

ORIGINAL ARTICLE

Comparative Efficacy of Low-Dose Ketamine Versus Midazolam Co-Induction on Hemodynamic Stability and Early Neurocognitive Recovery in Geriatric Anesthesia: A Randomized Double-Blind Pilot Trial

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ABSTRACT

Background. Older patients are prone to hypotension after induction and to early postoperative cognitive decline. Midazolam, the conventional co-induction sedative, may prolong sedation in older adults; ketamine preserves sympathetic tone.

Objective. To compare low-dose ketamine with midazolam co-induction for hemodynamic stability, propofol requirement, and early neurocognitive recovery in older surgical patients.

Methods. In this randomized, double-blind pilot trial, 32 patients aged ≥ 65 years (ASA II–III) undergoing elective surgery under general anesthesia received ketamine 0.3 mg/kg (Group K, $n = 16$) or midazolam 0.075 mg/kg (Group M, $n = 16$) before titrated propofol induction. The primary outcome was the change in Mini-Mental State Examination (MMSE) score from baseline to 1 hour after extubation. Secondary outcomes were mean arterial pressure (MAP), hypotension, propofol dose, and extubation time.

Results. The MMSE declined by 1.1 ± 0.8 points in Group K and 4.2 ± 1.4 points in Group M ($p < 0.001$); cognitive dysfunction (decline > 2 points) occurred in 18.8% and 68.8% ($p = 0.004$). Post-induction MAP was 88.5 ± 7.4 and 76.2 ± 8.8 mmHg ($p < 0.001$), and hypotension occurred in 12.5% and 56.3% (relative risk 0.222, 95% confidence interval 0.057–0.872; $p = 0.009$). Group K needed 32.1% less propofol (1.12 ± 0.18 vs. 1.65 ± 0.22 mg/kg, $p < 0.001$) and was extubated sooner (8.4 ± 2.1 vs. 14.2 ± 3.5 minutes, $p < 0.001$).

Conclusion. In this pilot trial, ketamine co-induction was associated with more stable hemodynamics, less propofol, and a smaller early MMSE decline than midazolam.

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1. Introduction

The number of older adults presenting for surgery is rising, and anesthesiologists must protect a brain that is already vulnerable.¹ The population aged 65 years and above is projected to double by 2050,² and more octogenarians and nonagenarians with several comorbidities now undergo complex procedures.³ Perioperative risks include acute organ failure, long hospital stays, loss of independence, and death,⁴ and the underlying cause is homeostenosis, the gradual loss of physiological reserve.⁵ The central nervous system is particularly fragile.⁶ Cerebral aging brings atrophy, synaptic pruning, reduced neurotransmitter synthesis, poorer microvascular compliance, and a less intact blood-brain barrier,⁷ and older surgical patients face emergence delirium, postoperative delirium, and prolonged postoperative cognitive dysfunction.⁸ Persistent impairment is diagnosed weeks or months after surgery, but the deviation begins in the first hours after emergence,⁹ and slow cognitive recovery in the post-anesthesia care unit (PACU) may be an early sign of neuroinflammation and cerebral hypoperfusion.¹⁰

Induction of general anesthesia in an older patient demands adequate hypnosis without hemodynamic instability.¹¹ Propofol is the standard induction agent,¹² but its dose-dependent myocardial depression and vasodilation often produce hypotension,¹³ which is amplified by arterial stiffness, impaired baroreceptor sensitivity, and a contracted circulating volume.¹⁴ Chronic hypertension shifts the cerebral autoregulatory threshold to the right, so watershed ischemia becomes likely once mean arterial pressure falls below the lower limit.¹⁵ Co-induction, in which an adjuvant given just before propofol lowers the induction dose, is the usual answer.¹⁶ Midazolam, a short-acting benzodiazepine that modulates gamma-aminobutyric acid type A (GABA-A) receptors,¹⁷ has long been used for its anxiolytic and amnestic effects,¹⁸ but its safety in older patients is increasingly questioned.¹⁹ Greater body fat and lower hepatic clearance lengthen its context-sensitive half-life,^{20,21} and GABAergic overload on a depleted cholinergic background may worsen cognitive fragmentation and delirium.²²

Ketamine, an uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist,²³ keeps sympathetic tone at

sub-anesthetic doses (0.3 to 0.5 mg/kg) and offsets the vasodilation and cardiodepression caused by propofol.²⁴ It may also be neuroprotective by limiting glutamate-mediated calcium influx and excitotoxicity,²⁵ and it may reduce microglial inflammatory signaling and cytokine release.²⁶ Clinical evidence in older patients is, however, conflicting, especially for early emergence and immediate cognitive recovery.²⁷ Large trials using high intraoperative doses reported inconsistent effects on delirium and concern about hallucinations,²⁸ most geriatric anesthesia trials come from Western cohorts,²⁹ and ethnic differences in body composition and cytochrome P450 polymorphisms (CYP2B6, CYP3A4) may change the pharmacology of both drugs.^{30,31} Geriatric surgical care in Southeast Asia faces constraints that differ from those of resource-rich systems.^{1,32} Guidelines written in North America or Western Europe often assume target-controlled infusion systems, processed electroencephalographic monitors, and staff trained in delirium assessment, which many Indonesian referral hospitals lack.³³ Induction strategies that rely on predictable pharmacology are therefore valuable.^{32,34} Cognitive assessment in the immediate postoperative period is also underappreciated. Late measures at 30 to 90 days are affected by many non-anesthetic factors,^{10,35} whereas the first hour after extubation isolates the immediate effect of induction and emergence,³⁶ and a patient who wakes clear and oriented can report pain, allow early recognition of stroke, protect the airway, and cooperate with respiratory care.^{10,36} To our knowledge, few trials have combined detailed hemodynamic profiling with cognitive testing in the first hour after emergence in an older Southeast Asian cohort.^{33,35}

We therefore compared low-dose ketamine (0.3 mg/kg) with midazolam (0.075 mg/kg) co-induction in older patients having elective surgery under general anesthesia. The primary objective was to determine whether ketamine preserves early neurocognitive recovery, measured with the Mini-Mental State Examination (MMSE) 1 hour after extubation, better than midazolam. The secondary objective was to compare intraoperative hemodynamic stability.³⁶

