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CLINICAL TRIAL REPORT

Effects of Remimazolam on Perioperative Inflammatory Response and Neurocognitive Disorders in Elderly Patients Undergoing Video-Assisted Thoracic Surgery: A Randomized Controlled Trial

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Purpose: The systemic inflammatory response triggered by video-assisted thoracic surgery (VATS) is associated with the risk of perioperative neurocognitive disorders (PND). Remimazolam, a newer benzodiazepine anesthetic, has unknown anti-inflammatory properties and uncertain effects on elderly patients. This study investigated the effects of remimazolam on postoperative inflammation and neurocognitive disorders in elderly patients undergoing VATS.

Patients and Methods: Ninety-two patients aged 60 years or older scheduled for VATS were randomized to receive either remimazolam (induction: 0.25 mg/kg; maintenance: 0.5–1.5 mg/kg/h) or propofol (induction: 2 mg/kg; maintenance: 4–6 mg/kg/h). The primary outcome was the serum C-reactive protein concentration at 24 h postoperatively. Secondary outcomes included the incidence of PND, assessed using the 3-Minute Diagnostic Confusion Assessment Method and the Mini-Mental State Examination on postoperative days 1, 3, 5, and 7. Exploratory outcomes included inflammatory cells (leucocytes and neutrophil counts), cytokines (IL-6, TNF-α, S100β), stress markers, and the systemic inflammatory response index. Other measures comprised hemodynamic parameters, anesthesia parameters, and potential adverse events.

Results: All 92 patients completed the intention-to-treat analysis. At 24h postoperation, the remimazolam group showed significantly higher CRP, IL-6, leukocyte counts, neutrophil counts, and systemic inflammatory response index than the propofol group. No differences were found in TNF-α, S100β, or PND incidence (8.7% vs 6.5%). Stress marker levels were comparable between groups at all time points. Additionally, the remimazolam group demonstrated shorter anesthesia awakening time (P<0.001), with reduced incidence of hypotension (P <0.001) and injection pain (P = 0.015).

Conclusion: Although remimazolam is less effective than propofol in suppressing the early postoperative inflammatory response in elderly patients undergoing VATS, it did not increase the risk of PND or infection. It has significant advantages in hemodynamic stability, facilitates faster recovery, and reduces injection pain, establishing it as a preferred anesthetic option for geriatric VATS, though its inflammatory mechanisms require clarification.

Keywords: remimazolam, propofol, elderly, inflammatory, neurocognitive disorders, thoracic surgery

Introduction

Perioperative Neurocognitive Disorders (PND), particularly postoperative delirium, delayed neurocognitive recovery, and postoperative neurocognitive disorders, not only hinder recovery and significantly impair patients' self-care ability and

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quality of life but also increase the risk of postoperative complications and mortality.[1] Previous studies have identified several factors associated with PND, including age, preoperative comorbidities (such as hypertension and diabetes), perioperative medication use, anesthesia techniques, and surgical methods.[2] Systemic inflammatory responses triggered by surgical trauma and the subsequent neuroinflammation may be key factors in the pathogenesis of PND, with the mechanism of this neuroinflammation being closely linked to age.[3,4] Additionally, neuronal damage, stress response, and glucocorticoids, oxidative stress, and blood-brain barrier (BBB) impairment are also recognized as underlying mechanisms of PND.[2,5] As a representative minimally invasive technique, video-assisted thoracic surgery (VATS) reduces surgical trauma and systemic immune-inflammatory responses, and has become an important approach for thoracic procedures in elderly patients.[6] However, ischemia-reperfusion injury, mechanical traction, and surgical stress induced by One-Lung Ventilation (OLV) are also risk factors for postoperative cognitive dysfunction.[7,8] Intraoperative hypoperfusion, hypoventilation, pulmonary edema, and increased blood loss further exacerbate hypoxia exposure, activating inflammatory pathways and contributing to postoperative cognitive impairment.[9] Therefore, reducing the incidence of PND and improving the quality of life in elderly patients undergoing VATS has become a major challenge in our aging society.

Anesthetic management plays a crucial role in regulating perioperative inflammation. Through appropriate selection of anesthesia techniques and medications, as well as optimized analgesic strategies, levels of pro-inflammatory cytokines can be reduced, effectively suppressing excessive inflammatory responses and directly influencing patient outcomes.[10] Propofol, as a mainstream anesthetic-sedative agent in VATS, exerts anti-inflammatory effects by suppressing the nuclear factor kappa B (NF-κB) signaling pathway, thereby downregulating the expression of TNF-α and IL-6.[11] However, its cardiovascular depressive properties lead to a high incidence of hypotension (up to 40%-60%), limiting its use in hemodynamically unstable elderly patients.[12] Additionally, injection pain (occurring in 15%-30% of cases) also adversely affects patient experience.[13] Remimazolam, as a novel benzodiazepine-class drug, demonstrates promise in geriatric anaesthesia due to its minimal circulatory depression, absence of injection pain, availability of a specific antagonist (flumazenil), and rapid recovery.[14] By modulating γ-aminobutyric acid (GABA)A receptors, it suppresses reactive oxygen species generation and enhances antioxidant defences, potentially mitigating cellular apoptosis and offering neuroprotection.[15] Nevertheless, its impact on postoperative inflammation and cognition remains controversial: some studies report elevated inflammatory markers without increased complications,[16] while others found no significant difference in cytokine levels compared to propofol.[17] More importantly, although benzodiazepines are historically linked to PND risk in the elderly, recent evidence suggests no association between intraoperative use and PND.[18–20] These discrepancies may stem from variations in drug dosage, surgical type, and timing of assessment.

