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CLINICAL TRIAL REPORT

Comparison of Remimazolam and Dexmedetomidine on Postoperative Delirium and Emergence Agitation in Elderly Patients Undergoing Thoracoscopic Surgery: A Randomized, Double-Blind, Non-Inferiority Trial

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Background and Aim: Postoperative delirium (POD) and emergence agitation (EA) are common complications in older patients undergoing video-assisted thoracoscopic surgery (VATS), significantly impacting recovery. This study was designed to examine whether remimazolam is noninferior to dexmedetomidine for preventing POD and EA in elderly patients following VATS.

Patients and Methods: A total of 176 elderly patients scheduled for VATS due to lung cancer were randomly assigned to receive either dexmedetomidine (Group D, n = 88) or remimazolam (Group R, n = 88). Group D received dexmedetomidine at 0.5 μg/kg/h starting 3 minutes before anesthesia induction until surgery completion. Group R received remimazolam at 0.5 mg/kg/h over the same period. The primary outcomes were the incidence of EA and POD within 5 days after surgery. Secondary outcomes included Quality of Recovery-15 (QoR-15) score, Athens Insomnia Scale (AIS), and numeric rating scale (NRS) for pain. Correlations among hypotension, EA, and POD were also analyzed.

Results: The incidence of POD and EA in Group R was non-inferior to that in Group D (non-inferiority $P < 0.01$), with overall rates of 20.73% vs 18.75% and 10.98% vs 8.75%, respectively. No significant differences were observed in QoR-15 or NRS scores between groups, though Group D had lower AIS scores on postoperative day 1. Group R demonstrated more stable intraoperative hemodynamics with reduced requirements for opioids and vasopressors, and shorter extubation times. Hypotension and EA were significantly correlated with POD.

Conclusion: Remimazolam was non-inferior to dexmedetomidine in preventing POD and EA in elderly patients undergoing VATS while providing improved hemodynamic stability and reducing the need for intraoperative opioids and vasopressors.

Keywords: remimazolam, postoperative delirium, emergence agitation, thoracoscopic surgery

Introduction

Lung cancer is on the rise globally and is the most common cause of cancer-related deaths.[1] Video-assisted thoracoscopic surgery (VATS) is widely used in pulmonary surgeries due to its advantages such as minimal trauma and rapid postoperative recovery. It has now become the definitive standard for diagnostic and therapeutic practices in thoracic surgery.[2] Postoperative delirium (POD), an acute confusional state characterized by impaired attention and cognition, is a common complication in elderly surgical patients.[3] POD incidence in elderly surgical patients ranges from 10% to 60%.[4] Emergence agitation (EA) is an acute, self-limiting, non-fluctuating state of psychomotor excitement confined to the emergence period following general anesthesia.[5] EA is a strong predisposing factor for POD, associated with increased postoperative pulmonary complications, prolonged hospital stay and mortality.[6]

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Dexmedetomidine, an α2-adrenergic receptor agonist, possesses sedative, analgesic, anti-stress, and hemodynamic-stabilizing properties.[7] It acts on presynaptic α2-adrenergic receptors, exerting sympatholytic effects by regulating adrenaline release through a negative feedback mechanism, thereby reducing anxiety and agitation.[8] Studies have indicated that dexmedetomidine can reduce the incidence of POD and EA in geriatric patients under general anesthesia,[9,10] making it a classic and effective drug for the prevention or treatment of POD and EA in clinical practice. However, dexmedetomidine has certain drawbacks, including transient hypertension, bradycardia, and hypotension.[11] The administration of dexmedetomidine to patients with limited compensatory reserves, such as those with preexisting severe left ventricular failure, is associated with a higher incidence of severe bradycardia and hypotension.[12]

Remimazolam is a new ultra-short acting benzodiazepine, featuring rapid onset, rapid metabolism, no accumulation and hemodynamic stability.[13,14] In recent years, it has demonstrated promising application prospects in anesthesia for elderly patients. It has exhibited safe and effective sedation in endoscopic surgeries.[15,16] Moreover, remimazolam has been shown to reduce oxidative stress and inflammation in experimental models.[17] Recent studies demonstrate that remimazolam is non-inferior to propofol for general anesthesia efficacy,[18,19] and comparable to dexmedetomidine in improving early postoperative cognitive dysfunction (POCD).[20]

If the benefits of dexmedetomidine in preventing POD and EA can be attained by another anesthetic agent without the reported adverse effects, it could expand the options for anesthetic approaches. In this investigation, we sought to compare the impact of remimazolam and dexmedetomidine on the incidence of POD and EA in elderly patients undergoing VATS.

