Dexamethasone and dexmedetomidine as adjuvants to local anesthetic mixture in intercostal nerve block for thoracoscopic pneumonectomy: a prospective randomized study

Panpan Zhang,1 Shijiang Liu,2 Jingming Zhu,2 Zhuqing Rao,2 Cunming Liu2

ABSTRACT
Background and objectives Perineural dexamethasone or dexmedetomidine prolongs the duration of single-injection peripheral nerve block when added to the local anesthetic solution. In a randomized, controlled, double-blinded study in patients undergoing thoracoscopic pneumonectomy, we tested the hypothesis that combined perineural dexamethasone and dexmedetomidine prolonged the duration of analgesia as compared with either perineural dexamethasone or perineural dexmedetomidine after intercostal nerve block (INB).

Methods Eighty patients were randomized to receive INB using 28 mL 0.5% ropivacaine, with 2 mL normal saline (R group), with 10 mg dexamethasone in 2 mL (RS group) or 1 µg/kg dexmedetomidine in 2 mL (RM group), or with 1 µg/kg dexmedetomidine and 10 mg dexamethasone in 2 mL (RSM group) administrated perineurally. The INB was performed by the surgeon under thoracoscopic direct vision; a total of six intercostal spaces were involved, each with an injection of 5 mL. The primary outcome was the duration of analgesia. Secondary outcomes included total postoperative fentanyl consumption, visual analog scale pain score and safety assessment (adverse effects).

Results The duration of analgesia in RSM (824.2±105.1 min) was longer than that in RS (611.5±133.0 min), RM (602.5±108.5 min) and R (440.0±109.6 min) (p<0.001). Total postoperative fentanyl consumption was lower in RSM (106.0±84.0 µg) compared with RS (243.0±175.2 µg), RM (237.0±98.7 µg) and R (369.0±134.2 µg) (p<0.001). No significant difference was observed in the incidences of adverse effects between the four groups.

Conclusion The addition of combined perineural dexamethasone and dexmedetomidine to ropivacaine for INB seemed to be an attractive method for prolonged analgesia with almost no adverse effects.

Trial registration number ChiCTR-IOR-17012183.

INTRODUCTION
Single-injection peripheral nerve block (PNB) is commonly used for perioperative analgesia and anesthesia.1 Although PNB are beneficial for improved early postoperative pain management, it often is insufficient, as postoperative pain may persist for several days. The aim of prolonging the duration of PNB to treat postoperative pain is a key issue in regional anesthesia. Three approaches for extending the duration of PNB include continuous PNB with catheter-based techniques, novel local anesthetics delivery systems and addition of novel adjuvants to local anesthetics.2

Adjuvants that are frequently added to local anesthetics to prolong analgesia following single-injection PNB include epinephrine, opioids, tramadol, ketamine, midazolam, magnesium, clonidine, dexamethasone and dexmedetomidine, but often with limited success and unproven safety.3–6 Studies of perineural bupivacaine, dexmedetomidine and dexamethasone have most consistently demonstrated prolongation of PNB.5

Dexamethasone is a potent long-acting steroid that has shown efficacy as an adjuvant to local anesthetics in various studies.7 8 Dexmedetomidine enhances PNB when added to local anesthetics, providing better quality of anesthesia as well as postoperative analgesia.9 10 The mechanism by which dexamethasone and dexmedetomidine prolong the duration of local anesthetics are not completely understood and may arise from various factors. Both dexamethasone and dexmedetomidine can reduce local inflammation and prolong the duration of nerve block through vasoconstriction by maintaining the local concentration of the local anesthetic.11–14 Vasoconstriction also inhibits the nociceptive impulse transmission along myelinated C fibers.15 Possible mechanisms of dexmedetomidine in prolonging the duration of nerve blocks may also include the inhibition of the hyperpolarization-activated cation current (Ih current).16 Some research suggests that dexmedetomidine may provide local anesthetic action that blocks the conduction of nerve signals through C and Aδ fibers, not through α2 action, and may stimulate the release of enkephalin-like substances at peripheral sites.17

Due to the different mechanisms of action, we hypothesized that ropivacaine combined with both perineural dexamethasone and dexmedetomidine could further prolong the duration of PNB. Therefore, we performed a prospective, randomized, double-blinded, controlled trial to investigate whether the addition of two adjuvants (dexmedetomidine and dexamethasone) to ropivacaine for INB prolongs block duration and therefore improves postoperative analgesia, as compared with each adjuvant alone with ropivacaine.

