [a]Compare with R Group, $P<0.05$; [b]Compare with RD_{iv} Group, $P<0.05$.
Abbreviation: LANSS, Leeds Assessment of Neuropathic Symptoms and Signs.

Table 2 Outcomes Between Groups

Outcome	R Group (n=53)	RD_{iv} Group (n=51)	$RD_{0.5}$ Group (n=50)	$RD_{1.0}$ Group (n=51)	*P*
VAS score at rest (median, IQR)					
1h	2.0 (1.0–3.0)	2.0 (1.0–3.0)	2.0 (1.0–3.0)	2.0 (2.0–2.0)	0.988
3h	2.0 (2.0–3.0)	2.0 (2.0–3.0)	2.0 (2.0–3.0)	2.0 (2.0–3.0)	0.791
6h	3.0 (2.0–4.0)	3.0 (2.0–4.0)	3.0 (2.0–3.0)	3.0 (3.0–3.0)	0.892
12h	3.0 (3.0–3.0)	3.0 (2.0–3.0)[a]	2.0 (2.0–3.0)[ab]	2.0 (1.0–2.0)[abc]	0.000
24h	2.0 (1.0–3.0)	2.0 (1.0–2.0)[a]	1.0 (1.0–2.0)[ab]	1.0 (1.0–1.0)[abc]	0.000
48h	1.0 (1.0–2.0)	1.0 (1.0–1.0)	1.0 (1.0–1.0)	1.0 (1.0–1.0)	0.116
VAS score at movement (median, IQR)					
1h	3.0 (2.5–3.0)	3.0 (3.0–3.0)	3.0 (3.0–3.0)	3.0 (3.0–3.0)	0.586
3h	4.0 (3.5–4.0)	4.0 (3.0–4.0)	4.0 (3.0–4.0)	3.0 (3.0–4.0)	0.948
6h	4.0 (4.0–4.5)	4.0 (4.0–4.0)	4.0 (3.0–4.0)	4.0 (3.0–4.0)	0.218
12h	5.0 (4.0–5.0)	4.0 (4.0–4.0)[a]	4.0 (3.0–4.0)[ab]	3.0 (2.0–4.0)[abc]	0.000
24h	4.0 (3.0–4.0)	3.0 (3.0–3.0)[a]	3.0 (2.0–3.0)[ab]	3.0 (2.0–3.0)[ab]	0.000
48h	2.0 (2.0–3.0)	2.0 (2.0–3.0)	2.0 (1.8–3.0)	2.0 (1.0–3.0)	0.360
Prince-Henry Pain(median, IQR)					
1h	2.0 (2.0–3.0)	2.0 (2.0–3.0)	2.0 (2.0–3.0)	3.0 (1.0–3.0)	0.909
12h	3.0 (3.0–4.0)	3.0 (3.0–3.0)[a]	3.0 (2.0–3.0)[ab]	2.0 (2.0–2.0)[abc]	0.000
24h	3.0 (2.0–3.0)	2.0 (2.0–3.0)[a]	1.0 (1.0–3.0)[ab]	2.0 (1.0–2.0)[ab]	0.000
48h	2.0 (1.0–3.0)	2.0 (1.0–2.0)	2.0 (1.0–2.0)	2.0 (1.0–2.0)	0.634
QoR-15(median, IQR)					
Pre	134.0 (126.0–140.0)	132.0 (124.0–139.0)	135.0 (129.5–140.0)	136.0 (126.0–140.0)	0.954
POD1	100.0 (91.5–100.0)	110.5 (107.0–115.0)[a]	119.0 (113.0–125.8)[ab]	119.0 (113.0–128.0)[ab]	0.000
POD2	125.0 (118.0–130.5)	125.0 (120.0–130.0)	124.5 (120.0–132.5)	125.0 (120.0–134.0)	0.606
Number of PCIA Attempts(median, IQR)					
0–24h	2.0 (0.0–3.0)	2.0 (0.0–2.0)	1.0 (1.0–2.0)	2.0 (1.0–2.0)	0.976
24–48h	1.0 (0.0–2.0)	1.0 (1.0–1.0)	1.0 (1.0–1.0)	1.0 (1.0–1.0)	0.847
Total	2.0 (1.0–4.0)	3.0 (1.0–3.0)	2.0 (1.8–3.0)	2.0 (2.0–3.0)	0.979
Number of Rescue Analgesia Received	1.0 (1.0–1.0)	1.0 (1.0–2.0)	1.0 (0.8–1.0)	1.0 (1.0–1.0)	0.947
Anti-emetics required, n (%)	3 (5.7)	3 (5.9)	3 (6.0)	4 (7.8)	0.980
Intraoperative OME	45.0 (39.70–51.6)	35.6 (30.3–39.3)[a]	33.7 (27.9–40.1)[a]	33.4 (30.0–37.3)[a]	0.000
Postoperative OME					
0–24 h	34.1(31.1–38.0)	24.1(20.0–28.1)[a]	17.5 (15.5–23.9)[ab]	19.1(16.1–22.5)[ab]	0.000
24–48 h	17.1 (15.5–20.1)	16.7 (14.8–19.1)	16.6 (15.4–18.5)	16.1 (15.1–18.1)	0.506
Total	52.0 (47.8–56.0)	41.4 (37.8–46.1)[a]	35.5 (32.0–40.4)[ab]	35.6 (33.2–39.9)[ab]	0.000

