Comparison of dexmedetomidine and dexamethasone as adjuvant for ropivacaine in ultrasound-guided erector spinae plane block for video-assisted thoracoscopic lobectomy surgery: a randomized, double-blind, placebo-controlled trial

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Background: Adding an adjuvant, such as dexmedetomidine or dexamethasone, to a nerve block improves its quality and reduces perioperative opioid consumption. We aimed to compare the effect of dexmedetomidine and dexamethasone as an adjuvant for the erector spinae plane block (ESPB) to control postoperative pain after video-assisted thoracoscopic lobectomy surgery (VATLS).

Methods: Ninety patients, aged 20–65 years who were scheduled to undergo VATLS were enrolled in this trial. The visual analogue scale (VAS) score changes at various time points [waking up in post-anesthesia care unit (PACU) and 2, 4, 6, 8, 12, 24, 48, 72 h after surgery], duration of sensory block, first request to use the patient controlled analgesia (PCA) device, total PCA use, postoperative nausea and vomiting (PONV), rate of rescue analgesia use, and post-surgical hospital stay were recorded.

Results: VAS score was lower in the ropivacaine with dexmedetomidine (RM) group at wake up and at postoperative 2, 4, 12, and 24 h. The median duration of sensory blockade was significantly longer in the RM group (P=0.001). First request to use the PCA machine in the RM group was prolonged significantly compared with that in the ropivacaine alone (R) group and ropivacaine with dexamethasone (RS) group (P<0.001). Total PCA use, post-surgical hospital stay, and rate of rescue analgesia use in The RM group were reduced significantly compared with those in the R and RS groups.

Conclusions: Using dexmedetomidine (1 μg/kg), instead of dexamethasone (10 mg), as an adjuvant of ESPB with ropivacaine, prolonged sensory block duration, provided effective acute pain control, and required lesser rescue analgesia and shorter hospital stays.

Keywords: Dexmedetomidine; dexamethasone; adjuvant; erector spinae plane block (ESPB); analgesia

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Introduction

Video-assisted thoracic surgery (VATS) has been widely used to treat lung cancer, since it is minimally invasive, more effectively reduces postoperative pain and complications than open thoracotomy, and shortens operation time and hospital stay (1). However, postoperative pain management, particularly early postoperative pain, remains a matter of concern for several anesthesiologists and thoracic surgeons (2). Erector spinae plane block (ESPB) is an interfascial plane block that successfully deposits a local anesthetic deep into the erector spinae muscle that lies adjacent to transverse processes. Emerging research

demonstrated that ESPB can be employed as a simple and safe alternative analgesic technique to address acute post-surgical, post-traumatic, and chronic neuropathic thoracic pain in adults (3) and children (4,5). Fortunately, its efficacy to ameliorate incisional pain has already been confirmed in clinical studies (6,7).

Since it is not always feasible to admit patients to a ward with indwelling peripheral nerve catheters, it is imperative to employ methods to increase the duration of analgesia with single-shot peripheral nerve blocks.

Dexmedetomidine is a potent α2 agonist and is now emerging as an adjuvant to regional anesthesia and analgesia. It can prolong the duration of the nerve block anesthesia when used with a local anesthetic, and only has a few side effects (8,9). Dexamethasone is considered to work by reducing the release of inflammatory mediators and by inhibiting potassium channel-mediated discharge of C-fibers. Results of human studies proved that the dexamethasone-treated group demonstrated longer duration of sensory and motor blockade than the control (10,11). Considering a number of studies on the efficacy of dexmedetomidine or dexamethasone as an adjuvant for ropivacaine in the erector spinae plane, we designed a double-blind randomized control study to compare the ESPB characteristics and side effects following erector spinae plane ropivacaine versus erector spinae plane ropivacaine supplemented with either dexmedetomidine or dexamethasone in patients scheduled for video-assisted thoracoscopic lobectomy surgery (VATLS).

Methods

The study was approved by the Ethics Committee of First Affiliated Hospital of Anhui Medical University (kuai 2019-02-12) and registered at clinicaltrials.gov (ChiCTR1800020041). The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This randomized, controlled, double-blind study enrolled patients scheduled for lobectomy under video-assisted thoracoscopic surgery (VATS) at the first affiliated hospital of Anhui medical university (Hefei, China); all patients provided written informed consent.

