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CLINICAL TRIAL REPORT

Remimazolam versus Sevoflurane for Paediatric Circumcision: A Randomised Controlled Trial Evaluating Emergence Delirium

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Background: Emergence delirium complicates up to 40% of paediatric sevoflurane anaesthetics. Remimazolam is an ultra-short-acting benzodiazepine with organ-independent esterase metabolism, offering rapid and predictable recovery. We tested whether remimazolam monotherapy could serve as a volatile-free alternative to reduce emergence delirium.

Methods: We conducted a prospective, randomised, assessor-blinded trial (ChiCTR2500095974). One hundred children aged 3–12 years (ASA I–II) undergoing circumcision were randomised 1:1 to remimazolam (0.3 mg kg^{-1} induction; 0.75 mg kg^{-1} h^{-1} maintenance) or sevoflurane (8% induction; 1.5–2.5 MAC maintenance). All received penile nerve block. The co-primary outcomes were induction and emergence times. The key secondary outcome was emergence delirium (PAED score ≥12).

Results: Emergence was faster with remimazolam (10.7 [SD 3.9] vs 13.5 [3.7] min; P<0.001). Induction was slower (80.8 [9.8] vs 52.3 [8.2] s; P<0.001) due to the slow-injection protocol. Emergence delirium occurred in 6/50 (12%) remimazolam patients versus 18/50 (36%) sevoflurane patients (relative risk 0.33; 95% CI 0.14–0.77; P=0.009; NNT 4.2). PACU stay was shorter (33.4 [8.5] vs 40.7 [10.9] min; P<0.001). Guardian anxiety reduction was threefold greater with remimazolam. Hypotension occurred in 6/50 (12%) remimazolam versus 1/50 (2%) sevoflurane patients (P=0.11); all cases were fluid-responsive.

Conclusion: Remimazolam monotherapy reduced emergence delirium by 67% compared with sevoflurane, yielding faster recovery and improved family experience. However, a trend towards transient hypotension warrants appropriate preoperative fluid management. Larger multicentre trials are needed to confirm safety and broader applicability.

Plain Language Summary:

- Emergence delirium affects up to 40% of children after sevoflurane anaesthesia, causing distress to patients and families.
- Remimazolam monotherapy reduced emergence delirium from 36% to 12% versus sevoflurane (relative risk 0.33; NNT 4.2).
- Remimazolam provided faster emergence (21% reduction) and shorter PACU stay (18% reduction).
- Transient hypotension occurred more frequently with remimazolam (12% vs 2%) but responded to fluid therapy.
- These findings support remimazolam as a volatile-free alternative for paediatric ambulatory anaesthesia.

Keywords: anaesthesia, paediatric, anaesthetics i.v., remimazolam, anaesthetics volatile, sevoflurane, complications, emergence delirium, randomised controlled trial

Introduction

Emergence delirium is a transient behavioural disturbance that occurs during recovery from general anaesthesia. It is characterised by inconsolable agitation, disorientation, and non-purposeful motor activity. In children, the reported incidence ranges from 10% to 80%, depending on anaesthetic technique, patient age, and diagnostic criteria.[1–3] Sevoflurane, the most widely used volatile agent for paediatric induction, is consistently associated with elevated

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emergence delirium risk.[4] This phenomenon causes substantial clinical burden: children may sustain self-injury, intravenous catheters and surgical dressings may be dislodged, nursing workload increases, and parents experience considerable distress when witnessing their child's dysphoric emergence.[5]

Current preventive strategies include prophylactic administration of propofol, opioids, α_2-agonists, or benzodiazepines. Each approach carries drawbacks including respiratory depression, delayed emergence, or residual sedation.[6] A more fundamental approach would be to replace sevoflurane entirely with an intravenous agent that offers inherently smoother emergence characteristics.

Remimazolam besylate is an ultra-short-acting benzodiazepine that is metabolised by tissue esterases to an inactive carboxylic acid metabolite. Unlike sevoflurane, whose elimination depends on alveolar ventilation and can be unpredictable in agitated children, this metabolic pathway yields context-insensitive pharmacokinetics independent of hepatic or renal function.[7–9] Its rapid offset allows predictable emergence without the ventilation-dependent washout variability that characterises volatile agents. Adult studies have shown favourable haemodynamic stability, and the availability of flumazenil reversal provides an additional safety margin.[10,11] Paediatric pharmacokinetic data now support weight-based dosing across the 3–12 year age range, with clearance rates comparable to those in adults.[12,13]

Cai and colleagues[14] recently showed that adding remimazolam to sevoflurane reduces emergence delirium in children undergoing laparoscopic surgery. Their work established proof-of-concept but left unanswered whether remimazolam could serve as the primary anaesthetic, thereby eliminating volatile agents entirely. This distinction has practical significance: total intravenous anaesthesia (TIVA) with remimazolam may suit resource-limited settings that lack scavenging infrastructure, reduce operating room pollution, and address ongoing concerns regarding volatile anaesthetic neurodevelopmental effects in young children.[15]

We hypothesised that intravenous remimazolam monotherapy would significantly reduce emergence delirium incidence compared with sevoflurane in children undergoing ambulatory surgery. We further postulated that this benefit would remain robust when accounting for potential confounders such as preoperative anxiety and postoperative pain. The co-primary objectives were to compare anaesthetic induction and emergence times. The key secondary objective was to evaluate emergence delirium incidence and quality of recovery.

Methods

Ethics and Registration

This prospective, randomised, assessor-blinded, parallel-group trial was approved by the Ethics Committee of Wanzhou District Maternal and Child Health Hospital (Reference 2024–44) and registered at the Chinese Clinical Trial Registry (ChiCTR2500095974; 15 January 2025; https://www.chictr.org.cn/showproj.html?proj=247814) before recruitment commenced. The published protocol contains full methodological details.[16] Written informed consent was obtained from guardians; children provided assent when developmentally appropriate. Remimazolam lacks paediatric licensing; its off-label use was explicitly disclosed. The study adhered to the Declaration of Helsinki (2024) and is reported according to CONSORT 2025 guidelines. The CONSORT Harms 2022 checklist is provided as Supplementary Material.

Patient and Public Involvement

No patients or members of the public were involved in the design, conduct, or reporting of this research. Guardians of participants were not consulted regarding study design or outcome selection. This represents a limitation of our study. However, guardian satisfaction was included as a secondary outcome measure to capture family perspectives on the perioperative experience.

Participants

Children aged 3–12 years, ASA physical status I–II, scheduled for elective circumcision under general anaesthesia at Wanzhou District Maternal and Child Health Hospital (July–November 2025) were screened for eligibility. Exclusion criteria comprised: anticipated difficult airway; allergy to study drugs; personal or family history of malignant

hyperthermia; developmental delay precluding PAED assessment; upper respiratory infection within 14 days; or concurrent enrolment in another trial.

