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CLINICAL TRIAL REPORT

Efficacy of Dexmedetomidine as an Adjuvant to Ropivacaine for Intercostal Nerve Block in Elderly Patients Undergoing Video-Assisted Thoracoscopic Esophagectomy: A randomized Double-Blinded Trial

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Background: Esophagectomy is associated with significant postoperative pain and a pronounced perioperative stress response. Dexmedetomidine (DEX) has been widely recognized as an effective adjuvant to regional anesthesia across various surgical procedures. However, its efficacy and safety as an adjuvant to ropivacaine in elderly patients undergoing thoracoscopic esophagectomy remain unclear. This study aimed to evaluate the effectiveness and safety of DEX.

Methods: A total of 89 patients with the American Society of Anesthesiologists (ASA) physical status I–III were randomly assigned to two groups. The DR group received an intercostal nerve block with a mixture of 20 mL of 0.25% ropivacaine and 2 μg/kg of DEX, while the RP group received 20 mL of 0.25% ropivacaine alone. Plasma levels of epinephrine (E), norepinephrine (NE), and cortisol (COR) were measured perioperatively. Postoperative analgesia was assessed using the Visual Analog Scale (VAS), the cumulative dose of rescue analgesics, and the pump pressure required for rescue analgesia. Additionally, adverse events and satisfaction scores from both patients and thoracic surgeons were recorded. The Shapiro–Wilk test was applied for uniformly distributed. The values for baseline information were presented as the mean ±standard (SD), and compared using one-way ANOVA. Enumeration data were expressed as percentages or frequencies and compared using the Chi-square test.

Results: Postoperatively, plasma levels of E, NE, and COR decreased significantly in the DR group compared to the RP group. The duration of analgesia was longer in the DR group, with fewer requirements for rescue analgesia and a significantly extended time to the first analgesic request. VAS scores were significantly lower in the DR group. No significant adverse events were observed, and patient satisfaction with analgesia was significantly higher in the DR group.

Conclusion: DEX, when used as an adjuvant to intercostal nerve block, prolongs analgesic duration, improves pain control, and attenuates the perioperative stress response in elderly patients undergoing thoracoscopic esophagectomy.

Keywords: dexmedetomidine, ropivacaine, intercostal nerve block, analgesia, esophagectomy

Introduction

Video-assisted thoracoscopic surgery (VATS) has been widely adopted for the treatment of esophageal carcinoma due to its minimally invasive nature. Compared with open thoracotomy, VATS is associated with reduced postoperative pain, a lower inflammatory response, and faster recovery.[1,2] However, early postoperative pain and perioperative stress responses remain significant challenges for anesthesiologists after VAST.[3,4] Postoperative pain can exacerbate the stress response, leading to immune and endocrine dysfunction. Excessive stress responses after VATS may induce tachycardia, hypertension, increased oxygen consumption, and delayed recovery by perpetuating inflammatory processes.[5,6] Numerous studies claim that pain and stress response free in postoperative period helps in early mobilization and

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recovery of surgical patients, thereby reducing postoperative complications.[7–9] Thus, effective analgesia is essential for preventing postoperative complications and promoting rehabilitation.

Recent clinical studies suggest that optimal postoperative pain management involves a multimodal analgesic approach, combining pharmacological agents and regional interventions.[10,11] Systemic opioid administration with patient-controlled devices has been widely utilized in VATS multimodal pain management; however, its effectiveness is often limited, and it is associated with side effects such as drowsiness, nausea, and vomiting.[12] So, multimodal analgesic strategies, particularly those incorporating peripheral nerve blocks, have shown promise in alleviating postoperative pain in VATS. Peripheral nerve blocks, a vital component of a multimodal analgesic regimen, effectively alleviate incision-related pain and reduce opioid consumption.[13] Intercostal nerve block (ICNB) is particularly suited for thoracic surgical incisions, providing localized anesthesia by injecting local anesthetics between the rib and pleura.[14] Compared with systemic opioid administration alone, ICNB offers superior analgesia, attenuates the stress response, and is associated with fewer complications.[15] Moreover, previous research found that ICNB could provide more effective analgesia and was more suitable for VATS patients compared to thoracic epidural analgesia.[16] But, effect of dexmedetomidine (DEX) as an adjuvant of ICNB was not clear.

