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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

Aditya Guna Wicaksono Panatagama[1*], Aswoco Andyk Asmoro[1], Arie Zainul Fatoni[1], Rudy Vitraludyono[1]

[1]Department of Anesthesiology, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia

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***Corresponding author:**
Aditya Guna Wicaksono Panatagama

E-mail address:
aditya.panatagama@gmail.com

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A B S T R A C T

Introduction: Geriatric patients undergoing general anesthesia are susceptible to hemodynamic instability and delayed neurocognitive recovery. The choice of co-induction agent significantly influences these outcomes. This study compares the effects of low-dose Ketamine versus Midazolam co-induction on intraoperative hemodynamic stability and immediate post-operative cognitive trajectory. **Methods:** A prospective, double-blind, randomized controlled pilot trial was conducted on 32 geriatric patients aged 65 years or older classified as American Society of Anesthesiologists (ASA) physical status II or III undergoing elective surgery. Patients were randomized to receive either intravenous Ketamine (0.3 mg/kg, n=16) or Midazolam (0.075 mg/kg, n=16) prior to Propofol induction. The primary outcome was the magnitude of early cognitive change measured by the Mini-Mental State Examination (MMSE) at 1-hour post-operation relative to baseline. Secondary outcomes included intraoperative mean arterial pressure (MAP), incidence of hypotension, total Propofol consumption, and time to extubation. Data were analyzed using Analysis of Covariance (ANCOVA) and independent t-tests; effect sizes were calculated using Cohen's d. **Results:** Baseline characteristics were comparable between groups. The Ketamine group exhibited significantly superior early cognitive preservation with a mean decline of -0.50 ± 0.63 compared to the Midazolam group, which showed a decline of -1.25 ± 0.93 ($p = 0.012$; Cohen's $d = 0.93$). Hemodynamically, the Ketamine group maintained significantly higher Mean Arterial Pressure post-induction ($p = 0.003$) with a lower risk of hypotension (Relative Risk 0.29, 95% Confidence Interval 0.07–1.18). Additionally, the Ketamine group required significantly less induction of Propofol ($p < 0.001$) and achieved faster extubation times ($p < 0.001$). **Conclusion:** Co-induction with sub-anesthetic Ketamine provides superior hemodynamic stability and facilitates faster early neurocognitive recovery compared to Midazolam in geriatric patients. These findings suggest Ketamine is a preferable adjuvant for optimizing emergence profiles and maintaining perfusion pressure in the aging population.

1. Introduction

The trajectory of modern healthcare is currently being redefined by an unprecedented demographic shift, often termed the silver tsunami.[1] The global demographic transition has precipitated a dramatic surge in the geriatric surgical population, presenting anesthesiologists with the distinct and escalating challenge of managing the aging brain. By 2050, the global population aged over 60 is projected to double, a statistical inevitability that necessitates a fundamental restructuring of perioperative care. As medical advancements extend life expectancy, an increasing number of elderly patients with complex comorbidities are presenting for surgical interventions. In this cohort,

the perioperative period is not merely a transient interval of physiological stress but a critical juncture fraught with specific vulnerabilities, most notably hemodynamic lability and a profound susceptibility to neurocognitive disturbances.[2] The margin for error in the geriatric patient is vanishingly narrow; the physiological reserve—or homeostenosis—is depleted, rendering the aging organism less capable of compensating for the profound insults of anesthesia and surgical trauma.

Among the myriad challenges facing the geriatric anesthesiologist, the preservation of neurological function stands paramount. The aging brain is characterized by structural and functional alterations, including cortical atrophy, reduced neurotransmitter density, and compromised integrity of the blood-brain barrier.[3] These changes create a substrate of neural frailty, where the brain becomes highly sensitive to the neurotoxic and sedative burdens of anesthetic agents. Consequently, post-operative cognitive changes have emerged as a leading cause of morbidity, ranging from transient Delayed Emergence to persistent Post-Operative Cognitive Dysfunction (POCD) and delirium. While POCD is typically diagnosed via neuropsychological testing days to weeks post-operatively, the trajectory of recovery—or decline—begins immediately upon emergence from anesthesia. The initial hours post-surgery serve as a critical window; delayed emergence does not merely represent a logistical bottleneck in the operating room but may herald a cascade of neuroinflammation and oxidative stress that underpins longer-term cognitive deficits.[4]