Site and Interventionist Eligibility

This was a single-centre trial conducted at Wanzhou District Maternal and Child Health Hospital. All anaesthesia providers were board-certified anaesthesiologists with a minimum of five years' paediatric anaesthesia experience. Each had completed standardised training in remimazolam administration including at least 20 supervised cases before enrolling patients in this trial. Penile nerve blocks were performed by attending anaesthesiologists with documented competency in regional anaesthesia techniques.

Randomisation and Blinding

A statistician who was not involved in clinical care generated a computer-derived randomisation sequence stratified by age (3–6 vs 7–12 years) using permuted blocks of four. Allocations were sealed in sequentially numbered opaque envelopes that were opened after consent was obtained. Anaesthesia providers could not be blinded to drug administration route. Implementation bias was minimised through standardised protocols for both arms, identical monitoring, and application of mint-flavoured lip balm to all participants to mask sevoflurane odour. PACU assessors remained physically separated from the operating theatre and were prohibited from viewing anaesthetic records. Data analysts were blinded until database lock. We did not formally assess blinding success, which is a limitation of this study.

Anaesthetic Protocol

Standard fasting guidelines were followed. Monitoring comprised ECG, non-invasive blood pressure, pulse oximetry, and capnography. Baseline modified Yale Preoperative Anxiety Scale (mYPAS) and guardian State-Trait Anxiety Inventory (STAI-S) were recorded. No anxiolytic premedication was administered to avoid confounding emergence assessment.

In the remimazolam group, intravenous access was established after topical EMLA cream application. Remimazolam besylate 0.3 mg kg^{-1} was administered over a strictly timed 60-second period to minimise respiratory depression. This was followed by maintenance infusion. (MOAA/S) ≤1. If inadequate sedation (MOAA/S >1) persisted at exactly 120 s after the start of induction, a single rescue dose of remimazolam 0.1 mg kg^{-1} was administered (maximum total induction 0.4 mg kg^{-1}). The 0.3 mg kg^{-1} starting dose was based on recent ED_{95} data.[13]

In the sevoflurane group, inhalational induction was performed using 8% sevoflurane in oxygen via facemask. The concentration was then reduced to 1.5–2.5 MAC in oxygen/air for maintenance, titrated to MOAA/S ≤1. Rescue at 120 s comprised increasing sevoflurane to 4–6%.

In both groups, all patients received penile nerve block with 1% lidocaine (maximum 4 mg kg^{-1}) once adequate sedation was achieved. Airway was secured with a laryngeal mask airway. Mechanical ventilation maintained end-tidal CO_2 at 35–45 mmHg. Anaesthesia was discontinued at skin closure, and patients were transferred to the PACU upon return of spontaneous ventilation and protective reflexes.

Sedation depth was assessed using the MOAA/S scale rather than processed EEG. The MOAA/S correlates with bispectral index (r=0.57–0.66)[17] and avoids the practical challenges of paediatric electrode adhesion and the debated reliability of proprietary algorithms in children.[18] We acknowledge that this pragmatic choice cannot ensure equivalent anaesthetic states across pharmacologically distinct drug classes.

Outcomes

The co-primary outcomes were: (1) induction time, defined as the interval from drug administration to MOAA/S ≤1; and (2) emergence time, defined as the interval from drug discontinuation to MOAA/S=5.

The key secondary outcome was emergence delirium incidence, defined as peak Paediatric Anaesthesia Emergence Delirium (PAED) score ≥12 during PACU stay.[1] Trained nurses (inter-rater κ>0.8) assessed PAED at PACU arrival and then every 5 min until 30 min and at discharge. If delirium persisted, assessments continued beyond 30 min.

Other secondary outcomes included: peak PAED score; PACU duration; pain assessed using the FLACC scale at surgery end (T3) and PACU discharge (T4); guardian STAI-S post-emergence; guardian satisfaction (10-point VAS); and

adverse events including hypotension (MAP decrease >20%), hypoxaemia (SpO_2 <90% for >30 s), bradycardia (HR <60 or decrease >30%), and postoperative nausea and vomiting (PONV).

Changes to Trial Protocol

No changes were made to the trial protocol after commencement of recruitment. All outcomes and analyses were prespecified in the published protocol and statistical analysis plan.[16]

Statistical Analysis

Sample size was calculated based on the co-primary outcome of emergence time. Pilot data indicated a mean difference of 3 min (SD 4 min). At α=0.05 (two-sided) and 90% power, 44 patients per group were required. Anticipating 10% dropout, we enrolled 50 per group. The two co-primary outcomes were interpreted jointly rather than independently because they represented complementary dimensions of the same clinical question (induction and emergence kinetics); therefore, formal α-adjustment was not applied, which was consistent with our published protocol.[16]

No interim analyses were planned or conducted. No formal stopping rules were prespecified. The Data Safety Monitoring Board reviewed aggregate safety data after 50 participants (50% enrolment) without unblinding; no safety concerns were identified and the trial continued without modification.

Continuous data are presented as mean (SD) or median [IQR]; comparisons used independent *t*-tests or Mann–Whitney *U*-tests as appropriate. Categorical data are presented as n (%); comparisons used χ^2 or Fisher's exact tests. Relative risk (RR) with 95% CI was calculated for binary outcomes. Number needed to treat (NNT) was calculated as 1/absolute risk reduction. Effect sizes are reported as Cohen's d. Kaplan-Meier curves were constructed for time to emergence, with Cox proportional hazards regression used to estimate hazard ratios and Log rank tests for between-group comparison. Exploratory age-stratified subgroup analyses tested for interaction. Sensitivity analyses adjusted for baseline mYPAS. Post-hoc power exceeded 80% for the observed emergence delirium difference. Analyses used SPSS 26.0 on an intention-to-treat basis. P<0.05 was considered statistically significant. There were no missing data for any outcome.

Results

Participants

Between July and November 2025, 112 children were screened. Twelve were excluded (8 ineligible; 4 declined). One hundred were randomised (50 per group), and all completed the study without protocol deviation (Figure 1). All 100 participants received their assigned intervention and were included in the intention-to-treat analysis. Baseline characteristics were balanced (Table 1): age 7.6 (2.8) vs 7.4 (2.6) years; weight 25.8 (8.2) vs 24.6 (7.5) kg; mYPAS 36.8 (12.4) vs 37.2 (11.8); guardian STAI-S 50.4 (8.6) vs 50.8 (9.2).

Co-Primary Outcomes

Emergence time was 21% faster with remimazolam: 10.7 (3.9) vs 13.5 (3.7) min (mean difference −2.8 min; 95% CI −4.3 to −1.4; P<0.001; d=0.74). Kaplan-Meier analysis showed earlier emergence with remimazolam (hazard ratio 1.68; 95% CI 1.18–2.40; log-rank P<0.001; Supplementary Figure S2). Induction time was longer with remimazolam: 80.8 (9.8) vs 52.3 (8.2) s (mean difference +28.5 s; 95% CI 25.0–32.1; P<0.001). This difference reflected the mandatory 60-second injection protocol rather than pharmacological delay (Figure 2).