2. Methods

2.1. Study design and reporting

This was a single-center, prospective, randomized, double-blind, parallel-group pilot trial with 1:1 allocation, reported according to the CONSORT statement.³² An independent biostatistician generated a computer-based permuted block sequence (block size four).³⁷ Allocation was concealed in sequentially numbered, opaque, sealed envelopes kept in the clinical trial pharmacy and opened only after enrollment and baseline testing.³⁸ An independent research pharmacist, who took no part in clinical care or outcome assessment, prepared the study drugs in identical 5 mL polypropylene syringes diluted with sterile 0.9% saline: preservative-free racemic ketamine hydrochloride 0.3 mg/kg of total body weight for Group K, or midazolam hydrochloride 0.075 mg/kg for Group M.^{39,40} Both solutions were clear and colorless. A quality-assurance pharmacist checked each syringe for clarity, particulates, and volume (5.0 mL), and labels showed only the randomized subject identifier.³⁸ Anesthesiologists, surgeons, nurses, patients, and the cognitive assessor were blinded to allocation,⁴¹ and a technical assistant recorded the monitor screens so that clinicians would not need to speculate about allocation.³⁹

2.2. Setting

The study took place at Dr. Saiful Anwar Regional General Hospital, a tertiary academic referral center affiliated with the Faculty of Medicine, Universitas Brawijaya, Malang, East Java, Indonesia,³³ between January 2025 and December 2025. Attending anesthesiologists, residents, and PACU nurses received protocol training before recruitment, in line with Good Clinical Practice.³²

2.3. Participants and eligibility

Consecutive patients aged 65 years or older, scheduled for elective major non-cardiac surgery under general endotracheal anesthesia with an expected operative time above 120 minutes, were eligible.⁴² Eligible patients were ASA physical status II (mild, controlled systemic disease) or III (severe, non-incapacitating systemic disease),⁴³ with a baseline MMSE of at least 24 of 30 at the pre-anesthesia visit 24 hours before surgery.⁴⁴ Exclusion criteria were a history of cerebrovascular accident (ischemic stroke, intracranial hemorrhage, or transient ischemic attack); neurodegenerative disease (Alzheimer's disease, Parkinson's disease, or vascular dementia); uncontrolled hypertension (systolic pressure > 180 mmHg or diastolic pressure > 110 mmHg); unstable coronary artery disease or severe arrhythmia; chronic psychiatric disorders treated with antipsychotic or mood-stabilizing drugs; advanced hepatic or renal impairment; known hypersensitivity to ketamine, midazolam, or propofol; and severe visual, auditory, or language barriers that prevent standardized cognitive testing.⁴⁵

2.4. Sample size

A pilot-study framework was used because few data describe acute 1-hour post-extubation MMSE change after co-induction in older Asian patients.³³ Assuming a standard deviation of 1.1 points and a clinically meaningful difference of 1.2 points in Delta MMSE, a two-tailed independent t test with alpha 0.05 and power 85% requires at least 16 patients per group (15.1, rounded up). Allowing for 10% dropout would require 18 per group, so the 32 patients enrolled (16 per arm) leave no margin for dropout.³⁷

2.5. Variables and operational definitions

The primary outcome was early neurocognitive recovery, measured with the Indonesian-validated MMSE (30 points; orientation, registration, attention and calculation, recall, and language),³⁶ by an independent neuropsychological evaluator blinded to group. Testing took place 24 hours before surgery in the ward (T0) and 1 hour after extubation in the PACU (T1), after the patient was fully conscious and hemodynamically stable with a modified Aldrete score $\geq$ 8.⁴⁴ Delta MMSE was T1 minus T0, and early cognitive dysfunction was a decline of more than 2 points from the individual baseline.³⁹ Secondary outcomes were MAP and heart rate (HR) at baseline (TBase), 3 minutes after induction (TInd), and 1 minute after intubation (TIntub);¹⁷ hypotension, defined as a fall in MAP of more than 20% from baseline or an absolute MAP below 65 mmHg,^{17–19} with the dose of ephedrine and crystalloid used for rescue;^{13,14} induction propofol dose (mg/kg); and time to extubation, from discontinuation of sevoflurane to extubation.²⁸

2.6. Data sources and measurement

Monitoring comprised 5-lead electrocardiography, non-invasive oscillometric blood pressure with a calibrated cuff of appropriate size on the non-dominant upper arm at heart level, pulse oximetry, end-tidal capnography, and

Bispectral Index (BIS) monitoring (Aspect Medical Systems, Norwood, MA, USA).^{2,18} Baseline HR and MAP were the mean of three readings at 2-minute intervals after 10 minutes of supine rest.¹⁷ Patients were pre-oxygenated with 100% oxygen at 8 L/min for 3 minutes.¹⁸ The study drug was given as an intravenous bolus over 30 seconds,²³ followed 2 minutes later by fentanyl 2 µg/kg to blunt the response to intubation.²⁴ Anesthesia was induced with 1% propofol by infusion pump at 30 mg/kg/hour, not as a fixed bolus, until verbal contact and the eyelash reflex were lost and BIS was below 60.¹² The cumulative propofol dose divided by body weight gave the induction dose.²⁸ Rocuronium 0.6 mg/kg was given, and an experienced senior anesthesiologist intubated 90 seconds later.¹¹ Maintenance used sevoflurane at 0.8–1.2 minimal alveolar concentration in oxygen/air (FiO₂ 0.50) with BIS 40–60,¹⁶ volume-controlled ventilation to end-tidal CO₂ 35–40 mmHg, and fentanyl 0.5 µg/kg when hemodynamic values rose more than 20% above baseline. Under a predefined protocol, each episode of hypotension received ephedrine 5 mg and lactated Ringer's solution 200 mL over 5 minutes, ephedrine was repeated if hypotension persisted after 2 minutes,¹³ and bradycardia (HR < 50 beats/min) received atropine 0.5 mg.¹⁴ Sevoflurane was stopped at the last skin suture, and ventilation was switched to 100% oxygen.²⁹ After return of spontaneous breathing and a Train-of-Four ratio ≥ 0.9, neuromuscular block was reversed with neostigmine 0.04 mg/kg and atropine 0.02 mg/kg.³⁰ The trachea was extubated when the patient opened the eyes to command, moved purposefully, lifted the head for more than 5 seconds, and breathed with tidal volumes above 6 mL/kg. The evaluator stayed outside the operating theater, entered the PACU only after extubation and a modified Aldrete score ≥ 8, had no access to anesthesia records or group assignment, and placed the sealed score sheets in a locked repository.^{36,44}