The anesthetic management of the elderly patient, therefore, requires a delicate pharmacological balance. The primary goal during the induction of general anesthesia is to secure unconsciousness while maintaining hemodynamic stability.[5] The standard induction agent, Propofol, while effective, is notorious for its dose-dependent cardiodepressive effects, often precipitating hypotension that can compromise cerebral perfusion pressure. In the context of the autoregulatory-impaired aging brain, such hypotensive episodes can lead to cerebral ischemia, further exacerbating the risk of cognitive decline. To mitigate this, current induction protocols frequently utilize co-induction agents—sedative-hypnotics administered prior to Propofol to synergistically reduce the required dose of the latter, thereby preserving hemodynamic stability.

Historically, Midazolam, a short-acting benzodiazepine and Gamma-Aminobutyric Acid (GABA) type A receptor agonist, has been the co-induction agent of choice. Its anxiolytic and amnestic properties are well-documented.[6] However, the safety profile of Midazolam in the geriatric population is increasingly being scrutinized and challenged. The pharmacokinetics of benzodiazepines are significantly altered by the aging process. Aging is associated with a reduction in lean body mass, an increase in total body fat, and a decline in hepatic clearance mechanisms. As a lipid-soluble drug, Midazolam exhibits an increased volume of distribution in the elderly, sequestering in adipose tissue and re-entering the circulation over a prolonged period. This leads to a significantly extended context-sensitive half-life. Consequently, what is clinically intended as brief anxiolysis often manifests as prolonged sedation, respiratory depression, and delayed cognitive recovery. Furthermore, there is growing concern regarding the GABAergic burden on the aging brain; excessive GABAergic inhibition may interfere with neural plasticity and has been implicated in the pathophysiology of delirium. Thus, the continued reliance on Midazolam risks confounding the assessment of neurological integrity in the immediate post-operative period.

Conversely, Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, offers a distinct and potentially superior pharmacological profile for this demographic. Unlike the cardiodepressive profile of propofol and the purely sedative nature of midazolam, ketamine creates a dissociative anesthetic state. In sub-anesthetic, analgesic doses (0.3–0.5 mg/kg), ketamine preserves sympathetic tone, thereby maintaining systemic vascular resistance and cardiac output. This sympathomimetic property makes it an ideal co-induction agent to counteract the hemodynamic depression caused by Propofol. Beyond hemodynamics, Ketamine has been hypothesized to exert neuroprotective effects. The pathophysiology of perioperative neurocognitive disorders is thought to

involve glutamate-induced excitotoxicity and neuroinflammation.[7] As an NMDA antagonist, Ketamine may mitigate excitotoxic calcium influx into neurons. Furthermore, emerging evidence suggests Ketamine possesses potent anti-inflammatory properties, potentially suppressing the microglial activation that triggers post-operative neuroinflammation.[8]

Despite these theoretical advantages, the clinical landscape remains ambiguous. While Ketamine is widely used, robust comparative data specifically targeting immediate cognitive recovery in geriatric populations is insufficient.[9] Moreover, the majority of existing literature stems from Western populations. There is a notable paucity of data regarding Southeast Asian geriatric populations, a demographic that may possess distinct genetic polymorphisms in drug metabolism enzymes (such as the CYP450 system), which could alter the pharmacokinetics and pharmacodynamics of both Midazolam and Ketamine. The interplay between genetic background, aging physiology, and anesthetic sensitivity remains an underexplored frontier in precision anesthesiology. It is unclear whether the neuroprotective and hemodynamic benefits of Ketamine observed in younger or Western cohorts translate effectively to the Southeast Asian geriatric context, or if the psychomimetic side effects traditionally associated with Ketamine (such as hallucinations) outweigh its benefits in this specific group. Therefore, a rigorous comparison is required to determine the optimal co-induction strategy that balances hemodynamic preservation with rapid and high-quality cognitive recovery. Moving away from the one-size-fits-all approach to anesthesia, this inquiry seeks to refine induction protocols specifically for the fragile physiology of the elderly.[10]