Emergence Delirium

Emergence delirium (PAED ≥12) occurred in 6 of 50 patients (12%) in the remimazolam group versus 18 of 50 (36%) in the sevoflurane group (RR 0.33; 95% CI 0.14–0.77; P=0.009). The absolute risk reduction was 24% (8.4–39.6%), corresponding to an NNT of 4.2 (2.5–11.1). Peak PAED scores were lower with remimazolam: 5.4 (3.4) vs 9.4 (4.2); median 4 [3–6] vs 11 [5–13] (P<0.001; d=1.04; Supplementary Figure S1). Sensitivity analysis using PAED ≥10 confirmed consistency of results (RR 0.33; P<0.001; Supplementary Table S2).

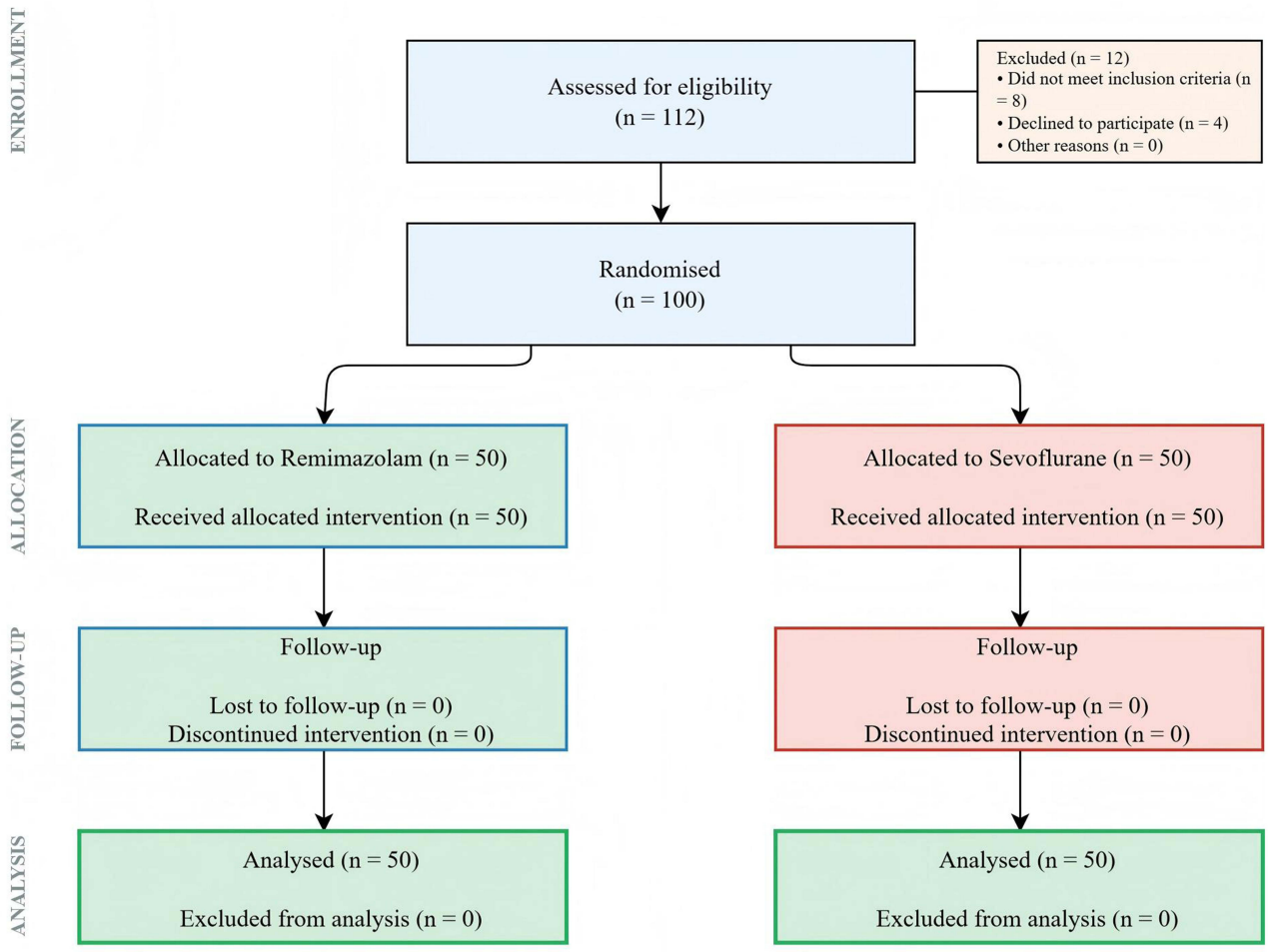

Figure 1 CONSORT flow diagram. All 100 randomised patients completed the study and were included in the intention-to-treat analysis.

Subgroup Analysis

The direction of effect was consistent across age strata (Figure 3). Among preschool children (3–6 years), emergence delirium was observed in 2 of 15 (13%) vs 8 of 21 (38%) patients (RR 0.35; P=0.14). Among school-age children (7–12 years), the incidence was 4 of 35 (11%) vs 10 of 29 (35%) (RR 0.33; P=0.035). The interaction P-value was 0.89, indicating no effect modification by age. However, these subgroup analyses were underpowered and should be considered hypothesis-generating (Supplementary Table S1).

Pain and Delirium

FLACC scores at surgery end were comparable (1.5 [0.8] vs 1.8 [1.2]; P=0.06), confirming equivalent penile block analgesia. At PACU discharge, FLACC scores were lower in the remimazolam group (0.22 [0.91] vs 1.18 [2.06]; P=0.003). The correlation between FLACC at PACU arrival and peak PAED was moderate (r=0.49; R^2=0.24; P<0.001), indicating that pain explained only 24% of PAED variance. This finding suggests that factors beyond analgesia, likely drug-specific emergence characteristics, contributed to the observed difference.

