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Original Article

Comparative analysis of esketamine versus remimazolam in adult and pediatric surgical patients: a multimodal monitoring evaluation

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Abstract: Objective: To evaluate the anesthetic effects of esketamine and remimazolam across different age groups, optimizing personalized anesthesia strategies. Methods: This retrospective study analyzed 264 surgical patients (esketamine n = 135, remimazolam n = 129) stratified by age (adults n = 141, children n = 123). Seventeen key perioperative parameters were assessed. Two-way analysis of variance (ANOVA) was performed to examine drug-specific, population-dependent, and interaction effects, while point-biserial correlation analysis was employed to assess relationships between parameters. Results: Remimazolam demonstrated superior pharmacokinetic profiles, with a shorter time to sedation target, shorter recovery time, and lower dosage requirements compared to esketamine (all $P < 0.001$). However, it was associated with more pronounced respiratory depression, a higher incidence of intraoperative body movements, and hemodynamic suppression. Conversely, esketamine provided greater hemodynamic stability, minimal respiratory impact, and a significantly lower incidence of postoperative restlessness ($P < 0.001$). Pediatric patients showed a higher incidence of postoperative nausea and vomiting (PONV) with both agents. Significant drug-population interactions ($P < 0.05$) were observed for sedation onset, respiratory depression, and recovery time. Conclusion: Remimazolam offers faster onset and recovery but carries higher cardiorespiratory risks. Esketamine provides superior hemodynamic stability and is associated with less restlessness. The anesthetic effects show significant age-dependent variations, necessitating individualized drug selection based on patient age, physiological status, and surgical type.

Keywords: Esketamine, remimazolam, adult, pediatric, anesthetic efficacy, multimodal analysis

Introduction

The selection and administration of general anesthetics significantly influence surgical safety and patient outcomes [1]. Recent advancements in perioperative multimodal monitoring have expanded the clinical evaluation of anesthetic agents beyond traditional sedation and analgesia to encompass hemodynamic stability, organ protection, postoperative recovery quality, and neurocognitive functions [2, 3]. This broader perspective is underscored by investigations into how anesthetics can modulate molecular pathways critical for cognitive processes, such as memory consolidation [4]. Esketamine [5] and remimazolam [6], as novel intravenous anesthetics, exhibit distinct clinical advantages in adult and pediatric populations through different mechanisms. Esketamine acts as an N-methyl-D-aspartate (NMDA) receptor antagonist, while remimazolam is a γ-aminobutyric acid type A (GABA-A) receptor agonist. However, their age-dependent pharmacological profiles and comprehensive clinical effects require further investigation.

As the S-enantiomer of ketamine, esketamine provides potent analgesia with mild sympathomimetic effects and minimal respiratory depression. Its applications in pediatric anesthesia are particularly notable. Intramuscular administration (0.5-1 mg/kg) achieves rapid sedation while preserving spontaneous ventilation, making it valuable for uncooperative children or those requiring non-invasive induction [7]. Its hemodynamic-stabilizing effects may also benefit hypovolemic or hypotensive patients [8]. In contrast, remimazolam, an ultra-short-acting

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benzodiazepine derivative metabolized by plasma esterases, offers rapid onset, predictable recovery, and minimal cardiovascular depression [9, 10]. Clinical research in adults has demonstrated its potential to reduce postoperative delirium for anesthetic induction and maintenance in frail elderly patients [11].

Despite accumulating evidence, current research predominantly examines isolated populations without directly comparing age-specific pharmacokinetics or clinical outcomes. Moreover, most studies focused on limited endpoints rather than conducting systematic evaluations that integrate hemodynamic stability, respiratory function, and recovery quality. To address these gaps, this retrospective study analyzes clinical data from adult and pediatric surgical patients, aiming to delineate optimal clinical scenarios for intramuscular esketamine versus intravenous remimazolam. It also seeks to validate remimazolam's potential advantages in reducing vasopressor requirements, thereby facilitating its adoption in high-risk populations. By systematically comparing the comprehensive perioperative profiles of both agents, our findings are expected to provide evidence for optimizing agent selection based on patient age and specific clinical needs.

Materials and methods

General data

This retrospective study analyzed 264 surgical patients (141 adults and 123 children) who underwent surgery at our hospital between January 2022 and January 2025. Baseline characteristics showed no significant differences between esketamine and remimazolam groups in either adult or pediatric patients (all $P > 0.05$) (**Tables 1** and **2**). The sample size was calculated using the formula:

$$n = \frac{2\left(Z_{\alpha/2} + Z_{\beta}\right)^2 \cdot \sigma^2}{\Delta^2}$$

Where $Z_{\alpha/2} = 1.96$, $Z_{\beta} = 0.84$, and the pooled standard deviation (σ) = 4.53. The estimated required sample size was 37 per group, confirming that the total of 264 cases provided sufficient statistical power. The study was approved by the Medical Ethics Committee of Xianning Central Hospital, and the requirement for informed consent was waived due to the retrospective nature of the analysis.