2.7. Statistical analysis

Analyses used SPSS Statistics version 26.0 (IBM Corporation, Armonk, NY, USA) and Python (SciPy, Statsmodels). Normality was checked with the Shapiro-Wilk test and Q-Q plots. Continuous variables are shown as mean ± standard

deviation (SD) and were compared with independent-samples *t* tests; categorical variables are shown as *n* (%) and were compared with Pearson's chi-square or Fisher's exact test. Analysis of covariance (ANCOVA) compared T1 MMSE with T0 as covariate, to adjust for baseline cognition and regression to the mean. Effect sizes were Cohen's *d* and relative risk (RR) with 95% CI. Secondary outcomes, the multivariable binary logistic regression for early cognitive dysfunction (adjusted for group, post-induction hypotension, propofol dose, age, and baseline MMSE), and the correlation analyses were exploratory. All tests were two-tailed, and *p* < 0.05 was considered significant.³⁸

2.8. Ethics

The Health Research Ethics Committee of the Faculty of Medicine, Universitas Brawijaya, approved the protocol (reference 400/182/KEPK/302/2025). The study followed the Declaration of Helsinki. Written informed consent was obtained from each participant or from a legally authorized surrogate after the objectives, procedures, and risks had been explained.³⁴

3. Results

3.1. Participant flow and baseline characteristics

Between January 2025 and December 2025, 38 older patients were screened. Six were excluded before randomization: four did not meet inclusion criteria (two with baseline MMSE < 24, one with uncontrolled hypertension, and one with a history of transient ischemic attack) and two declined to participate. The remaining 32 patients were randomized to Group K (*n* = 16) or Group M (*n* = 16), completed the protocol without deviation, adverse drug reaction, or attrition, and were all analyzed (Figure 1). Baseline characteristics were similar (Table 1): age 71.4 ± 4.2 vs. 70.8 ± 3.9 years, body mass index 24.5 ± 3.1 vs. 25.1 ± 2.8 kg/m², baseline MMSE 27.2 ± 1.8 vs. 27.0 ± 2.1, ASA III 37.5% vs. 43.8%, controlled hypertension 50.0% vs. 56.3%, and type 2 diabetes mellitus 25.0% vs. 31.3%. Anesthesia time (145.5 ± 22.4 vs. 151.2 ± 25.6 minutes) and surgery time (128.0 ± 19.5 vs. 134.5 ± 21.0 minutes) did not differ.

Table 1. Baseline characteristics of the study patients (*n* = 32).

Characteristic	Group K (ketamine, <i>n</i> = 16)	Group M (midazolam, <i>n</i> = 16)
Age, years	71.4 ± 4.2	70.8 ± 3.9
Sex, male / female, <i>n</i> (%)	9 (56.3) / 7 (43.8)	8 (50.0) / 8 (50.0)
Body mass index, kg/m ²	24.5 ± 3.1	25.1 ± 2.8
ASA physical status, <i>n</i> (%)		
ASA II	10 (62.5)	9 (56.3)
ASA III	6 (37.5)	7 (43.8)
Baseline MMSE score (T0)	27.2 ± 1.8	27.0 ± 2.1
Formal education, years	9.4 ± 3.2	9.1 ± 2.8
Comorbidities, <i>n</i> (%)		
Controlled essential hypertension	8 (50.0)	9 (56.3)
Type 2 diabetes mellitus	4 (25.0)	5 (31.3)
Duration of anesthesia, minutes	145.5 ± 22.4	151.2 ± 25.6
Duration of surgery, minutes	128.0 ± 19.5	134.5 ± 21.0

Notes: Values are mean ± SD or *n* (%). ASA, American Society of Anesthesiologists; MMSE, Mini-Mental State Examination. The baseline test statistics and *p* values of the submitted table were removed (CONSORT discourages significance tests of baseline differences in a randomized trial); the ASA chi-square, printed as 0.154 (*p* = 0.694), is 0.130 (*p* = 0.719) on recomputation.