Recovery and Guardian Outcomes

PACU stay was 18% shorter with remimazolam: 33.4 (8.5) vs 40.7 (10.9) min (P<0.001). Clinically significant pain (FLACC ≥4) at discharge was less frequent in the remimazolam group: 1 of 50 (2%) vs 8 of 50 (16%) (P=0.031). Guardian post-emergence STAI-S was lower with remimazolam (29.2 [5.8] vs 43.7 [7.4]; P<0.001), and anxiety

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Table 1 Baseline Demographic and Clinical Characteristics

Characteristic	Remimazolam (n=50)	Sevoflurane (n=50)	P value
Demographics			
Age, years	7.6 ± 2.8	7.4 ± 2.6	0.712
Age group			0.296
Preschool (3–6 y) *School-age (7–12 y)* Weight, kg BMI, kg/m^2	15 (30%) 35 (70%) 25.8 ± 8.2 16.4 ± 2.1	21 (42%) 29 (58%) 24.6 ± 7.5 16.2 ± 1.9	 0.445 0.618
Clinical Status			
ASA physical status			0.841
ASA I *ASA II*	42 (84%) 8 (16%)	41 (82%) 9 (18%)	
Preoperative Anxiety			
mYPAS score Guardian STAI-S score	36.8 ± 12.4 50.4 ± 8.6	37.2 ± 11.8 50.8 ± 9.2	0.868 0.684
Baseline Haemodynamics			
Heart rate, bpm MAP, mmHg SpO_2, %	108 ± 15 82 ± 9 99 [98–100]	110 ± 14 81 ± 8 99 [98–100]	0.492 0.554 0.918
Surgical Details			
Duration of surgery, min Duration of anaesthesia, min	18.4 ± 4.2 28.6 ± 5.1	17.9 ± 3.8 27.8 ± 4.7	0.527 0.411

Notes: Table 1. Baseline demographic and clinical characteristics of participants. No significant differences were observed between groups for any baseline variable, confirming successful randomisation. Continuous variables were compared using independent *t*-tests or Mann–Whitney *U*-tests; categorical variables were compared using chi-square or Fisher's exact tests.

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; bpm, beats per minute; IQR, interquartile range; MAP, mean arterial pressure; mYPAS, modified Yale Preoperative Anxiety Scale; SD, standard deviation; SpO_2, peripheral oxygen saturation; STAI-S, State-Trait Anxiety Inventory, state subscale.

reduction (ΔSTAI-S) was threefold greater (21.2 [2.6] vs 7.1 [3.5]; P<0.001; d=4.56). Satisfaction was higher in the remimazolam group (8.6 [1.0] vs 7.4 [2.0]; P<0.001) (Figure 4 and Table 2).

Safety

No serious adverse events occurred in either group. No deaths, cardiac arrests, or unplanned intensive care admissions were observed. Hypotension (MAP decrease >20%) was more frequent with remimazolam: 6 of 50 (12%) vs 1 of 50 (2%) (RR 6.0; 95% CI 0.75–48; P=0.11). Affected patients had a mean nadir MAP of 58 (4) mmHg at a median of 3 min post-induction. None of these episodes was accompanied by bradycardia, which suggests that the mechanism was reduced systemic vascular resistance (benzodiazepine-mediated sympatholysis) rather than cardiac depression. All six patients responded to 10 mL kg^{-1} crystalloid within 5 min. No vasopressors were required, and discharge was not delayed.

Perioperative haemodynamic trajectories are detailed in Supplementary Figure S3.

Hypoxaemia (SpO_2 <90% for >30 s) occurred with equal frequency (4 of 50 [8%] vs 4 of 50 [8%]) and resolved with airway repositioning. Bradycardia was rare (1 of 50 [2%] vs 2 of 50 [4%]). PONV was absent with remimazolam (0 of 50

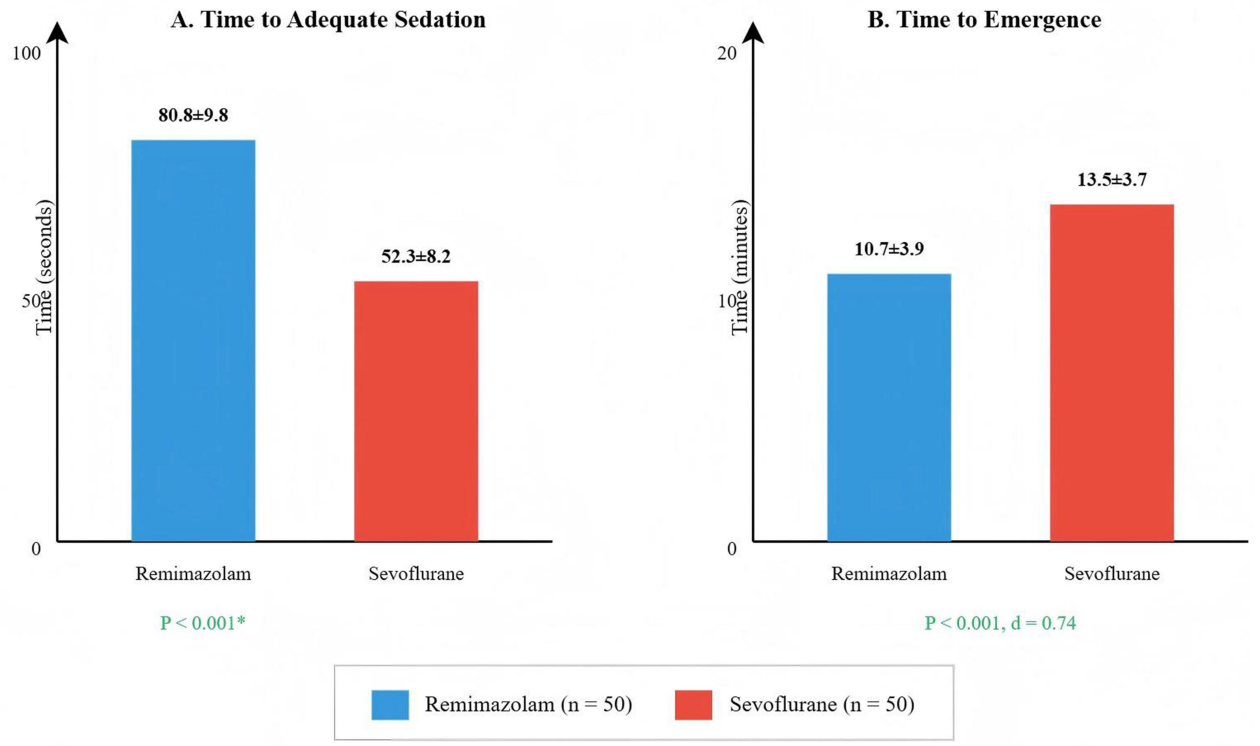

Figure 2 Timing outcomes. (**A**) Induction time (drug administration to MOAA/S ≤1). The longer remimazolam interval reflects the protocol-mandated 60-second injection. (**B**) Emergence time (drug discontinuation to MOAA/S=5). Values are mean (SD). *P<0.05.