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Figure 1  Patient enrollment, inclusion and exclusion process. PICA, patient-controlled intravenous analgesia.

METHODS

Trial design and participants

After providing written informed consent, patients with American Society of Anesthesiologists (ASA) physical status classes I and II, aged 28–68 years and scheduled for thoracoscopic pneumonectomy between September 2017 and April 2018 were considered eligible to participate in this prospective, randomized, double-blinded clinical trial. Major exclusion criteria were: hypertension; ischemic heart disease; psychiatric disorders; preoperative heart rate (HR) less than 50 beats/min with or without cardiac conduction or rhythm abnormalities; diabetes mellitus; neuromuscular and endocrine diseases; coagulation disorders; adrenoreceptor agonist or antagonist therapy; chronic pain treatment or chronic steroid therapy; allergy to the study drugs and refusal to participate in the study. Individuals who had an estimated intraoperative blood loss of more than 500 mL were subsequently excluded from the study. Those who were transferred to an open chest operation, those who required a second operation for postoperative hemorrhage and those who presented severe postoperative infection were also subsequently excluded from the study.

Randomization and blinding

A computer-generated random numbers list was used to randomize consented study participants on a 1:1:1:1 ratio to receive INB with trial medication.

Table 1  Demographic data and surgical characteristics

<table>
<thead>
<tr>
<th></th>
<th>Group R</th>
<th>Group RS</th>
<th>Group RM</th>
<th>Group RSM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>53.3±7.8</td>
<td>54.5±9.3</td>
<td>53.9±6.7</td>
<td>55.6±10.3</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.6±2.0</td>
<td>22.8±2.5</td>
<td>22.1±2.4</td>
<td>23.5±2.1</td>
</tr>
<tr>
<td>Gender (F/M)</td>
<td>9/11</td>
<td>12/8</td>
<td>13/7</td>
<td>14/6</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>132.4±51.9</td>
<td>126.7±19.4</td>
<td>119.6±49.7</td>
<td>136.4±29.7</td>
</tr>
<tr>
<td>Extubation time (min)</td>
<td>19.5±11.2</td>
<td>22.2±6.3</td>
<td>25.8±9.5</td>
<td>23.7±10.1</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SD or numbers. There were no significant differences between groups.

BMI, body mass index; F, female; M, male; R, ropivacaine; RM, ropivacaine+dexmedetomidine; RS, ropivacaine+dexamethasone; RSM, ropivacaine+dexamethasone+dexmedetomidine.
All patients received PCIA for postoperative analgesia. PCIA was administered for VAS ≥4. Statistical analysis was performed with SPSS V.24.0 for Windows and GraphPad Prism 6 (GraphPad Software, La Jolla, California, USA). For duration of analgesia, total postoperative fentanyl consumption and VAS data, ANOVA was selected and grouped into four groups, with adjustment for multiple comparisons. Repeated measures were assessed before surgery (baseline) and at 6 hours, 12 hours, 24 hours, 36 hours and 48 hours after surgery. Side effects such as bradycardia (HR <50 beats/min), hypoxemia (SpO₂ <90%), hypotension (systolic blood pressure <90 mmHg or more than 20% decline from the baseline), respiratory depression (RR <10 beats/min lasting for more than 10 min), headache, pruritus, nausea, vomiting and neurotoxicity were recorded after surgery, whereas hypotension was treated with fluid loading, intravenous ephedrine or phenylephrine. In addition, bradycardia was treated with atropine. Respiratory depression was treated with oxygen or naloxone until RR ≥15 beats/min.

