

Comparison of dexmedetomidine or sufentanil combined with ropivacaine for epidural analgesia after thoracotomy: a randomized controlled study

This article was published in the following Dove Press journal:
Journal of Pain Research

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Background: Thoracotomy is frequently accompanied with moderate-to-severe postoperative pain, and excellent pain management is important for early rehabilitation. The purpose of this study is to investigate the effects of dexmedetomidine combined with ropivacaine for epidural analgesia after thoracotomy.

Methods: One hundred and thirty patients undergoing elective lung lobectomy were enrolled in the double-blind study and randomly divided into two groups. Group A received 0.5 µg/mL of dexmedetomidine plus 0.1% ropivacaine for postoperative analgesia, and group B (control group) received 0.5 µg/mL of sufentanil plus 0.1% ropivacaine for postoperative analgesia. Hemodynamic parameters were monitored. Pain intensity at rest was assessed using a visual analog scale (VAS) at 2, 4, 6, 8, 12, 24, and 48 hrs postoperatively. Ramsay sedation score (RSS), analgesic consumption, postoperative respiratory depression, nausea and vomiting, pruritus, and bradycardia were recorded.

Results: The VAS values at rest during the postoperative 6–48 hrs were lower in group A than those in group B ($P<0.05$), and the RSS values were higher in group A during the postoperative 4–48 hrs compared to group B ($P<0.05$). Side effects were similar between the groups ($P>0.05$).

Conclusion: Dexmedetomidine combined with ropivacaine may provide better postoperative analgesia and sedative effect in patients undergoing thoracic surgery with fewer side effects. It is superior to sufentanil in analgesic effect during postoperative analgesia after thoracotomy.

Keywords: dexmedetomidine, sufentanil, ropivacaine, epidural, analgesia

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Introduction

Thoracotomy is frequently accompanied with moderate-to-severe postoperative pain, and excellent postoperative analgesia is important for early rehabilitation.¹ Epidural analgesia is a common technique for pain relief in patients undergoing thoracotomy. The local anesthetic combined with opioids may decrease obviously its concentration and reduce the incidence of hypotension and motor block.² However, Lorenzini et al³ found that adding an opioid to local anesthetic could offer good analgesia, but increased the incidence of pruritis, nausea, and vomiting, even it was reported that thoracic epidural analgesia was insufficient in up to 24% of the patients.⁴ Hence, superior postoperative analgesia is necessary for patients undergoing open thoracotomy. Dexmedetomidine, an α_2 -adrenoceptor agonists, possesses anxiolytic, sedative, sympatholytic, and analgesic properties without

causing respiratory depression.^{5,6} Documents reported that dexmedetomidine was safely used for epidural analgesia with good analgesic effect and stable hemodynamics.^{7–11} However, the studies of dexmedetomidine for epidural analgesia are fewer in patients undergoing thoracotomy. We hypothesized that dexmedetomidine was superior to sufentanil in terms of analgesic effects and side effects in patients undergoing thoracotomy during postoperative period. This study was designed to assess the effects of dexmedetomidine in combination with ropivacaine for epidural postoperative analgesia in patients undergoing thoracotomy.

Methods

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee (Chairman Prof Yin) of Zhejiang hospital on 5 May 2, 2016. The written informed consent forms were obtained from all patients. The trial was registered at www.chictr.org.cn (Registration number: ChiCTR-ONC16008376, date of registration: May 3, 2016). From May 2016 to December 2017, we chose 130 patients undergoing elective open lung lobectomy with ASA grade II, age ranged from 35 to 60 years, weight 55–80 kg, and maximal ventilation volume (MMV) >70 L/min to include in this prospective, double-blind study. Exclusive criteria were as follows: patients with cardiovascular disease, liver and kidney dysfunction, allergy to dexmedetomidine, and contraindications to epidural anesthesia. One hundred and twenty-eight patients were randomly assigned to the control group (group B, n=64) and group A (n=64) using computer-generated random number code.