We designed a single-center, randomized controlled trial to test the primary hypothesis that, for elderly patients undergoing VATS, the use of remimazolam for anesthesia induction and maintenance might be inferior to propofol in suppressing the level of early postoperative inflammatory response. Simultaneously, we investigated the secondary hypothesis that remimazolam does not increase the incidence of PND within 7 days after surgery in these elderly patients.

Methods

Study Design and Patient Enrollment

This study was conducted in accordance with the Declaration of Helsinki (2013 revision). The research protocol for this randomized controlled trial was approved by the Ethics Committee of Chongqing University Three Gorges Hospital (Approval No: 2024 Scientific Review 78) and registered at the Chinese Clinical Trial Registry (Registration No: ChiCTR2400094127). This study will enroll patients scheduled for elective VATS between February 2024 and June 2025. Each participant gave written informed consent.

Participants

Inclusion criteria: ① Age ≥60 years; ② American Society of Anesthesiologists (ASA) physical status classification II–III; ③ Preoperative Mini-Mental State Examination (MMSE) score ≥27, and 3-Minute Diagnostic Confusion Assessment Method (3D-CAM) was negative; ④ Signed informed consent. Exclusion criteria: ① Allergy or contraindications to

study medications; ② Severe cardiovascular/cerebrovascular diseases (NYHA class III–IV heart failure, severe arrhythmia, stroke within 6 months); ③ Severe respiratory diseases (acute chronic obstructive pulmonary disease exacerbation, pulmonary infection); ④ Hepatic/renal dysfunction (Child-Pugh grade ≥B or eGFR <60 mL/min/1.73m^2); ⑤ Long-term use of sedative and analgesic medications; ⑥ History of neuropsychiatric disorders (eg, schizophrenia, epilepsy); ⑦ Other conditions deemed inappropriate for participation. Elimination criteria: ① Conversion to open thoracotomy; ② Protocol discontinuation due to severe adverse events; ③ Withdrawal of informed consent.

Randomization and Blinding

We generated random sequences using SPSS 27 and allocated participants in a 1:1 ratio to either the remimazolam group or the propofol group. The group assignments were sealed in opaque envelopes and maintained throughout the study period. While anesthesia providers and intraoperative data collectors were not blinded (due to visible differences in medication coloration), postoperative follow-up assessors, laboratory technicians, and patients remained unaware of group allocation. In emergencies (eg, occurrence of severe adverse reactions or rapid clinical deterioration during surgery), anesthesiologists were permitted to adjust or discontinue drug administration. Unblinding was strictly performed only when clinically imperative.

Anaesthesia, Perioperative Care, and Intervention

Preoperative fasting was performed for 8 hours (solid food) and 2 hours (clear fluids). Intraoperative monitoring included: Heart rate (HR), Pulse oxygen saturation (SpO_2), Invasive blood pressure[systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP)], End-tidal carbon dioxide tension ($PETCO_2$), Bispectral index (BIS), Nasopharyngeal temperature, Urine output.

Both groups underwent general anesthesia with double-lumen endobronchial intubation. For anesthesia induction, the remimazolam group received intravenous remimazolam 0.25 mg/kg for sedation,[21,22] while the propofol group received intravenous propofol 2 mg/kg for sedation.[21] Subsequently, both groups administered sequential intravenous boluses of sufentanil 0.5 μg/kg and rocuronium 0.6 mg/kg, followed by mask ventilation with 100% oxygen. When the BIS decreased below 60, orotracheal intubation was performed under video-laryngoscopy guidance, with double-lumen tube position confirmed by fiberoptic bronchoscopy. For maintenance, the remimazolam group received continuous remimazolam infusion at 0.5–1.5 mg/kg/h,[20,23] and the propofol group received continuous propofol infusion at 4–6mg/kg/h.[21] Both groups received remifentanil 0.08–0.2 μg/kg/min for analgesia, with intermittent sufentanil and rocuronium boluses as needed. Anesthetic depth was maintained at BIS 40–60. At the end of surgery, the anesthetic infusion was discontinued, and parecoxib sodium was administered intravenously, followed by transfer to the post-anesthesia care unit (PACU). Upon PACU admission, the remimazolam group received flumazenil 3mL (0.3 mg) as a remimazolam antagonist, while the propofol group received an equivalent volume of normal saline (3 mL). In the PACU, non-invasive blood pressure, HR, and SpO_2 were monitored for at least 30 minutes. Patients were discharged from the PACU when their Steward score exceeded 4. Patient-controlled intravenous analgesia (PCIA) was employed with sufentanil 4μg/kg (maximum 250μg), tropisetron 10 mg, diluted with normal saline to 200 mL. The PCIA settings included a background infusion of 4mL/h, a bolus dose of 3mL, and a lockout interval of 15 minutes, maintained for 48 hours. The use of ketamine and dexmedetomidine was prohibited during the perioperative period. During the study, all patients were not given an epidural or other regional anesthesia. All patients received standard prophylactic antibiotics within 0.5 to 1 hour before surgery and for one day postoperatively.

Data Collection

Primary Indicators

The primary outcome was the serum C-reactive protein (CRP) concentration at 24 h postoperatively. Venous blood samples (5 mL) were obtained from all patients three times: preoperatively, at the end of surgery, and 24 hours postoperatively. The samples were collected in EDTA-coated tubes, allowed to stand for 30 min, and then centrifuged (3000 rpm, 5 min). The supernatant was stored at −80°C until analysis. Serum CRP concentrations were determined using an immunoturbidimetric assay.