All patients were aged 20–65 years, had an American Society of Anesthesiologists physical status (ASA) of I or II, and were scheduled for VATLS. The exclusion criteria were as follows: refusal to ESPB, presence of coagulopathy or bleeding disorder, bradycardia, cardiac conduction block, were administered β-adrenergic antagonist or an antiplatelet agent, local infection at the injection site, hypersensitivity to local amide anesthetics, or were hypersensitive or allergic to dexmedetomidine. Patients were also excluded if they had central neuropathy, a body mass index >35 kg/m^2, uncontrolled diabetes mellitus, significant cardiopulmonary disease, or psychiatric disease.

After obtaining a written informed consent, all patients were taught to evaluate their own pain by using a 10-cm visual analog pain scale (0= no pain, 10= maximum pain imaginable) and how to use the patient controlled analgesia (PCA) device at the preoperative visit. All patients were then randomized to one of three groups using computer-generated random numbers and a 1:1:1 allocation ratio. Allocation concealment was fulfilled by an assistant not involved in the study, and randomization was achieved in sequentially numbered, sealed, opaque envelopes, which were opened after patient's arrival to the operation room. Blinding of research personnel was maintained throughout the study, including postoperative follow-ups.

Patients were placed in a standard lateral position to apply ESPB before inducing anesthesia. An assistant, who was neither involved in the study nor was participating in the perioperative period or the postoperative follow-up, prepared study drugs. Groups received 0.5% ropivacaine 30 mL (R) or 0.5% ropivacaine 30 mL with 10 mg dexamethasone (RS) or 0.5% ropivacaine 30 mL with 1 μg/kg dexmedetomidine (RM), deep to the erector spinae muscle adjacent to transverse processes.

We performed ESPB in the preoperative block area following standardized monitoring, which included noninvasive blood pressure (BP), electrocardiogram (EKG), and pulse oximetry (PO). Oxygen (2–3 L/min) was supplied through the nasal cannula, and midazolam IV (0.025 mg/kg) was administered. All blocks were performed by the same three senior attending doctors with considerable experience in ultrasonic-guided nerve blocks. They were performed at the T5 level of the spine using an in-plane approach. A real-time ultrasound machine (SonoSite M-Turbo, Bothell, WA, USA) was used to evaluate block performance. A high-frequency linear ultrasound probe was placed longitudinally at a distance of 3 cm from the midline. After identifying the erector spinae muscle and transverse processes, we inserted a 22 G, 120-mm needle (stimuplex D; B. Braun Melsungen AG, Melsungen, Germany) after standard skin disinfection. It was inserted in a caudad-to-cephalad direction using a sterile probe cover until the tip lay in the

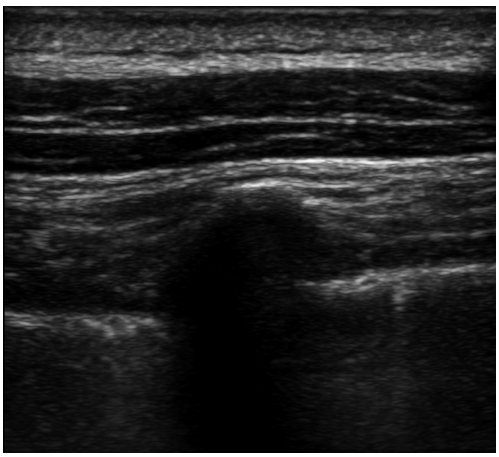

Figure 1 Ultrasound image taken before the erector spinae plane block (ESPB).

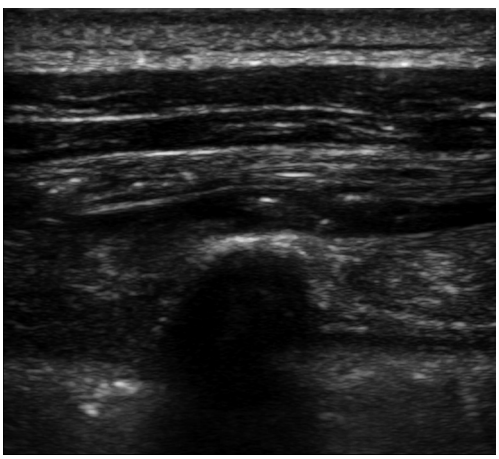

Figure 2 Ultrasound image taken after the erector spinae plane block (ESPB).

interfacial plane deep into the erector spinae muscle (*Figure 1*). This plane was opened following hydrolocalization with normal saline. We administered 30 mL of 0.5% ropivacaine, with or without adjuvants, to ensure block performance (*Figure 2*). Sensory block of the 5th intercostal space in the midaxillary line was assessed by bilaterally using cold perception for 30 min after applying the nerve block. The patient was excluded from the study if sensory blockade was unsuccessful.