Materials and Methods

Study Design and Ethics

Conducted as a prospective, randomized, double-blind study, this trial received ethics approval (XYFY2024-KL506-01) from Xuzhou Medical University Affiliated Hospital and was registered (ChiCTR2500101977). All participants or legal representatives provided informed consent in accordance with the Declaration of Helsinki.

Patients

Between May and July 2025, 210 patients were assessed for eligibility. After exclusions, 176 patients were enrolled and randomly assigned to groups (88 to Group R and 88 to Group D) (Figure 1).

Inclusion criteria: (1) Patients undergoing elective unilateral VATS for primary lung cancer (No restrictions were placed on the number of ports or the extent of pulmonary resection); (2) Age ≥ 65 years; (3) ASA classification I–III. Exclusion criteria: (1) BMI < 18 kg/m² or >30 kg/m²; (2) Patients with language comprehension disorders, mental illnesses, inability to cooperate, or preoperative cognitive impairment (Mini-Mental State Examination (MMSE): illiterate ≤17; primary school ≤20; secondary school ≤22; university ≤23); (3) Ejection fraction < 40%, heart rate (HR) < 50 beats/min, or arrhythmias other than first-degree atrioventricular block; (4) Epilepsy and related mental disorders, chronic stress, or psychological disorders; (5) History of alcohol abuse, analgesic drug dependence, or long-term sedative use; (6) Allergy to study drugs or declined informed consent.

Randomization and Blinding

Randomization was conducted using computer-generated block randomization sequences (block lengths of 4 or 6). Patients were randomized to the dexmedetomidine group (Group D) or remimazolam group (Group R) at a 1:1 ratio via an independent online randomization system. Researchers obtained allocation information through the system after enrolling subjects, with no advance knowledge of the next assignment of subject. Surgeons, patients, anesthesiologists, and follow-up investigators were blinded to group allocation. A study-independent nurse prepared the study drugs in 50 mL syringes, which were indistinguishable between groups. Syringes were filled with dexmedetomidine (1 μg/mL) or remimazolam (1 mg/mL), and administered by anesthesiologists at an infusion rate of 0.5 mL/kg/h (corresponding to 0.5 μg/kg/h for Group D and 0.5 mg/kg/h for Group R).

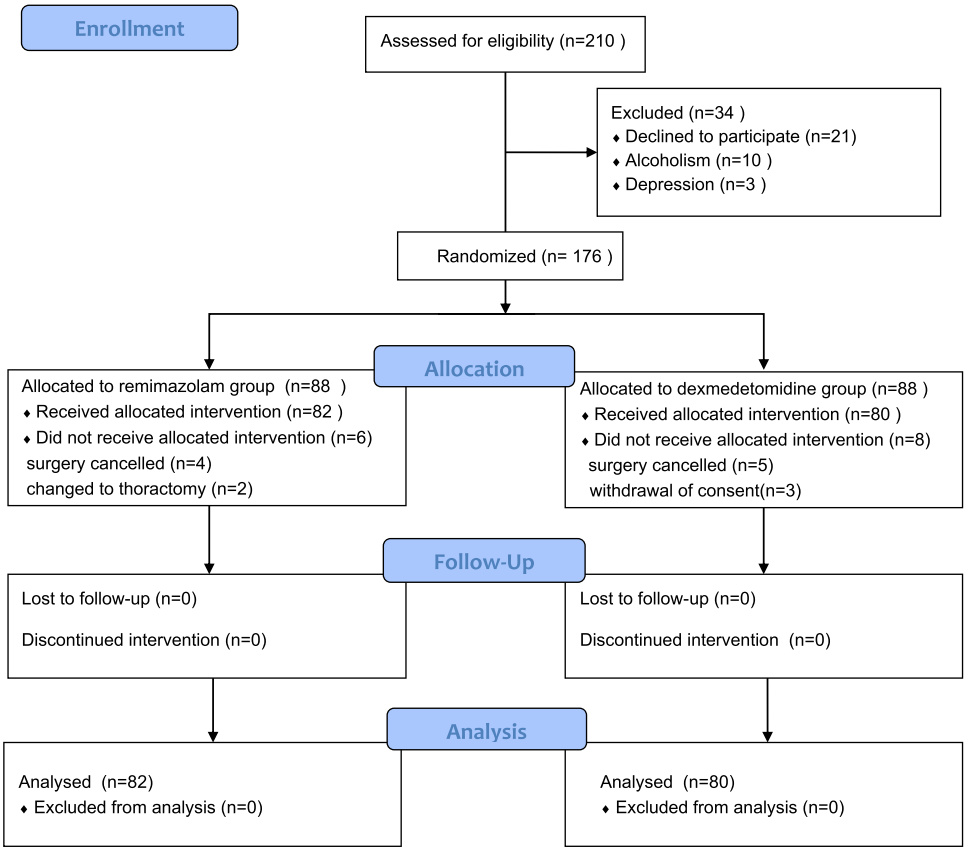

Figure 1 CONSORT diagram describing each stage of the randomized trial.