Secondary Indicators

All PND assessments were performed by the same anesthesiologist, who was blinded to the group assignments and trained in the use of the 3D-CAM and MMSE by the Department of Neurology. Trained assessors evaluated PND once daily (between 8:00 and 10:00 AM) on postoperative days 1, 3, 5, and 7 using the MMSE and 3D-CAM. The presence of PND is established when either the MMSE score is less than 27 or delirium is detected through a positive 3D-CAM assessment. Inflammatory cells (leucocytes and neutrophil counts), cytokines (IL-6, TNF-α, S100β), stress markers (β-endorphin, malondialdehyde, cortisol, and norepinephrine), and the systemic inflammatory response index were designated as exploratory outcome measures. Serum levels of IL-6, TNF-α, S100β, and stress markers were measured using enzyme-linked immunosorbent assay (ELISA). The venous blood levels of leucocytes, neutrophils, lymphocytes, and monocytes in both groups were measured using the electrical impedance method before surgery and 24 hours after surgery. The Systemic Inflammatory Response Index (SIRI) was calculated as follows: SIRI = neutrophil count × monocyte count/lymphocyte count.

Intraoperative vital signs (HR, SBP, DBP, MAP, and SpO_2) were recorded at predefined time points: before anesthesia induction (T0), 2 minutes after drug administration (T1), 5 minutes after drug administration (T2), at surgical incision (T3), 60 minutes after anesthesia induction (T4), and at the end of surgery (T5). The following anesthesia-related parameters were also documented: time to loss of eyelash reflex (defined as no blink response after three consecutive stimulations of the lateral corneal margin with a sterile cotton swab), time for the BIS value to decrease and stabilize at ≤60 after induction, anesthesia awakening time (from discontinuation of anesthetics to eye opening on verbal command), PACU length of stay, and the incidence of perioperative adverse events.

Adverse event monitoring was conducted from the initiation of anesthesia until 7 days postoperatively, specifically including: ① Injection pain: Patient-reported pain in the hand or arm during anesthesia induction. ② Hypotension: A decrease in MAP (mean arterial pressure) exceeding 20% from baseline. ③ Bradycardia: HR <60 beats per minute. ④Respiratory depression: Defined as SpO_2< 90% or respiratory rate (RR) < 8 breaths/min requiring respiratory support. ⑤ Postoperative nausea and vomiting (PONV): Nausea (subjective feeling of discomfort) or vomiting (forceful expulsion of gastric contents) occurring within 24 hours postoperatively. ⑥ Pulmonary infection: Postoperative fever (>38°C) with radiological evidence of new pulmonary infiltrate. ⑦ Surgical site infection (SSI): Purulent discharge from the surgical incision within 7 days postoperatively, or local inflammation (erythema, swelling, heat, or pain) requiring antibiotic therapy/surgical intervention.

Sample Size Calculation

The sample size was calculated using PASS 15.0 software. The sample size estimation was calculated based on the 24-hour postoperative CRP levels (primary outcome measure) from the first 20 enrolled patients (10 per group). The mean serum CRP concentrations at 24 hours postoperatively were 38.6±17.3 mg. L^{-1} in the propofol group and 52.3±29.0 mg. L^{-1} in the remimazolam group. Using PASS 15 software with a power of 0.8, a type I error rate of 0.1, and accounting for a 15% dropout rate, a total of 92 patients were required, with 46 patients to be randomly allocated to each group.

Statistical methods

The data were analyzed using SPSS version 27.0 software. For the primary outcome measures, an intention-to-treat analysis (ITT) was employed. The balance of baseline data between groups was assessed using the absolute standardized difference, defined as the absolute difference in means, medians, or proportions divided by the pooled standard deviation. Baseline variables with an absolute standardized difference≥0.409 ($1.96\times\sqrt{1/n1+1/n2}$) were considered imbalanced.[24] Normally distributed continuous variables are presented as mean ± SD and compared between groups using an independent samples *t*-test. Within-group changes before and after treatment were assessed with paired *t*-test. Non-normally distributed continuous variables are expressed as median (interquartile range). The Mann–Whitney *U*-test was used for between-group comparisons, and the Friedman test was used for within-group comparisons across multiple time points. If the Friedman test indicated a significant difference, post-hoc pairwise analyses were conducted using the Wilcoxon signed-rank test, with the *P*-values adjusted for multiple comparisons using the Bonferroni method.

Categorical variables are summarized as number (percentage), and comparisons were made using the Chi-square test, Yates' correction for continuity, or Fisher's exact test, as appropriate. A two-sided *P* value of < 0.05 was considered statistically significant, except for post-hoc pairwise comparisons, where Bonferroni-adjusted *P* values are reported and significance was maintained at the < 0.05 level after adjustment.

Results

From February 2024 to June 2025, a total of 214 patients were assessed for eligibility. Ultimately, 92 patients were successfully enrolled and randomly assigned to the remimazolam group (n=46) or the propofol group (n=46). No loss of follow-up occurred during the study, and all 92 patients were included in the ITT (Figure 1).

General Information and Inflammatory Parameters

The two groups were well balanced on baseline characteristics (Table 1). Serum levels of CRP, IL-6, leucocyte count, neutrophil count, and SIRI increased 24 hours postoperatively compared to preoperative values in both groups ($P<0.001$) (Figure 2). Notably, serum IL-6 concentrations showed an upward trend immediately after surgery ($P<0.001$) (Figure 2). At the 24-hour postoperative mark, the remimazolam group exhibited higher concentrations of CRP ($P=0.044$), IL-6 ($P=0.021$), leucocyte count ($P=0.028$), neutrophil count ($P=0.031$), and SIRI ($P=0.049$) compared to the propofol group (Figure 2). However, no statistically significant differences were observed between the two groups in S100β ($P=0.381$) *and* TNF-α ($P=0.318$) concentrations (Figure 2). Levels of surgical stress markers, cortisol ($P<0.001$), and malondialdehyde ($P<0.01$) increased significantly by the end of surgery in both groups and remained elevated for β-endorphin, cortisol, and norepinephrine at 24 hours ($P<0.001$) (Figure 2). No significant intergroup differences were detected in these markers at any time point (Figure 2).