We connected the peripheral intravenous (IV), right internal jugular vein, and radial artery catheters while transferring the patients to the operating room. Electrocardiogram (leads II and V5), invasive blood pressure, central venous pressure, heart rate, pulse oximetry, and the bispectral index (BIS) (Vista; Aspect Medical Systems Inc., Norwood, MA, USA) were monitored throughout the procedure. Propofol (Diprivan; AstraZeneca plc, London, UK) was administered in a target-controlled infusion according to Marsh pharmacokinetic model (12) (Graseby 3500; Smiths Medical, Wat-ford, UK) while administering the anesthetic. After achieving an initial target concentration of 1.0 μg/mL, it was progressively increased by 0.3 μg/mL until the BIS value reached 40–60. Following which, 0.03 mg/kg midazolam and 0.5 μg/kg of sufentanil were intravenously injected. Rocuronium bromide (0.9 mg/kg) was used to facilitate double-lumen endobronchial intubation. After tracheal intubation, lungs were ventilated with 100% oxygen, and a volume-cycled ventilator was applied with the following settings: tidal volume of 8 mL/kg ideal body weight; inspiratory-to-expiratory ratio of 1:2; and a respiratory frequency of 8 breaths/min. Propofol and remifentanil were continuously infused to maintain anesthesia, and sufentanil and cisatracurium were administered as needed. BIS values were maintained from 40 to 60 throughout the surgery by changing the effect site concentration of propofol. The ventilation mode was switched to one-lung ventilation before the surgical procedure, and the frequency and tidal volume were adjusted to maintain pulse oximetry and end-tidal carbon dioxide. Propofol and remifentanil were discontinued upon adding the last skin suture. Neostigmine (20 μg/kg) and atropine (5–10 μg/kg) were administered according to tidal volume and frequency to reverse residual muscle relaxation at the end of surgery. Patients were admitted to the post-anesthesia care unit (PACU) until spontaneous breathing was recovered. Patients were extubated in the PACU according to standard extubation protocols and subjects were moved from the PACU on receiving a Steward recovery score of >4.

Sufentanil (0.1–0.2 μg/kg) and flurbiprofen (50 mg) were intravenously administered, followed by patient-controlled analgesia (PCA) pump use before the end of the surgery. PCA capacity was 250 mL and contained 7.5 μg/kg sufentanil and 250 mg flurbiprofen. The infusion rate was maintained at 2 mL/h, and the patient-controlled bolus was 2 mL with a lockout interval of 15 min. They were trained to press for an additional bolus if a 10 cm visual analog scale (VAS) for postoperative pain exceeded 3, and first time request for pressing PCA was recorded. In the situation when the VAS score remained ≥4 after using the PCA, the patients received tramadol 100 mg intramuscularly injection

as rescue analgesic.

We performed a cold perception test in comparison with the contralateral intercostal area. Duration of sensory block was the time period from establishing the block to 100% cold perception in all sensory areas (100%= no difference to the contra-lateral side; 0%= complete sensory loss).

While under the influence of the anesthesia, mean arterial pressure (MAP) was maintained between –20% and +20% of the baseline value. A drop of 20% below the baseline MAP or a MAP<60 mmHg lasting more than 30 s was defined as hypotension. Phenylephrine (40 μg) was administered intravenously when fluid therapy was not appropriate. Atropine (0.3 mg) was administered intravenously for bradycardia, which was defined as an HR <60 bpm. Ephedrine (3–6 mg) was administered intravenously to treat bradycardia and hypotension.