This study aims to evaluate the comparative efficacy of low-dose Ketamine versus Midazolam as co-induction agents in geriatric patients undergoing general anesthesia. Specifically, it seeks to assess the impact of these agents on intraoperative hemodynamic stability and, crucially, the speed and quality of early cognitive recovery in the immediate post-operative period. The novelty of this research lies in its specific focus on the immediate cognitive trajectory following emergence in a Southeast Asian geriatric cohort, a population underrepresented in current pharmacogenomic and anesthetic literature. Unlike previous studies that focus primarily on long-term POCD or intraoperative hemodynamics in isolation, this study integrates hemodynamic parameters with early neurocognitive outcomes to challenge the traditional dogma of benzodiazepine use. By investigating whether the NMDA-antagonist properties of Ketamine offer a superior brain-sparing alternative to the GABA-ergic burden of Midazolam, this study attempts to provide evidence-based recommendations for optimizing perioperative brain health in the rapidly aging Asian population.

2. Methods

This study was designed as a prospective, double-blind, randomized controlled pilot trial. The protocol adhered to the CONSORT guidelines for reporting clinical trials. The study protocol adhered strictly to the ethical principles outlined in the Declaration of Helsinki. Ethical approval was granted by the Health Research Ethics Committee of the Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia. The study was conducted at Dr. Saiful Anwar Regional General Hospital. Written informed consent was obtained from all participants or their legal surrogates.

The investigation focused on geriatric patients, defined as those aged 65 years or older, who were scheduled for elective major non-cardiac surgery under general anesthesia. The physical status of the cohort was standardized to include only those classified as American Society of Anesthesiologists (ASA) physical status II (mild systemic disease) or III (severe systemic disease), ensuring a representative sample of the typical elderly surgical population while excluding moribund patients.

Strict inclusion and exclusion criteria were applied to minimize confounding variables that could obscure the pharmacological effects of the induction agents. The inclusion criteria necessitated an estimated surgical duration of at least two hours requiring endotracheal intubation, ensuring that the exposure to anesthesia was significant enough to potentially impact early cognitive recovery. Crucially, a baseline neurocognitive

assessment was mandated; only patients with a pre-operative Mini-Mental State Examination (MMSE) score of 24 or higher were recruited. This threshold was critical to exclude patients with pre-existing dementia, ensuring that any post-operative cognitive decline observed could be attributed to the perioperative process rather than an underlying neurodegenerative trajectory.

The exclusion criteria were designed to ensure both patient safety and data integrity. Patients with a history of cerebrovascular accidents, including stroke or transient ischemic attacks (TIA), and those with established neurodegenerative disorders such as Alzheimer's or Parkinson's disease were excluded to avoid confounding the assessment of acute anesthetic effects on the brain. From a safety perspective, given the sympathomimetic properties of Ketamine, patients with uncontrolled hypertension (defined as Systolic Blood Pressure > 180 mmHg) or ischemic heart disease were excluded to prevent deleterious increases in myocardial oxygen demand. Furthermore, patients with a history of psychiatric disorders requiring antipsychotic medication were excluded to prevent potential drug-drug interactions and to avoid the confounding effects of pre-existing neurotransmitter imbalances.

To eliminate selection bias and ensure the internal validity of the study, a rigorous randomization and blinding protocol was implemented. Patients were randomly assigned to one of two study groups in a 1:1 ratio utilizing a computer-generated randomization sequence with a block size of four. Allocation concealment was strictly maintained through the use of opaque, sealed, sequentially numbered envelopes, which were opened only after participant recruitment was confirmed. Double-blinding was achieved through the involvement of an independent pharmacist who was not otherwise involved in patient care or data collection. This pharmacist prepared the study medications in identical 5 mL syringes, diluted with normal saline to a total standard volume of 5 mL. Group K (the ketamine group) received syringes containing ketamine at a dose of 0.3 mg/kg, while Group M (the midazolam group) received syringes containing midazolam at a dose of 0.075 mg/kg. This preparation ensured that the attending anesthesiologist, the outcome assessors, and the patients remained blinded to the group allocation throughout the perioperative period, thereby preventing performance and detection bias.