Inclusion criteria included: 1) adult patients aged ≥ 18 years or pediatric patients aged 1 month-17 years; 2) American Society of Anesthesiologists (ASA) physical status level I-III undergoing elective surgery; 3) intraoperative use of esketamine or remimazolam as the primary intravenous sedative/anesthetic, with clearly documented administration routes, dosages, and timing; 4) complete intraoperative monitoring data and 48-hour postoperative follow-up records. Exclusion criteria were: 1) known hypersensitivity to esketamine, remimazolam, or their excipients; 2) severe comorbidities (e.g., hepatic or renal insufficiency, significant neurological disorders); 3) occurrence of major intraoperative adverse events; 4) excessively short or long surgical duration; or 5) incomplete monitoring data due to technical interruptions.

Anesthetic regimen

All anesthetic management followed protocols approved by the Department of Anesthesiology and was administered by senior anesthesiologists to ensure consistency.

The esketamine protocol utilized the drug's potent analgesic and hemodynamic-stabilizing properties. For adult induction, combined intravenous agents were used: midazolam (0.02-0.03 mg/kg) followed sequentially by esketamine (0.5-1 mg/kg), fentanyl (2-3 μg/kg), and rocuronium (0.6 mg/kg). Hemodynamically compromised patients received esketamine as the primary induction agent (0.5-1.5 mg/kg). Maintenance involved continuous esketamine infusion (0.25-0.5 mg/kg/h) with propofol or remifentanil, optionally supplemented with inhaled anesthetics. For postoperative analgesia, an esketamine infusion (0.125-0.25 mg/kg/h) was initiated 30-40 minutes before surgical closure. Pediatric induction utilized intramuscular administration (3-5 mg/kg with anticholinergics) for uncooperative children, or intravenous dosing (0.5-1 mg/kg). Maintenance infusions (0.25-1 mg/kg/h) were titrated according to age and surgical stimulus. This protocol was also applied for diagnostic procedure sedation.

The remimazolam protocol was based on the drug's rapid onset, predictable recovery, and

Table 1. Comparative analysis by anesthetic agent in children

Parameter	Esketamine (n = 63)	Remimazolam (n = 60)	t/X^2	*P*
Age (year)	4.0 ± 1.71	3.98 ± 1.75	0.046	0.964
Weight (kg)	22.8 ± 4.86	22.0 ± 5.05	0.767	0.445
Operation duration (min)	27.5 ± 7.29	27.2 ± 9.55	0.175	0.862
Drug dosage (mg/kg)	1.51 ± 0.19	0.21 ± 0.03	44.35	< 0.001
Time to sedation target (min)	5.01 ± 0.48	3.15 ± 0.43	18.78	< 0.001
Heart rate fluctuation (%)	0.14 ± 0.03	-0.15 ± 0.05	33.52	< 0.001
SBP (%)	0.16 ± 0.03	-0.14 ± 0.05	36.82	< 0.001
MAP (%)	0.15 ± 0.03	-0.15 ± 0.05	37.76	< 0.001
Minimum respiratory rate (bpm)	21.1 ± 1.50	15.2 ± 2.54	12.92	< 0.001
Minimum SpO_2 (%)	0.99 ± 0.01	0.96 ± 0.01	14.19	< 0.001
Duration of SpO_2 < 90% (s)	1.38 ± 2.37	27.1 ± 8.79	18.98	< 0.001
Recovery time (min)	10.1 ± 1.01	7.15 ± 0.91	14.70	< 0.001
ASA classification (I) [n (%)]	45 (71.4%)	42 (70%)	0.173	0.863
ASA classification (II) [n (%)]	18 (28.6%)	18 (30%)		
ASA classification (III) [n (%)]	0 (0%)	0 (0%)		
Body movements (0) [n (%)]	45 (71.4%)	23 (38.3%)	4.181	< 0.001
Body movements (1) [n (%)]	18 (28.6%)	26 (43.3%)		
Body movements (2) [n (%)]	0 (0%)	11 (18.3%)		
PONV (present) [n (%)]	55 (87.3%)	52 (86.7%)	0.105	0.917
PONV (absent) [n (%)]	8 (12.7%)	8 (13.3%)		
Restlessness (present) [n (%)]	50 (79.3%)	60 (100%)	3.721	< 0.001
Restlessness (absent) [n (%)]	13 (20.6%)	0 (0%)		

Note: SBP, systolic blood pressure; MAP, mean arterial pressure; SpO_2, peripheral oxygen saturation; ASA, American Society of Anesthesiologists; PONV, postoperative nausea and vomiting.

cardiovascular stability. Adult induction employed a loading dose (0.1-0.3 mg/kg over > 30 seconds) with mandatory opioids and neuromuscular blockers. Maintenance infusion (0.5-1.5 mg/kg/h or 0.1-0.25 mg/kg/min) was titrated to effect, with typical emergence within 5-15 minutes after discontinuation. Flumazenil was available for reversal. Pediatric dosing was age-stratified: infants < 1 year received 0.3-0.4 mg/kg, while children ≥ 1 year received 0.2-0.3 mg/kg, both with concomitant opioids. Maintenance infusions (0.5-2 mg/kg/h) were precisely titrated according to age and surgical requirements. Its favorable pharmacokinetic profile supports expanded pediatric application.