Study Procedures

On the day before surgery, non-invasive blood pressure and HR were recorded in the ward. Additionally, MMSE was administered to assess cognitive function, and the Hospital Anxiety and Depression Scale-Anxiety subscale (HADS-A) was used to evaluate anxiety status.

Upon entering the operating room, all patients immediately had an intravenous access established and received routine monitoring of electrocardiogram and peripheral capillary oxygen saturation (SpO_2), as well as an indwelling urinary catheter as per institutional protocol for thoracic surgery. Radial artery cannulation was carried out under local anesthesia for the monitoring of invasive blood pressure and end-tidal carbon dioxide, while bispectral index (BIS) was used to assess anesthetic depth. Anesthesia induction was conducted with sufentanil 0.5 μg/kg, etomidate 0.3 mg/kg, and rocuronium 0.6 mg/kg. A double-lumen endobronchial tube was inserted after BIS dropped below 60 and adequate muscle relaxation was confirmed, with its position verified by fiberoptic bronchoscopy. Mechanical ventilation was initiated in volume-controlled mode with a tidal volume of 6–8 mL/kg, modified to 4–6 mL/kg during one-lung ventilation (OLV), maintaining airway pressure <30 cmH_2O and $PaCO_2$ at 35–45 mmHg.

In Group D, dexmedetomidine was administered 3 minutes before anesthesia induction and maintained at a constant dosage (0.5μg/kg/h) until the conclusion of surgery. In Group R, remimazolam was given following the same timing (3 minutes pre-induction) and duration (until surgery end) at a fixed dose of 0.5 mg/kg/h. All patients received surgical-side thoracic paravertebral block (TPVB) 30 minutes before anesthesia induction: under ultrasound guidance, 20 mL of 0.375% ropivacaine hydrochloride solution was injected slowly after confirming the paravertebral space. Anesthesia was maintained with remifentanil (0.1–0.3 μg/kg/min) and sevoflurane. Remifentanil dose was titrated by surgical stimulation and vital signs (with±0.05 μg/kg/min adjustment triggered by HR/MAP deviations persisting >1 minute), while sevoflurane doses and intraoperative fluids were adjusted based on the same two factors. Rocuronium 0.3 mg/kg was administered intermittently to keep BIS at 40–60. Hypotension (mean arterial pressure (MAP) <80% of baseline for

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>1 minute) was managed by reducing anesthetic depth or administering phenylephrine 0.5–1 μg/kg until MAP ≥80% of baseline. At surgery completion, tropisetron 2 mg was given for antiemesis, remifentanil and study drugs were discontinued. Intravenous administration of flurbiprofen axetil 50 mg was performed for preemptive analgesia prior to transfer to the post-anesthesia care unit (PACU). Residual muscle relaxation was reversed with sugammadex 2 mg/kg, and the tracheal tube was removed after meeting extubation criteria.

Outcome Measures

EA was assessed using the Riker Sedation-Agitation Scale (SAS) in the PACU. The Riker SAS was applied 1 minute post-extubation and repeated every 15 minutes throughout the PACU stay. A score exceeding 4 at any time point was classified as EA. POD was assessed using the Confusion Assessment Method (CAM) from postoperative day 1 to day 5; CAM evaluations were conducted twice daily (morning and evening) until postoperative day 5. Additionally, the association between the incidence of POD and EA/hypotension-associated factors was investigated.

Postoperative day 3 assessments included the total score of the Quality of Recovery-15 (QoR-15) (scoring range 0–150 points, where higher scores signify better postoperative recovery quality), the Athens Insomnia Scale (AIS) (a total score <4 indicating no sleep disorder, 4–6 suggesting possible insomnia, >6 denoting insomnia), and the Numeric Rating Scale (NRS) for evaluating postoperative pain intensity (where 0 represents no pain and 10 represents the most severe pain imaginable). When the postoperative NRS pain score was ≥4, patients were administered 50 mg of tramadol hydrochloride. Additionally, postoperative nausea and vomiting (PONV), extubation time, and delayed emergence (defined as failure to regain consciousness 90 minutes after the end of general anesthesia, excluding cerebrovascular accidents) were recorded. Intraoperative adverse events comprised hypoxemia (SpO_2 <90%), hypertension, hypotension, bradycardia, and tachycardia. The intraoperative consumption of sufentanil and remifentanil, fluid balance, and the durations of anesthesia, surgery, and OLV were also documented. Hemodynamic parameters such as MAP, HR, and SpO_2 were recorded at various time points: before the induction of anesthesia (T0), after the induction of anesthesia (T1), immediately after intubation (T2), at skin incision (T3), 20 minutes (T4) and 40 minutes (T5) into OLV, at the end of surgery (T6), and during extubation (T7). End-tidal sevoflurane concentrations were measured at T3, T4, T5, and T6. The usage rate of tramadol hydrochloride, the postoperative pulmonary complication incidence, the time of Chest tube removal, and postoperative hospital stay were all recorded.

