Research Square

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Cerebral hemodynamic effects of remimazolam versus propofol during anesthesia induction: a randomised controlled exploratory physiological study

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Abstract

Background: The comparative cerebral hemodynamic effects of remimazolam and propofol during anesthesia induction are poorly characterized. We explored these effects using continuous transcranial color-coded duplex sonography.

Methods: In this single-center, randomised, open-label, blinded-endpoint exploratory trial, 52 adults (ASA I–II, 18–65 years) scheduled for major abdominal surgery were randomised to induction with remimazolam 0.3 mg/kg (n = 26) or propofol 2 mg/kg (n = 26). The primary outcome was the adjusted between-group difference in middle cerebral artery mean flow velocity (MCAvm) from baseline to 1, 3, 5, and 10 min after intubation (T1–T4), analysed with a linear mixed-effects model (baseline MCAvm as covariate, group-by-time interaction) under a treatment-policy strategy. The full analysis set comprised the 44 participants with retrievable data (remimazolam 20, propofol 24). Secondary and exploratory outcomes were not adjusted for multiplicity. Trial registration: NCT07303985.

Results:MCAvm decreased from baseline by approximately 12 cm/s in both groups. Adjusted between-group differences (remimazolam minus propofol) were +3.88 (95% CI −3.21 to 10.97), +0.63 (−6.46 to 7.72), −1.37 (−8.57 to 5.83), and −1.09 (−8.38 to 6.21) cm/s at T1–T4 (group-by-time interaction p = 0.206). A post-hoc equivalence analysis (margin ±10 cm/s) yielded a 90% CI of −6.26 to 6.36 cm/s for the baseline-to-T4 change difference. Mean arterial pressure and estimated effective cerebral perfusion pressure were nominally higher with remimazolam at T1 only.

Conclusions: No significant between-group difference in MCAvm was detected in this small exploratory sample; the study was underpowered for differences smaller than approximately 10.5 cm/s. Findings are hypothesis-generating and require confirmation in adequately powered trials.

Key message

• In this small exploratory physiological study, middle cerebral artery mean flow velocity decreased by approximately 12 cm/s (about 19%) from an elevated pre-induction baseline after induction with either remimazolam or propofol; no significant between-group difference was detected.

Introduction

Post-induction hypotension (PIH) occurs frequently and has been linked to organ injury. A reduction in cerebral blood flow (CBF) may accompany PIH [1, 2]. This reduction is multifactorial, primarily reflecting systemic vasodilation and decreased cardiac output induced by anesthetic agents. An excessive or prolonged decrease in CBF may disturb the cerebral oxygen supply–demand balance, potentially increasing the risk of cerebral ischemia and neurological dysfunction in susceptible patients [2], such as elderly patients and those with cardiovascular disease. These considerations motivate the study of how commonly used induction agents affect cerebral hemodynamics.

Propofol, a mainstay intravenous anesthetic that potentiates GABAergic neurotransmission, provides rapid and reliable hypnosis. It decreases intracranial pressure and the cerebral metabolic rate of oxygen (CMRO2), but also causes dose-dependent systemic hypotension and bradycardia, which may compromise perfusion of vital organs [3, 4]. Remimazolam, another GABA_A receptor agonist, is an ultra-short-acting benzodiazepine that is rapidly hydrolyzed by tissue esterases and induces less cardiovascular depression than propofol [5]. Several trials have found remimazolam to be non-inferior to propofol for general anesthesia with a lower incidence of systemic hypotension [6–8]. Anesthetic-induced PIH can be treated with vasopressors [9]; however, the comparative effects of these two agents on cerebral hemodynamics during induction remain unclear.

We therefore conducted an exploratory physiological study comparing the effects of remimazolam and propofol on cerebral and systemic hemodynamics during induction of general anesthesia in relatively healthy adults (ASA I–II, 18–65 years) undergoing major abdominal surgery. The research question is deliberately narrow: we asked whether, in this population and during the induction period only, the two agents produce different trajectories of middle cerebral artery flow velocity and derived cerebral hemodynamic indices. Our findings should not be extrapolated to elderly patients or to patients at high cardiovascular or cerebrovascular risk, and—because the maintenance regimens necessarily differed between groups—any between-group contrast reflects the entire induction-plus-maintenance regimen rather than the induction bolus alone.

Methods

Study design, ethics, and registration

This was a single-center, prospective, randomised, open-label, blinded-endpoint (PROBE) exploratory trial with a 1:1 allocation ratio, conducted at Fudan University Shanghai Cancer Center (FUSCC). The protocol was approved by the Institutional Review Board of FUSCC (approval number 2510-Exp296), and written informed consent was obtained from all participants before enrollment. The study was conducted in accordance with the Declaration of Helsinki. The trial was registered at ClinicalTrials.gov (NCT07303985; public release 12 December 2025; first participant enrolled 29 December 2025; principal investigator Jun Zhang). Participants were recruited from 29 December 2025 to 28 February 2026. This report follows the CONSORT 2025 statement [22]; the analysis framework was guided by the ICH E9(R1) estimands addendum [23]. Deviations from the protocol and registration are disclosed below (“Protocol and registration”).

Patient population

Adult patients (18–65 years, ASA physical status I–II) scheduled for major abdominal surgery under general anesthesia were eligible. Exclusion criteria were: history of cardiac or brain surgery; cerebrovascular or cardiovascular disease; pregnancy; refusal to participate; and failure to detect the

middle cerebral artery (MCA) through the temporal window. The protocol version 1.0 (8 August 2025) specified age > 18 years without an upper limit and only two exclusion criteria (intracranial lesions/carotid stenosis/head trauma; allergy or contraindication to the study drugs); the additional eligibility criteria applied in the manuscript were introduced without a documented protocol amendment (see “Protocol and registration”).

Randomisation and blinding

Enrolled patients were randomly allocated (1:1) to remimazolam or propofol using minimization implemented in MinimPy2 software (version 2.0, OSDN, Columbus, OH, USA), executed by a research nurse who did not otherwise participate in the study. The stratification factors entered into the minimization algorithm and the random component were not documented in the retrievable trial records; this is acknowledged as a reporting limitation. Allocation was performed by the independent research nurse after enrollment, providing separation between sequence generation and enrollment; group assignments were not placed in sequentially numbered sealed envelopes, and formal allocation-concealment documentation was not retained. Participants and the data analyst were blinded to group assignment; all sonographic measurements were performed by a single experienced sonographer (XL) blinded to allocation; the anesthesiologists responsible for perioperative management were aware of the allocation.

Anesthetic intervention

Remimazolam group (group R)

induction with intravenous remimazolam 0.3 mg/kg, sufentanil 0.4 μg/kg, and rocuronium 0.6 mg/kg; maintenance with remimazolam 1–3 mg/kg/h and remifentanil target-controlled infusion (TCI) 1 ng/ml, titrated to a Narcotrend Index (NCI) of 27–60.