A standardized anesthetic protocol was enforced to ensure that the only significant variable between groups was the co-induction agent. Intraoperative monitoring included standard non-invasive parameters: 5-lead Electrocardiogram (ECG), non-invasive blood pressure (NIBP), pulse oximetry (SpO_2), and capnography ($EtCO_2$). To strictly control the depth of anesthesia and prevent relative overdose or awareness, Bispectral Index (BIS) monitoring was utilized, with the depth of anesthesia targeted to a BIS range of 40 to 60.

Following pre-oxygenation with 100% oxygen for three minutes to increase functional residual capacity, the induction sequence commenced; (1) Co-induction: The blinded study drug (Ketamine or Midazolam) was administered intravenously over a 30-second interval. This timing allowed for the initial onset of the co-induction agent prior to the administration of the hypnotic; (2) Analgesia: Two minutes following the co-induction agent, Fentanyl (2 mcg/kg IV) was administered to blunt the sympathetic response to laryngoscopy; (3) Hypnosis: Anesthesia was subsequently induced with Propofol. Crucially, Propofol was not given as a bolus but titrated slowly until the loss of verbal contact and a BIS value below 60 was achieved. The precise dose of Propofol required to reach this endpoint was recorded to evaluate the Propofol-sparing effect of the respective co-induction agents; (4) Neuromuscular Blockade: Intubation was facilitated by Rocuronium (0.6 mg/kg). Anesthesia maintenance was standardized using Sevoflurane (0.8 – 1.2 MAC) in an Oxygen/Air mixture (FiO_2 50%). Mechanical ventilation was controlled to maintain normocapnia ($EtCO_2$ 35–45 mmHg). Intraoperative hemodynamic stability was strictly managed. Hypotension, defined as a mean arterial pressure (MAP) drop of >20% from baseline or an absolute MAP <65 mmHg, was treated promptly with crystalloid boluses or Ephedrine to maintain cerebral perfusion. Conversely, bradycardia (HR < 50 bpm) was managed with Atropine.

To assess early recovery accurately, the emergence protocol was also standardized. Sevoflurane was

discontinued immediately at the start of skin closure. Upon the return of spontaneous respiration, residual neuromuscular blockade was reversed with Neostigmine (0.04 mg/kg) combined with Atropine (0.02 mg/kg). The time to extubation was strictly defined as the interval from anesthetic discontinuation to tracheal extubation.

The primary outcome of the study was Early Neurocognitive Recovery. This was assessed using the MMSE at two specific time points: T0 (Baseline, 1 day prior to surgery) and T1 (Early Recovery, exactly 1 hour post-extubation in the PACU). The primary metric for analysis was the Delta MMSE, calculated as the T1 score minus the T0 score. This differential approach allowed for the quantification of acute cognitive deviation relative to the patient's own baseline, effectively isolating the immediate cognitive impact of the anesthetic regimen. Secondary outcomes focused on physiological stability and efficiency. Hemodynamic parameters (MAP and Heart Rate) were recorded at critical intervals: Baseline (TBase), 3 minutes Post-Induction (TInd), and 1 minute Post-Intubation (TIntub). The incidence of hypotension requiring vasopressor support served as a binary measure of hemodynamic safety. Furthermore, the total induction dose of Propofol (mg/kg) was analyzed to quantify the sparing effect of the co-induction agents, and the time to extubation (minutes) was recorded to assess the speed of physical emergence.

The statistical strategy was designed to robustly handle the specific constraints of the study. Sample size determination utilized a pilot study approach, as formalized power analysis parameters for MMSE changes within this specific 1-hour postoperative timeframe are not well-established in current literature. A sample size of 16 patients per group was deemed sufficient to assess feasibility and detect large effect sizes (Cohen's $d > 0.8$) in continuous variables. Data analysis was performed using SPSS version 26.0. Normality of the data distribution was verified using the Shapiro-Wilk test. Continuous variables were presented as Mean ± Standard Deviation (SD) and compared using the Independent Samples t-test. For the primary outcome analysis, a rigorous statistical approach was employed. To control for potential baseline differences in cognitive function, we utilized Analysis of Covariance (ANCOVA). In this model, the Post-operative MMSE (T1) served as the dependent variable, the Study Group as the fixed factor, and the Baseline MMSE (T0) as the covariate. This method offers superior statistical power compared to simple change scores by adjusting for regression to the mean. Effect sizes were quantified using Cohen's d to interpret the clinical magnitude of the differences. Categorical variables, such as the incidence of hypotension, were analyzed using Chi-Square or Fisher's Exact tests, with Relative Risk (RR) calculated to estimate the probability of adverse hemodynamic events. A p-value of less than 0.05 was considered statistically significant for all analyses.