Sample Size Calculation

According to published study,[21] the incidences of POD and EA with dexmedetomidine were 16.7% and 22.1%, respectively. Sample size was calculated for each endpoint (68 per group for EA, 79 for POD), and the larger POD-based estimate was used. With one-sided α=0.025, power (1-β)=80%, and a 20% non-inferiority margin for relative risk, 79 patients per group were needed. Accounting for 10% dropout, 88 patients per group (total 176) were recruited.

Statistical Analysis

Statistical analyses were performed using SPSS version 26.0 and R version 4.5.1. First, missing data were handled via multiple imputation for continuous variables to ensure data integrity. Subsequently, data normality was first evaluated via histogram observation and the Shapiro–Wilk test. Continuous variables with normal distribution were presented as mean and standard deviation ($\bar{x} \pm s$), and intergroup comparisons were performed using the *t*-test. Non-normally distributed variables were described by median and interquartile range [M(P25, P75)], with Mann–Whitney *U*-test used for between-group comparisons. Categorical data were expressed as percentages (%), and intergroup differences were analyzed via the chi-square test. Statistical significance was defined as $P < 0.05$. For the non-inferiority test of primary outcomes, the 95% confidence interval (CI) of the incidence difference between groups was compared against the predefined non-inferiority margin, with $P < 0.025$ considered statistically significant for non-inferiority validation.

Univariate analysis was conducted for all independent variables to evaluate their correlation with POD. Following this, logistic regression analysis was performed on the shortlisted independent variables with statistically significant univariate results. To strengthen the reliability of the findings, sensitivity analyses were implemented by incorporating additional covariates, including age, gender, and the presence of comorbidities such as hypertension, diabetes, coronary

heart disease, or cerebrovascular disease. All statistical tests were two-sided, with statistical significance defined as $P < 0.05$. The findings for all secondary outcomes are considered exploratory and are presented for descriptive purposes, with inferences made accordingly.

Results

Between May and July 2025, a total of 210 patients who met the inclusion criteria were evaluated. Of these, 34 patients were excluded prior to randomization. Finally, 176 patients were randomly assigned to Group R (n=88) and Group D (n=88). In these 176 patients, 3 chose to withdraw midway, 9 had their surgeries canceled, and 2 were converted to open thoracotomy. Ultimately, data from 162 participants (82 in Group R and 80 in Group D) were included in the final analysis of this study (Figure 1).

Participant Characteristics

Baseline characteristics and intraoperative data are presented in Table 1. Patient and surgical baseline characteristics were well balanced between Group R and Group D.

Primary Outcomes and Assessment Scales

The 95% CI for the overall POD incidence difference between Group D and Group R was (−0.142 to 0.104), with the upper limit of the 95% CI rate difference below the predefined non-inferiority margin (0.2) (non-inferiority $P<0.01$). The

Table 1 Demographic Characteristics and Intraoperative Data

	Group R (n=82)	Group D (n=80)	*P*-value
Male, n (%)	33(40.2)	29(36.3)	0.601
Age, (y)	69(67,71)	68(67,72)	0.679
BMI, (kg/m^2)	24.3±2.6	24.1±2.4	0.468
ASA classification, n (%)			0.906
I	25(30.5)	27(33.8)	
II	44(53.7)	41(51.2)	
III	13(15.8)	12(15.0)	
TNM staging, n (%)			0.827
I	49(59.7)	44(55.0)	
II	25(30.5)	27(33.7)	
III	8(9.8)	9(11.3)	
Education level, n (%)			0.803
Illiterates	22(26.8)	20(25.0)	
Primary school	25(30.5)	20(25.0)	
Junior high school	20(24.4)	22(27.5)	
University or higher	15(18.3)	18 (22.5)	
Hypertension, n (%)	39(52.5)	42(47.6)	0.530
Diabetes, n (%)	13(15.9)	10(12.5)	0.541
Coronary artery disease, n (%)	9(11.0)	11(13.8)	0.591
Cerebrovascular disease, n (%))	15(18.3)	13(16.3)	0.731
Smoker, n (%)	23(28)	21(26.3)	0.797
Duration of operation, (min)	92.8±38.7	91.9±38.5	0.887
Duration of anesthesia, (min)	126.7±42.2	122.0±41.9	0.479
Duration of OLV, (min)	89.8±38.9	87.3±38.4	0.687
HADS-A	6(5,7)	6(5,7)	0.916
AIS	3(2.75,4)	3(2,4)	0.426
MMSE	27(26,28)	27(27,28)	0.242
QoR-15	134(131,135)	132(131,135)	0.326

Notes: Values are shown as percentages, mean ± standard deviation, or median (interquartile range).
Abbreviations: BMI, body mass index; ASA, American Society of Anesthesiologists; TNM, Tumor Node Metastasis; OLV, one-lung ventilation; HADS-A, Hospital Anxiety and Depression Scale - Anxiety subscale; AIS, Athens Insomnia Scale; MMSE, Mini-Mental State Examination; QoR-15, Quality of Recovery-15.