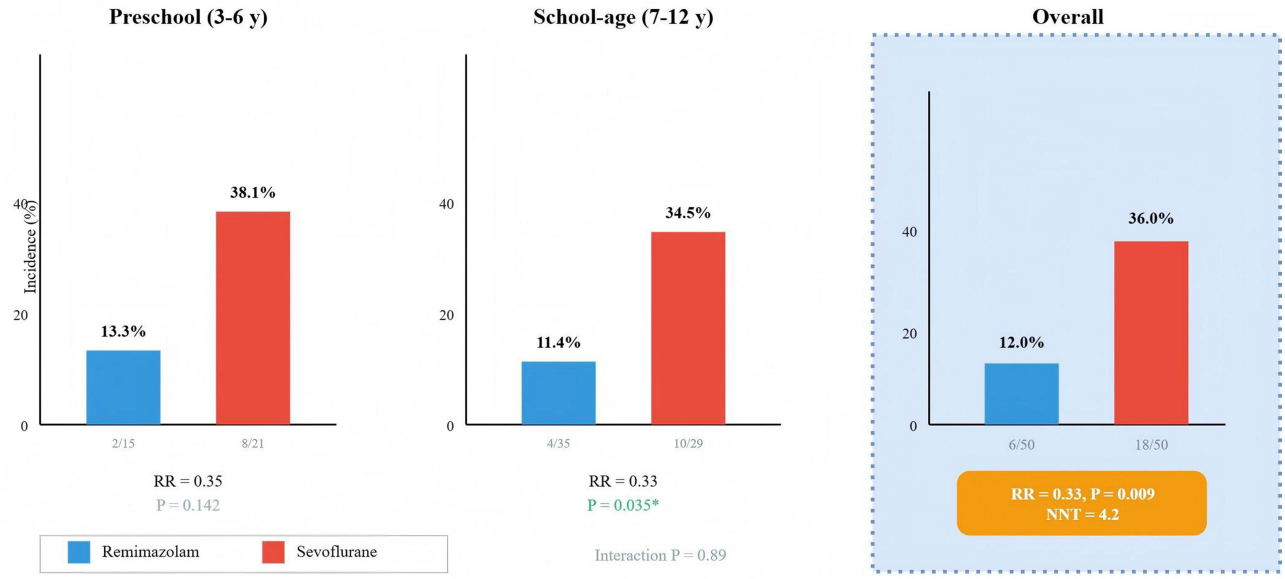

Figure 3 Emergence delirium incidence (PAED ≥12) by age stratum. Overall: 12% vs 36% (P=0.009); school-age: 11% vs 35% (P=0.035); preschool: 13% vs 38% (P=0.14). Interaction P=0.89. *P<0.05.

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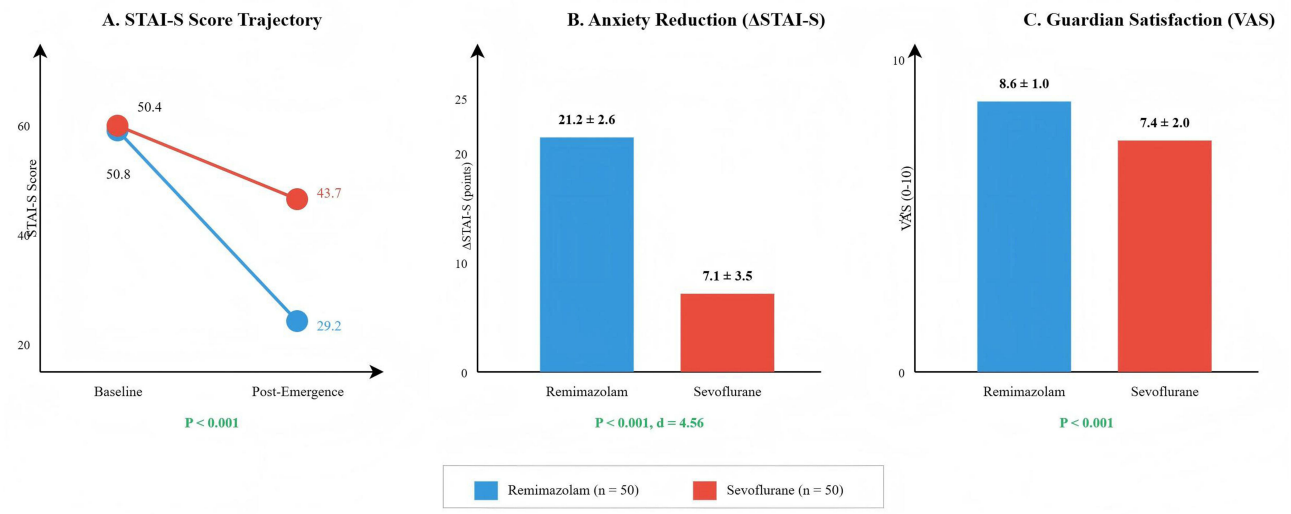

Figure 4 Guardian outcomes. (**A**) STAI-S trajectory. (**B**) Anxiety reduction magnitude. (**C**) Satisfaction scores.

[0%]) versus 5 of 50 (10%) with sevoflurane (P=0.06). No laryngospasm, bronchospasm, or allergic reactions occurred in either group (Figure 5).

A comprehensive summary of treatment effects across all outcomes is presented in Figure 6.

Discussion

This randomised trial shows that remimazolam monotherapy is associated with a 67% reduction in emergence delirium compared with sevoflurane in children undergoing ambulatory surgery. The number needed to treat was 4.2, meaning that for approximately every four children who receive remimazolam instead of sevoflurane, one emergence delirium episode is prevented.

Table 2 Primary and Secondary Outcomes

Outcomes	Remimazolam (n=50)	Sevoflurane (n=50)	Effect Estimate (95% CI)	Effect Size	P value
Co-Primary Outcomes					
Time to sedation, s Time to emergence, min	80.8 ± 9.8 10.7 ± 3.9	52.3 ± 8.2 13.5 ± 3.7	+28.5 (25.0–32.1) **−2.8 (−4.3 to −1.4)**	d = 3.15 d = 0.74	**<0.001** **<0.001**
Key Secondary Outcomes					
ED incidence (PAED ≥12)	6 (12%)	18 (36%)	**RR 0.33 (0.14–0.77)**	NNT = 4.2	**0.009**
Other Secondary Outcomes					
Peak PAED score Peak PAED score (median) PACU stay, min	5.4 ± 3.4 4 [3–6] 33.4 ± 8.5	9.4 ± 4.2 11 [5–13] 40.7 ± 10.9	**−4.0 (−5.5 to −2.5)** — **−7.3 (−11.2 to −3.5)**	d = 1.04 — d = 0.75	**<0.001** **<0.001** **<0.001**
Pain Outcomes					
FLACC at surgery end (T3) FLACC at PACU discharge (T4) FLACC ≥4 at discharge	1.46 ± 0.79 0.22 ± 0.91 1 (2%)	1.84 ± 1.17 1.18 ± 2.06 8 (16%)	−0.38 (−0.78 to 0.02) **−0.96 (−1.59 to −0.33)** **RR 0.13 (0.02–0.96)**	d = 0.38 d = 0.60 —	0.06 **0.003** **0.031**
Guardian-Reported Outcomes					

(*Continued*)

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Table 2 (Continued).