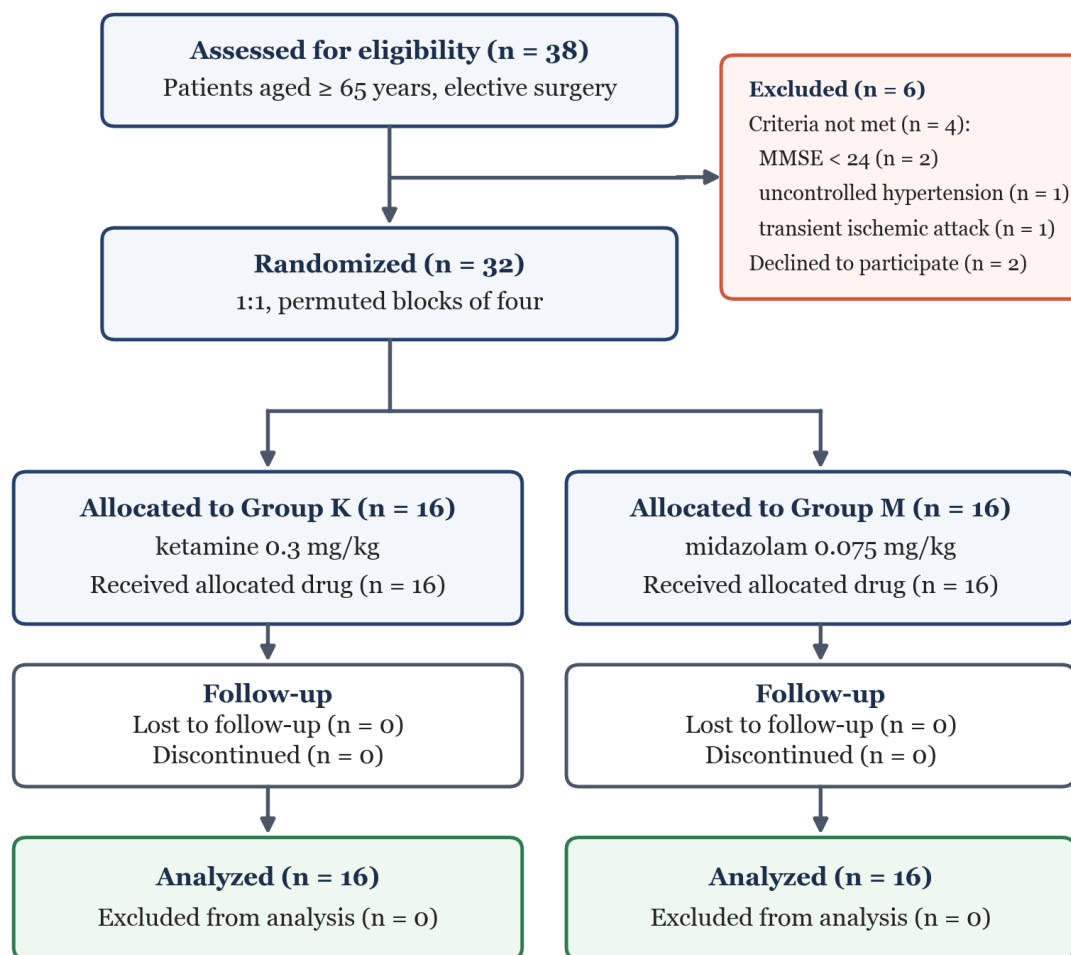


Figure 1. Flow of participants through the trial according to the CONSORT statement.

3.2. Primary outcome

The MMSE at 1 hour after extubation was 26.1 ± 2.0 in Group K and 22.8 ± 2.5 in Group M (Table 2, Figure 2). Delta MMSE was -1.1 ± 0.8 points in Group K and -4.2 ± 1.4 points in Group M (mean difference 3.1 points, 95% CI 2.3 to 3.9; $t = 7.69$, $p < 0.001$). After adjustment for baseline score, the ANCOVA-adjusted T1 MMSE was 26.04 (95% CI 25.32 to 26.76) in Group K and 22.86 (95% CI 22.14 to 23.58) in Group M ($F = 59.48$, $p < 0.001$; partial $\eta^2 = 0.672$).

Cohen's d was 2.72 (95% CI 1.76 to 3.68). Early cognitive dysfunction occurred in 3 of 16 patients (18.8%) in Group K and 11 of 16 (68.8%) in Group M (Pearson $\chi^2 = 8.13$, $p = 0.004$; Fisher's exact $p = 0.011$; RR 0.273, 95% CI 0.093 to 0.797; absolute risk reduction 50.0%, 95% CI 20.3% to 79.7%; number needed to treat 2.0). The median Delta MMSE was -1.0 (interquartile range -1.5 to -0.5) in Group K and -4.0 (-5.0 to -3.0) in Group M (Mann-Whitney $U = 12.5$, $Z = 4.412$, $p < 0.001$), with ranges of -3.0 to 0.0 and -7.0 to -2.0 .

Table 2. Primary outcome: Mini-Mental State Examination (MMSE) scores and early cognitive dysfunction.

Outcome	Group K (n = 16)	Group M (n = 16)	Test statistic	p value
MMSE at baseline (T0)	27.2 ± 1.8	27.0 ± 2.1	$t = 0.289$	0.774
MMSE at 1 h after extubation (T1)	26.1 ± 2.0	22.8 ± 2.5	$t = 4.123$	< 0.001
Delta MMSE (T1 – T0)	-1.1 ± 0.8	-4.2 ± 1.4	$t = 7.690$	< 0.001
Delta MMSE, median (IQR)	-1.0 (-1.5 to -0.5)	-4.0 (-5.0 to -3.0)	$U = 12.5$	< 0.001
Adjusted T1 MMSE (ANCOVA), mean (95% CI)	26.04 (25.32–26.76)	22.86 (22.14–23.58)	$F = 59.48$	< 0.001
Cohen's d for Delta MMSE (95% CI)	2.72 (1.76–3.68)	—	—	—
Early cognitive dysfunction, n (%)	3 (18.8)	11 (68.8)	$\chi^2 = 8.13$	0.004
Fisher's exact test	—	—	—	0.011
Relative risk (95% CI)	0.273 (0.093–0.797)	1 (reference)	$Z = -2.38$	0.017
Absolute risk reduction, % (95% CI); NNT	50.0 (20.3–79.7); 2.0	—	—	—

Notes: Values are mean $\pm$ SD unless stated. Early cognitive dysfunction was a decline of more than 2 points from baseline. IQR, interquartile range; NNT, number needed to treat. t statistics and p values were recomputed from the printed means and SDs ($n = 16$ per group); the submitted values differed slightly (for example $t = 7.712$ for Delta MMSE). The submitted Fisher p (0.005) and Z (2.45; $p = 0.018$) did not match the counts. [Author query: individual Delta MMSE values are needed to verify the IQR, range, and effect size.]