Notes: [a]Compare with R Group, $P<0.05$; [b]Compare with RD_{iv} Group, $P<0.05$; [c]Compare with $RD_{0.5}$ Group, $P<0.05$. Values are means (SD), median (IQR) or number of patients.
Abbreviations: VAS, visual analog scale; PCIA, patient controlled intravenous analgesia; OME, oral morphine equivalent; QoR-15, Quality of Recovery-15; POD1, Postoperative day 1; POD2, Postoperative day 2.

Table 3 The Incidence of Adverse Effects at 24 h After Surgery

Index	R Group (n=53)	RD_{iv} Group (n=51)	$RD_{0.5}$ Group (n=50)	$RD_{1.0}$ Group (n=51)	$\chi 2$	*P*
Nausea, n (%)	7 (13.2)	9 (17.6)	9 (18.0)	10 (19.6)	0.833	0.842
Vomiting, n (%)	6 (11.3)	7 (13.7)	6 (12.0)	7 (13.7)	0.210	0.976
Hypoxemia, n (%)	0	0	1 (2.0)	1 (2.0)	2.191	0.490
Bradycardia, n (%)	1 (1.9)	2 (3.9)	2 (4.0)	4 (7.8)	2.109	0.531
Dizziness, n (%)	2 (3.8)	4 (7.8)	4 (8.0)	5 (9.8)	1.631	0.686
Drowsiness, n (%)	0	2 (3.9)	1 (2.0)	7 (13.7)[abc]	9.820	0.008
Delirium, n (%)	0	0	0	0	–	/
Intraoperative awareness, n (%)	0	0	0	0	–	/
TPVB puncture site hematoma, n (%)	0	0	0	0	–	/

Notes: [a]Compare with R Group, $P<0.05$; [b]Compare with RD_{iv} Group, $P<0.05$; [c]Compare with $RD_{0.5}$ Group, $P<0.05$; Values are number of patients (%).
Abbreviations: TPVB, Thoracic paravertebral nerve block.

Discussion

This randomized study was designed to evaluate the two administration routes of dexmedetomidine on acute pain and chronic NeuP prevention compared with no dexmedetomidine. This trial is the first to compare the incidence of chronic NeuP between the two routes of dexmedetomidine administration in TPVB in patients undergoing thoracic surgery. In addition, two concentrations of dexmedetomidine (0.5 ug·kg^{-1} and 1.0 ug·kg^{-1}) were compared for the perineural administration route. Both perineural and IV dexmedetomidine groups effectively reduced acute pain, resulting in lower perioperative analgesic drug consumption and prolonged duration of analgesia compared with patients receiving ropivacaine alone. Nonetheless, only perineural dexmedetomidine reduced the incidence of chronic NeuP at 3-month after surgery.