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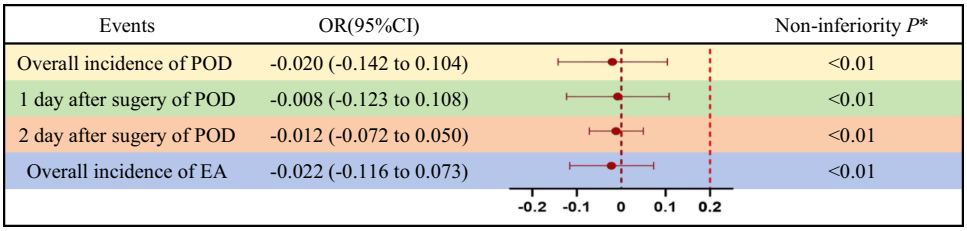

Figure 2 Primary Outcomes. *The upper limits of the 95% (CI) for the differences in POD and EA incidence between Group D and Group R were below the non-inferiority margin (0.2), with non-inferiority $P<0.025$. X-axis: Values <0 indicate lower incidence in Group R (favours remimazolam); values >0 indicate lower incidence in Group D (favours dexmedetomidine); the vertical dashed line at X=0.2 is the predefined non-inferiority margin.
Abbreviations: CI, Confidence Interval; POD, Postoperative Delirium; EA, Emergence Agitation.

95% CI upper limits for POD incidence differences at POD1 (95% CI −0.123 to 0.108) and POD2 (95% CI −0.072 to 0.050) both remained below the non-inferiority margin (0.2) (non-inferiority $P<0.01$). For EA incidence, the 95% CI of the difference between groups was (−0.116 to 0.073), with the 95% CI upper limit of the rate difference lower than the non-inferiority margin (0.2) (non-inferiority $P<0.01$). In conclusion, remimazolam can be considered non-inferior to dexmedetomidine in efficacy (Figure 2).

Overall, the POD incidence in this trial was 19.75%, with 15 cases in Group D and 17 in Group R (18.75% vs 20.73%, $P=0.715$). POD incidence did not differ significantly on postoperative days 1 to 5 ($P=0.888$, $P=0.670$, $P=1$, $P=1$, $P=1$, respectively). POD primarily occurred within the first 2 postoperative days, with the highest incidence on day 1. The overall incidence of Emergence agitation was 9.87%, with 7 cases in Group D (8.75%) and 9 in Group R (10.98%), showing no statistical difference between groups ($P=0.635$). No significant intergroup differences were observed in QoR-15 or NRS scores from postoperative days 1 to 3. Group D had a lower AIS score than Group R on postoperative day 1 ($P<0.05$), with no significant differences observed on days 2 and 3 (Table 2).

Table 2 Primary Outcomes and Associated Assessment Scales

	Group R (n=82)	**Group D (n=80)**	***P*-value**
Postoperative delirium incidence, n (%)	17(20.73)	15(18.75)	0.715
1 day after surgery	14(17.07)	13(16.25)	0.888
2 day after surgery	3(3.66)	2(2.5)	0.670
3 day after surgery	0	0	1
4 day after surgery	0	0	1
5 day after surgery	0	0	1
Emergence agitation, n (%)	9(10.98)	7(8.75)	0.635
QoR-15			
1 day after surgery	101(98,103)	101(99,103)	0.691
2 day after surgery	105(102,108)	105(102,108)	0.933
3 day after surgery	113(110,117)	115(111,117)	0.192
AIS			
1 day after surgery	3(2.75,4)	3(2,4)	0.044
2 day after surgery	3(3,4)	3(2,4)	0.356
3 day after surgery	2(2,3)	2(2,2.75)	0.615
NRS			
1 day after surgery	2(1,3)	2(2,2)	0.607
2 day after surgery	1(1,1)	1(1,1.25)	0.962
3 day after surgery	1(0,1)	0.5(0,1)	0.524

Notes: Values are shown as percentages or median (interquartile range).
Abbreviations: QoR-15, Quality of Recovery-15; AIS, Athens Insomnia Scale; NRS, Numeric Rating Scale.