Data collection

Preoperative demographic and clinical characteristics, including age, weight, and ASA physical status, were extracted from the electronic medical record system. Intraoperative parameters, comprising operation duration, drug dosage, time to target sedation, heart rate fluctuation, systolic blood pressure (SBP), mean arterial pressure (MAP), minimum respiratory rate, and peripheral oxygen saturation (SpO_2), were continuously monitored and recorded. Postoperative outcomes recorded within 24 hours included recovery time, incidence of body movements, postoperative nausea and vomiting (PONV), and restlessness. To ensure data integrity and accuracy, two independent investigators performed blinded data extraction with cross-verification, reconciling any discrepancies or missing values through a systematic review of the original records.

Definition of serious adverse events

Significant respiratory depression: SpO_2 < 90% persisting for > 30 seconds.

Significant hypotension: A decrease in MAP of > 30% from the baseline level.

PONV requiring intervention: Nausea, retching, or vomiting within 24 hours postoperatively necessitating rescue intervention (e.g., intrave-

Table 2. Comparative analysis by anesthetic agent in adults

Parameter	Esketamine (n = 72)	Remimazolam (n = 69)	t/X^2	*P*
Adult				
Age (year)	48.2 ± 9.46	48.9 ± 8.20	0.350	0.727
Weight (kg)	68.5 ± 4.94	70.2 ± 5.21	1.610	0.109
Operation duration (min)	30.9 ± 10.0	33.5 ± 10.4	1.264	0.208
Drug dosage (mg/kg)	4.04 ± 0.40	0.16 ± 0.01	62.14	< 0.001
Time to sedation target (min)	4.04 ± 0.40	2.56 ± 0.34	19.33	< 0.001
Heart rate fluctuation (%)	0.09 ± 0.02	-0.09 ± 0.03	40.27	< 0.001
SBP (%)	0.11 ± 0.02	-0.08 ± 0.02	40.22	< 0.001
MAP (%)	0.10 ± 0.02	-0.09 ± 0.02	40.22	< 0.001
Minimum respiratory rate (bpm)	15.3 ± 1.17	13.3 ± 2.81	4.785	< 0.001
Minimum SpO_2 (%)	0.98 ± 0.01	0.95 ± 0.02	7.374	< 0.001
Duration of SpO_2 < 90% (s)	3.04 ± 4.56	20.9 ± 9.88	11.56	< 0.001
Recovery time (min)	9.17 ± 1.09	5.63 ± 0.90	18.77	< 0.001
ASA classification (I) [n (%)]	36 (50%)	35 (50.7%)	0.02	0.988
ASA classification (II) [n (%)]	27 (37.5%)	25 (36.2%)		
ASA classification (III) [n (%)]	9 (12.5%)	9 (13%)		
Body movements (0) [n (%)]	38 (57.8%)	30 (43.5%)	43.101	< 0.001
Body movements (1) [n (%)]	34 (47.2%)	17 (24.6%)		
Body movements (2) [n (%)]	0 (0%)	22 (31.9%)		
PONV (present) [n (%)]	62 (86.7%)	59 (86%)	0.103	0.918
PONV (absent) [n (%)]	10 (13.3%)	10 (14%)		
Restlessness (present) [n (%)]	62 (86.7%)	69 (100%)	3.212	0.001
Restlessness (absent) [n (%)]	10 (13.3%)	0 (0%)		

Note: SBP, systolic blood pressure; MAP, mean arterial pressure; SpO_2, peripheral oxygen saturation; ASA, American Society of Anesthesiologists; PONV, postoperative nausea and vomiting.

nous ondansetron 4 mg or additional fluid replacement). Symptoms not requiring intervention were excluded.

Severe restlessness: Defined as meeting any of the following criteria: (1) Riker Sedation-Agitation Scale score ≥ 6; (2) Hazardous behaviors, such as attempts to remove intravenous lines, drainage tubes, or monitoring devices; (3) Requirement for physical restraint or pharmacological intervention due to agitation. Cases involving only mild uneasiness alleviated by verbal reassurance were excluded.

Two-way analysis of variance (ANOVA)

Two-way ANOVA was performed using R statistical software to examine the interaction effects between anesthetic agents (esketamine vs. remimazolam) and patient populations (adults vs. children). The linear model was specified as: outcome variable - drug * population (data = RDATA), where the * operator simultaneously incorporated main effects and their interaction term. Model fitting was performed using the aov() function, with variance components extracted via the summary() function. The significance of interaction effects was determined by evaluating the *F*-statistic and corresponding *P*-value of the drug:population term, with $P < 0.05$ considered statistically significant. For models demonstrating significant interaction effects, post hoc analyses were conducted using the emmeans package. Estimated marginal means were computed via the emmeans() function with the model specification - drug * population, followed by multiple comparisons using the contrast(..., method = "tukey") function. The interaction patterns were visualized through effect plots to facilitate clinical interpretation.

Statistical analysis

All statistical analyses were performed using SPSS version 27.0 and R version 4.4.3.