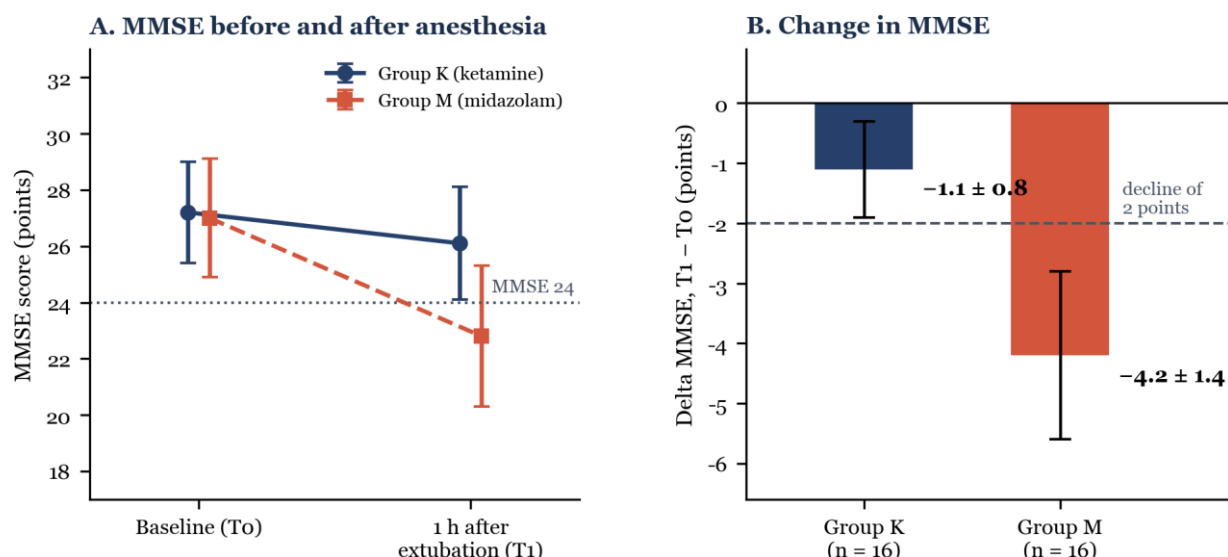


Figure 2. Mini-Mental State Examination (MMSE) before surgery (T0) and 1 hour after extubation (T1). (A) Mean $\pm$ SD by group. (B) Delta MMSE (T1 - T0), mean $\pm$ SD; the dashed line marks the 2-point decline used to define early cognitive dysfunction (n = 16 per group).

3.3. Secondary and exploratory analyses

Baseline MAP and HR were similar (Table 3, Figure 3). At 3 minutes after induction, MAP was 88.5 ± 7.4 mmHg in Group K and 76.2 ± 8.8 mmHg in Group M (mean difference 12.3 mmHg, 95% CI 6.4 to 18.2; $p < 0.001$), a fall from baseline of $6.05 \pm 5.12\%$ and $18.76 \pm 7.34\%$. HR at that time was

78.4 ± 8.1 vs. 71.2 ± 6.9 beats/min ($p = 0.011$). After intubation, MAP (98.4 ± 10.2 vs. 92.1 ± 11.5 mmHg) and HR (84.6 ± 9.2 vs. 79.5 ± 8.4 beats/min) did not differ. MAP was recorded at three time points only, so the lowest value is unknown.

Table 3. Mean arterial pressure (MAP) and heart rate (HR) across induction and intubation.

Variable	Group K (n = 16)	Group M (n = 16)	Test statistic	p value
MAP, mmHg				
Baseline (TBase)	94.2 $\pm$ 8.5	93.8 $\pm$ 9.1	t = 0.128	0.899
3 min after induction (TInd)	88.5 $\pm$ 7.4	76.2 $\pm$ 8.8	t = 4.279	< 0.001
1 min after intubation (TIntub)	98.4 $\pm$ 10.2	92.1 $\pm$ 11.5	t = 1.639	0.112
HR, beats/min				
Baseline (TBase)	72.5 $\pm$ 6.8	74.1 $\pm$ 7.2	t = -0.646	0.523
3 min after induction (TInd)	78.4 $\pm$ 8.1	71.2 $\pm$ 6.9	t = 2.707	0.011
1 min after intubation (TIntub)	84.6 $\pm$ 9.2	79.5 $\pm$ 8.4	t = 1.638	0.112

Notes: Values are mean $\pm$ SD. t statistics and p values were recomputed from the printed means and SDs (independent t test, $df = 30$); the submitted values differed in the third decimal. [Author query: reference point of TInd.]

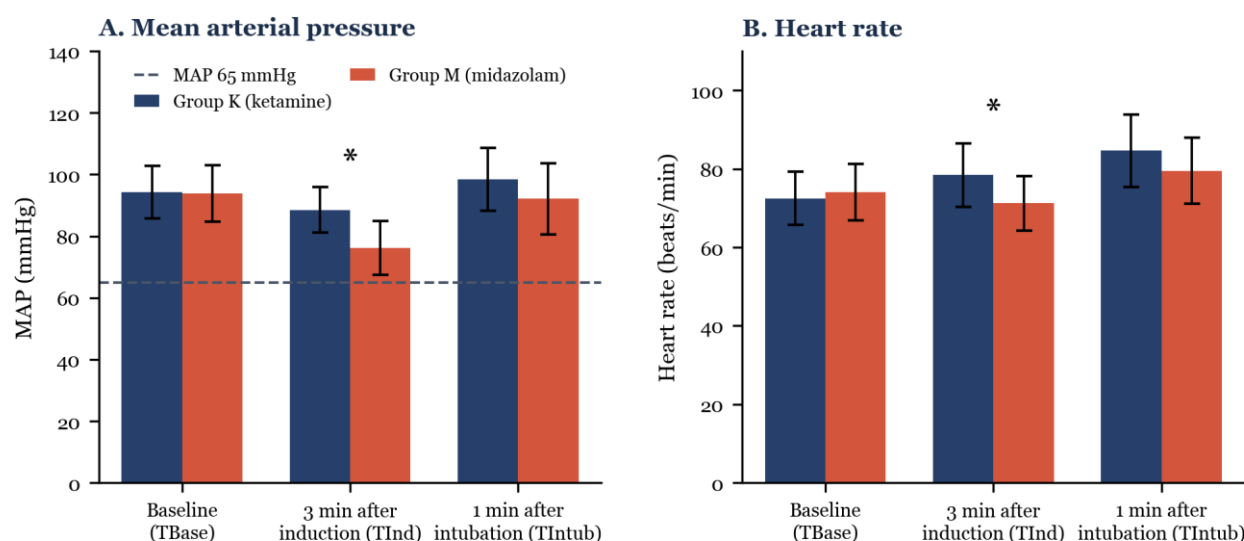


Figure 3. Mean arterial pressure (A) and heart rate (B) at baseline (TBase), 3 minutes after induction (TInd), and 1 minute after intubation (TIntub); mean $\pm$ SD, n = 16 per group. * $p < 0.05$ between groups.