All patients were pre-medicated with midazolam 5 mg given orally 1 hr before surgery. After entering operating room, routine monitoring included an electrocardiogram, invasive arterial blood pressure (BP), heart rate (HR), pulse oxygen saturation (SpO₂) using anesthesia monitor, and venous access was established. The bispectral index (BIS) was monitored continuously using a BIS monitor (Model A2000, Aspect Medical Systems Inc., Natick, MA, USA). With the patients in the left lateral position, the epidural space was identified at the level of T_{5–6} with an 18-gauge Tuohy needle using the method of decreasing resistance to air. An epidural catheter was inserted 3–4 cm cephaladly into epidural space, and then patients were turned supine. A test dose of 3 mL of 1.5% lidocaine was administered to exclude the epidural catheter in the blood vessel or subarachnoid space. Subsequently, 10 mL of 0.25% ropivacaine was given as loading dose and a bolus

of 5 mL of 0.25% ropivacaine was administered every 60 mins. The height level of sensory block was measured with pinprick at 2-min intervals within 30 mins after administration. After pre-oxygenation, general anesthesia was induced using intravenous propofol 2 mg/kg, fentanyl 4 ug/kg, and rocuronium 0.6 mg/kg to facilitate endobronchial intubation with direct laryngoscope. Propofol at a rate of 6–8 mg/kg/hr and remifentanyl at a rate of 0.2–0.5 ug/kg/min were infused continuously to keep the BIS value between 40 and 55. Rocuronium was administered intermittently to maintain stable neuromuscular block during surgery.

Patient's trachea was intubated with a double-lumen endobronchial tube (37 F for women and 39 F for men). After intubation, we identified the correct position of the endobronchial tube with a fiber-optic bronchoscope (Olympus Corporation, Tokyo, Japan). The lungs were initially ventilated with volume-controlled ventilation mode, and the respiratory variables were set as follows: inspiratory tidal volume of 8 mL/kg, inspiratory to expiratory ratio of 1:2, respiratory frequency of 12–14 breaths/min, oxygen flow rate of 1 L/min, inspiratory oxygen fraction of 1.0, and position end-expiratory pressure=zero. One-lung ventilation was started at skin incision, and double-lung ventilation was alternately applied if SpO₂ was below 91% lasting for 30 s during one-lung ventilation. The lungs were manually inflated at the end of surgery. The surgery was performed by the same surgeons, and the skin incision length was about 20 cm. After muscles were separated, the intercostal space was opened with rib spreader, and retention period of the chest drain was 7 days after surgery. Ringer's solution was infused at a rate of 6–8 mL/hr during the operative period. All patients were transferred to the post-anesthesia care unit (PACU) at the end of the operation and were discharged from PACU when the modified Aldrete score¹² ≥9. Patients were attached to an electronic infusion pump (ShangHai Bochuang Corporation, China) for patient-controlled epidural analgesia (PCEA) at the end of surgery. Patients were followed up for the postoperative analgesia-associated complications. The investigators were blind to the patient allocation and components of analgesics.

PCEA regimen consisted of 0.5 µg/mL of dexmedetomidine +0.1% ropivacaine in group A and 0.5 µg/mL of sufentanil +0.1% ropivacaine in group B (total volume of 250 mL). The electronic infusion pump was programmed to deliver at a rate of 4 mL/hr with a lock-out at 20-min intervals and a bolus infusion of 4 mL. All patients received 4 mL loading dose immediately after the

electronic infusion pumps were attached. A rescue bolus of the analgesics was administered when visual analog scale (VAS) ≥ 5 (0=no pain, 10=maximum imaginable pain) within the postoperative 48 hr.

Postoperative BP, HR, and SpO₂ were monitored at 5-min intervals. Pain intensity was evaluated with VAS at 2, 4, 6, 8, 12, 24, and 48 hrs postoperatively, and the level of analgesic satisfaction was defined as follows: bad, VAS >7, moderate VAS=4–7, and good VAS ≤ 3 . The adverse effects were also recorded, if any, such as hypotension, nausea and vomiting, shivering, excessive sedation, respiratory depression, and bradycardia. Respiratory depression was defined as SpO₂<90% and respiratory rate <10 breaths/min. Hypotension was defined as the systolic blood pressure <80% of the baseline values (at time of leaving PACU) and bradycardia was defined as heart rate <80% of the baseline or 60 beats/min, respectively.