Continuous variables following a normal distribution were presented as mean ± standard deviation ($\bar{X} \pm SD$)), while categorical data were expressed as n (%). Between-group comparisons were conducted using independent samples *t*-tests and chi-square tests. Point-biserial correlation analysis was employed to examine relationships between binary and continuous variables. Data visualization was generated using the ggplot2 package in R. A *P*-value < 0.05 was considered statistically significant.

Results

Comparative analysis by anesthetic agent

Baseline characteristics (age, weight, operation duration, ASA classification) were comparable between the esketamine and remimazolam groups. Pharmacological comparisons revealed notable differences. Remimazolam demonstrated significant pharmacokinetic advantages, with a substantially shorter time to sedation target and recovery time compared to esketamine (all $P < 0.001$), while requiring a lower dosage. However, it was associated with more pronounced respiratory depression, evidenced by a lower minimum respiratory rate, lower minimum SpO_2, and a longer duration of $SpO_2 < 90\%$. Hemodynamic suppression (negative fluctuations in heart rate and blood pressure) and a significantly higher incidence of intraoperative body movements (especially Grade 2) were also observed in the remimazolam group. Conversely, esketamine, despite its slower onset and recovery, provided superior hemodynamic stability (mild positive fluctuations in heart rate and blood pressure) with minimal respiratory impact. Regarding adverse events, the esketamine group showed a significantly lower incidence of postoperative restlessness in both pediatric and adult populations. The incidence of PONV was similar between the two groups (**Tables 1** and **2**).

Population-specific comparative analysis

The utilization rates of anesthetic agents were similar between adults and children, while baseline characteristics (age, weight, ASA classification) differed significantly. Pharmacological responses exhibited age-dependent patterns: with esketamine, children required a longer time to sedation target and higher weight-adjusted doses; whereas with remimazolam, adults achieved the sedation target faster and recovered more quickly, but children exhibited more pronounced body movements (Grade 2 in 36.7% of pediatric cases). Hemodynamically, esketamine showed mild sympathomimetic effects in both groups, while remimazolam induced slight circulatory depression in adults. Regarding respiratory effects, the minimum respiratory rate was generally higher in children. Notably, in the remimazolam group, the duration of $SpO_2 < 90\%$ was significantly longer in adults than in children. For postoperative recovery, recovery time was generally shorter in adults. Among adverse events, PONV incidence was significantly higher in children for both anesthetics, while no significant population-based difference was observed for postoperative restlessness (**Tables 3** and **4**).

Interaction effect analysis

The type of anesthetic agent had a highly significant main effect ($P < 0.001$) on dosage, time to sedation target, cardiovascular responses, respiratory effects, body movements, recovery time, and restlessness. Population type demonstrated significant main effects ($P < 0.05$) on ASA classification, operation duration, dosage, time to sedation target, heart rate/respiratory rate/SpO_2 patterns, body movements, recovery time, and PONV. Notably, the pharmacological effects on cardiovascular parameters (heart rate, blood pressure, and SpO_2) maintained consistent directional trends across both populations without significant interaction effects. However, drug-specific impacts on sedation onset, respiratory depression, body movements, recovery time, PONV, and restlessness exhibited substantial population-dependent variations (**Table 5**; **Figure 1**).

Correlation analysis

Point-biserial correlation analysis revealed that anesthetic drug type demonstrated strong negative correlations with dosage, time to sedation target, and cardiovascular parameters including heart rate fluctuation, SBP, and MAP. Patient population showed strong negative correlations with age and weight. Strong positive correlations were observed among cardiovascular parameters, including heart rate fluctuation, SBP and MAP. Respiratory and recovery metrics showed strong inverse relationships with minimum respiratory rate and minimum SpO_2,

Table 3. Comparative analysis by population group with esketamine

Parameter	Adults (n = 72)	Children (n = 63)	t/X^2	*P*
Age (year)	48.3 ± 9.46	4 ± 1.71	32.35	< 0.001
Weight (kg)	68.5 ± 4.94	22.8 ± 4.86	44.24	< 0.001
Operation duration (min)	30.9 ± 10.0	27.5 ± 7.52	1.876	0.063
Drug dosage (mg/kg)	1.08 ± 0.1	1.51 ± 0.19	-14.38	< 0.001
Time to sedation target (min)	4.04 ± 0.40	5.01 ± 0.48	10.50	< 0.001
Heart rate fluctuation (%)	0.09 ± 0.02	0.14 ± 0.03	7.762	< 0.001
SBP (%)	1.11 ± 0.02	0.16 ± 0.03	10.54	< 0.001
MAP (%)	0.10 ± 0.02	0.15 ± 0.03	10.71	< 0.001
Minimum respiratory rate (bpm)	15.3 ± 1.17	21.1 ± 1.50	19.31	< 0.001
Minimum SpO_2 (%)	0.98 ± 0.01	0.99 ± 0.01	6.952	< 0.001
SpO_2 (s)	3.04 ± 4.56	1.38 ± 2.37	12.003	< 0.001
Recovery time (min)	9.17 ± 1.09	10.14 ± 1.01	4.768	< 0.001
ASA classification (I) [n (%)]	36 (50.0%)	45 (71.4%)	3.283	0.001
ASA classification (II) [n (%)]	27 (37.5%)	18 (28.6%)		
ASA classification (III) [n (%)]	9 (12.5%)	0 (0%)		
Body movements (0) [n (%)]	42 (58.3%)	41 (65.1%)	1.749	0.072
Body movements (1) [n (%)]	30 (41.7%)	22 (34.9%)		
Body movements (2) [n (%)]	0 (0%)	0 (0%)		
PONV (present) [n (%)]	58 (80.6%)	59 (93.7%)	2.233	0.026
PONV (absent) [n (%)]	14 (19.4%)	4 (6.3%)		
Restlessness (present) [n (%)]	59 (81.9%)	53 (88.9%)	0.337	0.737
Restlessness (absent) (n (%))	13 (18.1%)	10 (11.1%)		