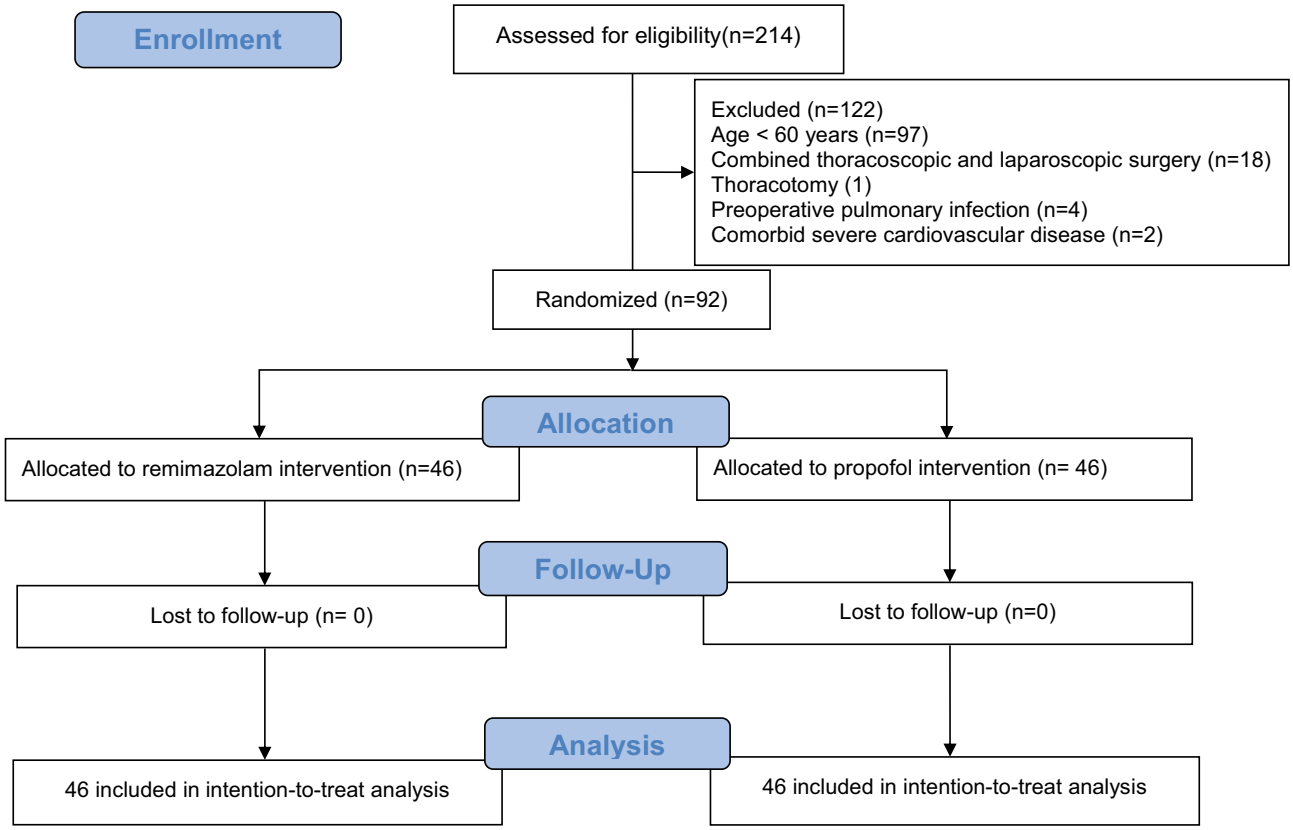

Figure 1 Trial diagram.

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Table 1 Baseline Clinical Characteristics of the Patient

Characteristics	Propofol (n=46)	Remimazolam (n=46)	ASD	*P* value
Age (years)	67 (62–71)	69 (65–72)	0.351	0.204[a]
Gender				
Female	20 (43.5)	26 (56.5)	0.260	0.297[b]
Male	26 (56.5)	20 (43.5)		
BMI (kg/m^2)	22.7 (21.3–25.0)	23.0 (21.0–24.2)	0.123	0.748[a]
ASA classification				
II	28(60.9)	25(54.3)	0.131	0.673[b]
III	18(39.1)	21(45.7)		
Comorbidities				
Hypertension	10(21.7)	9(19.6)	0.052	>0.999[b]
Diabetes mellitus	6(13.0)	6(13.0)	<0.001	>0.999[b]
COPD	4(8.7)	6(13.0)	0.138	0.739[b]
Coronary heart disease	3(6.5)	2(4.3)	0.097	>0.999[b]
Laboratory tests				
Albumin	41.60±3.08)	41.99±2.56)	0.139	0.507[c]
Alanine Aminotransferase	18.04±8.45)	16.97±9.39)	0.120	0.570[c]
Aspartate Aminotransferase	21.69±6.11)	20.24±5.10)	0.258	0.219[c]
Creatinine	69.91±13.78)	70.22±13.91)	0.022	0.916[c]
Total Hemoglobin	13.60±1.40)	13.39±1.46)	0.150	0.475[c]
Surgery type				
Wedge resection	2(4.3)	2(4.3)	<0.001	0.816[b]
Segment resection	7(15.2)	4(8.7)	0.200	
Lobectomies	37(80.4)	38(82.6)	0.056	
Lung bulla resection	0(0.0)	1(2.2)	0.211	
Thymectomy with enlargement	0(0.0)	1(2.2)	0.211	
Educational Attainment				
Illiterate	3(6.5)	8(17.4)	0.336	0.302[b]
Primary School	23(50.0)	23(50.0)	<0.001	
Junior High School	16 (34.8)	10 (21.7)	0.291	
High School	4 (8.7)	4 (8.7)	<0.001	
College	0 (0.0)	1 (2.2)	0.211	
Operative time (min)	100 (85–120)	105 (84–122)	0.137	0.707[a]
Anesthesia time (min)	150(128–166)	151(125–170)	0.024	0.500[a]
Intraoperative fluid infusion volume (mL)	1000(800–1300)	1000(1000–1200)	<0.001	0.998[a]
Intraoperative blood loss volume (mL)	90(50–100)	90(50–100)	<0.001	0.516[a]
Urine output (mL)	300(200–300)	200(200–300)	0.202	0.170[a]
Preoperative cognitive dysfunction	0(0.0)	0(0.0)	<0.001	>0.999[b]
Preoperative delirium	0(0.0)	0(0.0)	<0.001	>0.999[b]