Hypotension needing rescue occurred in 2 of 16 patients (12.5%) in Group K and 9 of 16 (56.3%) in Group M (Pearson $\chi^2 = 6.79$, $p = 0.009$; Fisher's exact $p = 0.023$; RR 0.222, 95% CI 0.057 to 0.872; absolute risk reduction 43.8%, 95%

CI 14.5% to 73.0%; number needed to treat 2.3) (Table 4). Group M received more ephedrine (6.25 ± 5.92 vs. 1.25 ± 3.54 mg, $p = 0.007$) and crystalloid (218.8 ± 175.9 vs. 62.5 ± 120.4 mL, $p = 0.006$).

Table 4. Hypotension, vasopressor and fluid requirement, propofol dose, and time to extubation.

Outcome	Group K (n = 16)	Group M (n = 16)	Test statistic	p value
Hypotension needing rescue, n (%)	2 (12.5)	9 (56.3)	$\chi^2 = 6.79$	0.009
Fisher's exact test	—	—	—	0.023
Relative risk (95% CI)	0.222 (0.057–0.872)	1 (reference)	$Z = -2.16$	0.031
Odds ratio (95% CI)	0.111 (0.019–0.659)	1 (reference)	—	—
Absolute risk reduction, % (95% CI); NNT	43.8 (14.5–73.0); 2.3	—	—	—
MAP fall at TInd from baseline, %	6.05 ± 5.12	18.76 ± 7.34	$t = -5.681$	< 0.001
Total ephedrine, mg	1.25 ± 3.54	6.25 ± 5.92	$t = -2.900$	0.007
Crystalloid boluses, mL	62.5 ± 120.4	218.8 ± 175.9	$t = -2.933$	0.006
Induction propofol, mg/kg	1.12 ± 0.18	1.65 ± 0.22	$t = -7.458$	< 0.001
Time to extubation, minutes	8.4 ± 2.1	14.2 ± 3.5	$t = -5.684$	< 0.001

Notes: Values are n (%) or mean $\pm$ SD. Hypotension was a fall in MAP of more than 20% from baseline or MAP below 65 mmHg. NNT, number needed to treat. The submitted chi-square (6.827, $p = 0.018$ for both Pearson and Fisher) was recomputed from the counts; derived effect measures were recomputed with the log method. [Author query: please confirm with the software output.]

The induction propofol dose was 1.12 ± 0.18 mg/kg in Group K and 1.65 ± 0.22 mg/kg in Group M (mean difference -0.53 mg/kg, 95% CI -0.68 to -0.38 ; $p < 0.001$), a 32.1% reduction (Figure 4A). Time to extubation was $8.4 \pm$

2.1 and 14.2 ± 3.5 minutes (mean difference -5.8 minutes, 95% CI -7.9 to -3.7 ; $p < 0.001$), 40.8% shorter in Group K (Figure 4B). Adverse events such as agitation, delirium, or hallucinations were not tabulated.

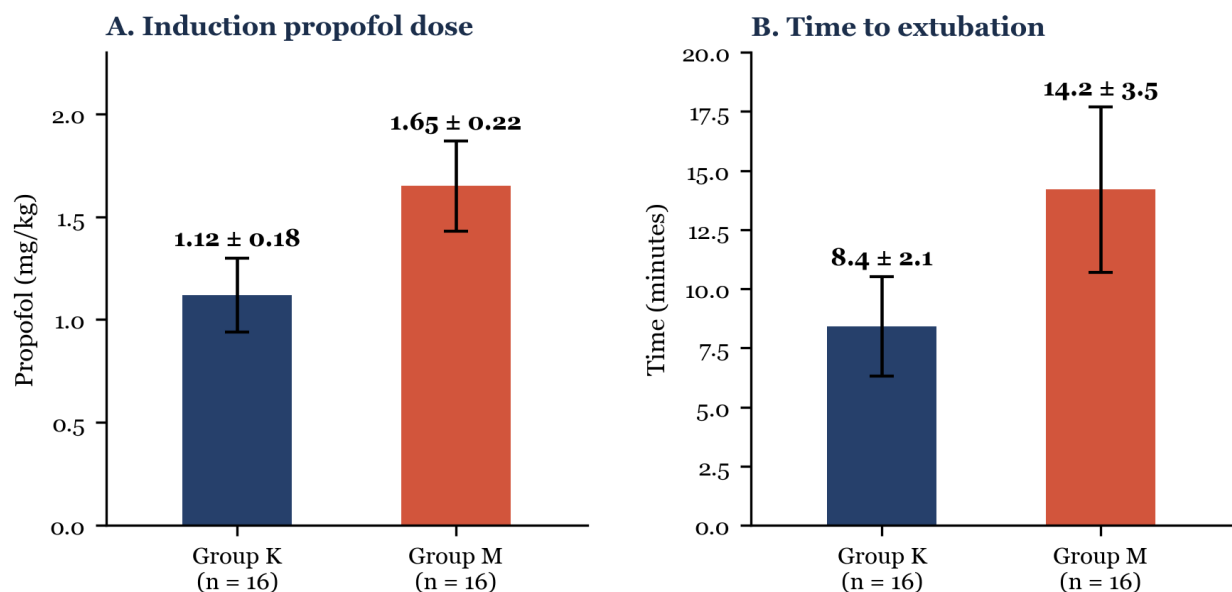


Figure 4. Induction propofol dose (A) and time to extubation (B); mean $\pm$ SD, $n = 16$ per group.

In an exploratory logistic regression for early cognitive dysfunction (14 events; Table 5), ketamine co-induction was associated with lower odds (crude odds ratio, OR, 0.105, 95% CI 0.020 to 0.548; adjusted OR 0.128, 95% CI 0.021 to 0.784, $p = 0.026$) and post-induction hypotension with higher odds (crude OR 5.833, 95% CI 1.182 to 28.784; adjusted OR 4.821, 95% CI 1.142 to 20.354, $p = 0.032$). Propofol dose (adjusted OR 1.412 per 0.1 mg/kg, 95% CI 0.985 to 2.024, $p = 0.061$), age (adjusted OR 1.045, $p = 0.706$), and baseline MMSE (adjusted OR 0.948, $p = 0.803$)

were not significant. The omnibus test was $\chi^2 = 16.48$ ($p = 0.005$), the Hosmer-Lemeshow test $\chi^2 = 4.12$ ($df = 8$, $p = 0.846$), and Nagelkerke $R^2 = 0.548$. Across the whole cohort ($N = 32$), post-induction MAP correlated with Delta MMSE (Pearson $r = 0.548$, $p = 0.001$; Spearman $\rho = 0.582$, $p < 0.001$), the percentage fall in MAP correlated with the 1-hour MMSE (Pearson $r = -0.612$, $p < 0.001$), and propofol dose correlated with time to extubation ($r = 0.684$, $p < 0.001$) and with the 1-hour MMSE ($r = -0.495$, $p = 0.004$).