Propofol group (group P)

induction with propofol 2 mg/kg, sufentanil 0.4 μg/kg, and rocuronium 0.6 mg/kg; maintenance with propofol 4–12 mg/kg/h and remifentanil TCI 1 ng/ml, titrated to an NCI of 27–60.

If the NCI could not be kept ≤ 60, or signs of insufficient anesthesia appeared, despite maximum infusion rates (remimazolam 3 mg/kg/h; propofol 12 mg/kg/h), sevoflurane was permitted and the case was withdrawn from the study (this withdrawal rule was pre-specified in the protocol).

Anesthetic management and co-interventions

Patients fasted for at least 8 h. Standard monitoring (electrocardiography, non-invasive blood pressure, pulse oximetry) was applied on arrival. Before induction, a radial arterial line was placed for continuous

invasive blood pressure monitoring and intermittent blood gas analysis, and a single-lumen central venous catheter was inserted via the right internal jugular vein. A Narcotrend monitor (MT MonitorTechnik GmbH & Co. KG, Germany) was connected with surface electrodes placed symmetrically 3 cm lateral to the frontal midline; recording epochs with a Noise/Clutter Interference index exceeding 30% were excluded. Ventilation used a tidal volume of 8 ml/kg and a rate of 10–12 breaths/min, targeting end-tidal carbon dioxide (PetCO2) of 35–40 mmHg. Intraoperative goal-directed fluid therapy was guided by pulse pressure variation (threshold PPV > 11%) and applied identically in both groups.

Hypotension was defined as mean arterial pressure (MAP) < 65 mmHg. In the executed procedure, patients who developed MAP < 65 mmHg persisting for ≥ 3 min without spontaneous recovery were treated with intravenous phenylephrine 80 μg (if heart rate [HR] ≥ 60 bpm) or ephedrine 6 mg (if HR < 60 bpm), and were withdrawn from further study-drug titration; atropine 0.5 mg was given if HR fell below 45 bpm. Per-group totals of fluid administration and vasopressor doses were not systematically recorded in the retrievable dataset and therefore cannot be reported; this is acknowledged as a limitation.

Monitoring of cerebral circulation

Cerebral hemodynamics were monitored continuously with a transcranial color-coded duplex (TCCD) sonography system (Rocvue T7; Shenzhen Krinwave Technology Co., Ltd., Guangdong, China) equipped with a 1.4-MHz SP3 phased-array transducer. The main trunk of the MCA was insonated through the transtemporal window at a depth of 45–60 mm [11]. Two-dimensional B-mode imaging with color flow mapping allowed anatomical localization and continuous angle correction; the insonation angle was kept < 60°. A custom-designed fixation headframe stabilized the transducer. Middle cerebral artery systolic flow velocity (MCAvs), diastolic flow velocity (MCAvd), and mean flow velocity (MCAvm), pulsatility index (PI), and resistance index (RI) were recorded by the blinded sonographer. MCAvm is used throughout as a continuous surrogate for dynamic changes in global CBF, acknowledging that velocity is not flow because MCA cross-sectional area was not measured.

Derived hemodynamic indices

Critical closing pressure (CrCP) was estimated with a multiparameter model [12, 13]:

$$CrCP = MAP - [MCAvm \times (MAP - DAP)] / (MCAvm - MCAvd)$$

where DAP is diastolic arterial pressure. The estimated effective cerebral perfusion pressure (CPPe) was calculated as MAP − CrCP; it is a model-based estimate that incorporates the cumulative downstream zero-flow pressure and is not equivalent to conventional cerebral perfusion pressure (MAP − intracranial pressure), because intracranial pressure was not measured [14]. Cerebrovascular resistance (CVR) was calculated as CPPe divided by MCAvm and is reported in $mmHg \cdot s \cdot cm^{-1}$ [13]. PI and RI were calculated by standard Doppler formulae [15]. CrCP, CPPe, and CVR are mathematically coupled (all derive from the

same MAP and velocity measurements) and are therefore interpreted together rather than as independent evidence.

Dynamic cerebral autoregulation was explored using the moving Pearson correlation coefficient between spontaneous slow-wave fluctuations in MAP and MCAvm (Mxa) [16]. Mxa was computed **post hoc** from the recorded signal pairs; the sampling frequency, filtering, window length, overlap, and averaging used to generate the stored Mxa values were not documented in the retrievable trial records, and Mxa was available in only a subset of participants (18 remimazolam, 20 propofol). Because the induction period is non-stationary and the conventional impairment threshold of 0.30 has not been validated in this setting, Mxa is reported descriptively as an exploratory index only.

Data collection

Systemic and cerebral hemodynamic indices were collected before induction (baseline, T0) and at 1 (T1), 3 (T2), 5 (T3), and 10 min (T4) after tracheal intubation. Cognitive function was assessed with the Montreal Cognitive Assessment (MoCA) preoperatively and at 24 h postoperatively (exploratory; see "Protocol and registration"). The time to first NCI ≤ 60 and the time from end of surgery to tracheal extubation were recorded.

Estimand and study endpoints

The primary estimand was defined post hoc, guided by ICH E9(R1) [23]:

- **Population**: adults undergoing elective major abdominal surgery randomised to remimazolam- or propofol-based induction in whom TCCD monitoring was feasible.
- **Treatments**: remimazolam-based versus propofol-based induction and maintenance regimen as specified above.
- **Variable**: MCAvm (cm/s) at T1–T4, expressed as change from the individual T0 baseline.
- **Population-level summary**: the adjusted mean between-group difference (remimazolam minus propofol) in MCAvm change from baseline at each post-intubation time point, with the group-by-time interaction as the overall primary test.
- **Intercurrent events**: persistent PIH and TCCD signal loss were handled with a treatment-policy strategy (all available observations retained regardless of the event) combined with a missing-at-random assumption in the mixed model; no data were imputed.

The **primary outcome** was MCAvm at T1–T4 as defined above. **Secondary outcomes** were MAP, HR, CPPe, CrCP, CVR, PI, and RI at T1–T4; time to NCI ≤ 60; and extubation time. **Exploratory outcomes** were the registered primary outcome MCAvs (reported as ΔMCAvs/ΔSBP and ΔMCAvm/ΔMAP ratios from T0 to each post-induction time point), Mxa, and the MoCA assessment.

Protocol and registration

The trial protocol (v1.0, 8 August 2025) and the ClinicalTrials.gov registration (NCT07303985) are not fully aligned with this report. We disclose the differences here; no protocol amendments were filed, and the reasons for several discrepancies cannot be reconstructed from retrievable records.