Secondary Outcomes

The usage of sufentanil and remifentanil in Group R was significantly lower than that in Group D during surgery ($P < 0.05$). The rocuronium dosage was similar between the two groups. Group D showed significantly higher incidences of intraoperative hypotension and bradycardia than Group R ($P < 0.05$). No significant intergroup differences were noted for intraoperative fluid balance, intraoperative hypertension, tachycardia, hypoxemia, postoperative tramadol hydrochloride usage rate, and incidence of PONV ($P > 0.05$).

Regarding vasoactive drugs, compared with patients in Group R, those in Group D had a higher dosage of phenylephrine (40 [0, 240] vs 200 [0, 400], $P < 0.05$) and a higher usage rate of ephedrine (3 [3.7%] vs 10 [12.5%], $P < 0.05$).

In terms of recovery quality, the awakening time in Group D was significantly prolonged compared with that in Group R ($P < 0.05$), while there was no significant difference in Riker SAS scores between the two groups. Additionally, 2 cases of delayed emergence occurred in Group R and 3 cases in Group D.

There were no significant differences in postoperative hospital stay, Chest tube removal time, or incidence of pulmonary complications between the two groups (Table 3). Only one pulmonary complication was observed (group R): mild postoperative atelectasis, confirmed by chest radiography on postoperative day 1. It resolved spontaneously within 48 hours with conservative management (incentive spirometry, early ambulation), requiring no additional interventions and causing no prolonged hospital stay.

Vital Signs and End-Expiratory Concentration of Sevoflurane

For hemodynamic parameters, no significant intergroup differences were observed in baseline MAP and HR (Figure 3). However, the results showed that the HR of patients in Group R was significantly higher than that in Group D at all time points after intubation ($P < 0.05$). The MAP in Group R was significantly higher at skin incision ($P < 0.05$), 20 minutes ($P < 0.01$) and

Table 3 Secondary Outcomes

	Group R (n=82)	Group D (n=80)	*P*-value
Drug dosage			
Sufentanil, (μg)	30(30,35)	35(30,40)	0.019
Remifentanil, (mg)	1.6(1.4,1.8)	1.8(1.3,2.1)	0.047
Rocuronium, (mg)	100(90,120)	100(81,125)	0.660
Ephedrine, n (%)	3(3.7)	10(12.5)	0.038
Phenylephrine, (μg)	40(0,240)	200(0,400)	0.006
Fluid balance			
Fluid intake, (mL)	1000(800,1100)	900(800,1100)	0.240
Blood loss, (mL)	40(25,55)	50(30,50)	0.642
Intraoperative adverse reactions			
Hypoxemia, n (%)	6(7.32)	5(6.25)	0.787
Hypotension, n (%)	13(15.9)	25(31.2)	0.021
Hypertension, n (%)	10(12.2)	6(7.5)	0.317
Bradycardia, n (%)	3(3.7)	12(15)	0.013
Tachycardia, n (%)	6(7.32)	3(3.75)	0.322
Quality of awakening			
Tracheal tube removal, (min)	19.09±9.06	23.36±7.68	0.001
Wake delay, n (%)	2(2.4)	3(3.75)	0.630
Riker SAS score	3.95±0.665	3.86±0.651	0.554
Tramadol hydrochloride, n (%)	3(3.7)	4(5)	0.718
PONV, n (%)	8(9.8)	6(7.5)	0.609
Postoperative hospital stay, (d)	3(3,5)	2(2,4)	0.965
Chest tube removal, (d)	3(3,5)	2(2,3)	0.207
Pulmonary complication, n (%)	1(1.2)	0	0.322

Notes: Values are shown as percentages, mean ± standard deviation, or median (interquartile range).
Abbreviations: Riker SAS, Riker Sedation-Agitation Scale; PONV, Post-operative nausea and vomiting.