Outcomes	Remimazolam (n=50)	Sevoflurane (n=50)	Effect Estimate (95% CI)	Effect Size	P value
STAI-S post-emergence	29.2 ± 5.8	43.7 ± 7.4	−14.5 (−17.1 to −11.9)	d = 2.18	<0.001
ΔSTAI-S (baseline - post)	21.2 ± 2.6	7.1 ± 3.5	+14.1 (12.9–15.3)	d = 4.56	<0.001
Satisfaction (VAS 0–10)	8.6 ± 1.0	7.4 ± 2.0	+1.2 (0.6–1.8)	d = 0.76	<0.001
Safety Outcomes					
Hypotension	6 (12%)	1 (2%)	RR 6.00 (0.75–48.0)	—	0.112
Hypoxaemia	4 (8%)	4 (8%)	RR 1.00 (0.27–3.73)	—	1
Bradycardia	1 (2%)	2 (4%)	RR 0.50 (0.05–5.30)	—	1
PONV	0 (0%)	5 (10%)	**RR 0.09 (0.01–1.60)**	—	0.056
Laryngospasm	0 (0%)	0 (0%)	—	—	—
Serious adverse events	0 (0%)	0 (0%)	—	—	—

Notes: Effect estimates for continuous outcomes represent mean differences (remimazolam minus sevoflurane); negative values favour remimazolam for time-based outcomes and anxiety scores. Cohen's d interpretation: 0.2 = small, 0.5 = medium, 0.8 = large effect. The key secondary endpoint (emergence delirium incidence) showed a statistically significant 67% relative risk reduction with remimazolam. All secondary efficacy outcomes favoured the remimazolam group. Hypotension occurred more frequently with remimazolam but did not reach statistical significance and was clinically manageable.

Abbreviations: CI, confidence interval; d, Cohen's d; ED, emergence delirium; IQR, interquartile range; NNT, number needed to treat; PACU, post-anaesthesia care unit; PAED, Paediatric Anaesthesia Emergence Delirium scale; PONV, postoperative nausea and vomiting; RR, relative risk; SD, standard deviation; STAI-S, State-Trait Anxiety Inventory, state subscale; VAS, visual analogue scale.

Our findings extend those of Cai and colleagues,[14] who showed that adding remimazolam to sevoflurane reduces emergence delirium. We now show that sevoflurane can be eliminated entirely while the anti-delirium benefit is preserved. This represents an advance over their approach: where Cai's approach required polypharmacy, our remimazolam monotherapy simplifies the anaesthetic regimen and may be particularly suitable for settings that lack vaporisers or scavenging systems.

The 36% emergence delirium incidence in our sevoflurane arm is consistent with published estimates of 30–50% for sevoflurane anaesthesia in preschool children undergoing urological procedures,[3,19] which supports the external validity of our findings. The 12% incidence with remimazolam approaches rates reported with propofol TIVA, which suggests

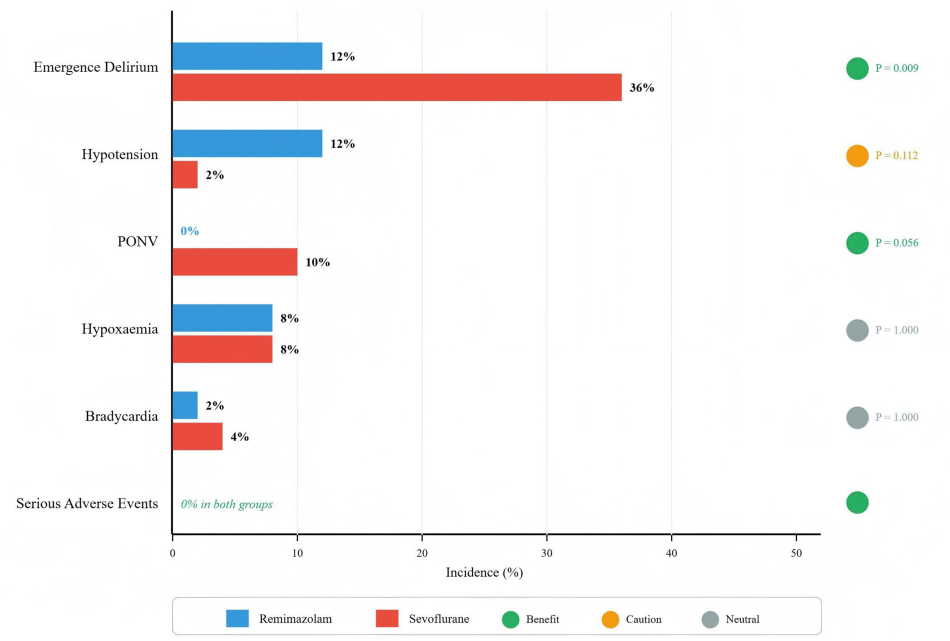

Figure 5 Adverse events. Green indicates benefit; Orange indicates caution; grey indicates neutral.

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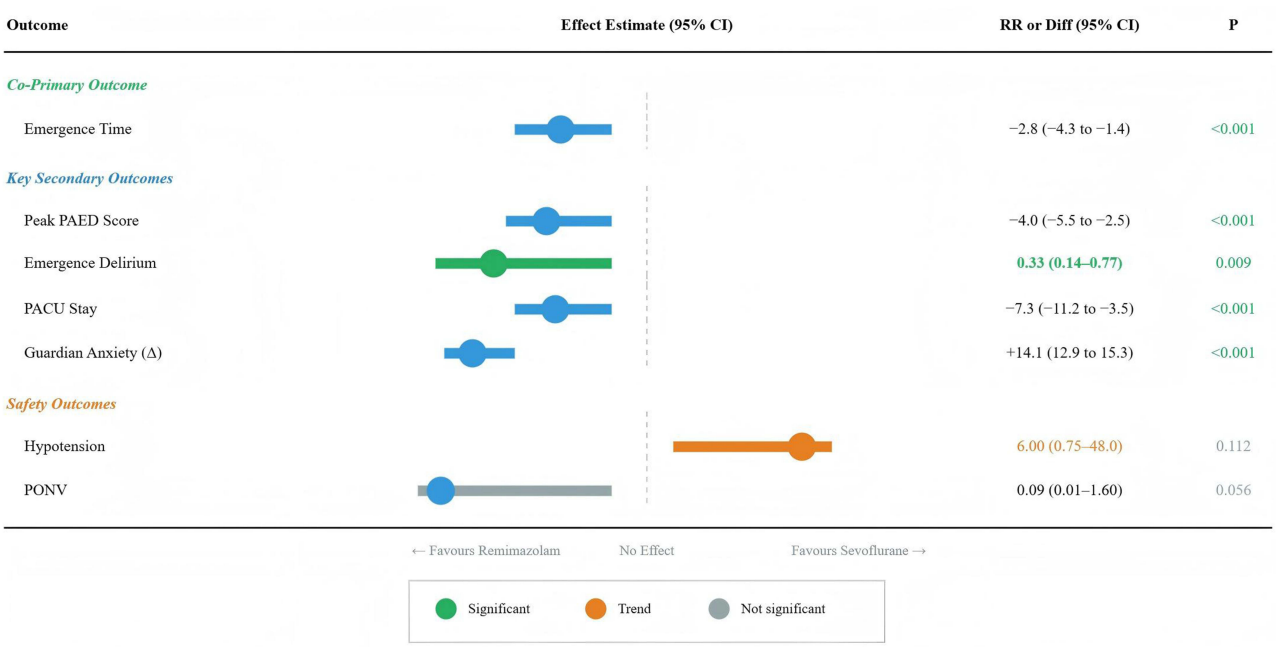

Figure 6 Forest plot summarising treatment effects. The vertical dashed line indicates no effect.

that remimazolam may share propofol's smooth emergence profile while offering the benzodiazepine advantages of flumazenil reversibility and potentially less injection pain.