1. **Primary outcome.** The registration lists MCA **systolic** flow velocity (MCAvs) as the primary outcome; protocol v1.0 specifies MCA **mean** flow velocity (MCAvm) at 1/3/5/10 min after intubation, which is the primary outcome of this report. MCAvs data are reported here as an exploratory outcome (Table 5). The sample-size assumptions in protocol v1.0 (peak systolic velocity 70 ± 10 cm/s, expected between-group difference 10 cm/s) and in the original manuscript planning (MCAvm 45 ± 5 cm/s, expected difference 5 cm/s, based on a pilot estimate from a prior trial by the first author in a different clinical setting [10]) also differ, consistent with the registration having been framed around MCAvs.
2. **Cognitive assessment.** The registration lists the Mini-Mental State Examination (MMSE); protocol v1.0 left the instrument undecided ("specific scale to be determined"); MoCA was used. A single MoCA measurement 24 h after surgery cannot diagnose postoperative cognitive dysfunction; these data are exploratory.
3. **Recovery endpoint.** The registration lists post-anesthesia care unit (PACU) length of stay; the protocol specified time to awakening; this report presents extubation time and time to NCI ≤ 60, which were the data collected.
4. **Eligibility.** The protocol specified age > 18 years without an upper limit and only two exclusion criteria; the executed study applied an upper age limit of 65 years and additional exclusions (cardiac/brain surgery history, cardiovascular or cerebrovascular disease, pregnancy, refusal, inadequate temporal acoustic window). These changes were not covered by a documented amendment.
5. **Sufentanil dose.** The protocol states sufentanil 4 μg/kg for induction; 0.4 μg/kg was administered in both groups. The protocol value is presumed to be a typographical error, but this cannot be verified.
6. **PIH management (protocol deviation).** Protocol v1.0 specified that MAP < 65 mmHg persisting for > 1 min should trigger intravenous norepinephrine 10 μg followed by infusion (initial 0.3 μg/kg/h)—a **treatment** trigger. In the executed study, MAP < 65 mmHg persisting for ≥ 3 min led to rescue vasopressor therapy (phenylephrine or ephedrine) **and withdrawal from the study**, and the four affected participants were excluded from the original analysis. This exclusion of randomised participants based on a post-randomization event was a protocol deviation performed without an amendment and without re-analysis in the randomised cohort. The deviation, its handling in the present re-analysis, and its consequences are reported in the Results and Limitations.

Table 5
Exploratory outcomes: registered primary outcome (MCAvs) ratios, autoregulation index, recovery, and cognition.

ΔMCAvs/ΔSBP (T0–T1)	Group R	Group P	p value
	0.3 [0.0, 0.8]	**0.4 [0.1, 0.9]**	**0.777**
ΔMCAvs/ΔSBP (T0–T2)	0.4 [0.2, 0.6]	0.5 [0.2, 0.7]	0.563
ΔMCAvs/ΔSBP (T0–T3)	0.5 [0.2, 0.8]	0.4 [− 0.1, 0.6]	0.448
ΔMCAvs/ΔSBP (T0–T4)	0.3 [0.2, 0.7]	0.4 [0.1, 0.7]	0.717
ΔMCAvm/ΔMAP (T0–T1)	0.3 [− 0.1, 0.6]	0.4 [0.2, 0.8]	0.346
ΔMCAvm/ΔMAP (T0–T2)	0.3 [0.2, 0.6]	0.5 [0.2, 0.6]	0.416
ΔMCAvm/ΔMAP (T0–T3)	0.4 [0.1, 0.7]	0.5 [0.1, 0.6]	0.950
ΔMCAvm/ΔMAP (T0–T4)	0.2 [0.2, 1.0]	0.4 [0.3, 0.7]	0.274
Mxa, median [IQR]	0.718 [0.184, 0.903] (n = 18)	0.705 [0.496, 0.863] (n = 20)	0.872
Mxa > 0.30, n/N (%)	12/18 (66.7)	16/20 (80.0)	0.488□
Time to first NCI ≤ 60 (min)	1.3 [0.5, 2.1]	0.8 [0.5, 1.5]	0.058
Extubation time (min)	15.2 [8.7, 23.6]	13.8 [7.1, 19.7]	0.080
MoCA < 26 at 24 h, n/N (%)	3/20 (15.0)	5/24 (20.8)	0.915

Data are median [IQR] or n/N (%). MCAvs: middle cerebral artery systolic flow velocity; SBP: systolic blood pressure; MCAvm: middle cerebral artery mean flow velocity; MAP: mean arterial pressure; Mxa: moving correlation coefficient between MAP and MCAvm; NCI: Narcotrend Index; MoCA: Montreal Cognitive Assessment. Ratio outcomes compare the change in flow velocity with the change in pressure from T0 to each time point. All outcomes in this table are exploratory; p values are nominal (Mann–Whitney U, chi-square, or Fisher exact test) without multiplicity adjustment. □ Proportion difference − 13.3 percentage points (95% CI − 41.3 to + 14.6).

Analysis sets and missing data

Fifty-two participants were randomised (26 per group). Twelve had no retrievable per-protocol hemodynamic dataset: six with failure to detect the MCA through the temporal window (four remimazolam, two propofol), two with inability to maintain NCI ≤ 60 at maximum infusion rates (both remimazolam), and four with persistent PIH (all propofol). The individual-level data file retained for re-analysis contained 44 participants (remimazolam 20, propofol 24); data for the remaining 8 randomised participants (the 6 acoustic-window failures and 2 NCI failures) were not retained, and the 4 propofol participants withdrawn for PIH could not be individually identified within the 24 propofol records because no subject identifiers or withdrawal flags were preserved.

We therefore defined: (i) a **full analysis set (FAS, n = 44)** of all randomised participants with retrievable data, analysed according to randomised allocation; and (ii) a **completer set (n = 40; 20 per group)** of

participants with complete TCCD data through T4 (for the propofol group this set, n = 20, is the closest reproducible approximation of the originally reported analysis cohort, although identity with that cohort cannot be verified). The primary analysis used the FAS. The 4 PIH withdrawals are acknowledged as post-randomization exclusions based on an intercurrent event; their induction-period data, where retained, are included in the FAS under the treatment-policy strategy.

Missing TCCD data within the FAS followed a monotone dropout pattern confined to the TCCD channel (RM: 2 participants missing from T3, 1 additional PI/RI value at T4; PP: 1 participant missing from T3, 4 at T4); MAP was complete at all time points. The linear mixed model uses all available observations under a missing-at-random assumption; no imputation was performed. A sensitivity analysis compared the full propofol set (n = 24) with the completer set (n = 20).

Statistical analysis

Analyses were performed in Python 3.12 (pandas/numpy/scipy/statsmodels) as an independent statistical re-analysis; the original analyses had been performed in SPSS version 26. Continuous variables are summarised as mean (SD) or median [IQR] and categorical variables as counts.

The primary outcome was analysed with a linear mixed-effects model (REML) with a random intercept per participant:

$$MCAvm_{it} = \beta 0 + \beta 1 \cdot (\text{baseline MCAvm}_i) + \text{time (T1–T4)} + \text{group} + \text{time} \times \text{group} + b0i + \varepsilon_{it}$$

Baseline MCAvm was included as a covariate (ANCOVA-type adjustment). The overall group-by-time interaction was tested by a likelihood-ratio test (df = 3) from a maximum-likelihood fit; a five-time-point model including T0 (df = 4) was fitted as a check. Adjusted between-group differences at each time point are reported with 95% confidence intervals. Within-group changes from baseline are presented descriptively only.