Notes: Data are mean ± SD, median (inter-quartile range), or n (%). An absolute standardized difference (ASD) >0.409 is considered imbalanced between the two groups. [a], Mann–Whitney *U*-test; [b], Chi-square test; [c], *t*-test.

Abbreviations: ASD, absolute standardized difference; BMI, body mass index; ASA, American Society of Anesthesiologists; COPD, Chronic Obstructive Pulmonary Disease.

Cognitive Function

The MMSE scores of both groups decreased on postoperative day 1 compared with preoperative values (P<0.001), but no statistically significant differences were observed between groups at any assessment time point (Figure 3). The 3D-CAM results also showed no significant difference (2.2% vs 4.3% positive rate, P>0.999) (Figure 3). The incidence of PND within 7 days was comparable between the remimazolam and propofol groups (8.7% vs 6.5%, P>0.999) (Figure 3).

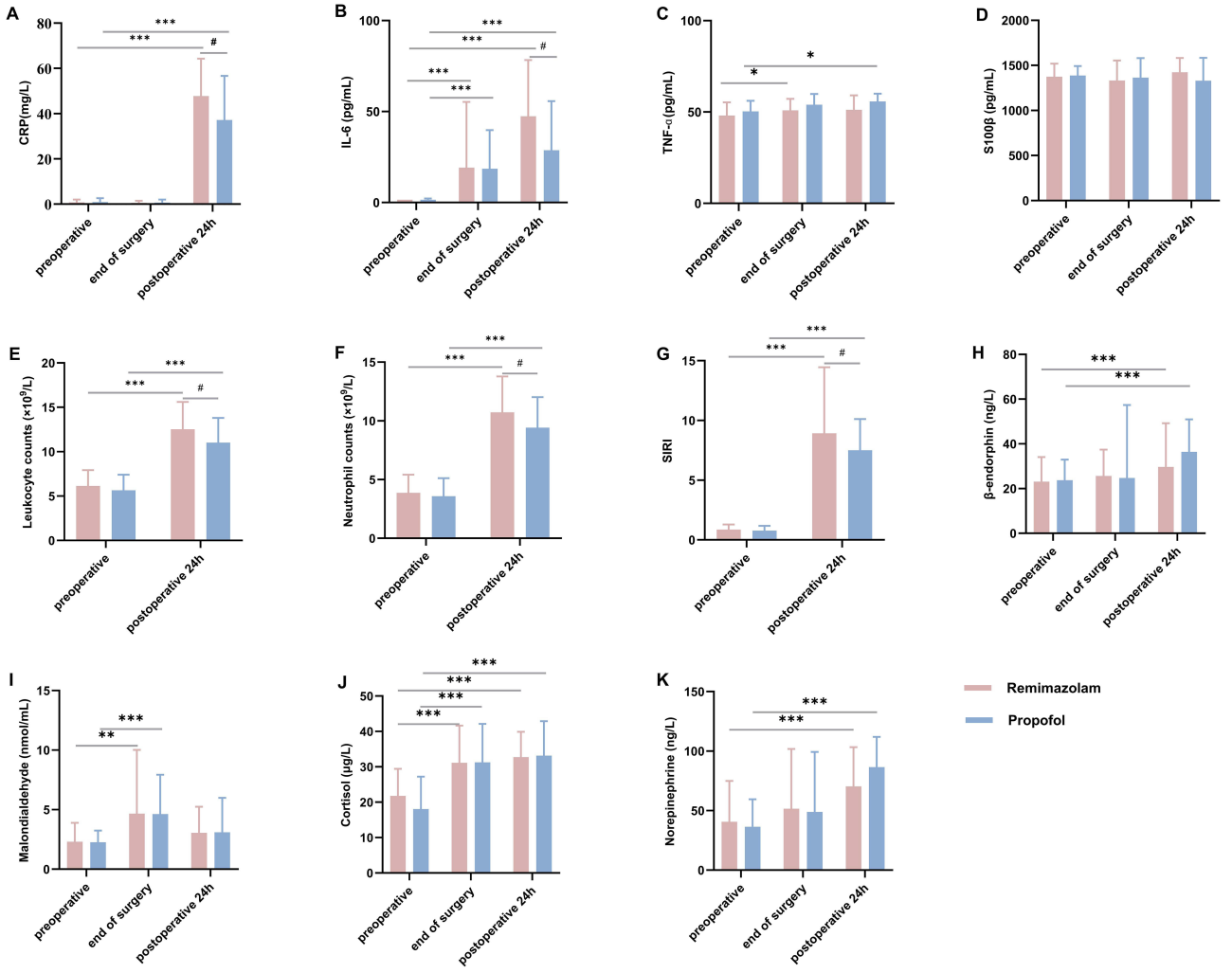

Figure 2 Inflammatory and stress indicators parameters at different time points between the two groups.
Notes: (**A**) CRP at different time points between the two groups; (**B**) IL-6 at different time points between the two groups; (**C**) TNF-α at different time points between the two groups; (**D**) S100β at different time points between the two groups; (**E**) Leukocyte counts at different time points between the two groups; (**F**) Neutrophil counts at different time points between the two groups; (**G**) SIRI at different time points between the two groups; (**H**) β-endorphin at different time points between the two groups; (**I**) Malondialdehyde at different time points between the two groups; (**J**) Cortisol at different time points between the two groups; (**K**) Norepinephrine at different time points between the two groups. *, $P<0.05$, compared to preoperative; **, $P<0.01$, compared to preoperative; ***, $P<0.001$, compared to preoperative; #, $P<0.05$, compared to the propofol group.
Abbreviations: CRP, C-reactive protein; IL-6, Interleukin-6; TNF-α, Tumor Necrosis Factor-α; SIRI, Systemic Inflammatory Response Index.