To further enhance the efficacy of regional anesthesia, various adjuvants have been combined with local anesthetics to prolong analgesia and improve block quality. However, commonly used adjuvants such as adrenaline, opioids, and dexamethasone are associated with adverse effects including pruritus, nausea, and hallucinations.[17–19] Dexmedetomidine has been increasingly used as an adjuvant due to its sedative, analgesic, and sympatholytic properties. DEX enhances the blockade of sodium ion channels by local anesthetics, thereby shortening onset time, prolonging analgesic duration, and reinforcing sedation. Nevertheless, concerns remain regarding its potential side effects in the local nerve block.[20,21] Currently, randomized controlled trials (RCTs) are being conducted to evaluate the efficacy and safety of DEX as an adjuvant in intercostal nerve infiltration for patients undergoing VATS.

Methods

This randomized, double-blinded study was conducted during March 2023–2025. The study was performed in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Affiliated Huaian No.1 Hospital of Nanjing Medical University (No. KY-2022-050-02) and registered in the Chinese Clinical Trial Registry (ChiCTR) (No. ChiCTR2300067299). The study protocol complied with the Declaration of Helsinki.

Characteristics of Participants

After obtaining written informed consent, 89 adult patients of both sexes, American Society of Anesthesiologists (ASA) I–III, scheduled for video-assisted thoracoscopic esophagectomy (VATE), and requiring postoperative analgesia were enrolled. The age range of the enrolled patients were confirmed according to previous studies.[22–24] A preanesthetic assessment of all patients was performed the day before surgery, and all subjects were thoroughly informed of the potential risks and benefits.

Inclusion Criteria

1. Age 60–75 years; 2) good compliance with the study protocols; 3) 18 kg/m^2 < body mass index (BMI) < 28 kg/m^2) Time of operation 2–4 h under general anesthesia.

Exclusion Criteria

1) History of drug allergy; 2) abnormal coagulation function; 3) history of mental and neurological disorders; 4) liver and kidney insufficiency; 5) poor compliance; 6) acute and chronic infectious diseases; 7) ASA grade >III.

Study Design

All patients were allocated into two groups according to the allocation sequences generated by a random number table and delivered in opaque coded envelopes. The DR group subjects who received intercostal nerve block with a mixture of ropivacaine and DEX and the RP group subjects who received the same volume of ropivacaine. All patients underwent

the same general anesthesia and operation procedure. The outcomes of the study were assessed by experimenters not involved in the intervention procedure. Thoracic surgeons and observers were blinded to the patient's allocation and drug-intervention program.

Procedure of Anesthesia

The patients underwent routine preoperative preparation. After they arrived at the operating room, all patients were monitored for their non-invasive blood pressure (NIBP), electrocardiography (ECG), and blood oxygen saturation (SpO_2) . Routine mask oxygen inhalation was administered at an oxygen flow rate of 2–3 L/min. Venous access was established with a 20-G indwelling needle for fluid supplementation. After that, continuous invasive blood pressure monitoring was established after radial artery puncture before the induction of anesthesia. Each group received the same anesthetic induction technique with 0.04 mg/kg midazolam (2 mL:10 mg, TMZ24104; Jiangsu Enhua Pharmaceutical Co., Ltd., China), 2 mg/kg of 1% propofol (20 mL: 0.2 g, H20223914, Jiangsu Yingke Biopharmaceutical Co., Ltd., China), 0.3 mg/kg of cisatracurium (5 mL: 10 mg, 241025XA, Jiangsu Hengrui Pharmaceutical Co., Ltd., China), and 0.3 μg/kg of sufentanil (1 mL: 50 μg, AB40803221, Hubei Renfu Pharmaceutical Co., Ltd., China). Next, 4–10 mg/kg/h of 1% propofol, 0.25–0.5 ug/kg/min of 1 mg remifentanil (AC4090031, Hubei Renfu Pharmaceutical Co., Ltd)., and 1–3 ug/kg/min of cisatracurium were administered via a computerized infusion pump to maintain the anesthetic state.