The sedative level was assessed with Ramsay sedation score (RSS)¹³ (1, patient anxious, agitated, or restless. 2, patient cooperative, oriented, and tranquil alert. 3, patient responds to commands. 4, asleep, but with brisk response to light glabellar tap or loud auditory stimulus. 5, asleep, sluggish response to light glabellar tap or loud auditory stimulus. 6, asleep, no response). The RSS values were recorded at 2, 4, 6, 8, 12, 24, and 48 hrs postoperatively. Excessive sedation was defined as RSS value >4.

Statistical analysis

The primary outcome was postoperative VAS value at rest in this study. The sample size was calculated according to our preliminary study and previous study,¹⁴ 62 patients in each group would have an 80% power to detect a difference of 0.6 in VAS value between the 2 groups using two-sided analysis with an error of 0.05. Sample size was increased to 65 to allow for dropouts.

Statistical analysis was applied with the SPSS 17.0 software (SPSS Inc., Chicago, USA). Quantitative variables were presented as mean \pm standard deviation (SD). Categorical data were presented as numbers or percents. Normally distributed data were analyzed by one-way ANOVA, and non-normally distributed data were analyzed by Mann–Whitney U test, categorical data were compared with χ^2 test. A $P < 0.05$ was considered as significant difference.

Results

A total of 130 patients were recruited in this study and two patients were excluded for hesitation in participating in this trial. One hundred twenty and eight patients finished

the study (Figure 1). There were no significant differences in age, weight, gender, maximal ventilation volume (MMV), the type of carcinoma, the height level of sensory block, blood loss, the duration of anesthesia and duration of operation between the groups ($P > 0.05$) (Table 1). There were significant differences in PCA bolus and the level of analgesic satisfaction between the groups (Table 1).

VAS values at rest were significantly lower in group A than in group B at 6, 8, 12, 24, and 48 hrs postoperatively (3.4 ± 0.62 vs 3.7 ± 0.51 , 3.6 ± 0.56 vs 4.2 ± 0.70 , 4.5 ± 0.95 vs 5.4 ± 1.30 , 4.2 ± 1.05 vs 5.3 ± 1.20 , 4.4 ± 0.9 vs 5.2 ± 1.10 , respectively, $P < 0.05$), but the VAS values at rest were similar between the groups during the postoperative 2–4 hrs (Figure 2). There were significant differences in VAS values between the groups during the postoperative 6–48 hrs, but no significant differences in VAS values within postoperative 2–4 hrs were observed. Besides, there were significant differences in RSS values during the postoperative 4–48 hrs ($P < 0.05$), but the RSS values were similar between the groups within postoperative 2 hrs (Figure 3).

The incidence of hypotension, bradycardia, shivering, nausea and vomiting, itching, and respiratory depression was similar between the groups (Table 2). There were no significant differences in adverse effects between the groups. Besides, no excessive sedation was observed in both groups.

Discussion

Superior analgesia may improve postoperative pulmonary function and reduce postoperative complications in patients undergoing thoracotomy. In this study, we found that adding dexmedetomidine to ropivacaine for epidural postoperative analgesia was safe and effective in patients undergoing thoracic surgery without excessive sedation and respiratory depression. It was superior to sufentanil in analgesic effect in patients undergoing thoracic surgery during postoperative period.

Our study showed that VAS values at rest were significantly lower in group A than those in group B during the postoperative 6–48 hrs, and the analgesic effects were better in group A compared to the group B. The reason was likely that dexmedetomidine activated α_2 -adrenoceptor in spinal cord and inhibited sympathetic nerve activity. Our findings were in accord with the results of Zhang et al.¹⁵

The VAS values were similar between the two groups within the postoperative 2–4 hrs, and the postoperative VAS values were all below 4 in both groups during postoperative 2–4 hrs. It was likely related with the residual