Hemodynamic Parameters

Compared with T_0, SBP, DBP, and MAP decreased at T_1-T_5, and HR decreased at T_2-T_3 in both groups ($P < 0.05$) (Figure 4). Additionally, HR at T_4 was also lower than at T_0 in the propofol group ($P < 0.001$) (Figure 4). The remimazolam group exhibited higher SBP, DBP, and MAP at T_1, T_2, and T_4, along with a higher HR at T_2 and T_4, compared to the propofol group ($P < 0.05$) (Figure 4). Although SpO_2 increased from baseline at all intraoperative time points in both groups ($P< 0.001$), there were no significant differences in SpO_2 between the groups at any time (Figure 4).

Anesthesia Parameters and Adverse Events

The consumption of intraoperative sufentanil (P=0.770), remifentanil (P=0.698), and rocuronium (P=0.580) was comparable between the two groups (Table 2). Compared to the propofol group, the remimazolam group showed a significantly longer time to loss of eyelash reflex and time to BIS reaching 60 (P<0.001) (Table 2). In contrast, anesthesia awakening time was shorter in the remimazolam group (P<0.001) (Table 2). No significant difference was

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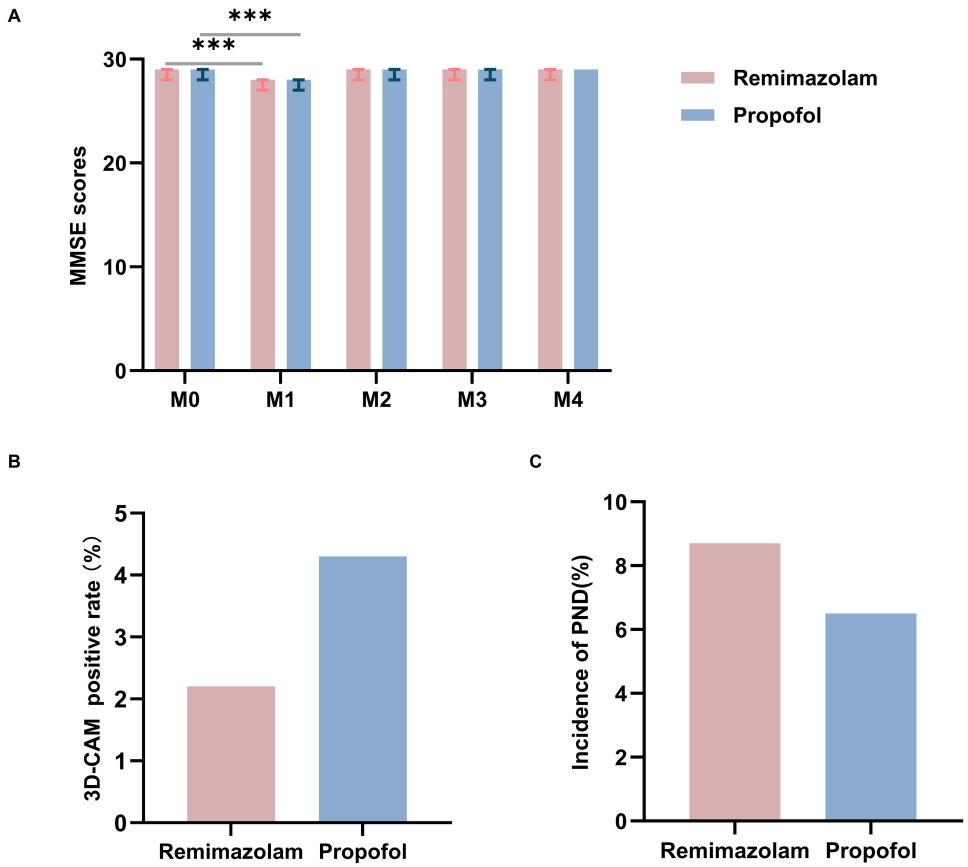

Figure 3 Compare the incidence rates of PND between the two groups, as assessed by the MMSE and 3D-CAM.
Notes: (**A**) MMSE scores at different time points between the two groups; (**B**) The 3D-CAM positive rate within 7 days after surgery in the two groups; (**C**) The incidence of PND within 7 days after surgery in the two groups. M0, 1 d before surgery; M1, 1 d after surgery; M2, 3 d after surgery; M3, 5 d after surgery; M4, 7 d after surgery. ***, *P*<0.001, compared to M0.
Abbreviations: MMSE, Mini-Mental State Examination; 3D-CAM, 3-Minute Diagnostic Confusion Assessment Method; PND, perioperative neurocognitive disorders.

observed in PACU length of stay between the two groups (*P*=0.936) (Table 2). The remimazolam group demonstrated a lower incidence of hypotension (*P* <0.001) and injection pain (*P*=0.015) than the propofol group (Table 2). There were no significant differences between the groups in the incidence of bradycardia, respiratory depression, nausea/vomiting, pulmonary infection, or surgical site infection (Table 2).

