Supplementary Material

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

Supplementary Table S1

Supplementary Table S1. Subgroup Analysis of Emergence Delirium Incidence by Age

Subgroup	n	Remimazolam n/N (%)	Sevoflurane n/N (%)	RR (95% CI)	ARR	P value
Overall	100	6/50 (12.0%)	18/50 (36.0%)	0.33 (0.14-0.77)	0.24	0.009
Preschool (3-6 y)	36	2/15 (13.3%)	8/21 (38.1%)	0.35 (0.09-1.41)	24.80%	0.142
School-age (7-12 y)	64	4/35 (11.4%)	10/29 (34.5%)	0.33 (0.12-0.94)	23.10%	0.035
Interaction P value (age × treatment):						0.89

Supplementary Table S1. Subgroup analysis of emergence delirium incidence by age. Both preschool and school-age subgroups showed similar effect magnitudes (65–67% relative reduction), supporting consistency of treatment effect across the paediatric age spectrum studied.

Abbreviations: ARR = absolute risk reduction; CI = confidence interval; PAED = Paediatric Anaesthesia Emergence Delirium scale; RR = relative risk.

Statistical methods: Relative risks calculated using the Newcombe-Wilson method without continuity correction. P values from Fisher's exact test for individual subgroups; interaction tested using logistic regression with age group × treatment term.

Caution: Subgroup analyses were underpowered and should be considered exploratory. The interaction P value of 0.89 suggests no meaningful effect modification by age, but confidence intervals for the preschool subgroup are wide due to limited sample size. These findings should inform hypothesis generation for future adequately powered studies rather than definitive conclusions.

Bold values indicate statistical significance (P < 0.05).

Supplementary Table S2

Supplementary Table S2. Sensitivity Analysis Using Alternative PAED ≥10 Threshold
Comparison of emergence delirium incidence using PAED ≥10 versus ≥12 thresholds

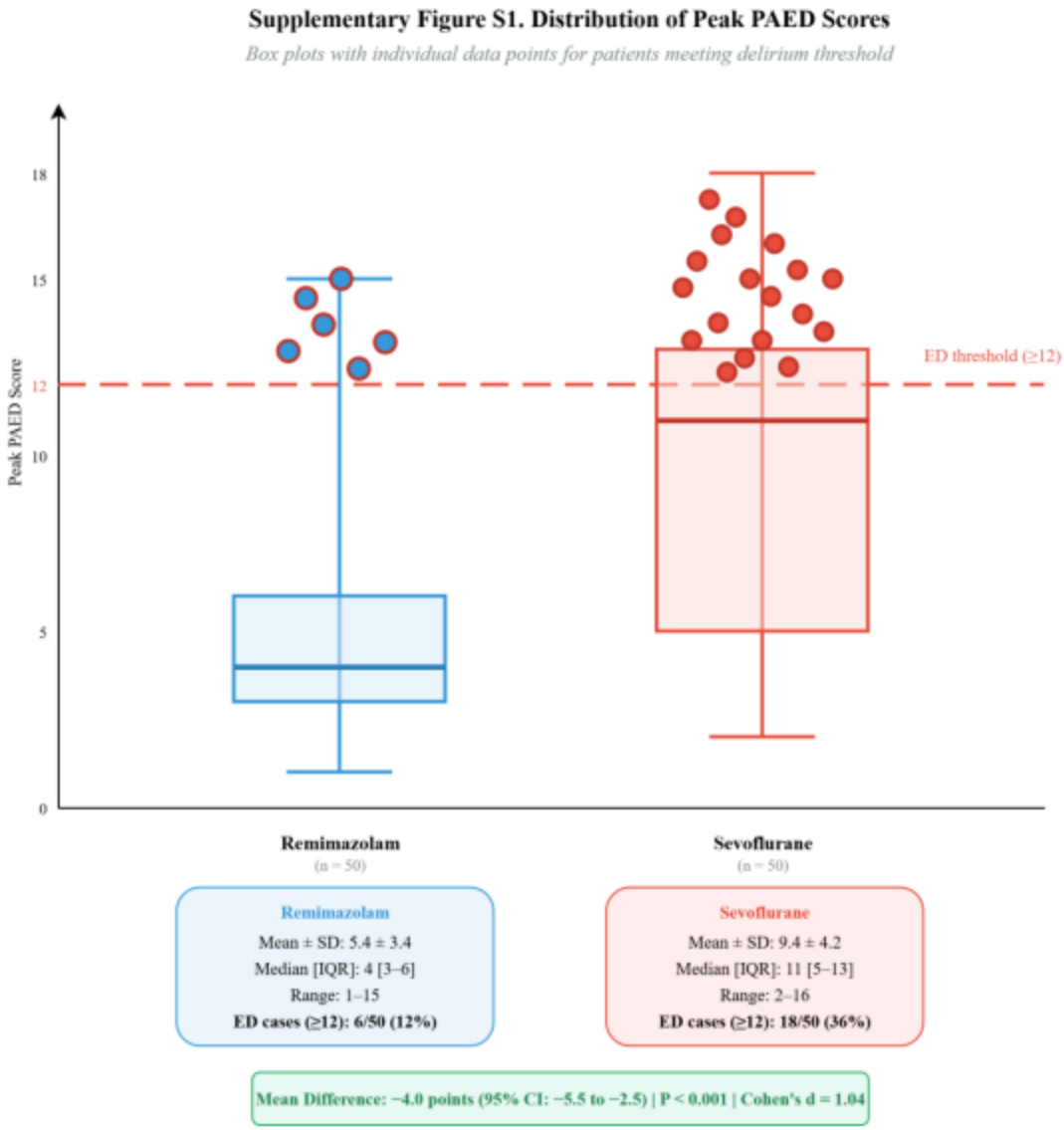
Threshold	Remimazolam (n=50)	Sevoflurane (n=50)	RR (95% CI)	P Value	NNT (95% CI)
PAED ≥12 (Primary)	6/50 (12.0%)	18/50 (36.0%)	0.33 (0.14–0.77)	0.009	4.2 (2.5–11.1)
PAED ≥10 (Sensitivity)	9/50 (18.0%)	27/50 (54.0%)	0.33 (0.18–0.63)	<0.001	2.8 (1.9–5.3)