Comparison with Propofol TIVA and Cost Implications

While propofol-based TIVA is a well-established strategy for ED prevention, remimazolam offers distinct advantages. Propofol is frequently associated with pain on injection, a significant source of distress in paediatric inductions, and carries a higher risk of respiratory depression and haemodynamic instability. In contrast, remimazolam causes negligible injection pain and its effects can be rapidly reversed with flumazenil. Regarding cost implications, the direct pharmacological cost of remimazolam currently exceeds that of sevoflurane. However, this initial expense may be offset by the economic benefits of an 18% shorter PACU stay and the decreased need for nursing interventions and pharmacological rescue associated with severe emergence delirium. Comprehensive cost-effectiveness analyses are required to confirm this economic balance.

Mechanistic Considerations

The mechanisms underlying the emergence quality advantage of remimazolam likely involve several factors. Benzodiazepines produce robust anterograde amnesia and anxiolysis through positive allosteric modulation at GABA-A receptors that contain α_1, α_2, α_3, or α_5 subunits. This broad receptor engagement may provide a buffer during emergence, attenuating the dysphoric arousal that can occur when consciousness returns before complete cortical reintegration.[20] In contrast, the mechanism of sevoflurane, while also involving GABA-A potentiation, includes additional actions at glycine receptors, NMDA receptors, and two-pore potassium channels. This produces a pharmacologically distinct state with a characteristically rapid, sometimes abrupt, offset.[21]

Remimazolam's ester-based metabolism by tissue carboxylesterases yields predictable, context-insensitive clearance that is unaffected by infusion duration.[7] The resulting smooth pharmacokinetic tail may prevent the irregular emergence trajectory seen with volatile agents, whose washout depends on alveolar ventilation, cardiac output, and tissue partition coefficients. This pharmacokinetic stability may be particularly advantageous in children, in whom ventilation variability is common.

The moderate correlation between pain and PAED scores (R^2=0.24) indicates that pain explains less than one-quarter of emergence delirium variance, which is consistent with previous work distinguishing emergence delirium from emergence pain.[22] The comparable intraoperative FLACC scores between groups confirms that our standardised penile block provided equivalent analgesia; the reduction in emergence delirium therefore reflects drug-specific effects rather than differential pain control.

Cardiovascular Considerations

The trend toward increased hypotension with remimazolam (12% vs 2%; P=0.11) requires comment. Although the difference was not statistically significant, this signal is consistent with the known sympatholytic effects of benzodiazepines, which can unmask hypovolaemia in fasted children. The absence of concurrent bradycardia in all six affected patients suggests that hypotension was caused by peripheral vasodilatation rather than myocardial depression, a pattern consistent with benzodiazepine pharmacology in adults, although paediatric data remain limited.[23] Given that all cases resolved promptly with crystalloid boluses, we recommend ensuring adequate preoperative hydration or administering 10 mL kg^{-1} crystalloid before remimazolam induction.

Clinical Implications

The faster emergence (21% reduction) and shorter PACU stay (18% reduction) have practical implications for the efficiency of high-throughput ambulatory surgery units. The substantially greater reduction in guardian anxiety (ΔSTAI-S 21 vs 7 points) underscores the family-centred value of smooth emergence: parents who witness their child waking calmly report a substantially better perioperative experience.

Beyond efficiency, remimazolam TIVA may address two broader concerns. Volatile anaesthetic pollution contributes to operating room air quality degradation and environmental greenhouse gas burden; an effective intravenous alternative would reduce both.[24] Additionally, while the clinical significance of anaesthetic neurotoxicity in human children remains debated, regulatory bodies have mandated warnings regarding repeated or prolonged anaesthetic exposure in children under 3 years.[15] For practitioners seeking to minimise volatile exposure in young children, remimazolam offers a pharmacologically sound alternative with demonstrated efficacy.

Strengths and Limitations

Strengths of this study include prospective registration, stratified randomisation, use of validated outcome instruments, 100% retention, and transparent reporting of methodological constraints. The large effect size (RR 0.33) and narrow confidence interval for emergence delirium support the clinical relevance of this finding despite its secondary endpoint status.

Several limitations should be acknowledged. First, complete blinding of anaesthesia providers was impossible due to the different administration routes, though assessor blinding mitigated this risk. Second, as a single-centre trial, our findings may lack generalisability to other surgical populations or settings. Third, the study was critically underpowered for subgroup analyses, and age-stratified results must be interpreted strictly as hypothesis-generating. Fourth, we did not apply statistical adjustments for multiple comparisons across our numerous secondary outcomes, which increases the risk of Type I errors. Absence of standardised premedication may have introduced baseline anxiety variability, although mYPAS was balanced between groups and was included in sensitivity analyses. As a single-centre trial in a specific surgical population with excellent regional block coverage, generalisability to other settings and procedures, particularly those with greater postoperative pain, requires confirmation. The study was underpowered for subgroup analyses, and age-stratified results should be interpreted as hypothesis-generating only. We used MOAA/S rather than processed EEG; while pragmatic, this approach cannot ensure equivalent anaesthetic depth across pharmacologically distinct drugs. Future trials should incorporate neurophysiological monitoring. This trial was not powered to detect differences in rare adverse events; the observed trends in hypotension and PONV require confirmation in larger studies. No patients or members of the public were involved in designing this research; future studies should incorporate stakeholder engagement. Finally, we did not assess long-term behavioural outcomes. While emergence delirium is typically self-limiting,

associations with postoperative maladaptive behaviours have been reported.[25] Whether the acute benefits of remimazolam translate into longer-term advantages warrants investigation.

Conclusion

Intravenous remimazolam monotherapy was associated with a 67% reduction in emergence delirium compared with sevoflurane in children undergoing circumcision. This was accompanied by faster emergence, shorter PACU stay, and improved guardian experience. However, the trend towards transient hypotension requires vigilant preoperative fluid optimisation. While these findings support remimazolam as a viable volatile-free alternative, larger multicentre trials are necessary to confirm its safety profile, generalisability to other procedures, and long-term neurodevelopmental outcomes.