Note: SBP, systolic blood pressure; MAP, mean arterial pressure; SpO_2, peripheral oxygen saturation; ASA, American Society of Anesthesiologists; PONV, postoperative nausea and vomiting.

while exhibiting strong positive correlations with recovery time (**Figure 2**).

Comparative analysis of adverse events associated with different anesthetic drugs

The incidence of significant respiratory depression was significantly higher in the remimazolam group (36.43%, 47/129) compared to the esketamine group (0.74%, 1/135) ($P < 0.001$). Significant hypotension was observed in 25.58% (33/129) of patients receiving remimazolam, whereas no cases (0%) were documented in the esketamine group ($P < 0.001$). The incidence rates of other serious adverse events were comparable between the two groups (**Table 6**).

Comparative analysis of serious adverse reactions among specific populations

A statistically significant age-related difference was found for significant hypotension. The pediatric group demonstrated a markedly higher rate (25.20%) compared to the adult group (1.42%) ($P < 0.001$). No statistically significant differences were observed for other serious adverse events between these two demographic groups ($P > 0.05$) (**Table 7**).

Discussion

This comprehensive investigation, employing two-way ANOVA, interaction effect modeling, and correlation analysis, systematically examines the synergistic influences of anesthetic type and patient population on pharmacological outcomes, providing a foundation for developing personalized anesthetic management. Our comparative approach addresses a critical need in anesthesiology, where high-quality evidence to guide the selection of even established agents for specific procedures can be lacking, as highlighted by a Cochrane review on intra-articular morphine for knee arthroscopy [12].

The study confirms distinct pharmacodynamic and pharmacokinetic profiles for both agents. Remimazolam, a benzodiazepine derivative

Table 4. Comparative analysis by population group with remimazolam

Parameter	Adults (n = 69)	Children (n = 60)	t/X^2	*P*
Age (year)	48.9 ± 8.20	4.0 ± 1.71	34.83	< 0.001
Weight (kg)	70.2 ± 5.21	22.8 ± 4.86	43.80	< 0.001
Operation duration (min)	33.5 ± 10.4	27.5 ± 7.52	2.954	0.004
Drug dosage (mg/kg)	0.16 ± 0.01	1.51 ± 0.19	12.07	< 0.001
Time to sedation target (min)	2.56 ± 0.34	5.01 ± 0.48	7.217	< 0.001
Heart rate fluctuation (%)	-0.09 ± 0.03	0.14 ± 0.03	8.443	< 0.001
SBP (%)	-0.08 ± 0.02	0.16 ± 0.03	8.982	< 0.001
MAP (%)	-0.09 ± 0.02	0.15 ± 0.03	8.982	< 0.001
Minimum respiratory rate (bpm)	13.3 ± 2.81	21.1 ± 1.50	3.456	< 0.001
Minimum SpO_2 (%)	0.95 ± 0.02	0.99 ± 0.01	0.478	0.634
SpO_2 (s)	20.9 ± 9.88	1.38 ± 2.37	3.172	0.002
Recovery time (min)	5.63 ± 0.90	10.14 ± 1.01	8.177	< 0.001
ASA classification (I) [n (%)]	35 (50.7%)	42(70.0%)	3.016	0.003
ASA classification (II) [n (%)]	25 (36.2%)	18 (30.0%)		
ASA classification (III) [n (%)]	9 (13.0%)	0 (0%)		
Body movements (0) [n (%)]	36 (52.2%)	17 (28.3%)	3.749	0.012
Body movements (1) [n (%)]	22 (31.9%)	21 (35%)		
Body movements (2) [n (%)]	11 (15.9%)	22 (36.7%)		
PONV (present) [n (%)]	54 (78.3%)	57 (95%)	2.732	0.006
PONV (absent) [n (%)]	15 (21.7%)	3 (5%)		
Restlessness (present) [n (%)]	69 (100%)	60 (100%)	0	1
Restlessness (absent) [n (%)]	0 (0%)	0 (0%)		

Note: SBP, systolic blood pressure; MAP, mean arterial pressure; SpO_2, peripheral oxygen saturation; ASA, American Society of Anesthesiologists; PONV, postoperative nausea and vomiting.

that potentiates GABA-A receptor activity, demonstrates rapid onset and esterase-mediated metabolism. However, it requires cautious administration in patients with compromised respiratory reserve or cardiovascular fragility due to its potential for respiratory depression and mild circulatory suppression [13, 14]. Conversely, esketamine's NMDA receptor antagonism, while associated with higher dose requirements and slower onset, provides cardiovascular stimulation and superior respiratory stability, making it suitable for hemodynamically unstable patients or those with limited pulmonary reserve [15, 16]. Correlation analyses further validated these pharmacological profiles, revealing strong interdependencies among dosage, sedation onset, hemodynamic fluctuations, and recovery time, which may collectively serve as composite endpoints for dynamic assessment of anesthesia depth.