Abbreviations: RR, relative risk; CI, confidence interval; NNT, number needed to treat; PAED, Paediatric Anaesthesia Emergence Delirium scale.

Note: The consistency of relative risk estimates across both thresholds (RR 0.33) reinforces the robustness of the findings.

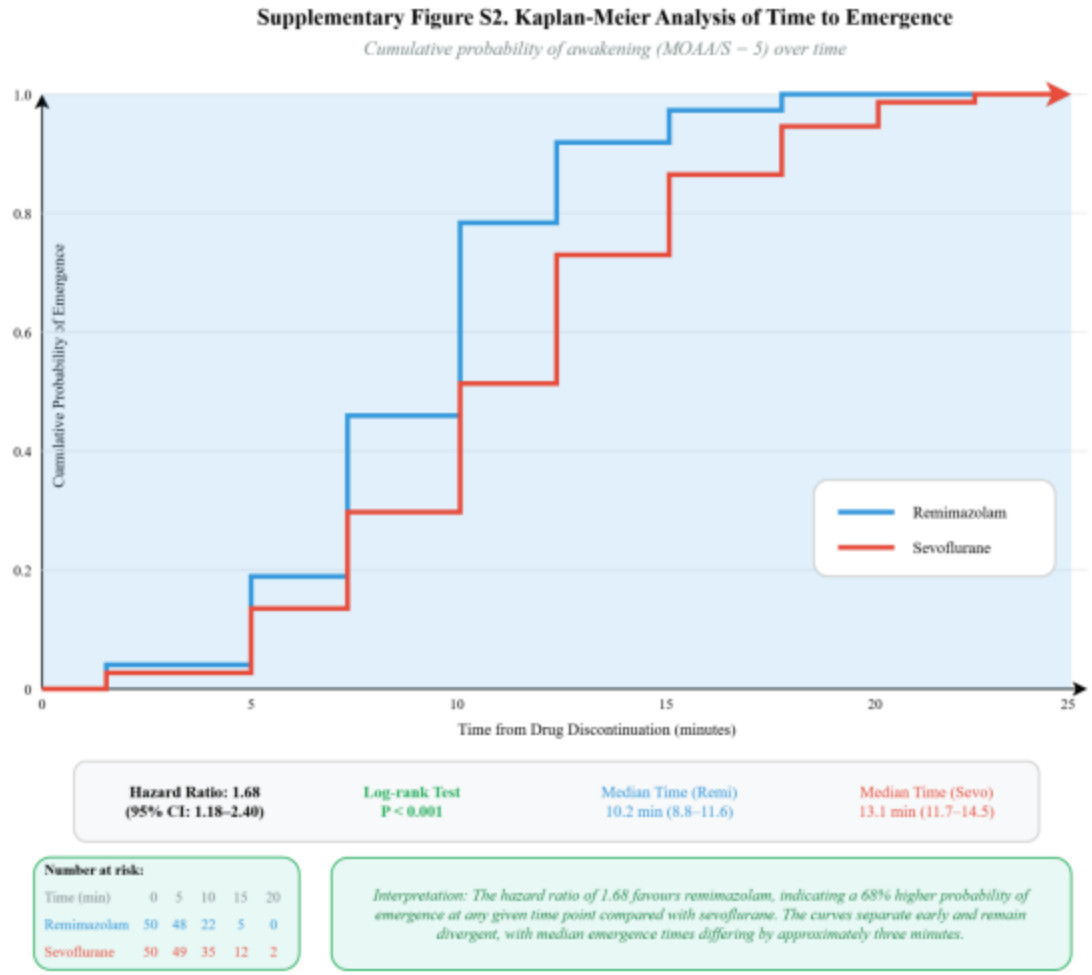
Bold values indicate statistical significance (P < 0.05).