Secondary hemodynamic outcomes were analysed with the same model structure. Secondary and exploratory outcomes were **not adjusted for multiplicity**; their p values are nominal and hypothesis-generating. A post-hoc exploratory equivalence analysis (two one-sided tests) was performed on the between-group difference in MCAvm change from T0 to T4, using an analyst-defined margin of ± 10 cm/s (approximately 15% of baseline MCAvm; not pre-registered). Categorical outcomes were compared with the chi-square or Fisher exact test, and skewed variables with the Mann–Whitney U test. Two-sided $p < 0.05$ was considered statistically significant for the primary test.

Sample size and post-hoc precision. The original sample-size calculation assumed MCAvm 45 ± 5 cm/s after induction and an anticipated between-group difference of 5 cm/s ($\alpha = 0.05$, power 0.80, 16 per group; inflated by 20% for dropout to a target of 40), based on a pilot estimate from a prior trial by the first author in a different clinical setting [10]. Observed baseline MCAvm was 62.9–65.0 cm/s and the observed SD of the MCAvm change was 11.6 cm/s—2.3 times the assumed SD. With n = 20 per group, the minimum detectable between-group difference in MCAvm change (two-sided $\alpha = 0.05$, 80% power)

was approximately 10.5 cm/s; achieving the originally targeted precision at the observed variance would require approximately 107 participants per group. The trial is therefore underpowered for differences smaller than about 10 cm/s, and this is reflected in the interpretation of all results.

Results

Participant flow and analysis sets

Of 100 patients assessed for eligibility, 52 were randomised (26 per group). Six were excluded before any analyzable TCCD recording because the MCA could not be insonated (four remimazolam, two propofol), and two (both remimazolam) because NCI ≤ 60 could not be maintained at maximum infusion rates; data for these 8 participants were not retained. Four propofol participants were withdrawn after persistent PIH (a protocol deviation, see Methods); their records are included, though not individually identifiable, in the propofol FAS of 24. The FAS thus comprised 44 participants (remimazolam 20, propofol 24) and the completer set 40 (20 per group) (Fig. 1).

Patient characteristics and baseline data

Demographic and clinical characteristics of the completer set are shown in Table 1; no significant between-group differences were observed, although mean age was descriptively higher in the remimazolam group (61.7 vs 55.2 years, p = 0.082).

Table 1
Demographic data and clinical characteristics (completer set, n = 40; data for the four participants withdrawn for PIH were not separately retrievable).

Age (yr)	**Group R (n = 20)**	**Group P (n = 20)**	**p value**
	61.7 (11.4)	**55.2 (12.4)**	**0.082**
Sex (Female/Male, n)	9/11	10/10	0.752
BMI (kg/m²)	23.9 (2.6)	22.9 (3.2)	0.239
ASA grade (I/II, n)	11/9	13/7	0.519
Hypertension (n)	5	6	0.723
Diabetes mellitus (n)	2	2	1.000
Smoking history (n)	5	7	0.490

Data are mean (SD) or number. BMI: body mass index; ASA: American Society of Anesthesiologists. Comorbidities are shown as number affected. Between-group comparisons by unpaired t-test, chi-square, or Fisher exact test as appropriate; p values are descriptive.

Baseline hemodynamics of the FAS are shown in Table 2. Baseline systolic blood pressure (SBP) was elevated in both groups (remimazolam 163.9 ± 26.0 mmHg; propofol 157.8 ± 24.7 mmHg; p = 0.432), with SBP ≥ 140 mmHg in 16/20 (80%) and 18/24 (75%) of participants, respectively. Baseline MAP (109.9 ±

18.4 vs 109.5 ± 17.1 mmHg; p = 0.941) and baseline MCAvm (62.9 ± 12.1 vs 65.0 ± 9.6 cm/s; p = 0.526) did not differ between groups.

Table 2
Baseline systemic and cerebral hemodynamics before anesthesia induction (full analysis set).

SBP (mmHg)	**Remimazolam (n = 20)**	**Propofol (n = 24)**	**p value**
	163.9 (26.0)	**157.8 (24.7)**	**0.432**
MAP (mmHg)	109.9 (18.4)	109.5 (17.1)	0.941
HR (bpm)	73.5 (13.8)□	73.8 (10.1)□	0.927□
MCAvm (cm/s)	62.9 (12.1)	65.0 (9.6)	0.526
PI	0.97 (0.21)	0.95 (0.22)	0.358□
RI	0.61 (0.07)	0.59 (0.07)	0.596□
CPPe (mmHg)	88.2 (32.8)	86.1 (29.5)	0.858□
CrCP (mmHg)	21.7 (21.9)	23.4 (24.3)	0.794□
CVR (mmHg·s·cm⁻¹)	1.81 (0.47)	1.71 (0.30)	0.408□

Data are mean (SD). □ HR values derive from the completer set (n = 20 per group); per-group HR for the four PIH-withdrawn participants was not retrievable. □ Between-group p value retained from the original completer-set comparison; FAS between-group differences were not significant (SBP p = 0.432; MAP p = 0.941; MCAvm p = 0.526 from the re-analysis). SBP: systolic blood pressure; MAP: mean arterial pressure; HR: heart rate; MCAvm: middle cerebral artery mean flow velocity; PI: pulsatility index; RI: resistance index; CPPe: estimated effective cerebral perfusion pressure; CrCP: critical closing pressure; CVR: cerebrovascular resistance.

Primary outcome: MCAvm

Descriptive MCAvm values are shown in Table 3 and Fig. 2. From elevated pre-induction baselines, MCAvm decreased by a mean of approximately 12 cm/s (about 19%) from T0 to T4 in both groups (remimazolam − 12.0 ± 10.8 cm/s; propofol − 12.0 ± 12.2 cm/s). Adjusted between-group differences (remimazolam minus propofol) were:

Time	**Adjusted difference (cm/s)**	**95% CI**	**p**
T1 (1 min)	+ 3.88	−3.21 to + 10.97	0.283
T2 (3 min)	+ 0.63	−6.46 to + 7.72	0.862
T3 (5 min)	−1.37	−8.57 to + 5.83	0.709
T4 (10 min)	−1.09	−8.38 to + 6.21	0.770

Table 3
Primary outcome and systemic hemodynamics over time (full analysis set; mean ± SD).

MCAvm (cm/s)	Group	T0	T1	T2	T3	T4
	R	**62.9 ± 12.1**	**51.9 ± 16.4**	**47.8 ± 14.9**	**49.6 ± 15.1 (n = 18)**	**50.7 ± 14.7 (n = 18)**
	P	65.0 ± 9.6	49.7 ± 13.0	48.8 ± 12.8	51.7 ± 14.7 (n = 23)	52.9 ± 14.2 (n = 20)
ΔMCAvm T0→T4 (cm/s)	R	—	—	—	—	−12.0 ± 10.8
	P	—	—	—	—	−12.0 ± 12.2
MAP (mmHg)	R	109.9 ± 18.4	94.0 ± 18.3	80.3 ± 11.9	78.7 ± 14.7	83.0 ± 16.8
	P	109.5 ± 17.1	83.3 ± 20.1	76.6 ± 14.7	75.9 ± 12.0	76.8 ± 12.3

R: remimazolam (n = 20); P: propofol (n = 24). Reduced n at T3/T4 reflects monotone loss of the TCCD signal; MAP was complete at all time points. Primary analysis (linear mixed model, baseline-adjusted): group-by-time interaction p = 0.206; adjusted between-group differences with 95% CIs are reported in the text and Fig. 3.