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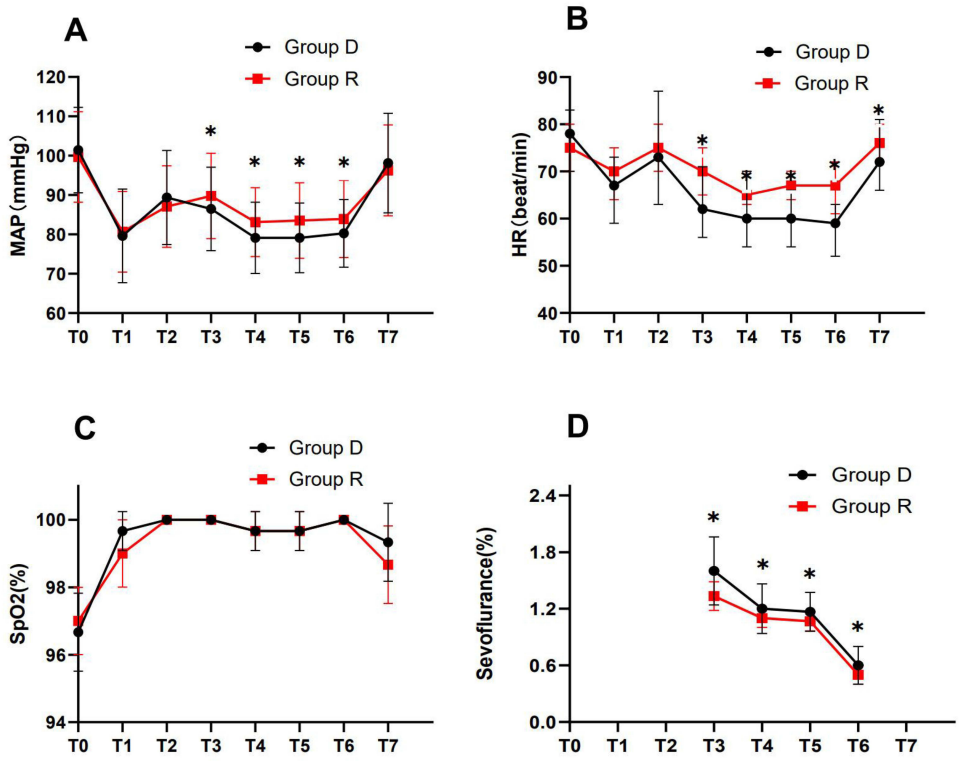

Figure 3 (**A**) MAP, (**B**) HR, (**C**) SpO_2, (**D**) Sevoflurane. Values are expressed as mean ± standard deviation (SD); error bars represent SD. *P <0.05 between the two groups at the same time point.

Abbreviations: T0, Before the induction of anesthesia; T1, After the induction of anesthesia; T2, Immediately after intubation; T3, At skin incision; T4, 20 minutes after one-lung ventilation (OLV); T5, 40 minutes after OLV; T6, At the end of surgery; T7, At extubation; HR, heart rate; MAP, mean arterial pressure; SpO_2, peripheral capillary oxygen saturation.

40 minutes ($P = 0.003$) of OLV, and the end of surgery ($P < 0.05$), with smaller fluctuations in MAP. The end-tidal sevoflurane concentrations in Group R were significantly lower than those in Group D at specific time points (T3, T4, T5, T6) ($P < 0.05$).

Logistic Regression Analysis of Risk Factors Related to POD

Logistic regression analysis identified multiple factors associated with POD risk. Intraoperative hypotension, higher HADS-A scores, longer surgery duration, and occurrence of EA were determined as risk factors for POD. However, a university degree or higher was a protective factor for POD (OR=0.039, 95% CI 0.002–0.653, P=0.024). To assess the stability of our results, two sensitivity analyses were conducted. The first sensitivity analysis incorporated age and gender as covariates, whereas the second analysis included four additional medical history-related covariates: hypertension, diabetes, coronary heart disease, and cerebrovascular disease. Both sensitivity analyses yielded consistent results, thereby validating the robustness of our findings (Table 4).

Table 4 Logistic Regression and Sensitivity Analysis

	Unadjusted			Adjusted 1			Adjusted 2		
	P	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***	**OR**	**95% CI**
University or higher	0.024	0.039	(0.002–0.653)	0.015	0.014	(0.000–0.438)	0.002	0.007	(0.000–0.167)
HADS-A	0.007	1.994	(1.212–3.283)	0.006	1.983	(1.217–3.232)	0.021	1.844	(1.096–3.103)
Duration of operation	0.000	1.048	(1.027–1.069)	0.000	1.046	(1.022–1.071)	0.000	1.056	(1.027–1.085)
Hypotension	0.004	1.005	(1.002–1.009)	0.018	1.005	(1.001–1.008)	0.001	1.006	(1.003–1.010)
Emergence Agitation	0.003	1.243	(1.076–1.436)	0.039	1.196	(1.009–1.417)	0.048	1.182	(1.001–1.395)

Notes: Adjusted 1: adjusted for age and gender. Adjusted 2: adjusted for hypertension, diabetes, coronary heart disease and cerebrovascular disease.
Abbreviation: HADS-A, Hospital Anxiety and Depression Scale - Anxiety subscale.