Supplementary Figure S1



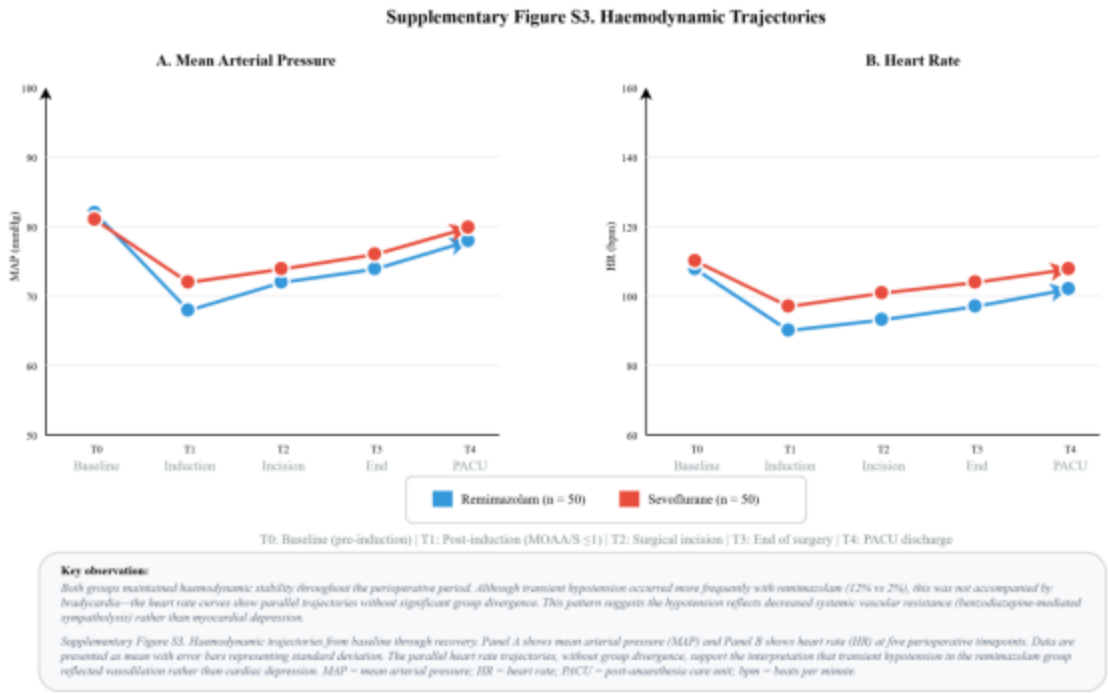
Supplementary Figure S1. Distribution of peak PAED scores. Box plots show median and interquartile range; individual data points are shown for patients meeting the delirium threshold (≥12).

Supplementary Figure S2



Supplementary Figure S2. Kaplan-Meier analysis of time to emergence. Hazard ratio 1.68 (95% CI 1.18 – 2.40) favours remimazolam, indicating 68% higher probability of emergence at any given time point. Log-rank P<0.001.

Supplementary Figure S3



Supplementary Figure S3. Haemodynamic trajectories from baseline through recovery. Panel A shows mean arterial pressure (MAP) and Panel B shows heart rate (HR) at five perioperative timepoints.