Intercostal Nerve Block

Intercostal nerve blocking was performed using an ultrasound machine (UMT-400, Mindray, Shenzhen, China) before the operation by an experienced anesthesiologist who was blinded to the grouping. The midaxillary line of the nerve root between the third and eighth ribs was selected as the puncture point and confirmed by the high linear transducer which was placed in a transverse orientation. Under continuous ultrasound guidance, the needle was inserted to deposit the anesthetics in-plane between the innermost intercostal muscle. When the puncture needle tip reached the extrapleural region close to the subcostal region, a local anesthetic agent was injected after confirming no return of blood from the suction syringe (Figure 1). For the DR group, 0.25% of ropivacaine (10 mL, 75 mg, Zhejiang Xianju Pharmaceutical Co., Ltd., China) and 2 μg/kg of DEX (1 m:2 mg, Nanjing Zhengdatianqing Pharmaceutical Co., Ltd., China; diluted with 0.9% normal saline up to a volume of 25 mL) was injected in successive rib spaces from the lower margin of the second rib to the upper margin of the seventh rib (5 mL each rib space). Meanwhile, the patients in the RP group were administered an equivalent volume of 0.25% ropivacaine.

Postoperative Pain Management

Intramuscularly, 2 mg butorphanol injection was administered as a rescue analgesic when the VAS score was >4. Immediately upon skin closure, the patients of both groups connected to the same patient-controlled intravenous analgesia (PCIA, diluted with 0.9% saline to 100 mL) contained 8 mg butorphanol plus 50 μg sufentanil for postoperative pain relief and 2 mL per demand (lockout time, 15 min), with a continuous infusion of 2 mL/h. Both the groups were

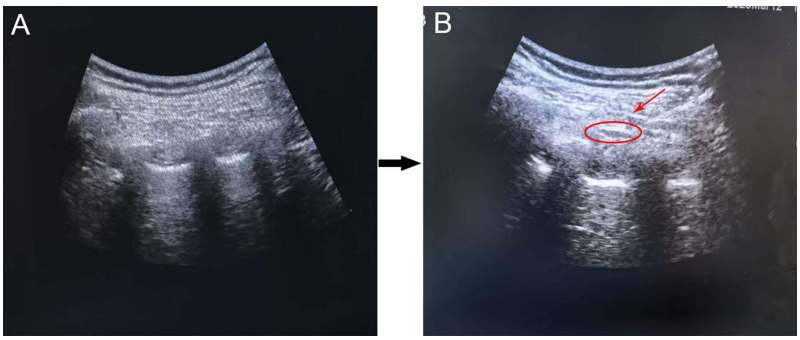

Figure 1 (**A**) Ultrasonography image of chest wall before ICNB. (**B**) Needle trajectory (red arrow) and drug spread in the intercostal space (Red circle).

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diluted with 0.9% normal saline to 100 mL, the infusion rate was adjusted to 2 mL/h, the locking time was 15 min, and one compression volume was 0.5 mL.

Outcome Measurement

Pain intensity was evaluated at 1 h (T_1), 6 h (T_2), 12 h (T_3), 24 h (T_4), and 48 h (T_5) after the completion of surgery by using a visual analog scale (VAS). A range of 0–10 was used to indicate the pain levels. A higher score represented more severe pain, ranging from 0 = no pain to 10 = worst possible pain. Rescue analgesic administration was recorded from the end of the operation to T_5.

Venous blood (5 mL) was collected before surgery (T_0), T_3, T_4, and T_5 after completion of surgery and centrifuged at 3000 rpm for 15 min to obtain serum samples in the supernatant. Cytokine concentration was assessed using ELISA kits specific for the level of epinephrine (E), norepinephrine (NE), and cortisol (COR) by ELISA kits (Abcam, Cambridge, MA, USA).

Adverse events were recorded from treated T_1 to T_5, including hypotension (systolic pressure<90 mmHg or 25% below baseline), bradycardia (<50 bpm or 25% below baseline), and hypoxemia (SpO2 <90%). Hypoxemia treatment options included oxygen supplementation or endotracheal intubation. The satisfaction survey of the patients and the thoracic surgeon to postoperative pain relief methods were recorded using questionnaires as well as with reference to the pain score: 0 = not at all satisfied; 10 = quite satisfied.

Statistical Analysis

Sample size calculated by Pass software version 15.0 (NCSS, Kaysville, UT, USA) was based on data from preliminary experiment. The study was Power of 0.90 and α=0.05. Considering a dropout rate of 20%, the estimated sample size was at least 28 patients were elected in each group, thus a total of 56 patients will be randomized. SPSS software version 19.0 (Chicago: SPSS Inc.) was used for data analysis. The Shapiro–Wilk test was applied for uniformly distributed. Non-parametric Wilcoxon Rank-sum tests or *t*-tests were used for analysis of continuous variables. The values for age, BMI, and duration of surgery were presented as the mean ±standard deviation(SD), compared using one-way ANOVA and Dunnett's post-tests when significance was achieved. Enumeration data were expressed as percentages or frequencies and compared using the Chi-square test. P value of <0.05 was considered statistically significant.