### Statistical analysis

Duration of analgesia was the primary outcome. We hypothesized that perineural dexamethasone and dexmedetomidine combined (RSM group) prolonged the duration of analgesia compared with single adjuvant groups of perineural dexamethasone (RS group) or perineural dexmedetomidine (RM group) after INB. In our preliminary study conducted with eight patients (two in each group), the mean duration of analgesia was 500±160 min, 570±226 min, 550±147 min, 767±184 min in groups R, RS, RM and RSM. Sample size calculation was performed with PASS V.11.0 (PASS, NCSS, USA) for Windows. One-way analysis of variance (ANOVA) was selected and grouped into four groups, with separate variances assumed. Hypothesized means were 570, 550 and 767 and SD were 226, 147 and 184, respectively. At a power of 0.8 and an alpha error of 0.05, the required sample size per group was calculated to be 15. Considering the dropouts and incomplete follow-up, suggested 20 patients per group and a total of 80 patients for this study.

### Results

A total of 151 patients were approached to participate in this study from September 2017 to April 2018; 54 patients were ineligible due to not meeting inclusion criteria or refusal to participate; 17 patients were excluded because of non-adherence to the protocol (three patients refused to participate in the study after surgery; two patients converted to open surgery; three patients hemorrhage need transfusion; four patients lost to follow-up; one patient underwent second surgery in 48 hours; two patients refused to use PICA after surgery; and two patients...
developed acteactasis in 24 hours); and finally, 80 patients were randomized and completed the study protocol (R group: n=20; RS group: n=20; RM group: n=20; and RSM group: n=20). Figure 1 represents the Consolidated Standards of Reporting Trials flow diagram depicting patient progress through the study phases.

A total of 80 patients were included for analysis in the study. No significant differences in patient characteristics were evident between each group (table 1).

The duration of analgesia was significantly longer in group RSM compared with the other three groups (p<0.001). Compared with group RS and group RM, the duration of analgesia was significantly shorter in group R (p<0.001). There was no significant difference between group RS and group RM (p=1.000) (table 2). The Kaplan-Meier survival analysis of the time to the first analgesic request was shown in figure 2. The log-rank test also suggested prolongation of the first analgesic request for group RSM compared with the other three groups (p<0.001). Compared with group RS and group RM, the first analgesic request was significantly shorter in group R (p<0.001). There was no significant difference between group RS and group RM (p=1.000).

Total postoperative fentanyl consumption in group RSM was lower than that of the other three groups (p<0.001). Compared with group RS and group RM, total postoperative fentanyl consumption was significantly higher in group R (p=0.016 and p=0.010, respectively). There was no significant difference between group RS and group RM (p=1.000) (table 2).

At 6 hours postoperatively, VAS in group R was higher than those in the other three groups (p<0.001). At 12 hours postoperatively, *p<0.001 group R compared with groups RS, RM and RSM. At 24 hours postoperatively, *p<0.001 group RSM compared with groups RS, RM and R. At 48 hours postoperatively, #p=0.043 between groups RSM and R. R, ropivacaine; RM, ropivacaine+dexmedetomidine; RS, ropivacaine+dexamethasone; RSM, ropivacaine+dexamethasone+dexmedetomidine; VAS, visual analog scale.

The duration of analgesia was significantly longer in group RSM compared with the other three groups (p<0.001). Compared with group RS and group RM, the duration of analgesia was significantly shorter in group R (p<0.001). There was no significant difference between group RS and group RM (p=1.000) (table 2). The Kaplan-Meier survival analysis of the time to the first analgesic request was shown in figure 2. The log-rank test also suggested prolongation of the first analgesic request for group RSM compared with the other three groups (p<0.001). Compared with group RS and group RM, the first analgesic request was significantly shorter in group R (p<0.001). There was no significant difference between group RS and group RM (p=1.000).

Total postoperative fentanyl consumption in group RSM was lower than that of the other three groups (p<0.001). Compared with group RS and group RM, total postoperative fentanyl consumption was significantly higher in group R (p=0.016 and p=0.010, respectively). There was no significant difference between group RS and group RM (p=1.000) (table 2).

At 6 hours postoperatively, VAS in group R was higher than those in the other three groups (p<0.001). At 12 hours postoperatively, VAS in group RSM was lower compared with group RS, group RM and group R (p<0.001). At 48 hours postoperatively, VAS was lower in group RSM compared with group R (p=0.043). There were no significant differences in VAS among the four groups at 24 hours and 36 hours postoperatively (p=0.645 and p=0.076, respectively) (figure 3).