Table 5. Exploratory multivariable logistic regression for early cognitive dysfunction (14 events).

Predictor	Crude OR (95% CI)	Adjusted OR	95% CI	p value
Ketamine (vs. midazolam) co-induction	0.105 (0.020–0.548)	0.128	0.021–0.784	0.026
Post-induction hypotension	5.833 (1.182–28.784)	4.821	1.142–20.354	0.032
Induction propofol, per 0.1 mg/kg	1.584 (1.142–2.198)	1.412	0.985–2.024	0.061
Age, per year	1.082 (0.884–1.325)	1.045	0.832–1.312	0.706
Baseline MMSE, per point	0.912 (0.642–1.295)	0.948	0.621–1.448	0.803

Notes: OR, odds ratio. Outcome: decline of more than 2 MMSE points at 1 hour after extubation. Omnibus test $\chi^2 = 16.48$ ($p = 0.005$); Hosmer-Lemeshow $\chi^2 = 4.12$, $df = 8$ ($p = 0.846$); Nagelkerke $R^2 = 0.548$. With 14 events and five predictors the model is likely overfitted, and the wide confidence intervals should be read with caution. These values are as submitted and could not be recomputed from the manuscript.

4. Discussion

4.1. Principal findings

In this pilot trial of 32 older patients, low-dose ketamine co-induction was associated with a smaller early MMSE decline than midazolam (–1.1 vs. –4.2 points), higher post-induction MAP (88.5 vs. 76.2 mmHg) with less hypotension (12.5% vs. 56.3%), 32.1% less induction propofol, and earlier extubation. The findings suggest that NMDA receptor antagonism may be an alternative to the GABAergic load of midazolam,^{2,3} but a pilot trial with a single early endpoint cannot show that midazolam co-induction should be abandoned.

4.2. Comparison with the published literature

Our result differs from trials using higher ketamine doses. In the PODCAST trial, ketamine 0.5 to 1.0 mg/kg did not prevent postoperative delirium and was linked to more hallucinations and nightmares in older surgical patients,²² and the B-Unaware and ENGAGES investigators noted that deep anesthesia and excess adjuvant can be harmful.^{2,3} We used a single pre-induction bolus of 0.3 mg/kg, which produced the expected sympathomimetic and propofol-sparing effects.^{23,24} Reviews of ketamine and cognition in older adults report conflicting findings and a dose-dependent balance between neuroprotection and psychomimetic effects,^{1,13,28,30} and our dose lies within the range thought to avoid psychomimetic reactions.^{23,28} The multicenter evidence on 0.25 to 0.35 mg/kg is limited, and only 0.3 mg/kg was tested here.

4.3. Interpretation and possible mechanisms

Several mechanisms may explain the difference, but none was measured. First, pharmacokinetics: aging increases body fat and reduces hepatic blood flow and cytochrome P450 3A4 activity,^{19,20} so midazolam may have a longer context-sensitive half-life and a sedative tail,^{21,24} whereas ketamine has a high hepatic extraction ratio and rapid alpha-phase redistribution.²³ Plasma concentrations were not measured, and extubation time was counted from sevoflurane discontinuation after surgery lasting more than 2 hours, so the longer extubation time in Group M may have other causes.²⁸ Second, pharmacodynamics: in a brain with reduced cholinergic transmission, midazolam may further suppress cholinergic and thalamocortical activity,^{18,22,42} whereas ketamine may preferentially inhibit GABAergic interneurons and increase acetylcholine and dopamine release.^{25,26,31} Third, perfusion: Group K kept higher MAP, and older hypertensive patients (over 50% of this cohort) may fall below the lower limit of cerebral autoregulation

at MAP of 70 to 75 mmHg.^{13–15,20} The exploratory regression suggested that post-induction hypotension was associated with cognitive dysfunction (adjusted OR 4.821), which is compatible with a hemodynamic second hit.^{18,29} Fourth, inflammation: surgical trauma releases interleukin-1 β , interleukin-6, and tumor necrosis factor- α , which may reach the brain through an aging blood-brain barrier and activate microglia,^{26,27,31} and ketamine reduces microglial nuclear factor kappa B signaling and glutamate excitotoxicity in animal models.^{15,23,25} No inflammatory biomarker was measured, and these pathways are summarized in Figure 5 as hypotheses.

4.4. Implications for practice

A single ketamine bolus needs only a syringe and may suit hospitals without target-controlled infusion, processed EEG monitoring, or delirium screening tools.^{32–34} In this trial midazolam co-induction was associated with more hypotension (56.3%), more ephedrine (6.25 vs. 1.25 mg), and later extubation (14.2 vs. 8.4 minutes).⁴² These findings should not change practice before confirmation in larger trials, because hallucinations, emergence agitation, and delirium were not systematically reported.^{23,40} Savings in nursing time, vasopressor cost, or theater capacity were not measured.^{28,32,33}

4.5. Strengths

Strengths include permuted-block randomization with concealed allocation, identical masked syringes prepared by an independent pharmacist, a standardized induction, maintenance, and emergence protocol, a predefined rescue protocol, fixed testing times, and a blinded cognitive assessor who had no access to anesthesia records.