The overall group-by-time interaction was not significant (likelihood-ratio p = 0.206 for the T1–T4 model; p = 0.498 for the five-time-point model including T0). The baseline MCAvm covariate was strongly associated with post-induction values (β = 0.767, SE 0.151, p < 0.001). All confidence intervals crossed zero (Fig. 3).

A post-hoc exploratory equivalence test (margin ± 10 cm/s, analyst-defined) on the between-group difference in MCAvm change from T0 to T4 gave a difference of + 0.05 cm/s with a 90% CI of − 6.26 to + 6.36 cm/s (TOST p = 0.006), entirely within the ± 10 cm/s margin. This is exploratory only: the trial was designed under a superiority framework, the margin was not pre-specified, and the CI does not exclude differences of 6–7 cm/s.

Sensitivity analysis: analysis-set dependence

Repeating the primary model with the propofol completer set (n = 20) instead of the full propofol set (n = 24) gave adjusted differences of + 3.11 (− 4.34 to 10.56), − 0.11 (− 7.56 to 7.34), − 2.50 (− 10.04 to 5.04), and − 1.86 (− 9.40 to 5.68) cm/s at T1–T4 (interaction p = 0.585). All point estimates remained within ± 4 cm/s and all CIs crossed zero; the primary conclusion was insensitive to the analysis-set definition.

Secondary hemodynamic outcomes

Descriptive values are shown in Tables 3 and 4 and Fig. 4; adjusted between-group differences are summarised below (remimazolam minus propofol; nominal p values, no multiplicity adjustment).

Table 4
Derived cerebral hemodynamic indices over time (full analysis set; mean ± SD).

CPPe (mmHg)	Group	T0	T1	T2	T3	T4
	R	**88.2 ± 32.8**	**70.3 ± 20.6**	**49.8 ± 11.3**	**51.9 ± 13.6**	**55.2 ± 20.1**
	P	86.1 ± 29.5	55.7 ± 21.2	51.1 ± 14.8	46.3 ± 12.4	48.7 ± 13.4
CrCP (mmHg)	R	21.7 ± 21.9	23.7 ± 18.0	30.5 ± 11.9	26.7 ± 12.1	28.5 ± 13.2
	P	23.4 ± 24.3	27.6 ± 12.8	25.5 ± 14.4	30.5 ± 10.8	27.4 ± 13.4
CVR (mmHg·s·cm⁻¹)	R	1.81 ± 0.47	1.94 ± 0.58	1.84 ± 0.69	1.70 ± 0.55	1.75 ± 0.52
	P	1.71 ± 0.30	1.78 ± 0.60	1.66 ± 0.52	1.59 ± 0.49	1.52 ± 0.41
PI	R	0.97 ± 0.21	0.90 ± 0.21	1.02 ± 0.20	0.97 ± 0.23	0.92 ± 0.21
	P	0.95 ± 0.22	1.04 ± 0.27	1.05 ± 0.20	1.05 ± 0.22	1.02 ± 0.20
RI	R	0.61 ± 0.07	0.56 ± 0.08	0.60 ± 0.07	0.58 ± 0.07	0.58 ± 0.08
	P	0.59 ± 0.07	0.60 ± 0.09	0.61 ± 0.06	0.61 ± 0.06	0.60 ± 0.06

R: remimazolam (n = 20); P: propofol (n = 24; n = 23 at T3 and n = 20 at T4 for TCCD-derived indices). CPPe: estimated effective cerebral perfusion pressure; CrCP: critical closing pressure; CVR: cerebrovascular resistance; PI: pulsatility index; RI: resistance index. Between-group nominal differences were confined to T1 (CPPe, PI, RI; see text); no multiplicity adjustment.

- **MAP**: group-by-time interaction p = 0.152. The adjusted difference was + 10.47 mmHg (95% CI 2.73 to 18.22; nominal p = 0.008) at T1, and + 3.49, + 2.55, and + 5.97 mmHg at T2–T4 (all CIs crossing zero).
- **CPPe**: interaction p = 0.069. Adjusted difference + 14.12 mmHg (5.35 to 22.90; nominal p = 0.002) at T1; differences at T2–T4 crossed zero.
- **CrCP**: interaction p = 0.350; no time point differed between groups.
- **CVR (mmHg·s·cm⁻¹)**: interaction p = 0.905; no time point differed.
- **PI**: interaction p = 0.041; adjusted difference − 0.15 (− 0.27 to − 0.04; nominal p = 0.010) at T1 only.
- **RI**: interaction p = 0.025; adjusted difference − 0.05 (− 0.09 to − 0.01; nominal p = 0.008) at T1 only.

Thus, between-group differences were confined to the first minute after intubation—a nominally shallower decrease in MAP and CPPe with remimazolam, accompanied by transiently lower PI and RI—

and were no longer detectable from T2 onward. Under a Bonferroni correction for the 24 secondary time-point tests (α ≈ 0.002), none of these nominal findings would remain clearly significant; they are hypothesis-generating.

Time to first NCI ≤ 60 (1.3 [0.5, 2.1] vs 0.8 [0.5, 1.5] min; p = 0.058) and extubation time (15.2 [8.7, 23.6] vs 13.8 [7.1, 19.7] min; p = 0.080) did not differ significantly between groups (Table 5).

Exploratory outcomes: MCAvs ratios, Mxa, and cognition

The registered primary outcome MCAvs is reported exploratorily as ΔMCAvs/ΔSBP ratios from T0 to each post-intubation time point; no between-group differences were detected (Table 5). ΔMCAvm/ΔMAP ratios likewise did not differ between groups. The ΔMV/ΔMBP ratio (T0–T1) showed very large dispersion (remimazolam 0.33 ± 0.86 vs propofol 0.61 ± 1.58) and is not interpretable.

Mxa was available in 18 remimazolam and 20 propofol participants: median 0.718 (IQR 0.184–0.903) versus 0.705 (IQR 0.496–0.863) (p = 0.872). The proportion with Mxa > 0.30 was 12/18 (66.7%; 95% CI 43.7–83.7) versus 16/20 (80.0%; 95% CI 58.4–91.9), a difference of − 13.3 percentage points (95% CI − 41.3 to + 14.6). Given incomplete sampling, undocumented signal-processing parameters, the non-stationary induction period, and the unvalidated 0.30 threshold, these data are descriptive only.