Discussion

This study reveals an intriguing dichotomy in the profile of remimazolam: it amplifies the early postoperative systemic inflammatory response yet preserves neurological outcomes comparably to propofol. Although remimazolam's anti-inflammatory effect is less pronounced than that of propofol, it did not increase the incidence of PND or the risk of infection (no pulmonary or surgical site infections occurred in either group). Furthermore, remimazolam demonstrated significant clinical advantages, including hemodynamic stability, reduced risk of hypotension, shorter recovery time, and a lower incidence of injection pain. Although the induction time was longer in the remimazolam group, it did not affect PACU stay duration, clinical anesthesia efficiency, or surgical turnover. In summary, remimazolam exhibits a paradoxical profile of "enhanced inflammation without impaired neurological outcomes" in elderly thoracoscopic anesthesia. Its advantages in hemodynamic stability and rapid recovery make it a preferred anesthetic option for this population. The following sections will further explore paradoxical immunomodulatory mechanisms and clinical implications.

The postoperative inflammatory response is a double-edged sword, integral to tissue repair yet potentially harmful when excessive.[16] CRP, IL-6, and TNF-α are key pro-inflammatory cytokines that reflect the severity of inflammatory responses and play a critical role in postoperative recovery and complications.[25] Our key finding is that remimazolam

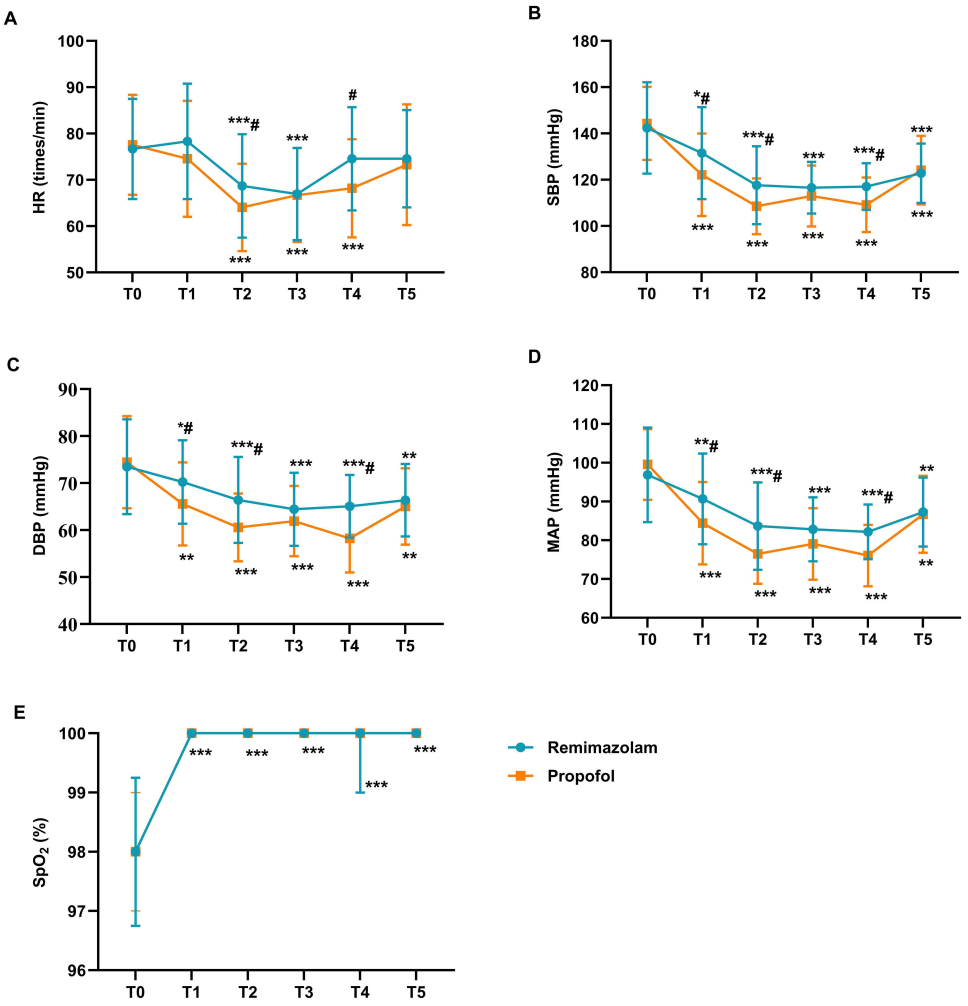

Figure 4 Vital signs at different time points between the two groups.
Notes: (**A**) HR at different time points between the two groups; (**B**) SBP at different time points between the two groups; (**C**) DBP at different time points between the two groups; (**D**) MAP at different time points between the two groups. (**E**) SpO_2 at different time points between the two groups. T0, preoperative; T1, 2 min after anesthesia induction intubation; T2, 5 min after anesthesia induction intubation; T3, beginning of operation; T4, 60 min after anesthesia induction intubation; T5, end of procedure. *, $P<0.05$, compared to T_0; **, $P<0.01$, compared to T_0; ***, $P<0.001$, compared to T_0; #, $P<0.05$, compared to the propofol group.
Abbreviations: HR, heart rate; SBP, systolic pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; SpO_2, Pulse oxygen saturation.

anesthesia resulted in a heightened early inflammatory response at 24 hours post-VATS, as evidenced by significantly elevated CRP, IL-6, leukocyte count, neutrophil count, and SIRI compared to propofol. Remimazolam may enhance the early inflammatory response through distinct immunomodulatory mechanisms, such as GABA-A receptor-mediated neutrophil activation.[26] In contrast, propofol appears to suppress NF-κB signaling and subsequent IL-6 production.[27] Remimazolam, however, may promote IL-6 secretion via potential activation of the TLR4/NF-κB pathway or direct stimulation of monocytes by its metabolite CNS7054.[28,29] Additionally, its more stable hemodynamic profile could improve oxygen supply–demand balance, potentially exacerbating oxidative stress and contributing to elevated levels of CRP and IL-6.[30] No intergroup difference was observed in TNF-α levels. While some studies report minimal perioperative changes in TNF-α following lung surgery,[10] recent evidence indicates elevated TNF-α in bronchoalveolar lavage after one-lung ventilation,[31] suggesting potential systemic effects or long-term implications.