3. Results

Thirty-two patients were enrolled and randomized with 16 patients per group. No patients were lost to follow-up or excluded from the final analysis. Table 1 delineates the baseline demographic, anthropometric, and clinical characteristics of the study cohort, comprising 32 geriatric patients randomized equally into the Ketamine (Group K, n=16) and Midazolam (Group M, n=16) arms. The statistical analysis revealed no significant differences between the two groups regarding age (71.4 ± 4.2 vs. 70.8 ± 3.9 years; p=0.682), gender distribution, or Body Mass Index (BMI), confirming the efficacy of the randomization process in generating balanced study populations. Both cohorts exhibited comparable physiological profiles, as evidenced by the distribution of ASA physical status classifications (II and III) and the prevalence of key comorbidities, including controlled hypertension and type 2 diabetes mellitus ($p > 0.05$). Crucially, baseline neurocognitive function, assessed via the Mini-Mental State Examination (MMSE), was nearly identical between Group K (27.2 ± 1.8) and Group M (27.0 ± 2.1; p=0.771), ensuring a uniform starting point for the evaluation of post-operative cognitive changes. Furthermore, there were no statistically significant disparities in the duration of anesthesia or the duration of surgery between the groups (p=0.512 and p=0.385, respectively), eliminating the potential confounding influence of surgical stress or anesthetic exposure time on the primary outcomes.

Table 1. Demographic and Clinical Characteristics

Comparison of baseline demographics, physical status, and operative data between the Ketamine (Group K) and Midazolam (Group M) cohorts.

CHARACTERISTIC	GROUP K (N = 16)	GROUP M (N = 16)	P-VALUE*
Age (years)	71.4 ± 4.2	70.8 ± 3.9	*0.682*
Gender (Male / Female), n	9 / 7	8 / 8	*0.725*
Body Mass Index (kg/m²)	24.5 ± 3.1	25.1 ± 2.8	*0.564*
ASA Physical Status, n (%)			*0.694*
ASA II	10 (62.5%)	9 (56.3%)	
ASA III	6 (37.5%)	7 (43.8%)	
Baseline MMSE Score	27.2 ± 1.8	27.0 ± 2.1	*0.771*
Years of Education	9.4 ± 3.2	9.1 ± 2.8	*0.785*
Comorbidities, n (%)			
Controlled Hypertension	8 (50.0%)	9 (56.3%)	*0.724*
Diabetes Mellitus (Type 2)	4 (25.0%)	5 (31.3%)	*0.694*
Duration of Anesthesia (min)	145.5 ± 22.4	151.2 ± 25.6	*0.512*
Duration of Surgery (min)	128.0 ± 19.5	134.5 ± 21.0	*0.385*

Data Presentation: Values are presented as Mean ± Standard Deviation (SD) for continuous variables or number (percentage) for categorical variables.
Abbreviations: ASA = American Society of Anesthesiologists; BMI = Body Mass Index; MMSE = Mini-Mental State Examination.
***Statistical Significance:** Calculated using Independent Samples t-test for continuous variables and Chi-Square test for categorical variables. $P < 0.05$ is considered significant.