The primary end point was postoperative PCA use during the first 72 h. Secondary outcomes included: (I) consumption of sufentanil, remifentanil, and propofol during anesthesia; (II) a 10 cm VAS for pain (0–10; 0, no pain; 10, worst imaginable pain) and changes in the VAS score at various time points: wake up in PACU and 2, 4, 6, 8, 12, 24, 48, 72 h after surgery; (III) optimum duration of sensory block; (IV) initial request for using PCA; and (V) incidence of postoperative nausea and vomiting (PONV) and rescue analgesia in the ward and the hospital stay after surgery.

All statistical data was analyzed primarily via SPSS, version 17.0 (SPSS Inc., Chicago, IL, USA) and GraphPad Prism version 5.01 (GraphPad Software, Inc., La Jolla, CA, USA). Calculations regarding the sample size were performed using an online power sample size calculator based on our previous pilot study showing a decreased mean effective pressing number of PCA for patients under general anesthesia combined with ESPB using ropivacaine with dexmedetomidine and ropivacaine with dexamethasone (2.6±2.2 and 3.2±2.7, respectively) compared with patients undergoing general anesthesia combined with ESPB using ropivacaine (7.4±5.0) at 72 h after surgery. To detect differences in postoperative PCA use 72 h with an SD of σ=4, the sample size was calculated as 21 per group at a power of 80% and a two-tailed α-error of 5%. We enrolled 99 patients in total (N=33/group) to countervail potential dropouts.

The Kolmogorov-Smirnov test was used to determine the normality of data distribution. The continuous variables were expressed as mean ± standard deviation, and median (25th–75th percentiles), and categorical variables as counts (percentages). We compared normally distributed continuous variables among the groups using one-way ANOVA, and used a least significant difference (LSD) procedure for post hoc comparisons, while non-normally distributed continuous variables among the groups were compared using the Kruskal-Wallis test. Mann-Whitney U tests were applied for intergroup comparisons when a significant difference was detected between the groups. Categorical variables were compared using chi-squared or Fisher's exact test (P<0.05 was considered statistically significant).

Results

The study flow is depicted in *Figure 3*. *Table 1* lists patient data. There was no significant difference in intraoperative characteristics among groups, which includes duration of surgery and the consumption of sufentanil, remifentanil, and propofol. *Table 2* shows that postoperative VAS scores at time-points of waking up in the PACU and 2, 4, 12, 24 h after surgery in group RM decreased significantly than that in group R. Group RM demonstrated longer durations of sensory block and delayed first time of using the PCA machine than that in group R and group RS. Group RM demonstrated reduced total PCA machine use, the requirement for rescue analgesia, and postoperative hospital stay than group R and RS. There was no significant difference in the PONV occurrence rate among the groups. No patient experienced block failure, pleural effusion, subjective symptoms of local anesthetic toxicity, infection, or hematoma at the insertion site.

Discussion

Erector spinal plane block (ESPB) is a novel regional anesthesia technique, which is a useful intervention in thoracic neuropathic pain and acute pain after thoracic surgery or trauma (3). ESPB has been considered as a viable peripheral nerve block in establishing postoperative analgesia as it ensures greater technical simplicity, lower incidence of hypotension, and the prevention of hematoma (13). Since it is neither ideal nor feasible to admit patients to the ward with indwelling peripheral nerve catheters, there is still a need for methods to extend the analgesic effect of the single-shot nerve block postoperatively. To the best of our knowledge, this is the