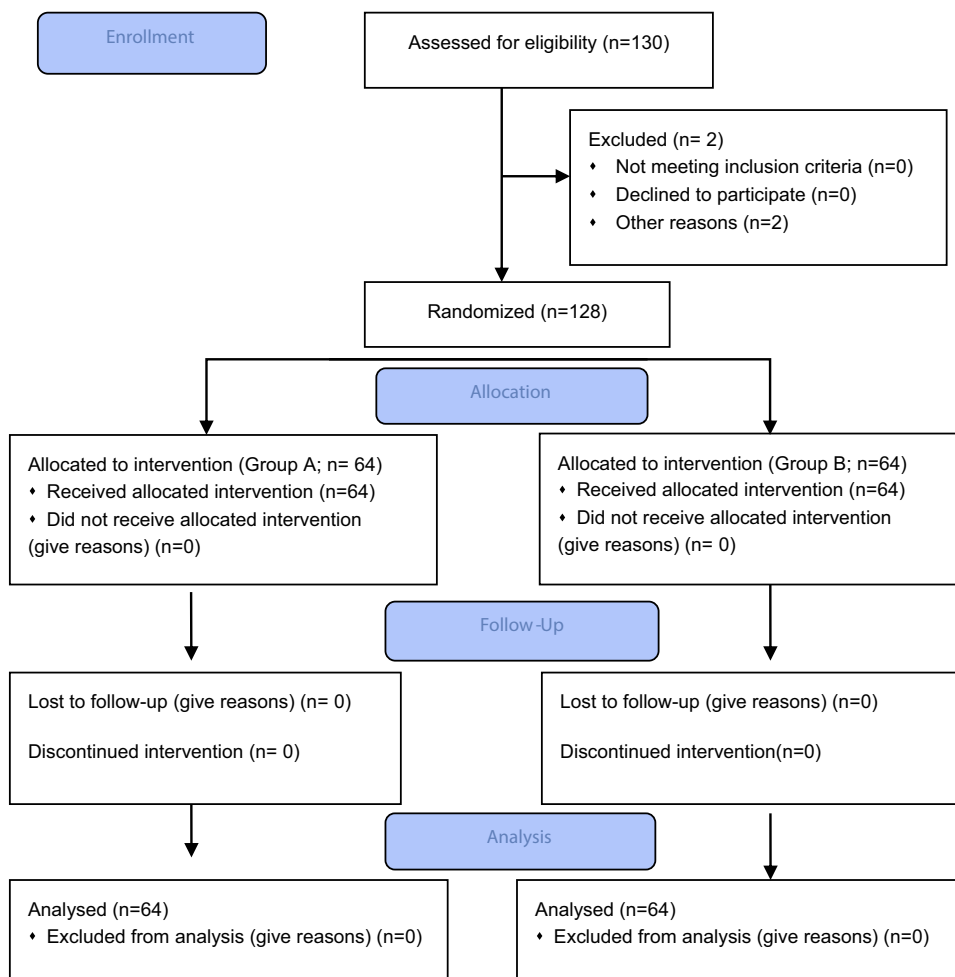


Figure 1 Flow diagram of study.

Table 1 Data of patients (n=64)

Index	Group A	Group B	P
Gender (male/female)	41/23	38/26	0.585
Weight (kg)	69.5±5.6	67.8±7.3	0.144
Height (cm)	171.5±3.8	170.4±4.1	0.120
MMV (L/min)	79.4±4.2	78.6±3.7	0.257
Type of carcinoma (central/peripheral)	45/19	41/23	0.451
Duration of anesthesia (min)	128.7±27.5	135.2±26.4	0.184
Duration of surgery (min)	117.9±22.5	123.1±24.3	0.213
Blood loss (mL)	290.5±36.7	283.2±31.4	0.231
PCA bolus	2 [1–6]	8 [3–12]	0.004
Level of analgesic satisfaction (bad/moderate/good)	0/22/42	0/36/28	0.013
Consumption of analgesics (mL)	213.8±19.6	228.4±21.5	0.001
Height level of epidural block (C5/C6)	31/33	34/30	0.596

Notes: Data were presented as mean±standard deviations or numbers. Compared with the control group, P>0.05.

Abbreviation: MMV, maximal ventilation volume.

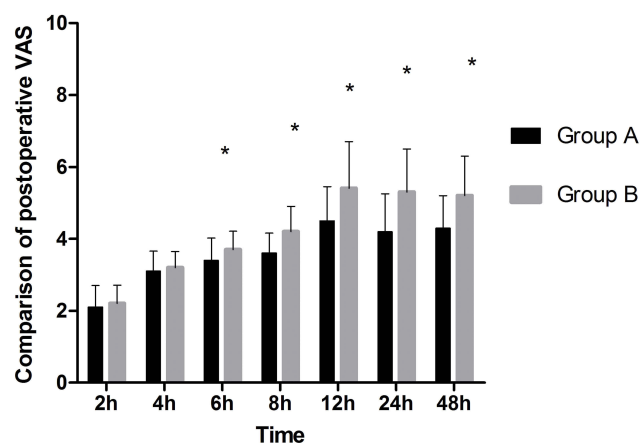


Figure 2 Comparison of VAS at rest between the groups. VAS values were significantly lower in group A than in group B at 6, 8, 12, 24, and 48 hrs postoperatively ($*P<0.05$), but the VAS values were similar between the groups during the postoperative 2–4 hrs ($P>0.05$).