Discussion

The present study demonstrates that remimazolam is non-inferior to dexmedetomidine in preventing POD and EA. Moreover, compared with dexmedetomidine, patients randomized to remimazolam maintained higher MAP at skin incision, 20 minutes of OLV, 40 minutes of OLV, and the end of surgery—indicating that remimazolam has less impact on the circulation of elderly patients and can maintain more stable hemodynamics. In addition, patients in the remimazolam group consumed less sevoflurane and phenylephrine, which is consistent with the findings of Zhou et al.[22] Furthermore, this trial identified a correlation between the incidence of POD and MAP, with an increase in low MAP being associated with a higher risk of POD, which is consistent with the research results of Liu et al.[23]

Delirium typically occurs within 24 to 48 hours postoperatively and is particularly common in elderly patients.[24] General anesthesia is indispensable for VATS; however, anesthetic agents and the anesthesia process itself may exert postoperative effects—including increased POD risk—on patients.[25] Our results showed no significant differences in POD incidence between the two groups on postoperative days 1–5, indicating remimazolam does not increase POD risk in elderly patients undergoing VATS, consistent with Liao et al's findings.[20] EA may lead to postoperative risks such as wound bleeding and aspiration, affect wound healing, prolong PACU stay, and even endanger patient safety.[26] Our study demonstrated EA is a risk factor for POD, aligning with Fields et al's results.[6] Dexmedetomidine has minimal impact on the cholinergic and γ-aminobutyric acid (GABA) systems, and may improve POCD, thereby reducing POD and EA incidence in high-risk populations.[27] Remimazolam enhances GABA receptor activity to promote chloride ion influx, inhibit neuronal activity, and thereby exerts sedative and amnestic effects—effects that facilitate synchronous brain function recovery and help alleviate EA symptoms.[28] Yang et al confirmed remimazolam can significantly reduce the likelihood of EA and POD following sevoflurane anesthesia.[29] These mechanisms may explain why remimazolam and dexmedetomidine result in similar POD and EA incidences.

Dexmedetomidine induces sympatholysis through central and peripheral mechanisms, inhibiting norepinephrine release, which in turn reduces blood pressure.[11] This may explain why the dexmedetomidine group had lower MAP than the remimazolam group in this trial. Furthermore, dexmedetomidine exerts sedative and hypnotic effects: by activating central α2-adrenergic receptors, it inhibits central nervous system excitability, keeping patients calm and mildly drowsy during anesthesia and postoperative recovery.[30] This may account for the prolonged extubation time and improved sleep on postoperative day 1 in the dexmedetomidine group. Although dexmedetomidine lowered the AIS score on postoperative day 1, no statistical difference in QoR-15 scores was observed between the two groups. As a benzodiazepine, remimazolam offers better sedation and fewer postoperative adverse reactions than midazolam.[31] Advanced age, stress, and inflammation are well-recognized risk factors for POD.[32] Acute intraoperative inflammation and harmful alveolar mechanical stress from one-lung ventilation can trigger pro-inflammatory cytokine release,[33] leading to inflammation and immunosuppression; this inflammatory response induces neuronal and synaptic dysfunction, thereby causing delirium.[34] Existing studies demonstrate remimazolam has significant anti-inflammatory effects in various animal models, including cerebral ischemia-reperfusion injury[35] and sepsis-related acute liver injury.[36]

TPVB has been routinely applied in VATS with confirmed efficacy.[37] In our study, postoperative tramadol use and NRS pain scores did not differ between the remimazolam and dexmedetomidine groups. Dexmedetomidine delivers analgesic effects by binding to central and peripheral α_2-adrenergic receptors, which inhibits pain transmission and reduces sensitivity to nociceptive stimuli.[38] Remimazolam, too, may ease neuropathic pain by suppressing pro-inflammatory factors and regulating bradykinin B1 receptor activity and autophagic pathways,[39] in turn lowering opioid requirements. Notably, while the remimazolam group used less intraoperative sufentanil and remifentanil, postoperative pain outcomes remained comparable between groups. This is likely explained by TPVB's reliable analgesic action[37] and the standardized ward analgesia protocols implemented, which helped minimize differences in pain control between the two groups.

The study has the following limitations: First, delirium was only assessed within 5 postoperative days without long-term follow-up; though most clinical delirium occurs on postoperative day 1, lack of long-term prognostic data remains a limitation. Second, the optimal remifentanil dosage with TPVB needs further exploration to reduce opioid-related adverse effects, and occasional ephedrine use (despite preferred phenylephrine) may be suboptimal for the elderly due to

potential tachycardia. Third, this small-sample, single-center trial, combined with significant individual heterogeneity among elderly patients, requires validation in future multi-center, large-sample prospective studies.

Conclusion

In elderly patients undergoing VATS, remimazolam was non-inferior to dexmedetomidine in preventing POD and EA while providing comparable recovery quality. It demonstrated superior hemodynamic stability, with a lower incidence of hypotension, bradycardia, and reduced vasopressor requirements. The remimazolam group also had a shorter extubation time and lower sevoflurane consumption, supporting its role as a viable alternative pending confirmation by larger multicenter trials.

Data Sharing Statement

Raw data will be provided to qualified researchers upon reasonable request to the corresponding author.

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Disclosure

The authors report no competing interests in this work.

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