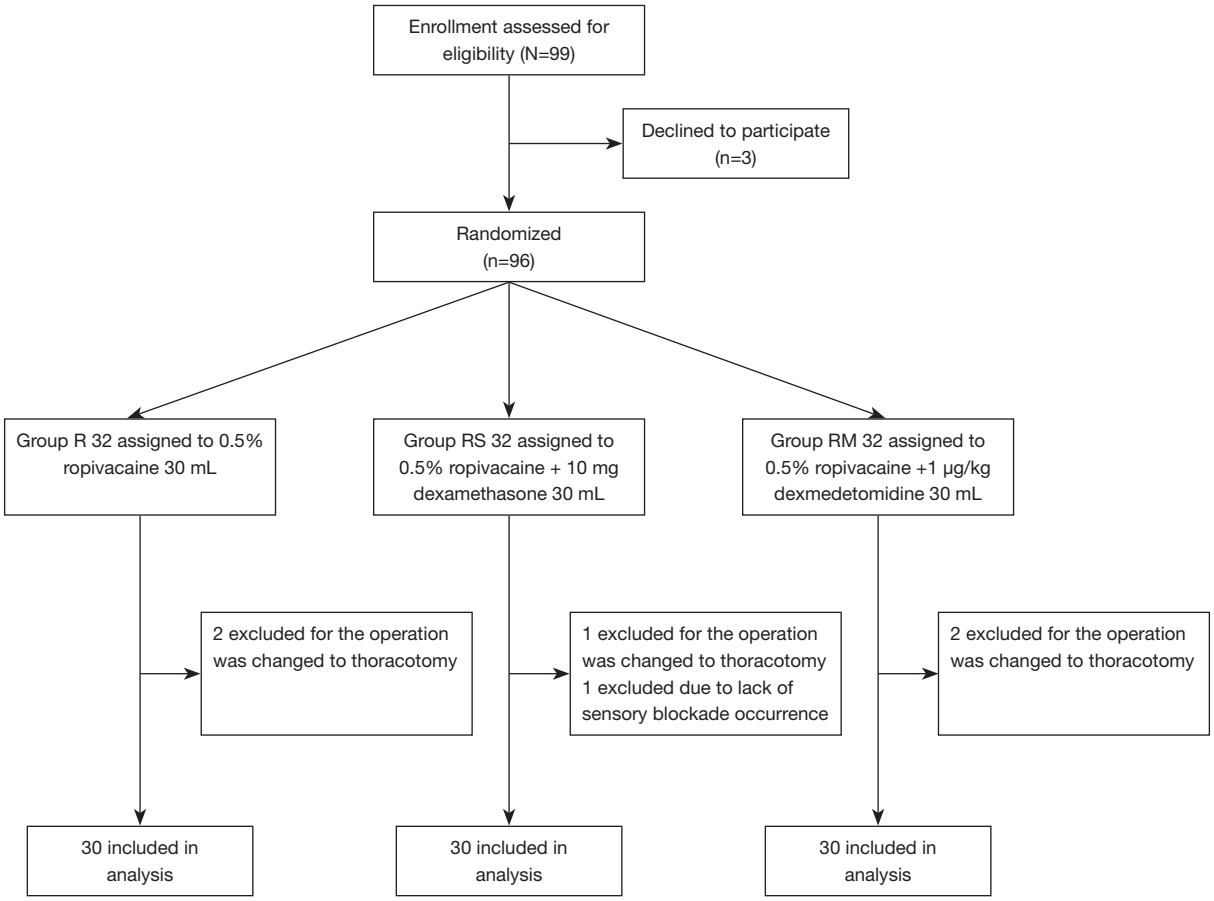

Figure 3 Flowchart of the study. R, 0.5% ropivacaine; RS, 0.5% ropivacaine and 10 mg dexamethasone; RM, 0.5% ropivacaine and 1 μg/kg dexmedetomidine.

Table 1 Patient characteristics and intraoperative data

Variables	Group R (n=30)	Group RS (n=30)	Group RM (n=30)	P value
Gender				0.836
Male	15 (50.0)	17 (56.7)	17 (56.7)	
Female	15 (50.0)	13 (43.3)	13 (43.3)	
Age (years)	56.3 (9.9)	58.1 (11,0)	56.9 (10.1)	0.787
Height (cm)	163 (7.8)	163 (8.1)	164 (8.1)	0.824
Weight (kg)	63.6 (10.2)	59.0 (9.7)	61.2 (9.8)	0.197
BMI (kg/m^2)	23.7 (2.91)	22.2 (3.3)	22.6 (2.6)	0.135
Duration of surgery (min)	184 (68.2)	158 (51.5)	165 (46.7)	0.169
Consumption of sufentanil (μg)	44.7 (9.5)	41.5 (7.4)	43.1 (8.1)	0.341
Consumption of remifentanil (mg)	1.7 (0.6)	1.4 (0.6)	1.7 (1.2)	0.303
Consumption of propofol (mg)	771 (311.5)	678.9 (245.4)	736.3 (214.6)	0.389

Data represent mean (SD) or number (%). P<0.05 is considered as a statistically significant difference. R, 0.5% ropivacaine; RS, 0.5% ropivacaine and 10 mg dexamethasone; RM, 0.5% ropivacaine and 1 μg/kg dexmedetomidine. BMI, body mass index.