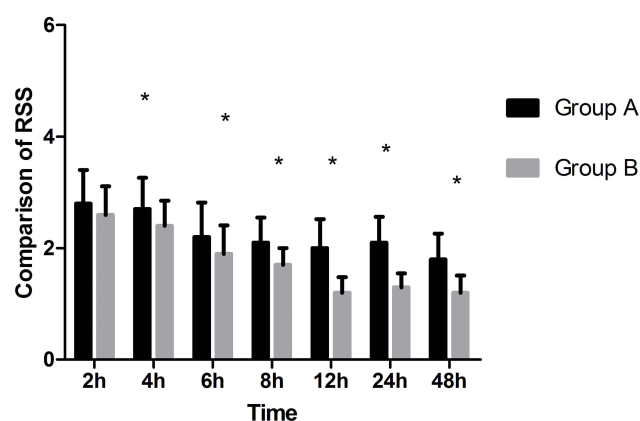


Figure 3 Comparison of RSS between the groups. The RSS values were greater in group A than group B during postoperative 4–48 hrs ($*P<0.05$), but the RSS values were similar between the two groups within postoperative 2 hrs ($P>0.05$).

Table 2 Side effects of postoperative analgesia

Index	Group A (n=64)	Group B (n=64)	P-value
Nausea and vomiting	1	3	0.61
Itching	0	2	0.48
Hypotension	1	1	0.99
Bradycardia	0	0	0.99
Respiratory depression	0	0	0.99
Shivering	0	1	0.99
Excessive sedation	0	0	0.99

Notes: Data were presented as numbers. Compared with the control group, $P>0.05$.

analgesic effects of epidural anesthesia and analgesics. Besides, the RSS values were greater in group A than group B during postoperative 4–48 hrs, but the RSS values

were similar between the two groups within postoperative 2 hrs, which was relevant to the residual sedative effect of anesthetics and analgesics administered intravenously. The greater RSS values in group A shown that dexmedetomidine could produce the excellent sedation effect by α_2 -adrenoceptors activation via the epidural route. Superior analgesia and sedation were beneficial to early rehabilitation in patients undergoing thoracic surgery.¹ Postoperative hemodynamic parameters were stable in both groups, and no hypotension and bradycardia were observed. It suggested that the incidence of hypotension and bradycardia was lower and these adverse effects might be dose-related when dexmedetomidine was administered by epidural route.

The common adverse effects of opioids for epidural analgesia were as follows: nausea, vomiting, itching, and respiratory depression.¹⁶ Our study shown that epidural dexmedetomidine had no itching and respiratory depression, it proved that dexmedetomidine did not result in itching and respiratory depression. It was consistent with the findings of Karnik et al¹⁷ and Zeng et al.¹⁸

This study is clearly not without limitations. On the one hand, the incidence of side effects related with postoperative analgesia is very low in both groups. On the other hand, the sample size is too small to compare these data between the groups. Moreover, a further large sample trial is needed to assess the adverse events of epidural dexmedetomidine with ropivacaine.

Conclusion

Dexmedetomidine combined with ropivacaine may provide better postoperative analgesia and sedative effect in patients undergoing thoracic surgery with fewer side effects. It is superior to sufentanil in term of analgesic effect in patients undergoing thoracic surgery.

Individual contribution

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Data sharing

Authors will allow sharing the data, such as pain scores, blood pressure, heart rate, and pain scores. No other study-related documents will be available. The data will be accessible 6 months after publication. The documents will be available online at a website (www.sina.com) where the documents will be placed.

Acknowledgment

We thank Chen Sheng, Gu Shui, and Li Zhong for the study design. This study was supported by the Department of Education of Zhejiang Province (JG20180421) and Health and Planning Commission of Zhejiang (2018KY167, 2018ZB128).

Disclosure

The authors report no conflicts of interest in this work.

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