PND encompasses cognitive decline occurring between pre-surgery and 12 months postoperatively.[1] While the Diagnostic and Statistical Manual of Mental Disorders-5th edition (DSM-5) is the gold standard for diagnosing perioperative PND, its routine use by non-psychiatric clinicians remains limited.[1] Accordingly, this study focused on in-hospital delirium and early neurocognitive recovery (up to 7 days), utilizing the practical 3D-CAM for delirium screening and the MMSE for cognitive assessment.[32,33] Neuroinflammation is a key driver of PND, with elevated levels of S100β

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Table 2 Anesthesia Parameters and Adverse Events in Both Groups

Indicator	Propofol (n=46)	Remimazolam (n=46)	*P* value
Sufentanil dose (μg)	40(30,50)	40(30,50)	0.770[a]
Remifentanil dose (μg)	1220(1000,1400)	1000(900,1500)	0.698[a]
Rocuronium dose (mg)	120(100,140)	120(100,140)	0.580 [a]
Time to lose eyelash reflex (s)	23.50±4.92	37.85±8.61	<0.001[c]
Time to BIS < 60 (s)	57.22±14.95	92.04±21.20	<0.001[c]
Anesthesia awakening time (min)	8.87±1.63	6.35±1.65	<0.001[c]
PACU length of stay (min)	60(55,70)	60(55,75)	0.936[a]
Injection pain	9(19.6)	1(2.2)	0.015[b]
Bradycardia	16(34.8)	15(32.6)	>0.999[b]
Hypotension	35(76.1)	18(39.1)	<0.001[b]
Respiratory depression	1(2.2)	0(0)	>0.999[b]
Nausea/vomiting	5(10.9)	2(4.3)	0.434[b]
Pulmonary infection	0(0.0)	0(0.0)	>0.999[b]
Surgical site infection	0(0.0)	0(0.0)	>0.999[b]

Notes: Data are mean ± SD, median (inter-quartile range), or n (%). [a], Mann–Whitney *U*-test; [b], Chi-square test; [c], *t*-test.

(reflecting blood-brain barrier disruption) and cytokines such as IL-6 and TNF-α serving as established biomarkers.[34–38] Paradoxically, despite observing elevated systemic inflammatory markers (CRP, IL-6, leukocyte counts, neutrophil counts, and SIRI), we found no corresponding increase in neuroinflammation (as indicated by similar S100β levels) or clinical sequelae such as PND or SSI. This dissociation may be attributed to several factors: first, the inflammatory response was either too transient or not of the specific type (eg, central neuroinflammation) required to trigger PND; second, uniform antibiotic prophylaxis in both groups could have suppressed the inflammatory response related to infection; third, a higher preoperative cognitive reserve (all patients had MMSE ≥27) might have buffered against short-term inflammatory insults;[39] and finally, in the remimazolam group, flumazenil reversal potentially reduced residual sedation-related cognitive impairment.[40] These clinical findings prompt further mechanistic investigation; future animal studies will explore how propofol and remimazolam differentially modulate inflammation and whether this difference mediates neurocognitive impairment via central nervous system injury.

The two drugs demonstrated comparable efficacy in modulating stress-related parameters. However, the remimazolam group demonstrated more stable hemodynamics with less fluctuation in blood pressure after anesthesia induction and during surgery, along with a lower incidence of hypotension compared to the propofol group. These findings are closely related to the pharmacological properties of remimazolam. Remimazolam exerts its sedative effects by enhancing GABA receptor activity, and its direct vasodilatory effect on vascular smooth muscle is weaker than that of propofol.[41] In contrast, propofol reduces blood pressure more abruptly by suppressing sympathetic tone and inducing calcium channel-mediated vasodilation.[42] This study further confirms the hemodynamic stability advantages of remimazolam for anesthesia induction and maintenance in elderly patients and those with cardiovascular diseases.[43] Additionally, the remimazolam group showed a longer time to loss of eyelash reflex and time to BIS <60 compared to the propofol group. However, due to the availability of flumazenil, the recovery time was shorter, and the incidence of injection pain was reduced. These results demonstrate that remimazolam offers superior hemodynamic stability and favorable safety for anesthesia induction and maintenance in elderly and cardiovascular-compromised patients.

This study has the following limitations. First, it was a single-center design, and the sample size was not estimated based on the incidence of clinical events. Second, we excluded emergency cases, ASA IV patients, and those with MMSE scores <27, so whether this population could benefit from remimazolam remains unclear. Third, inflammatory cytokines were only measured at a single time point (24 hours postoperatively), failing to reflect dynamic changes. Fourth, other important inflammatory/neuroinjury biomarkers (eg, IL-10, NfL, GFAP) were not assessed, and long-term cognitive follow-up (eg, 1–3 months or longer postoperatively) was lacking. We anticipate future multicenter, large-sample randomized controlled trials to evaluate its long-term inflammatory effects and safety in high-risk populations.

Conclusion

In summary, while remimazolam is less effective than propofol in suppressing the early postoperative inflammatory response after VATS in elderly patients, it does not increase the risk of PND or infection. Given its significant advantages in maintaining hemodynamic stability, promoting rapid postoperative recovery, and reducing injection pain, remimazolam represents a preferred anesthetic option for elderly patients undergoing VATS. However, the underlying mechanisms of its inflammatory effects still require further investigation.

Data Sharing Statement

The deidentified participant data that support the findings of this study are available from the corresponding author, Chun Liu, upon reasonable request, after the completion of a data sharing agreement.

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Disclosure

The authors report no conflicts of interest in this work.

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