The discrepancies of MAP and HR acquired at different time points were statistically significant (P < 0.001). No significant differences were observed between the study groups (P=0.242 and P=0.792, respectively) (figures 4 and 5).

The number of patients experiencing side effects was reported in table 3. No significant differences were observed in the incidences of hypotension, hypoxemia, respiratory depression, vomiting, nausea, pruritus or dizziness among the four groups. The RSS was two in all patients.

**DISCUSSION**

In this study, we demonstrated that ropivacaine combined with two perineural adjuvants (dexamethasone and dexmedetomidine) can further prolong the duration of analgesia and reduce the consumption of fentanyl compared with ropivacaine combined with a single perineural adjuvant (dexamethasone...
dose increases the duration of postoperative analgesia and delays the requirement of the first dose of analgesic. Although dexamethasone was widely used clinically, the optimal dose of dexamethasone as a local anesthetic adjuvant was inconsistent. Previous studies have shown that dexamethasone demonstrated significant beneficial dose-dependent effects as an adjuvant for local anesthesia. Recent studies have shown that perineural high doses of dexamethasone have no advantage, and low doses of dexamethasone are advocated. A recent meta-analysis showed very low quality evidence that there was a ceiling effect of dexamethasone at 4 mg. However, the latest research findings that both intravenous and perineural administered dexamethasone 4 mg has no clinically relevant effect on the duration of sensory block provided by ropivacaine applied to the ulnar nerve in volunteers. In addition, in the current study, we used a higher dose of dexamethasone than other experts have recommended. Although no permanent complications associated with nerve block could be attributed to the use of dexamethasone, considering that high doses of dexamethasone may increase potential risks, we no longer recommend high doses of dexamethasone administered perineurally. Therefore, the effective dose of dexamethasone as an adjuvant for local anesthesia needs further study.

There are a number of limitations associated with the present study. First, this study lacks an intravenous control. It would have required more than four groups by adding the intravenous group, making calculations and statistical analysis of the sample size more difficult. However, without intravenous control, we cannot ascertain whether the addition of either dexamethasone or dexmedetomidine was via systemic absorption or through perineural action. Second, we used a higher dose of dexamethasone than other experts have recommended. Third, VAS scores were measured only at rest, thus this reduces the usefulness of the results provided. Fourth, we did not assess the duration of the sensory block in patients using repeated neurological examinations. Considering that frequent testing of sensory block after surgery can affect patients’ rest, the time from the end of INB to the first use of fentanyl after operation indicates the duration of analgesia. Fifth, dexamethasone and dexmedetomidine are used off-label. Even though it is widely used on an international level and has been investigated in many scientific trials, the US Food and Drug Administration does not approve dexamethasone or dexmedetomidine for perineural administration. Regarding the inconclusive data on the safety of perineural dexamethasone and dexmedetomidine, we would like to remind clinicians that this ‘off-label’ use needs approval of the appropriate regulatory health institutions. Finally, our calculation of the number of patients who were needed in our study might not be adequate, so the study power cannot differentiate statistically significant differences between the dexamethasone and dexmedetomidine. Of course, further research is needed to confirm this.

CONCLUSIONS

We demonstrated that patients undergoing thoracoscopic pneumonectomy with the addition of perineural 10 mg dexamethasone and 1 µg/kg dexmedetomidine to 0.5% ropivacaine for INB had further increases in the duration of analgesia and decreases in postoperative fentanyl consumption compared with patients who did not receive this combination of drugs.

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**Contributors** All authors helped design the study. PZ, ZR and CL helped conduct the study. PZ, SL, ZR and CL helped recruit the patients. JZ, ZR and CL helped collect the data. PZ, SL, ZR and CL helped analyze the data. PZ, SL and CL was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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**Patient consent for publication** Not required.

**Ethics approval** The study protocol was approved by the Ethics Committee of The First Affiliated Hospital of Nanjing Medical University (Nanjing, Jiangsu Province, China) and was prospectively registered on Chinese Clinical Trial Registry (registration number ChiCTR-IOR-17012183).

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**Data availability statement** Data are available on reasonable request.

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**REFERENCES**