Patient age (adult vs. child) was identified as a critical variable contributing to pharmacological heterogeneity. Pediatric patients exhibited systematic differences in their response patterns to both drugs compared to adult patients. With esketamine, pediatric patients required higher weight-adjusted doses and had slower onset; whereas with remimazolam, pediatric patients displayed more pronounced intraoperative body movements. PONV incidence was significantly higher in pediatric patients for both anesthetics. These findings are consistent with previous reports indicating that pediatric patients exhibit heightened sensitivity to prescription opioids [17] and that distinct remimazolam pharmacokinetics exist between children and adults [18]. Our results further substantiate and extend these observations. Pharmacokinetically, children's immature hepatic enzyme systems coexist with enhanced metabolic rates, potentially necessitating higher relative esketamine concentrations despite lower absolute doses, as evidenced by significant interaction effects. Differences in respiratory physiology were also consequential. Children with elevated baseline respiratory rates but limited functional reserve maybe more sus-

Table 5. Results of interaction effects

Variable	Drug main effect	Population main effect	Interaction effect (drug:population)
Operation duration	$P = 0.386$	$P < 0.001$	$P = 0.300$
Drug dosage	$P < 0.001$	$P < 0.001$	$P < 0.001$
Time to sedation target	$P < 0.001$	$P < 0.001$	$P = 0.003$
Heart rate fluctuation	$P < 0.001$	$P = 0.037$	$P < 0.001$
SBP	$P < 0.001$	$P = 0.690$	$P < 0.001$
MAP	$P < 0.001$	$P = 0.470$	$P < 0.001$
Minimum respiratory rate	$P < 0.001$	$P < 0.001$	$P < 0.001$
Body movements	$P < 0.001$	$P = 0.009$	$P = 0.002$
Recovery time	$P < 0.001$	$P < 0.001$	$P = 0.048$
PONV	$P = 0.880$	$P = 0.004$	$P = 0.001$
Restlessness	$P < 0.001$	$P = 0.120$	$P = 0.130$

Note: SBP, systolic blood pressure; MAP, mean arterial pressure; PONV, postoperative nausea and vomiting.