MoCA scores below 26 at 24 h postoperatively occurred in 3/20 (15.0%) of the remimazolam group and 5/24 (20.8%) of the propofol group (p = 0.915); within-group changes from the preoperative assessment were not significant in either group. A single 24-h MoCA measurement cannot diagnose postoperative cognitive dysfunction; these data are exploratory.

Harms

Four participants (all propofol) experienced persistent PIH requiring vasopressor therapy and withdrawal (see above). Bradycardia requiring atropine did not occur. No other adverse events, and no postoperative cerebrovascular events, were recorded in either group. Systematic per-group recording of vasopressor doses and fluid volumes was not performed, and adverse-event ascertainment was limited to the intra- and immediate postoperative period; safety inferences cannot be drawn from this sample.

Discussion

In this exploratory physiological study, MCAvm decreased by approximately 12 cm/s (about 19%) from an elevated pre-induction baseline after induction of general anesthesia with either remimazolam or propofol, and no significant between-group difference in the MCAvm trajectory was detected. Secondary analyses suggested a nominally shallower decrease in MAP and CPPe with remimazolam confined to the first minute after intubation, which had resolved by 3 min. These T1 findings are consistent with the pharmacological expectation of slower onset and less cardiovascular depression with remimazolam [5–8], but they were not adjusted for multiplicity and should be regarded as hypothesis-generating.

The post-hoc equivalence analysis found that the 90% CI for the between-group difference in MCAvm change (− 6.3 to + 6.4 cm/s) lay within an analyst-defined ± 10 cm/s margin. This indicates that the data are precise enough to exclude differences of 10 cm/s or more, but not differences in the 6–10 cm/s range; it is exploratory evidence, not a formal equivalence conclusion, because the trial was designed as a superiority comparison and no margin was pre-specified.

Baseline SBP was markedly elevated in both groups (means 158–164 mmHg; three quarters of participants ≥ 140 mmHg), most plausibly reflecting pre-procedural anxiety, white-coat effects, and unmeasured background hypertension; no ward or resting blood pressure was recorded for comparison. Part of the observed post-induction decrease in blood pressure and flow velocity is therefore attributable to regression to the mean in addition to drug effect. Three considerations mitigate the threat to the between-group comparison: baseline SBP and MAP were balanced between groups ($p = 0.43$ and 0.94), so regression to the mean acts symmetrically; the correlation between baseline SBP and the T0–T1 SBP change across the sample was weak ($r = -0.10$, $p = 0.53$); and the primary analysis adjusted for baseline MCAvm (ANCOVA structure). Accordingly, within-group decreases should be interpreted cautiously, but the between-group comparison is not threatened by this mechanism.

Neither agent measurably changed CrCP, and CVR remained within a narrow range throughout induction in both groups. This appears inconsistent with the classical view that propofol increases cerebrovascular resistance [17]; however, propofol simultaneously lowers systemic pressure, triggering compensatory cerebrovascular dilation via autoregulation [5, 20], and the net effect on CVR depends on the balance between these opposing influences [17, 19]. Because CrCP, CPPe, and CVR are computed from the same underlying MAP and velocity signals, their trajectories are mathematically coupled and do not constitute independent confirmation of one another.

CPPe fell below 60 mmHg after induction in both groups. We deliberately avoid interpreting this against the conventional 60-mmHg cerebral perfusion pressure threshold: CPPe is a model-based estimate of MAP minus critical closing pressure, intracranial pressure was not measured, and no validated harm threshold exists for this index during anesthesia induction. The transient T1 between-group difference in CPPe diminished rapidly and was not accompanied by detectable differences in any downstream clinical measure in this small sample.

The Mxa findings are reported for completeness but are difficult to interpret: Mxa values were available in only a subset of participants, the signal-processing parameters used to compute them were not documented, the induction period violates the stationarity assumptions underlying correlation-based autoregulation indices [21], and the 0.30 threshold has not been validated in this context. We therefore refrain from any statement about impaired versus intact autoregulation. Similarly, the MoCA data—a single 24-h assessment without education adjustment or pre-specified intra-individual change analysis—cannot support any conclusion about postoperative cognitive dysfunction.

Limitations

This study has substantial limitations. **First**, four participants with persistent PIH (all propofol) were withdrawn after randomization and excluded from the original analysis. This was a deviation from protocol v1.0—which mandated vasopressor *treatment*, not withdrawal—and constitutes outcome-dependent exclusion of exactly the participants expected to show the least favorable hemodynamic response to propofol. Although the retained data of these participants are included in the FAS and the sensitivity analyses (PP24 vs PP20) did not change the neutral primary result, their data could not be individually identified, the analysis sets remain smaller than the randomised cohort, and attrition bias cannot be excluded. **Second**, data for 8 of the 52 randomised participants were not retained, so a true intention-to-treat analysis was impossible; the FAS (n = 44) is the largest reproducible set. **Third**, the trial was underpowered: the sample-size calculation used an SD (5 cm/s) 2.3 times smaller than observed (11.6 cm/s), yielding a minimum detectable difference of about 10.5 cm/s; equivalence margins below ± 7 cm/s are not supported. **Fourth**, discrepancies between the registration, the protocol, and this report (primary outcome MCAvs vs MCAvm; MMSE vs MoCA; PACU stay vs extubation time; eligibility criteria; sufentanil dose) arose without documented amendments and introduce a risk of selective reporting that disclosure can mitigate but not eliminate. **Fifth**, baseline blood pressures were elevated and a resting reference measurement was lacking; within-group decreases partly reflect regression to the mean. **Sixth**, PetCO2 was controlled but PaCO2 was not measured, MCA diameter was not measured (velocity substitutes for flow), and the drug-to-intubation timeline was not standardised beyond clinical routine. **Seventh**, the anesthesiologists were unblinded, although vasopressor administration was protocol-driven. **Eighth**, because the maintenance agents necessarily mirrored the induction agents, recovery endpoints (extubation time, MoCA) reflect the entire remimazolam- versus propofol-based regimen and cannot be attributed to the induction bolus. **Ninth**, the study population (ASA I–II, 18–65 years) excludes the elderly and cardiovascular/cerebrovascular high-risk patients in whom cerebral hemodynamic stability matters most; generalisation is not warranted. **Finally**, minimization factors, allocation-concealment mechanics, and per-group fluid/vasopressor totals were not documented, and no prospective statistical analysis plan existed; the statistical approach reported here was finalised after data collection.

Conclusion

In this small exploratory physiological study of relatively healthy adults, induction of general anesthesia with either remimazolam or propofol was followed by a decrease in MCAvm of approximately 12 cm/s from an elevated baseline, and no significant between-group difference in the post-intubation MCAvm trajectory was detected. Nominally smaller decreases in MAP and CPPe with remimazolam were confined to the first minute after intubation and are hypothesis-generating. The findings apply only to the induction period in ASA I–II patients and should not be extrapolated to elderly or high-risk populations. Adequately powered, prospectively registered trials with pre-specified estimands, retention and analysis of all randomised participants, and validated neuromonitoring methodology are needed.

Declarations

Ethical approval:

The protocol was approved by the Institutional Review Board of Fudan University Shanghai Cancer Center (approval number 2510-Exp296). Written informed consent was obtained from all participants.