Results

Total of 89 patients were assessed for eligibility, of whom 9 were excluded: 2 due to a history of neurological disorders, 2 due to a history of narcotic drug allergy, 3 who refused postoperative follow-up, and 2 with abnormal coagulation function (Figure 2). Demographic variables between the two groups showed no significant differences (Table 1).

No significant differences in VAS scores were observed between groups at baseline (T_0), T_1 and T_5. However, from T_2 to T_4, VAS scores in the DR group were significantly lower compared with the RP group (Table 2). Notably, no patients in the DR group and three patients in the RP group reported VAS scores >4 at T_1; similarly, two patients in the DR group and eight in the RP group had VAS scores >4 at T_4 ($P < 0.05$). The time to first request for rescue analgesia was significantly longer in the DR group compared to the RP group (Table 3). The cumulative dose of butorphanol used for rescue analgesia was also significantly lower in the DR group. Patient and thoracic surgeon satisfaction scores were significantly higher in the DR group ($P < 0.05$, Table 3).

The incidence of pulmonary atelectasis was significantly lower in the DR group than in the RP group (P<0.05). No significant differences were observed between groups regarding excessive sedation or sensory abnormalities in the nerve block area (Table 4, P<0.05).

Postoperatively, levels of E, NE, and COR were elevated in both groups; however, the increase was significantly less pronounced in the DR group. From T_2 to T_4, E, NE, and COR levels were significantly lower in the DR group compared to the RP group, indicating a suppressed stress response with the addition of DEX (Table 5, P<0.05).

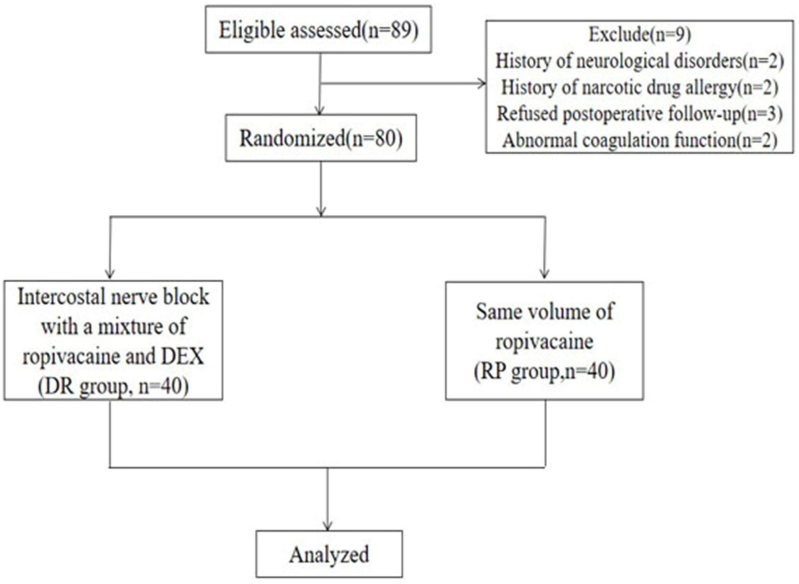

Figure 2 Details of clinical procedures of the study.

Discussion

Recently, VATE has become the preferred treatment for esophageal carcinoma, owing to advances in surgical techniques. However, despite its minimally invasive nature, VATE can still cause pleural injury, postoperative pain, and restricted breathing, leading to complications such as pulmonary infection, atelectasis due to impaired expectoration, and systemic stress responses.[25–27] Severe perioperative stress responses remain a significant concern in patients undergoing thoracoscopic esophagectomy, negatively impacting prognosis by increasing oxygen consumption and suppressing immune function.[28,29] Effective perioperative analgesia is essential for mitigating these effects and promoting recovery. In this

Table 1 Baseline Characteristics of Two Groups

Characteristics	DR Group (n=40)	RP Group (n=40)	*P* value
Gender (M/F)	24/16	21/19	0.49
Age (years)	67.87±5.22	69.02±4.73	0.31
BMI (kg/m^2)	22.59±2.40	23.64±2.52	0.06
Surgical duration (min)	174.54±21.83	170.69+24.56	0.46
Intraoperative infusion Volume (mL)	2064.65±368.28	2183.77±415.01	0.18

Note: Values are expressed as mean ± standard deviation(SD) or numbers.
Abbreviation: BMI, Body mass index.