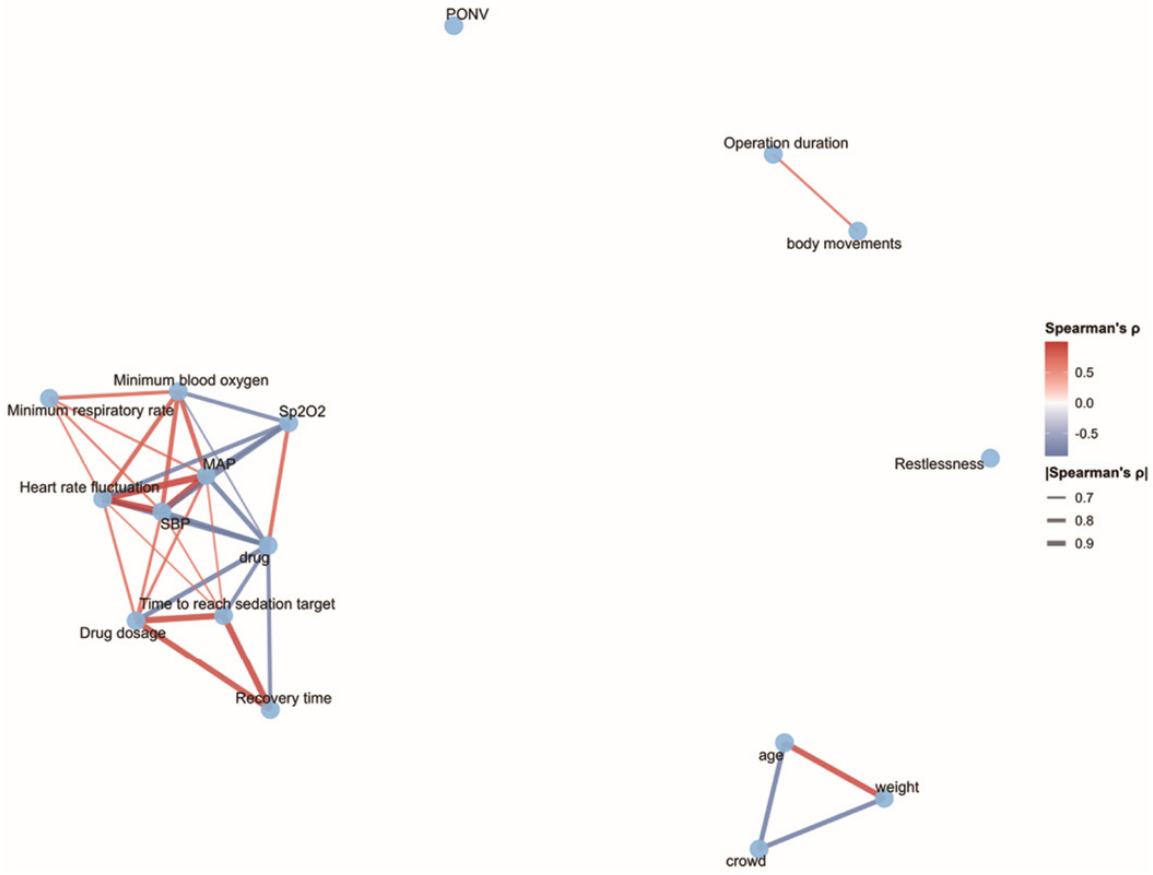

Figure 1. Interaction effect plot. Note: Node color indicates variable domain, edge color indicates correlation direction (blue: positive; red: negative), and edge thickness corresponds to the absolute correlation coefficient. Only correlations with $|r| > 0.6$ are displayed.

ceptible to remimazolam-induced respiratory depression. Adults demonstrated greater tolerance to esketamine's cardiovascular stimulation. The weak correlations between pediatric emergence agitation/movement and cardiorespiratory parameters suggest predominant

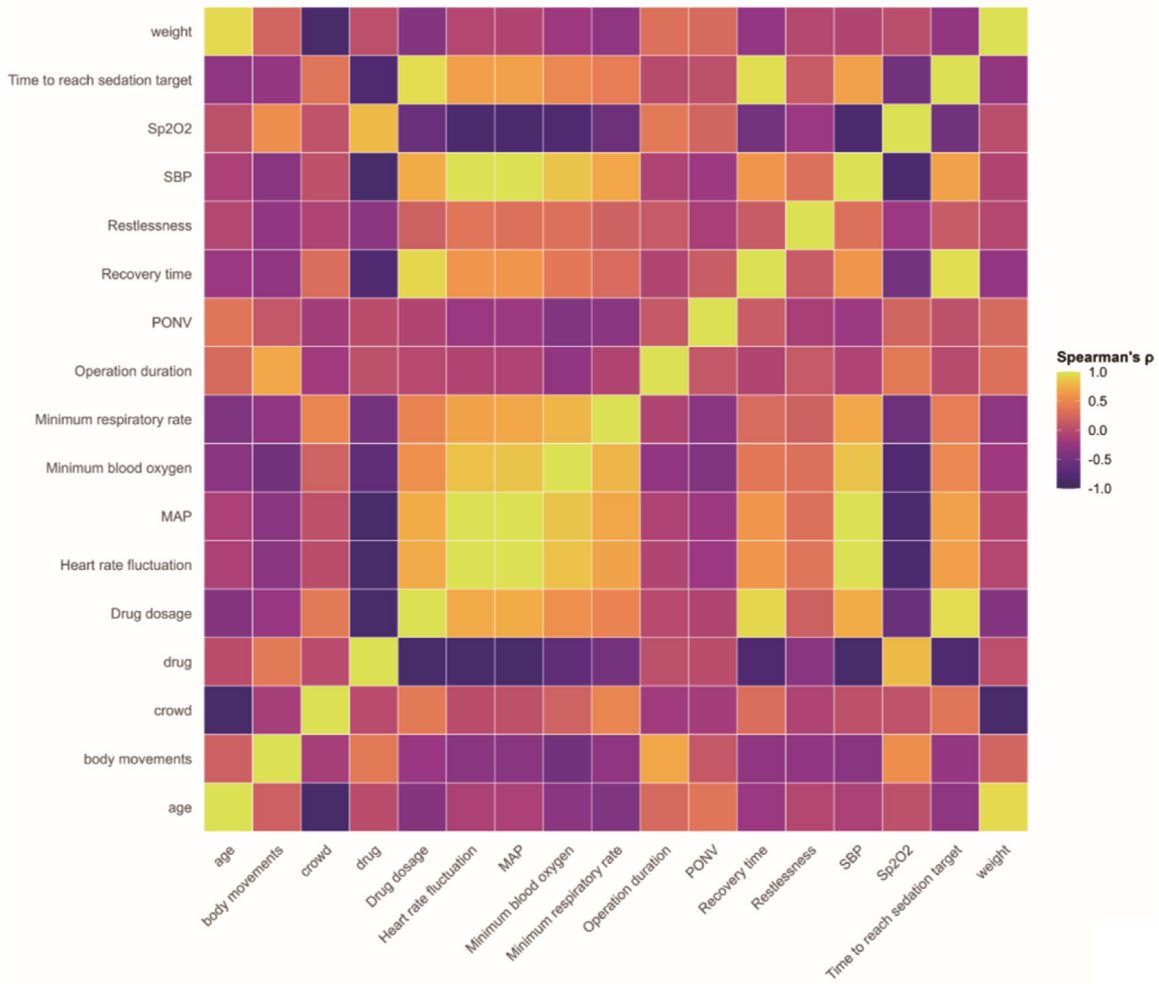

Figure 2. Correlation analysis heatmap. Note: Color intensity represents the strength and direction of the correlation.

influences from central sensitization and nociceptive processes, underscoring the need for adjunctive analgesia.