Table 2 Postoperative analgesia and postoperative hospital stays

Variables	Postoperative time	Group R (n=30)	Group RS (n=30)	Group RM (n=30)	P value
VAS	Wake up	0 (0–1)	0 (0–0)*	0 (0–0)*	0.016
	2 h	0 (0–1)	0 (0–0)	0 (0–0)*	0.016
	4 h	0 (0–1)	0 (0–0)	0 (0–0)*	0.029
	6 h	0 (0–1)	0 (0–1)	0 (0–0)	0.095
	8 h	0 (0–1)	0 (0–1)	0 (0–1)	0.386
	12 h	1 (0–1.8)	0.5 (0–1)	0 (0–1)*	0.021
	24 h	2 (1–4)	1 (1–3)	1 (0–2)*	0.015
	48 h	2 (0–4)	2 (1–3.5)	1 (0–3)	0.05
	72 h	2 (1–3.8)	1 (1–2.5)	1 (0–3)	0.261
Duration of sensory block (hour)		7.5 (3.3–11.8)	8 (6–10.5)	18 (7.5–22)*,#	0.001
First time request for PCA use (hour)		14.5 (9–20)	20 (2–24)	27 (18–47.2)*,#	<0.001
Sum of effective pressing numbers	72 h	9 (4.5–11.5)	6 (2.3–10)	2 (1–5)*,#	<0.001
Postoperative stay in hospital (day)		6 (4–7.8)	6 (4–8.3)	4 (3–5.2)*,#	0.032
Rescue analgesia		8 (26.7%)	7 (23.3%)	1 (3.3%)*,#	0.038
PONV		5 (16.7%)	6 (20%)	2 (6.7%)	0.311

Data are presented as median (interquartile range) or number (%). P<0.05 is considered as a statistically significant difference. *, P<0.05 compared with the group R; #, P<0.05 compared with the group RS. R, 0.5% ropivacaine; RS, 0.5% ropivacaine and 10 mg dexamethasone; RM, 0.5% ropivacaine and 1 μg/kg dexmedetomidine; PONV, postoperative nausea and vomiting.

first controlled trial to compare the use of dexamethasone or dexmedetomidine as adjuvants to local anesthetics (LAs) for ESPB. Clinical trials have previously indicated benefits of various adjuncts to local anesthetics, but none could satisfactorily prolong effective blockade duration (14,15). We noted block time of ESPB was prolonged approximately 120% by adding perineural dexmedetomidine (1 μg/kg) to 0.5% ropivacaine. Marhofer and Kettner demonstrated that it effectively doubled the estimated clinically meaningful prolongation of peripheral nerve block (PNB) to 60% (16). Furthermore, we observed that subjects of group RM showed delay in the first time use of the PCA machine, better postoperative analgesia, and less pain intensity at all-time points with lower total PCA use during the first 72 h postoperatively than those of group R and RS. Additionally, perineural dexmedetomidine was more effective in decreasing the need for rescue analgesia and duration of hospital stay after video-assisted thoracoscopic surgery than a single injection of ropivacaine, with or without dexamethasone. Postoperative hospital stay significantly reduced in group RM, due to a notable increase in ESPB duration. Consistent with other studies (17-20), our results demonstrated that a single-injection ESPB with ropivacaine or with 10 mg dexamethasone can provide a sensory block for 7–8 h. Introducing the block in the morning or early afternoon, has led to postoperative pain during night. Opioid use may cause opioid-induced side effects, including the inhibition of restorative sleep (21) and the potential for airway obstruction and desaturation (22-24). However, a single injection of ropivacaine with dexmedetomidine can extend the sensory block to 18 h and provide a comfortable analgesia throughout the first postoperative night. Adequate and analgesic-sparing postoperative analgesia patterns are beneficial for patients to ensure their comfort, early mobilization, and reduced risks of pulmonary complications, which lead to shorter hospital stays.