Table 2 Comparison of VAS Scores at Different Time in Two Groups ($\bar{x} \pm s$)

Time point Value	DR Group	RP Group	*P*
T_1	2.98±0.97	3.28±1.01	0.18
T_2	3.37±1.10	4.47±1.09	<0.001
T_3	4.10±0.96	5.93±1.21	<0.001
T_4	3.43±1.06	5.58±1.43	<0.001
T_5	2.52±0.51	3.83±0.85	0.06

Note: Values are expressed as mean ± standard deviation(SD).
Abbreviation: VAS, Visual Analogue Scale.

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Table 3 Comparison of Efficacy Parameters Between the Two Groups

Parameter	DP Group (n=40)	RP Group (n=40)	*P*value
Time to first rescue analgesic (h)	25.64±4.50	16.31±3.83	<0.001
VAS scores >4	2(5)	11(27.5)	0.006
Dose of butorphanol (mg)	7.93±2.83	12.40±3.57	<0.001
Rescue analgesic patient (%)	5(2)	14(6)	
Patients' satisfaction	8.97±0.95	8.52±0.93	0.04
Surgeon' satisfaction	9.0 ±1.01	8.15±1.17	0.001

Note: Values are expressed as mean ± standard deviation(SD) or numbers.
Abbreviation: VAS, Visual Analogue Scale.

Table 4 Frequency of Adverse Events in Two Groups[n(%)]

Characteristics	DP Group (n=40)	RP Group (n=40)	*P*value
Hypoxemia	4(10)	6(15)	0.49
Pulmonary atelectasis	4(10)	11(27.5)	0.04
Excessive sedation	2(5)	1(2.5)	0.56
Sensory abnormality	1(2.5)	1(2.5)	–
Hypotension	0(0)	1(2.5)	0.43
Bradycardia	0	0	–

Note: Values are numbers (percentage).

Table 5 Comparison of Stress Response at Different Time in Two Groups ($\bar{x} \pm s$)

Time point	DR group	RP group value	*P*
E(μg/L)			
T_0	0.45±0.09	0.41±0.15	0.29
T_1	2.32±0.81	2.70±1.02	0.71
T_2	5.05±1.29	5.69±1.21	0.02
T_3	6.28±1.12	7.18±1.92	0.01
T_4	6.03±1.61	6.89±1.73	0.03
T_5	2.69±0.76	2.98±0.77	0.10
NE(ng/L)			
T_0	31.56±5.56	33.62±6.49	0.13
T_1	79.93±11.25	87.33±16.59	0.02
T_2	104.26±13.86	111.67±18.82	0.04
T_3	128.0±22.11	141.73±28.57	0.02
T_4	124.99±15.87	151.60±21.9	<0.001
T_5	89.47±11.42	107.99±10.14	<0.001
COR(μg/L)			
T_0	50.50±6.82	47.62±8.30	0.09
T_1	84.19±12.33	89.19±15.01	0.11
T_2	103.46±14.95	116.26±12.21	<0.001
T_3	128.1±20.91	138.35±20.94	0.04
T_4	148.86±24.89	160.19±22.99	0.38
T_5	119.53 ±16.18	130.96±15.96	0.002

Note: Values are expressed as mean ± standard deviation(SD).
Abbreviations: E, epinephrine; NE, norepinephrine; and COR, cortisol.

study, we observed that levels of E, NE, and COR increased after surgery in both groups, indicating that surgical trauma triggers a systemic stress response that is not fully suppressed by general or local anesthesia alone.