Supplementary File 1: CONSORT 2025 Checklist

CONSORT 2025 Checklist

Section/Topic	No	CONSORT 2025 Checklist Item Description	Page No.	Comments
Title and structured abstract	1a	Identification as a randomised trial	1	Title includes 'Randomised Controlled Trial'
	1b	Structured summary of trial design, methods, results, and conclusions	1-2	Abstract with Background, Methods, Results, Conclusions
Trial registration	2	Name of trial registry, identifying number (with URL) and date of registration	2	ChiCTR2500095974; 15 January 2025
Protocol and statistical analysis plan	3	Where the trial protocol and statistical analysis plan can be accessed	2	Reference 16; BMC Anesthesiology
Data sharing	4	Where and how the individual de-identified participant data can be accessed	11	Available upon request 6-36 months post-publication
Funding and conflicts of interest	5a	Sources of funding and other support, and role of funders	11	Wanzhou District fund; no funder role
	5b	Financial and other conflicts of interest of the manuscript authors	11	None declared
Background and rationale	6	Scientific background and rationale	2-3	
Objectives	7	Specific objectives related to benefits and harms	3	Primary: timing; Secondary: ED, harms
Patient and public involvement	8	Details of patient or public involvement in the design, conduct and reporting of the trial	3	No PPI; acknowledged as limitation
Trial design	9	Description of trial design including type of trial, allocation ratio, and framework	3	Parallel, 1:1, superiority
Changes to trial protocol	10	Important changes to the trial after it commenced	5	No changes made

Trial setting	11	Settings and locations where the trial was conducted	3	Single centre, Chongqing, China
Eligibility criteria	12a	Eligibility criteria for participants	3	Age 3-12, ASA I-II, circumcision
	12b	Eligibility criteria for sites and for individuals delivering the interventions	3	Board-certified, ≥5 years experience, ≥20 remimazolam cases
Intervention and comparator	13	Intervention and comparator with sufficient details to allow replication	4	Doses, timing, titration described
Outcomes	14	Prespecified primary and secondary outcomes	4-5	MOAA/S, PAED, FLACC, STAI-S, VAS
Harms	15	How harms were defined and assessed	5	Predefined thresholds for each AE
Sample size	16a	How sample size was determined	5	90% power, α=0.05, 3 min difference
	16b	Explanation of any interim analyses and stopping guidelines	5	No interim analyses; DSMB review at 50%
Randomisation: Sequence generation	17a	Who generated the random allocation sequence and the method used	3	Independent statistician, computer-generated
	17b	Type of randomisation and details of any restriction	3	Stratified by age, blocks of 4
Allocation concealment mechanism	18	Mechanism used to implement the random allocation sequence	3	Sequentially numbered opaque envelopes
Implementation	19	Whether personnel who enrolled/assigned participants had access to sequence	3	Envelopes opened after consent
Blinding	20a	Who was blinded after assignment to interventions	3-4	Assessors, analysts; not providers
	20b	If blinded, how blinding was achieved and description of similarity of interventions	3-4	Physical separation, mint lip balm
Statistical methods	21a	Statistical methods used to compare groups for primary and secondary outcomes	5-6	t-test, χ^2, Fisher's, Cox regression
	21b	Definition of who is included in	5-6	ITT, all randomised

		each analysis		
	21c	How missing data were handled in the analysis	6	No missing data
	21d	Methods for any additional analyses	5-6	Age subgroups (prespecified), sensitivity
Participant flow	22a	Numbers randomly assigned, received intervention, and analysed	6	Figure 1; 50/50, all analysed
	22b	Losses and exclusions after randomisation, with reasons	6	None
Recruitment	23a	Dates defining the periods of recruitment and follow-up	3, 6	July–November 2025
	23b	Why the trial ended or was stopped	N/A	Completed per protocol
Intervention and comparator delivery	24a	Intervention and comparator as they were actually administered	6	All received assigned intervention
	24b	Concomitant care received during the trial for each group	4	Penile block, LMA, mechanical ventilation
Baseline data	25	A table showing baseline demographic and clinical characteristics	6 (Table 1)	Age, weight, BMI, ASA, anxiety scores
Numbers analysed, outcomes and estimation	26	For each outcome: participants analysed, results, effect size and precision	6-7	Mean diff, RR, 95% CI for all outcomes
Harms	27	All harms or unintended events in each group	7-8	Table 3, Figure 5; zero events reported
Ancillary analyses	28	Any other analyses performed, distinguishing pre-specified from post hoc	6-7	Age subgroups, PAED≥10 sensitivity
Interpretation	29	Interpretation consistent with results, balancing benefits and harms	8-10	67% ED reduction; hypotension trend
Limitations	30	Trial limitations, addressing sources of potential bias, imprecision, generalisability	10	Single-centre, unblinded providers, no PPI, underpowered for rare AEs

Citation: Hopewell S, Chan AW, Collins GS, et al. CONSORT 2025 Statement: updated guideline for reporting randomised trials. BMJ. 2025;388:e081123.