Conflicts of interest:

The authors declare no conflicts of interest.

CONSORT 2025 adherence statement

This report was prepared in accordance with the CONSORT 2025 statement [22]. A completed CONSORT 2025 checklist and the CONSORT flow diagram (Fig. 1) accompany this submission. Items that could not be fully reported because the underlying trial records were not retained (minimization factors and random component, allocation-concealment mechanics, per-group co-intervention volumes, and the reason certain randomised participants' data were not retained) are explicitly disclosed in the Methods and Limitations rather than omitted. The statistical approach was finalised after data collection and is described here in full; no prospective statistical analysis plan exists. The estimand framework follows ICH E9(R1) [23].

Formatting note for the editorial office

This document was prepared with double-equivalent (1.5-line) spacing and page numbering in the footer. Continuous line numbering is not supported by the Markdown-to-Word conversion pipeline used to prepare this file and is therefore not applied; line numbers can be added by the editorial office production system if required. Tables are formatted in three-line (booktabs) style.

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Author Contribution

Jun Zhang and Li Yang contributed to conception and design; Xueyan Li,Yijun Zheng and Zhiqin Chen contributed to data acquisition, methods, and analysis; Xueyan Li drafted the manuscript; Jun Zhang and Yijun Zheng critically revised it. All authors approved the final version.

Data availability:

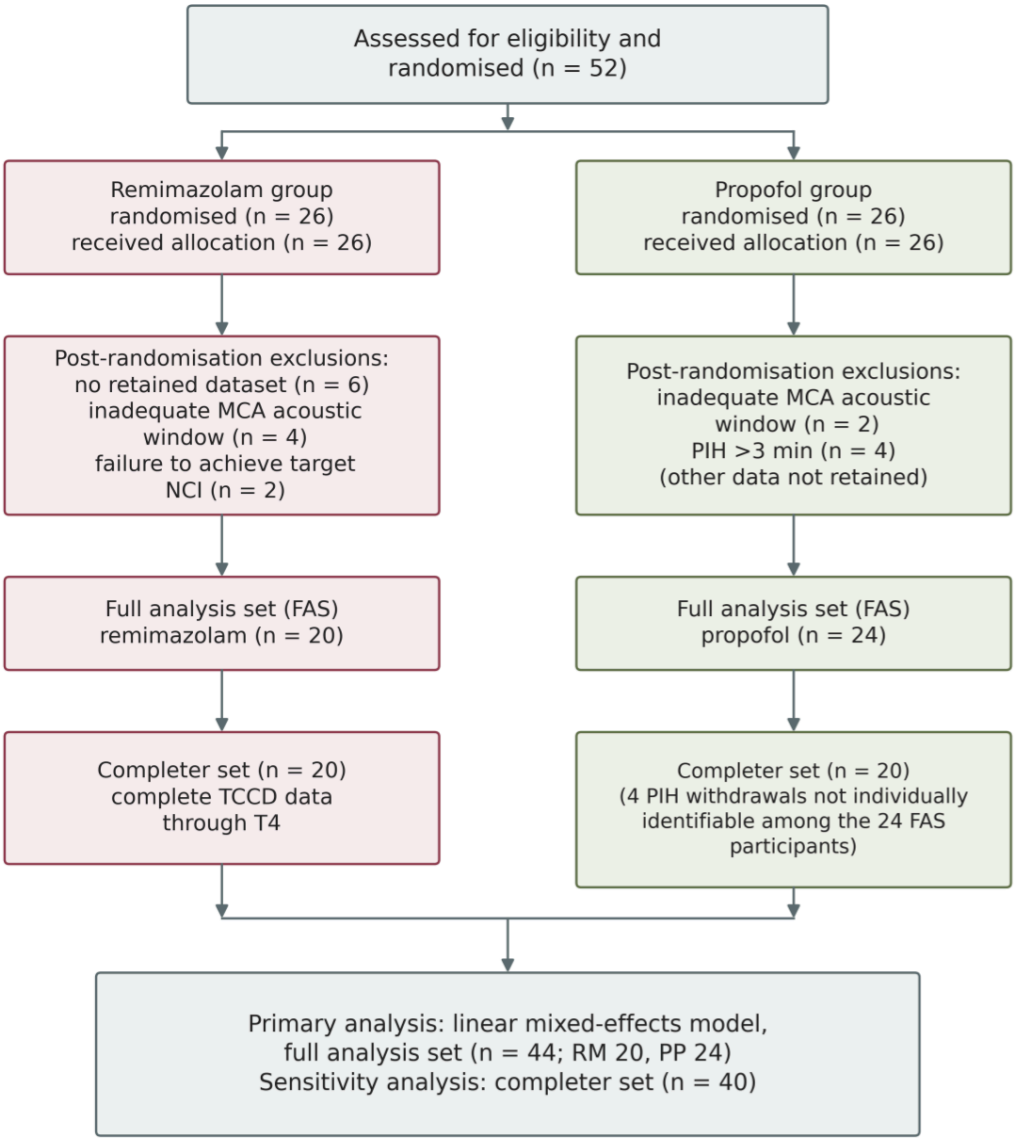
The de-identified dataset is available from the corresponding author upon reasonable request.

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Figures



MCA: middle cerebral artery; NCI: Narcotrend Index; PIH: post-induction hypotension; TCCD: transcranial color-coded duplex sonography; RM: remimazolam; PP: propofol.

Figure 1

CONSORT flow diagram of participant enrollment, randomization, withdrawal, and analysis-set construction.