4.6. Limitations

This was a single-center pilot trial with 32 patients; the effect on the primary outcome may be overestimated, and the study was not powered for rare adverse events or secondary outcomes.^{11,28} Cognition was assessed only in the first hour, and we did not follow patients for delirium at 72 hours or cognitive decline at 30 days.^{36,41} The MMSE is a screening test with ceiling effects, limited sensitivity to executive function and working memory, and a possible practice effect when repeated within 24 hours; residual sedation at 1 hour cannot be separated from cognitive injury.⁴⁴ Ketamine and midazolam may be distinguishable at induction, so blinding of the anesthesiologist may have been incomplete. The regression rested on 14 events, the correlations were pooled across arms, and several secondary outcomes were analyzed without correction. Pharmacogenetic variation (CYP2B6, CYP3A4) was not assessed.^{30,37}

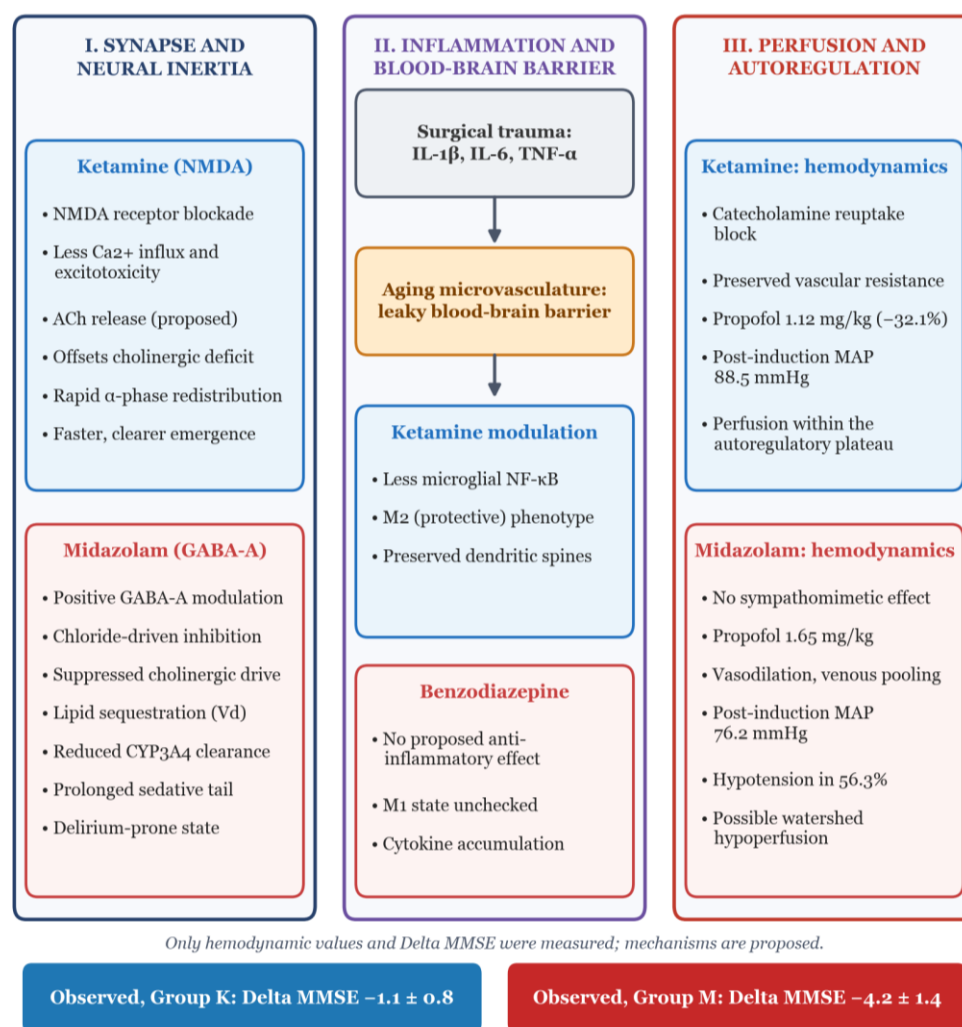


Figure 5. Hypothesized mechanisms by which ketamine and midazolam co-induction may influence early cognitive recovery. The pathways are drawn from the literature and were not measured; only the hemodynamic values and Delta MMSE were observed. ACh, acetylcholine; V_d , volume of distribution; MAP, mean arterial pressure.

4.7. Recommendations for future research

A confirmatory multicenter trial should register the protocol, prespecify one primary outcome and a minimal clinically important difference, use a validated delirium instrument and the Montreal Cognitive Assessment (MoCA) with processed EEG and biomarkers such as neurofilament light chain and S100B,³⁵ follow patients to 72 hours and 30 days, report adverse events, and measure plasma drug concentrations. As an illustration, with the assumed SD of 1.1 points, a difference of 1.0 point would need about 19 patients per group at 80% power and alpha 0.05, and more if the SD is larger.

5. Conclusion

In this randomized pilot trial of 32 older patients, low-dose ketamine (0.3 mg/kg) co-induction was associated with a smaller early decline in MMSE at 1 hour after extubation than midazolam (-1.1 ± 0.8 vs. -4.2 ± 1.4 points), together with higher post-induction mean arterial pressure, less hypotension, 32.1% lower propofol requirement, and earlier extubation. Larger multicenter trials with validated delirium and cognitive batteries, longer follow-up, and adverse-event reporting are needed before ketamine is recommended as a routine alternative to midazolam in older surgical patients.

6. Declarations

Ethical approval and consent to participate. The study was approved by the Health Research Ethics Committee, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia (reference 400/182/KEPK/302/2025). Written informed consent was obtained from all participants or their legally authorized surrogates. The study was conducted in accordance with the Declaration of Helsinki.

Consent for publication. Not applicable; no individually identifiable data are presented.

Availability of data and materials. The de-identified participant data and analysis code generated during this study are available from the corresponding author on reasonable request.

Artificial intelligence (AI) use statement. The authors declare that no generative artificial intelligence tool was used in the preparation of this manuscript.

Author contribution statement. A.G.W.P. conceived the study, recruited patients, performed the trial, acquired and analyzed the data, and wrote the original draft (Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Writing – original draft). A.A.A. oversaw the trial, validated the hemodynamic protocol, and managed

the project (Methodology, Validation, Project administration, Writing – review & editing). A.Z.F. validated the neurocognitive testing, verified the statistics, and edited the manuscript (Validation, Formal analysis, Writing – review & editing). R.V. supervised the clinical work and patient safety, oversaw ethical compliance, and approved the final version (Supervision, Project administration, Writing – review & editing). All authors read and approved the final manuscript.

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Conflict of interest (competing interests) statement. The authors declare that they have no competing interests.

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