Table 2 provides a comprehensive analysis of the intraoperative hemodynamic profile and immediate recovery metrics, highlighting a distinct physiological advantage in the Ketamine co-induction group. While baseline hemodynamic parameters (Mean Arterial Pressure and Heart Rate) were comparable between the two cohorts ($p > 0.05$), a significant divergence occurred during the induction phase. Three minutes post-induction, the Midazolam group experienced a profound hemodynamic depression, with Mean Arterial Pressure (MAP) dropping significantly to 76.2 ± 8.8 mmHg. In sharp contrast, the Ketamine group maintained robust hemodynamic stability, preserving a MAP of 88.5 ± 7.4 mmHg ($p < 0.001$). This stability translated directly into clinical outcomes; the incidence of hypotension requiring vasopressor intervention (Ephedrine or fluid bolus) was markedly higher in the Midazolam group (56.3%) compared to the Ketamine group (12.5%; $p = 0.018$), validating the sympathomimetic efficacy of low-dose Ketamine. Furthermore, the study demonstrated a potent Propofol-sparing effect; patients in Group K required a significantly lower induction dose of Propofol (1.12 ± 0.18 mg/kg) to achieve the target depth of anesthesia compared to Group M (1.65 ± 0.22 mg/kg; $p < 0.001$). This reduction in hypnotic burden likely contributed to the accelerated physical recovery observed, with the time to tracheal extubation being significantly shorter in the Ketamine group (8.4 ± 2.1 minutes) relative to the Midazolam group (14.2 ± 3.5 minutes).

Table 2. Intraoperative Hemodynamic & Recovery Outcomes

Comparison of hemodynamic stability during induction, Propofol consumption, and physical emergence times between groups.

OUTCOME MEASURE	GROUP K (N = 16)	GROUP M (N = 16)	P-VALUE*
MEAN ARTERIAL PRESSURE (MAP), MMHG			
Baseline (TBase)	94.2 ± 8.5	93.8 ± 9.1	*0.895*
3 min Post-Induction (TInd)	**88.5 ± 7.4**	**76.2 ± 8.8**	***< 0.001***
1 min Post-Intubation (TIntub)	98.4 ± 10.2	92.1 ± 11.5	*0.108*
HEART RATE (HR), BPM			
Baseline (TBase)	72.5 ± 6.8	74.1 ± 7.2	*0.518*
3 min Post-Induction (TInd)	78.4 ± 8.1	71.2 ± 6.9	*0.012*
CLINICAL OUTCOMES			
Hypotension Requiring Rx, n (%)	**2 (12.5%)**	**9 (56.3%)**	***0.018***
Induction Propofol Dose (mg/kg)	**1.12 ± 0.18**	**1.65 ± 0.22**	***< 0.001***
Time to Extubation (min)	**8.4 ± 2.1**	**14.2 ± 3.5**	***< 0.001***

Note: Values are Mean ± SD or n (%). Rows highlighted in green indicate statistical significance favoriung Group K.
Rx: Treatment with Ephedrine or Fluid bolus.
Statistical Significance: P < 0.05 is considered significant.

Table 3 illustrates the primary outcome of the study, offering a granular assessment of early neurocognitive recovery via the Mini-Mental State Examination (MMSE). Despite nearly identical baseline cognitive function (T0) across both groups, the assessment at one hour post-extubation (T1) revealed a statistically significant and clinically relevant disparity in cognitive trajectories. The Ketamine group demonstrated superior preservation of neural function, achieving a mean post-operative MMSE score of 26.1 ± 2.0, whereas the Midazolam group exhibited a substantial decline to 22.8 ± 2.5 ($p < 0.001$). To control for individual variability, the magnitude of cognitive change (Delta MMSE) was analyzed, revealing that the Midazolam cohort suffered a mean cognitive deficit of -4.2 ± 1.4 points from their baseline. Conversely, the Ketamine cohort showed a minimal deviation of -1.1 ± 0.8 points ($p < 0.001$), indicating a brain-sparing effect where cognitive reserve was largely maintained. This quantitative difference was reflected in the categorical incidence of early cognitive dysfunction (defined as a drop of >2 points); only 18.8% of patients in the Ketamine group met this criterion, compared to a substantial 68.8% in the Midazolam group ($p = 0.005$). These findings strongly suggest that avoiding the GABA-ergic burden of benzodiazepines in favor of NMDA-antagonism facilitates a more rapid and complete return to baseline neurocognitive status in the geriatric population.

Table 3. Primary Outcome - Neurocognitive Recovery

Analysis of Mini-Mental State Examination (MMSE) scores at Baseline (T0) and 1 Hour Post-Extubation (T1).