The analysis of serious adverse events reinforces the distinct risk profiles of these two anesthetics: remimazolam was associated with a significantly higher risk of respiratory depression and hypotension compared to esketamine. These clinical observations, particularly the greater susceptibility to hypotension in pediatric patients, align with the known pharmacological and physiological differences between the drugs. This underscores the principle that anesthetic agents can elicit unique and sometimes unexpected adverse effects, which may be dependent on the drug class, dosage, and patient population. For instance, beyond the cardiopulmonary effects observed here, other opioid-based analgesics like sufentanil have been linked to a distinct adverse outcome - maternal intrapartum fever - when used in neuraxial anesthesia for labor [19].

The interaction analysis provides clinically actionable insights for agent selection across different clinical scenarios. Firstly, while remimazolam demonstrates utility for brief pediatric procedures, it necessitates enhanced respiratory monitoring. In contrast, esketamine appears advantageous in complex surgical settings. These findings align with clinical evidence: remimazolam may induce respiratory distress [20, 21], whereas low-dose esketamine maintains safety and efficacy with minimal respiratory depression [22, 23]. Furthermore, adult patients at high risk for PONV may benefit from esketamine selection. Meanwhile,

Table 6. Comparative analysis of adverse events associated with different anesthetic drugs

Parameter	Esketamine (n = 135)	Remimazolam (n = 129)	t/X^2	*P*
Significant respiratory depression (present) [n (%)]	1 (0.74%)	47 (36.43%)		
Significant respiratory depression (absent) [n (%)]	134 (99.26%)	82 (63.57%)	7.516	< 0.001
Significant hypotension (present) [n (%)]	0 (0%)	33(25.58%)		
Significant hypotension (absent) [n (%)]	135 (100%)	96 (74.42%)	6.282	< 0.001
PONV requiring intervention (present) [n (%)]	6 (4.44%)	8 (6.20%)		
PONV requiring intervention (absent) [n (%)]	129 (95.56%)	121 (93.80%)	0.637	0.524
Severe restlessness (present) [n (%)]	8 (5.93%)	10 (7.75%)		
Severe restlessness (absent) [n (%)]	127 (94.07%)	119 (92.25%)	0.588	0.556

Note: PONV, postoperative nausea and vomiting.

Table 7. Comparative analysis of serious adverse reactions among specific populations

Parameter	Adults (n = 141)	Children (n = 123)	t/X^2	*P*
Significant respiratory depression (present) [n (%)]	24 (17.02%)	22 (17.89%)		
Significant respiratory depression (absent) [n (%)]	117 (82.98%)	101 (82.11%)	1.185	0.853
Significant hypotension (present) [n (%)]	2 (1.42%)	31 (25.20%)		
Significant hypotension (absent) [n (%)]	139 (98.58%)	92 (74.80%)	5.829	< 0.001
PONV requiring intervention (present) [n (%)]	8 (5.67%)	6 (4.88%)		
PONV requiring intervention (absent) [n (%)]	133 (94.33%)	117 (95.12%)	0.288	0.774
Severe restlessness (present) [n (%)]	11 (7.80%)	12 (9.76%)		
Severe restlessness (absent) [n (%)]	130 (92.20%)	111 (90.24%)	0.562	0.574

Note: PONV, postoperative nausea and vomiting.

remimazolam's predictable recovery profile makes it suitable for ambulatory surgeries, despite requiring vigilance against its potential cardiovascular inhibitory effects [24, 25]. Finally, regarding emergence agitation, the two agents demonstrate distinct mechanistic profiles. Remimazolam shows a greater propensity to provoke agitation, whereas esketamine exhibits anti-agitation properties potentially mediated through NMDA receptor modulation. This population-independent, drug-specific regulatory mechanism underscores the crucial role of the NMDA pathway in agitation control and warrants dedicated investigation.

Several limitations merit acknowledgment: 1) The broad age range within the pediatric cohort precluded assessment of pharmacokinetic differences between neonates and older infants. 2) Potential confounding by unmeasured variables (e.g., specific surgical type and adjuvant medications) cannot be ruled out. 3) Larger, prospective validation cohorts are needed to confirm the observed interaction effects. Future investigations should incorporate pharmacokinetic modeling for dose optimization and explore combination regimens to balance efficacy and safety.

In conclusion, this study systematically compares remimazolam and esketamine in adult and pediatric patients. Remimazolam offers pharmacokinetic efficiency but is accompanied by more pronounced cardiorespiratory depression and a higher risk of body movements. Esketamine provides greater hemodynamic stability and a lower incidence of restlessness. Pediatric patients exhibit unique response patterns, including higher risks of PONV and hypotension. The effects of the drugs show significant age-dependent interactions across multiple key parameters. These findings emphasize that clinical anesthesia practice must adopt an individualized approach to drug selection, comprehensively considering patient age, physiological status, comorbidities, and surgical type. This study provides evidence-based guidance for advancing towards more precise and safer perioperative management.

Disclosure of conflict of interest

None.

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