Our data was similar to results of previous studies that suggested perineural dexmedetomidine may extend block duration, delayed the time for first postoperative request for PCA use, and reduced the need for postoperative rescue analgesia (25-28). A number of studies on dexmedetomidine

as an adjuvant to LAs have reported that 0.5–1 μg/kg of peripheric dexmedetomidine was associated with an improved quality and duration of analgesia with no serious side effects (27). Using dexmedetomidine 100–150 μg as an adjuvant lowered the heart rate without influencing the blood pressure (29). Here, 1 μg/kg peripheric dexmedetomidine was extremely safe and effective for ASA I–II patients who underwent VATLS. Previous studies have provided possible mechanisms associated with the action of dexmedetomidine to improve blockade efficacy. First reason may be the interaction between dexmedetomidine and local anesthetics. Dexmedetomidine can cause vasoconstriction around the site of injection, which delays the absorption of the local anesthetic and prolongs the effect of the local anesthetics (30,31). Second, perineural dexmedetomidine directly affects peripheral nerve activity and attenuates acute local anesthetics-induced perineural inflammation without causing nerve damage and blocks the hyperpolarization-activated cation current (32). Finally, dexmedetomidine itself has analgesic effects and analgesic-sparing properties, and peripheral α_{2A}-ARs were responsible for mechanisms of dexmedetomidine to treat pain in peripheral nerve block (PNB). Presynaptic α_2 adrenoceptor activation inhibits the release of a transmitter from primary afferent fibers. Postsynaptic α_2 adrenoceptors stimulation at the level of the spinal cord increases acetylcholine concentrations in the superficial dorsal horn and inhibits nociceptive neurotransmission by reducing the release of -neurotransmitters such as substance P and glutamate (33,34).

We did not observe any evidence of the claim that dexamethasone prolonged sensory of perineurally applied ropivacaine to the ESPB. Furthermore, VAS score, first time request for PCA machine use and total PCA use, postoperative stay in hospital and the need for rescue analgesia and PONV were not significantly different between group RS subjects, who received dexamethasone as an adjuvant to LAs, than group R. Dexamethasone did not prolong the sensory block time of ESPB in our study, similar to that reported by Marhofer and colleagues while investigating the effects of dexamethasone as an adjuvant for ulnar nerve block. However, these results seem to contradict other main evidences: perineural dexamethasone has been reported to prolong loco-regional analgesia than controls without dexamethasone (35-38). Despite precise results, using the Grading of Recommendations Assessment, Development, and Evaluation system (GRADE), Heesen and Klimek graded the quality of above evidences for these primary outcome as low (14). Since dexamethasone cannot prolong the sensory block time of ESPB as well as dexmedetomidine, similar to the results of our study, the duration and effect of postoperative analgesia have been limited.

It is a possibility that dexamethasone may act as an additive to local anesthetics and may be useful in chronic pain therapy (e.g., neuropathic pain) by attenuating the release of inflammatory mediators, reducing ectopic neuronal discharge, and inhibiting potassium channel-mediated discharge of nociceptive C-fibers (39-41).

Limitation

Similar to previous studies (42,43), 1 μg/kg peripheric dexmedetomidine was extremely safe and effective for ASA level I–II patients. However, dexmedetomidine is associated with hypotension and bradycardia (44) and patients with significant cardiovascular diseases or prone to hypotension need to be cautioned against. The pain level and sensory blockade assessment methods used were limited to subjective perception of pain and cold. Although a commonly subjective measure has been used (38,45), it does not provide objective data regarding pain and sensory blockade. We acknowledge that our work is a small randomized double-blind trial and is designed to be closely integrated with clinical applications. However, there are only a few studies that have investigated the mechanism associated with peripheral dexmedetomidine and dexamethasone in ESPB. Therefore, there is a need to investigate preclinical toxicity and clinical application to elaborate on the mechanism and the safe optimal doses of dexmedetomidine used as an adjuvant to provide a maximum benefit while minimizing side effects in peripheral nerve block (PNB).

Conclusions

Dexmedetomidine, which was used as an adjuvant of ESPB with ropivacaine, prolonged sensory block duration, provided effective acute pain control after surgery, and reduced the need for rescue analgesia. It also shortened postoperative hospital stay for patients undergoing VATLS. However, dexamethasone had no clinically relevant effect on the duration of sensory block and postoperative pain control by ropivacaine at ESPB.

Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by the Ethics Committee of First Affiliated Hospital of Anhui Medical University (kuai 2019-02-12), all patients provided written informed consent.

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