Data Sharing Statement

De-identified individual participant data, data dictionary, and statistical analysis code will be available upon reasonable request to the corresponding author beginning 6 months after publication and ending 36 months after publication. Requestors must sign a data access agreement. The study protocol is available in the published protocol paper (Reference [16]).

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Sikich N, Lerman J. Development and psychometric evaluation of the pediatric anesthesia emergence delirium scale. *Anesthesiology*. 2004;100(5):1138–1145. doi:10.1097/00000542-200405000-00015
2. Vlajkovic GP, Sindjelic RP. Emergence delirium in children: many questions, few answers. *Anesth Analg*. 2007;104(1):84–91. doi:10.1213/01.ane.0000250914.91881.a8
3. Dahmani S, Delivet H, Hilly J. Emergence delirium in children: an update. *Curr Opin Anaesthesiol*. 2014;27(3):309–315. doi:10.1097/ACO.0000000000000076
4. Costi D, Cyna AM, Ahmed S, et al. Effects of sevoflurane versus other general anaesthesia on emergence agitation in children. *Cochrane Database Syst Rev*. 2014;2014(9):CD007084. doi:10.1002/14651858.CD007084.pub2
5. Reduque LL, Verghese ST. Paediatric emergence delirium. Continuing education in anaesthesia. *Crit Care Pain*. 2013;13(2):39–41. doi:10.1093/bjaceaccp/mks051
6. Dahmani S, Stany I, Brasher C, et al. Pharmacological prevention of sevoflurane- and desflurane-related emergence agitation in children: a meta-analysis of published studies. *Br J Anaesth*. 2010;104(2):216–223. doi:10.1093/bja/aep376
7. Kilpatrick GJ, McIntyre MS, Cox RF, et al. CNS 7056: a novel ultra-short-acting Benzodiazepine. *Anesthesiology*. 2007;107(1):60–66. doi:10.1097/01.anes.0000267503.85085.c0
8. Schüttler J, Eisenried A, Lerch M, Fechner J, Jeleazcov C, Ihmsen H. Pharmacokinetics and pharmacodynamics of remimazolam (CNS 7056) after continuous infusion in healthy male volunteers: part i. pharmacokinetics and clinical pharmacodynamics. *Anesthesiology*. 2020;132(4):636–651. doi:10.1097/ALN.0000000000003103
9. Zhou Y, Hu P, Huang Y, et al. Population pharmacokinetic/pharmacodynamic model-guided dosing optimization of a novel sedative HR7056 in Chinese healthy subjects. *Front Pharmacol*. 2018;9:1316. doi:10.3389/fphar.2018.01316

10. Rex DK, Bhandari R, Desta T, et al. A Phase III study evaluating the efficacy and safety of remimazolam (CNS 7056) compared with placebo and midazolam in patients undergoing colonoscopy. *Gastrointestl Endosc*. 2018;88(3):427–437.e6. doi:10.1016/j.gie.2018.04.2351
11. Xing Y, Lang Z, Wang X, et al. Anesthetic efficacy with remimazolam compared with propofol: a systematic review and meta-analysis of randomized controlled trials. *Int J Surg*. 2025;111(9):6384–6396. doi:10.1097/JS9.0000000000002737
12. Bai C, Xu M, Guo Y, Jin Y, Zhao X. Clinical application and research progress of remimazolam for pediatric patients. *Drug Des Devel Ther*. 2024;18:1221–1229. doi:10.2147/DDDT.S453440
13. Cai YH, Dong LQ, Zhong JW, et al. ED50 and ED95 of remimazolam for loss of consciousness in young children: a dose-finding study for induction of anaesthesia. *Br J Anaesth*. 2025;134(6):1709–1716. doi:10.1016/j.bja.2025.02.004
14. Cai YH, Zhong JW, Ma HY, et al. Effect of remimazolam on emergence delirium in children undergoing laparoscopic surgery: a double-blinded randomized trial. *Anesthesiology*. 2024;141(3):500–510. doi:10.1097/ALN.0000000000005077
15. Warner DO, Zaccariello MJ, Katusic SK, et al. Neuropsychological and behavioral outcomes after exposure of young children to procedures requiring general anesthesia: the mayo anesthesia safety in kids (MASK) study. *Anesthesiology*. 2018;129(1):89–105. doi:10.1097/ALN.0000000000002232
16. Zhang Y, Guo S, Wang L, Zeng Q, Cui H, Mo Y. Comparison of the anesthetic efficacy and recovery quality of remimazolam besylate versus sevoflurane for pediatric circumcision: a single-center,prospective,assessor-blinded,randomized controlled study protocol. *BMC Anesthesiol*. 2025;25(1):527. doi:10.1186/s12871-025-03378-3
17. Chernik DA, Gillings D, Laine H, et al. Validity and reliability of the observer's assessment of alertness/sedation scale: study with intravenous midazolam. *J Clin Psychopharmacol*. 1990;10(4):244–251.
18. Patel S, Vargo JJ, Trolli PA, et al. Comparison of a new bispectral index (BIS) algorithm to modified observer's assessment of alertness/sedation (MOAA/S) scale in moderate sedation (MS). *Gastrointest Endosc*. 2004;59:AB128.
19. Oofuvong M, Siripruekpong S, Naklongdee J, Hnookong R, Lakateb C. Comparison the incidence of emergence agitation between sevoflurane and desflurane after pediatric ambulatory urologic surgery. *J Med Assoc Thailand*. 2013;96(11):1470–1475.
20. Olsen RW, Sieghart W. GABA A receptors: subtypes provide diversity of function and pharmacology. *Neuropharmacology*. 2009;56(1):141–148. doi:10.1016/j.neuropharm.2008.07.045
21. Hemmings HC Jr, Akabas MH, Goldstein PA, Trudell JR, Orser BA, Harrison NL. Emerging molecular mechanisms of general anesthetic action. *Trends Pharmacol Sci*. 2005;26(10):503–510. doi:10.1016/j.tips.2005.08.006
22. Bajwa SA, Costi D, Cyna AM. A comparison of emergence delirium scales following general anesthesia in children. *Paediatr Anaesth*. 2010;20(8):704–711. doi:10.1111/j.1460-9592.2010.03328.x
23. Doi M, Morita K, Takeda J, Sakamoto A, Yamakage M, Suzuki T. Efficacy and safety of remimazolam versus propofol for general anesthesia: a multicenter, single-blind, randomized, parallel-group, phase IIb/III trial. *J Anesth*. 2020;34(4):543–553. doi:10.1007/s00540-020-02788-6
24. Sherman JD, MacNeill A, Thiel C. Reducing pollution from the health care industry. *JAMA*. 2019;322(11):1043–1044. doi:10.1001/jama.2019.10823
25. Kain ZN, Caldwell-Andrews AA, Maranets I, et al. Preoperative anxiety and emergence delirium and postoperative maladaptive behaviors. *Anesthesia Analg*. 2004;99(6):1648–1654. doi:10.1213/01.ANE.0000136471.36680.97