According to the recently updated criteria of CPSP, it is defined as either a continuation of acute postoperative pain or pain that occurs after an asymptomatic period, lasting for at least 3 to 6 months duration and significantly affecting the health-related quality of life.[30] A large proportion of CPSPs can be attributed to NeuP, which can be evaluate by LANSS score, as intraoperative intercostal nerve neuropraxia is the most common cause for CPSP following such procedures.[31,32] In the newly released ICD-11 classification, NeuP was defined as "pain initiated or caused by a primary lesion, dysfunction, or transitory perturbation of the peripheral or central nervous system".[7] An important classification of NeuP is NeuP after peripheral nerve injury.[7] Surgery, especially thoracic surgery, increases the risk of NeuP, which may involve different degrees of nerve injury, such as transection, stretching, and compression.[11,33–36] However, the precise mechanism underlying its occurrence remains elusive and likely involves a complex interplay between peripheral and central nervous system alterations.[37,38]

Our results suggested that chronic NeuP at 3 and 6-month after thoracic surgery were 41.5% and 11.3% with those receiving ropivacaine alone, respectively, which is compatible with that of previous studies.[24] At 3-month after surgery, perineural dexmedetomidine showed a significantly lower incidence of LANSS pain score > 12 in comparison to IV dexmedetomidine. This finding indicates that perineural administration of dexmedetomidine exhibits a certain degree of central and peripheral neuroprotective effects and contributes to the reduction in the incidence of chronic NeuP compared to IV administration.

Prolonged sensory block may provide longer analgesia and avoidance of premature return to moderate to severe pain. A recent meta-analysis revealed that perineural dexmedetomidine improves the postoperative pain severity of patients and prolongs the duration of analgesia in TPVB.[39] IV dexmedetomidine can also have the same effect as perineural dexmedetomidine in some studies.[19,21] This study revealed that compared with ropivacaine alone, perineural or IV dexmedetomidine can reduce VAS scores at rest and movement and Prince-Henry Pain scores at 12 and 24-h after surgery, and reduce the consumption of intraoperative and postoperative OME, which was consistent with previous studies.[40] QoR-15 is a validated quality assessment tool, and the results demonstrated that perineural and IV dexmedetomidine can improve the QOD-15 score at POD1 compared with ropivacaine alone, which has achieved minimum clinically important difference (MCID) (6.0).[41]

Another important result of our study was the effect of perineural dexmedetomidine compared to IV dexmedetomidine. Most importantly, perineural dexmedetomidine was found to reduce chronic NeuP at 3-month after surgery. In addition, compared with IV dexmedetomidine, perineural dexmedetomidine can reduce VAS scores at rest and movement and Prince-Henry Pain scores at 12 and 24-h after surgery, the consumption of postoperative OME and improve QOD-15 at POD1, which is in accordance with previous studies.[42] These findings suggest that compared with IV dexmedetomidine, perineural dexmedetomidine has analgesic advantages and can effectively reduce the incidence of acute pain and chronic NeuP.

The mechanism by which dexmedetomidine, as an adjuvant to local anesthetics, enhances the effect of analgesic is considered multifactorial and remains controversial. It was previously summarized in our review.[43] (1) Peripheral level: perineural dexmedetomidine can maintain the hyperpolarized state of cells by inhibiting the activation of I_h current (a non-inactivating, inwardly rectifying current carried by both $Na^+$and K^+ ions, which is also called the pacemaker current because it is believed to play a significant role in cell excitability) and activates α_2-adrenoceptor in peripheral blood vessels, constricting blood vessels around the injection site;[20,44] (2) Spinal cord level: dexmedetomidine inhibits the release of excitatory neurotransmitters such as glutamate and substance P in the spinal;[45] (3) Supraspinal level:

dexmedetomidine may have a certain amount of systemic absorption and inhibit the descending noradrenergic pathway in the medulla or reduce sympathetic nerve signals, thereby partly achieving its analgesic effect from the central level.[46] Due to this systemic absorption, perineural dexmedetomidine may have similar effects as IV administration.