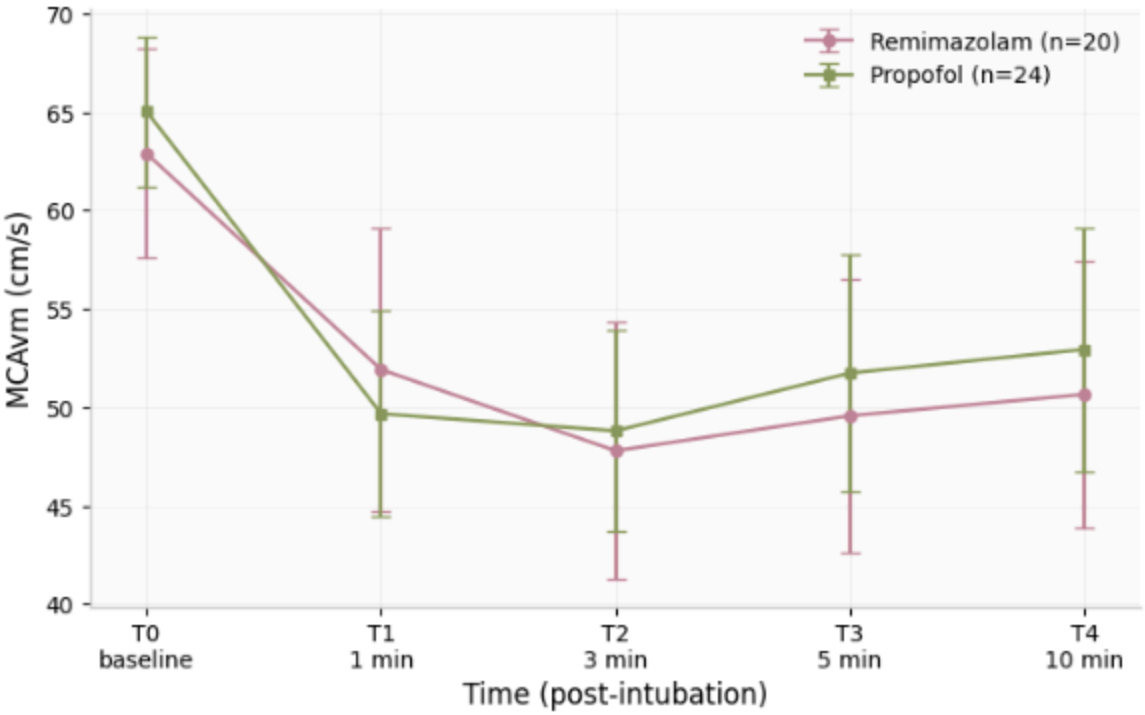


Figure 2

Middle cerebral artery mean flow velocity (MCAvm) over time in the remimazolam (n = 20) and propofol (n = 24) groups; means with 95% confidence intervals. T0: before induction; T1–T4: 1, 3, 5, and 10 min after intubation. Reduced denominators at T3/T4 (see Table 3) reflect loss of the TCCD signal.

MCAvm over time by group (mean ± 95% CI).

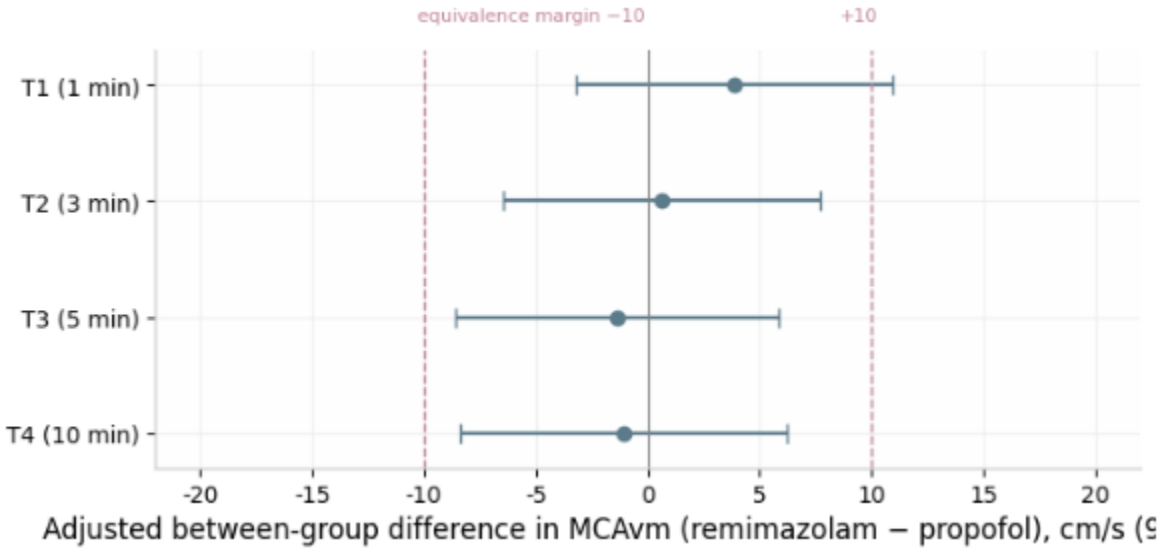


Figure 3

Adjusted between-group differences (remimazolam minus propofol) in MCAvm at T1–T4 with 95% confidence intervals from the baseline-adjusted linear mixed-effects model; dashed reference lines mark

the post-hoc analyst-defined equivalence margin of ±10 cm/s.

Adjusted between-group differences in MCAvm with 95% CIs.

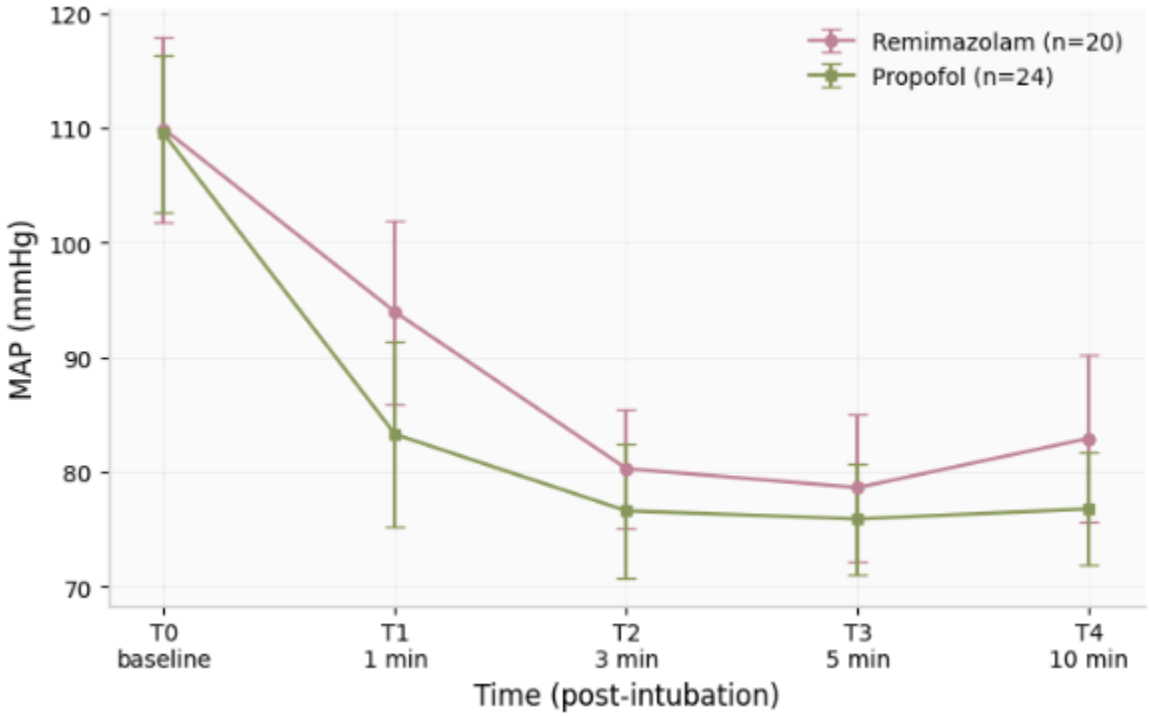


Figure 4

Mean arterial pressure (MAP) over time in the remimazolam and propofol groups; means with 95% confidence intervals. MAP was complete at all time points in both groups.

MAP over time by group (mean ± 95% CI).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- CONSORT2025Checklist.docx