The intercostal nerves are located between the costal pleura and intercostal muscles. ICNB aims to inhibit nociceptive transmission by injecting local anesthetics into the intercostal space, thereby alleviating stress responses and postoperative pain. However, single-agent ICNB often provides only limited and short-term analgesia, and simply increasing the concentration or dose of local anesthetics carries a high risk of toxicity.[30] Therefore, strategies to prolong anesthetic action without increasing drug concentration are necessary. One such approach is the addition of adjuvants to local anesthetics. Ropivacaine is a widely used and relatively safe local anesthetic for nerve blocks. DEX, a selective α2-adrenoreceptor agonist, exhibits sympatholytic, anxiolytic, and analgesic properties. Previous studies have demonstrated that DEX when used as an adjuvant to local anesthetics, can shorten onset time, extend the duration of analgesia, and enhance block quality.[31] In the present study, preoperative ICNB in both groups partially attenuated the postoperative elevations of E, NE, and COR, suggesting a reduction in the intraoperative stress response. Notably, patients in the DR group (receiving DEX combined with ropivacaine) showed significantly lower levels of E, NE, and COR from T_2 to T_4 compared with those in the RP group (receiving ropivacaine alone). These findings indicate that the addition of DEX to ropivacaine improves the quality and duration of ICNB, enhances stress response control, and reduces the requirement for additional local anesthetic administration.

With the advancement and widespread adoption of minimally invasive techniques in thoracic surgery, postoperative pain has been reduced compared to traditional thoracotomy. However, pain following thoracic surgery remains a common and unavoidable issue. Numerous studies have shown that a significant proportion of patients experience persistent pain after VATS, which may even progress to chronic pain.[32] Postoperative pain after VATE is often exacerbated by factors such as thoracic strap compression, intrathoracic drain traction, and respiratory movements, leading to spontaneous breathing resistance, protective breathing patterns, and reduced tidal volume.[33,34] These factors increase the risk of postoperative hypoxemia, pulmonary atelectasis, pulmonary infection, and, in severe cases, acute respiratory failure, which is a leading cause of mortality after thoracoscopic esophagectomy.[35] In this study, the incidence of pulmonary atelectasis was significantly higher in the RP group compared to the DR group, indicating that ropivacaine alone was insufficient to effectively block postoperative pain induced by multiple factors. Therefore, active and effective management of postoperative pain is essential.

DEX has been shown to prolong the duration of peripheral nerve blocks by inhibiting hyperpolarized cation currents, thereby delaying the restoration of the resting potential and preventing the conduction of new action potentials. This effect is thought to be more pronounced in C fibers (pain fibers) than A fibers (motor fibers).[36] Previous studies have demonstrated that DEX when used as an adjuvant to local anesthetics in various regional blocks (such as subarachnoid, paravertebral, or brachial plexus blocks), facilitates prolonged sensory block duration, extended postoperative analgesia, and shortened onset time.[37] VAS scores, a standard method for assessing pain intensity, were used at multiple time points in this study. The results demonstrated that the addition of DEX to ropivacaine in intercostal nerve blocks significantly prolonged the time to first rescue analgesia, reduced butorphanol consumption, and increased satisfaction among patients and thoracic surgeons. In this study, there was no significant difference of VAS scores at T_1 in two groups, which may be due to the residual effect of ropivacaine; however, VAS scores were significantly lower in the DR group at 6, 12, and 24 hours postoperatively which can be attributed to the fact that DEX prolonged the duration of analgesic action. Furthermore, significantly fewer patients in the DR group reported VAS scores greater at T_4 compared to the RP group. These findings suggest that DEX effectively intensify the analgesic action of ropivacaine for more than 12 h. likely through a peripheral mechanism. Adverse reactions, including excessive sedation and sensory abnormalities in the nerve block area, were mild in both groups. Drowsiness occurred in three patients in the RP group and four patients in the DR group, all of whom recovered spontaneously without intervention.

There were several limitations to this study. The small sample size may limit the generalizability of the findings; thus, future studies with larger sample sizes are needed to substantiate these results. Additionally, plasma concentrations of DEX and ropivacaine were not measured after administration, making it impossible to quantify the proportion and pharmacokinetics of DEX. Future research should explore the pharmacokinetic interactions between DEX and local anesthetics to further elucidate their combined mechanisms of action.

In conclusion, the addition of DEX to ropivacaine for intercostal nerve block significantly prolonged the duration of local anesthetic action, reduced VAS pain scores and perioperative stress responses, and improved patient and thoracic surgeon satisfaction with fewer adverse reactions compared to ropivacaine alone in patients undergoing VATE.

Data Sharing Statement

All data generated or analysed during this study are included in this published article.

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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.

Disclosure

The authors declare that they have no competing interests.

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