It is well-known that the contents of the thoracic paravertebral space include the intercostal neurovascular bundle.[47] TPVB is a technique used to block the conduction of somatosensory and motor nerves by injecting local anesthetics into the spinal nerve in the paravertebral space. The analgesic effects of perineural dexmedetomidine may be attributed to a combination of perineural effects as well as varying degrees of systemic absorption.[21]

Another important finding of our study was the effect of perineural dexmedetomidine 0.5 $\mu g \cdot kg^{-1}$ compared to 1.0 $\mu g \cdot kg^{-1}$. Our study revealed that compared with 0.5 $\mu g \cdot kg^{-1}$, 1.0 $\mu g \cdot kg^{-1}$ perineural dexmedetomidine could reduce VAS scores at rest at 12 and 24-h, VAS score in movement, and Prince-Henry Pain score at 12-h after surgery. Additionally, it is noteworthy that despite the presence of some intergroup disparities in postoperative acute pain, the Bonferroni correction *P*-values indicate that these variances are not clinically relevant. Consequently, increasing the dose of perineural dexmedetomidine to 1.0 $\mu g \cdot kg^{-1}$ is not necessary. Furthermore, 1.0 $\mu g \cdot kg^{-1}$ perineural dexmedetomidine could increase the incidence of drowsiness compared to 0.5 $\mu g \cdot kg^{-1}$. Two previous meta-analyses found that perineural dexmedetomidine was associated with a significant increase in postoperative sedation within 24 hours, which may contribute to an increase in drowsiness, which was consistent with our study.[48,49] 1.0 $\mu g \cdot kg^{-1}$ perineural dexmedetomidine can be rapidly absorbed into the blood, which may be related to the rapid absorption of the drug due to the abundant venous plexus in paravertebral space, thereby leading to drowsiness or excessive sedation. Many studies have shown that the maximum safe dose of dexmedetomidine is 2 $\mu g \cdot kg^{-1}$, but we should be aware of the risk of intraoperative transient bradycardia and hypotension.[50] According to our result, a dose of dexmedetomidine of 0.5 $\mu g \cdot kg^{-1}$ appears to provide an optimal balance between adequate postoperative analgesia and the adverse effects of TPVB in thoracic surgery.

Limitations

Nevertheless, the limitations of the present study should be acknowledged. Although this is a prospective randomized controlled study, it is a single-center trial with a relatively small sample size, which inevitably lacks external validity. In addition, several outcomes were subjective, such as the LANSS score and VAS score, which may have introduced variability and bias. In order to minimize these effects, the investigators provided the patients with a thorough preoperative explanation of the evaluation protocol after recruitment. Thirdly, the incidence of CPSP was not assessed in the long-term follow-up of patients undergoing thoracic surgery. While NeuP is a frequent component of CPSP after VATS and a marker of severity, some patients with CPSP after VATS do not have NeuP. Therefore, although we found that perineural dexmedetomidine decreased the incidence of NeuP at 3-month after surgery, its impact on the overall incidence of CPSP is unknown. Furthermore, despite setting an IV dexmedetomidine group and two groups of perineural dexmedetomidine, the optimal dose of dexmedetomidine for IV and perineural administration requires further study.

Conclusion

In conclusion, our results suggest that perineural and IV dexmedetomidine are both effective in reducing acute pain and the consumption of analgesics. However, only perineural dexmedetomidine can reduce chronic NeuP in the context of TPVB in patients undergoing thoracoscopic resection of lung lesions under GA. Moreover, considering postoperative complications such as drowsiness, 0.5 $\mu g \cdot kg^{-1}$ perineural dexmedetomidine may be a more appropriate choice.

Data Sharing Statement

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

Ethics Approval and Consent to Participate

The study was conducted with Institutional Review Board approval from the Second Hospital of Shandong University in China (No: KYLL-2022P254), and the guidelines outlined in the Declaration of Helsinki were followed. Written informed consent was obtained from all study participants.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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