Supplementary File 2: CONSORT Harms 2022 Checklist

CONSORT Harms 2022 Checklist

Remimazolam versus Sevoflurane for Paediatric Circumcision: A Randomised Controlled Trial

Section/Topic	Item No	Item Description	Page No.	Comments (Optional but Recommended)
Title and abstract	1b	Structured summary of trial design, methods, results of outcomes of benefits and harms, and conclusions	1-2	Abstract includes ED incidence (12% vs 36%), hypotension (12% vs 2%), and conclusions addressing both benefits and harms
Background and objectives	2b	Specific objectives or hypotheses for outcomes of benefits and harms	3	Objectives include emergence delirium (benefit) and safety outcomes including hypotension, hypoxaemia, bradycardia, PONV (harms)
Outcomes	6a	Completely defined prespecified primary and secondary outcomes, for both benefits and harms, including how and when they were assessed	4-5	Harms defined with specific thresholds: hypotension (MAP decrease >20%), hypoxaemia (SpO_2 <90% for >30s), bradycardia (HR <60 or decrease >30%), PONV (any episode)
	6c	Describe if and how non-prespecified outcomes of benefits and harms were identified, including any selection criteria, if applicable	N/A	All reported harms were prespecified in the published protocol (Reference 16). No non-prespecified harms were identified during the trial.
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes of benefits and harms) and how	3-4	Outcome assessors (PACU nurses) were blinded to group allocation; they assessed both efficacy (PAED) and safety (AEs). Providers were not blinded due to different administration routes. Data

				analysts blinded until database lock.
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes of both benefits and harms	5-6	Benefits: t-tests for continuous, χ^2 for categorical, RR with 95% CI. Harms: Fisher's exact test for binary safety outcomes due to low expected cell counts; RR with 95% CI reported.
Participant flow	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for outcomes of benefits and harms	6, Figure 1	Remimazolam: 50 randomised, 50 received, 50 analysed. Sevoflurane: 50 randomised, 50 received, 50 analysed. Same population analysed for both benefits and harms (ITT).
Recruitment	14a	Dates defining the periods of recruitment and follow-up for outcomes of benefits and harms	3, 6	Recruitment: July–November 2025. Follow-up for harms: from induction through PACU discharge (same day). No long-term harms follow-up.
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis of outcomes of benefits and harms and whether the analysis was by original assigned groups	6-8	n=50 per group for all analyses. ITT analysis by original assigned groups. No exclusions for safety analysis.
Outcomes and estimation	17a	For each primary and secondary outcome of benefits and harms, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	6-8	Benefits: ED 12% vs 36%, RR 0.33 (95% CI 0.14-0.77). Harms: Hypotension 12% vs 2%, RR 6.0 (95% CI 0.75-48); Hypoxaemia 8% vs 8%; Bradycardia 2% vs 4%; PONV 0% vs 10%.
	17a2	For outcomes omitted from the trial report (benefits and harms),	N/A	No outcomes were omitted from the report. All

		provide rationale for not reporting and indicate where the data can be accessed		prespecified efficacy and safety outcomes are reported in Tables 2-3 and Figure 5.
	17b	Presentation of both absolute and relative effect sizes is recommended, for outcomes of benefits and harms	6-8	Absolute: incidence per group (n/50, %). Relative: RR with 95% CI. NNT/NNH calculated where appropriate.
	17c	Report zero events if no harms were observed	7-8	Zero events explicitly reported for: laryngospasm (0/50 vs 0/50), bronchospasm (0/50 vs 0/50), allergic reactions (0/50 vs 0/50), serious adverse events (0/50 vs 0/50), PONV in remimazolam group (0/50).
Ancillary analyses	18	Results of any other analyses performed for outcomes of benefits and harms, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory	6-7	Subgroup analyses performed for efficacy (ED by age stratum) were prespecified. No subgroup analyses for safety outcomes due to low event rates - acknowledged as limitation.
Limitations	20	Trial limitations, addressing sources of potential bias related to the approach to collecting or reporting data on harms, imprecision, and, if relevant, multiplicity or selection of analyses	10	Explicitly acknowledged: (1) Trial underpowered for rare AEs; (2) Hypotension trend (P=0.11) requires confirmation in larger studies; (3) Short-term follow-up limits detection of delayed harms; (4) Single-centre may limit generalisability of safety findings.
Protocol	24	Where the full trial protocol and other relevant documents can be accessed, including additional data on harms	3, 11	Full protocol published: BMC Anesthesiology 2025;25:527 (Reference 16). Protocol includes

				complete list of prespecified safety outcomes and definitions.

Citation: Junqueira DR, Zorzela L, Golder S, et al. CONSORT Harms 2022 statement, explanation, and elaboration: updated guideline for the reporting of harms in randomised trials. BMJ. 2023;381:e073725.