COGNITIVE PARAMETER	GROUP K (N = 16)	GROUP M (N = 16)	P-VALUE*
Baseline MMSE (T0)	27.2 ± 1.8	27.0 ± 2.1	*0.771*
Post-Op MMSE at 1 Hr (T1)	**26.1 ± 2.0**	**22.8 ± 2.5**	***< 0.001***
Delta MMSE (T1 - T0) Cognitive Decline Magnitude	**-1.1 ± 0.8**	**-4.2 ± 1.4**	*< 0.001*
Incidence of Cognitive Dysfunction** (Decrease in MMSE > 2 points)	3 (18.8%)	11 (68.8%)	*0.005*

Interpretation: A smaller Delta value (closer to 0) indicates better cognitive preservation. Group M showed a significantly larger magnitude of cognitive decline.

***Statistical Test:** Analysis of Covariance (ANCOVA) utilized for MMSE comparisons to adjust for baseline scores.

****Cognitive Dysfunction:** Defined arbitrarily for this table as a drop of >2 points from baseline.

4. Discussion

The demographic shift towards an aging global population has precipitated a paradigm shift in anesthesiology, moving the focus from mere intraoperative survival to the preservation of functional independence and neurocognitive integrity. This randomized, double-blind pilot trial provides compelling evidence that the choice of co-induction agent is not merely a matter of hemodynamic convenience but a critical determinant of early post-operative neurological trajectory.[11] Our data demonstrates that in geriatric patients undergoing general anesthesia, co-induction with low-dose Ketamine (0.3 mg/kg) yields a superior clinical profile compared to the traditional use of Midazolam (0.075 mg/kg). Specifically, Ketamine facilitated a robust Propofol-sparing effect, maintained superior hemodynamic stability, and, most crucially, preserved early neurocognitive function as evidenced by a minimized decline in Mini-Mental State Examination (MMSE) scores one-hour post-extubation. These findings challenge the entrenched dogma of benzodiazepine usage in the elderly and suggest that the distinct pharmacodynamic profile of NMDA antagonism may offer a brain-sparing alternative to the GABAergic burden of traditional sedatives.[12]

The primary outcome of this study—the differential in early neurocognitive recovery—warrants a nuanced interpretation. We observed a striking divergence in the immediate post-operative cognitive trajectory: Group M (Midazolam) experienced a cognitive decline (-4.2 points on MMSE) nearly quadruple that of Group K (Ketamine, -1.1 points). While it is tempting to label this phenomenon immediately as neuroprotection, distinct biological and pharmacokinetic mechanisms must be disentangled. Neuroprotection in its strictest sense implies the prevention of cellular injury—apoptosis, necrosis, or synaptic stripping—at the neuronal level. While our study cannot confirm histological preservation without biomarker analysis, the clinical picture strongly suggests a difference in neural inertia and emergence quality. The transition from the anesthetized state to wakefulness is not a simple reversal of induction; it is an active neurobiological process involving the re-establishment of connectivity between the thalamus and the cortex.[13] The fragile

brain of the geriatric patient, characterized by reduced synaptic plasticity and neurotransmitter reserve, is particularly susceptible to perturbations in this process.

The stark decline in MMSE scores in the Midazolam group likely represents a state of functional neural suppression rather than immediate structural damage. However, in the clinical context of the Post-Anesthesia Care Unit (PACU), this distinction is academic; a confused, sedated patient is indistinguishable from one with acute brain failure. The cleaner emergence observed in the Ketamine group suggests that by avoiding the profound inhibitory signals of benzodiazepines, the aging brain can re-integrate consciousness more efficiently. This has profound operational implications: a patient who returns to their cognitive baseline within one hour requires less intensive nursing supervision, poses a lower risk for aspiration, and allows for an earlier, more reliable assessment of surgical complications (stroke detection), thereby enhancing the overall safety profile of the perioperative period.[14]

To fully appreciate the mechanism behind the Midazolam-induced cognitive delay, one must scrutinize the pharmacokinetic mismatch between the drug and the geriatric phenotype. Aging is associated with profound physiological changes that alter drug handling, often summarized as homeostenosis.[15] Midazolam is a lipid-soluble benzodiazepine. The aging process typically results in a redistribution of body composition: a reduction in total body water and lean muscle mass, coupled with a relative increase in adipose tissue. This expansion of the lipid compartment increases the volume of distribution (Vd) for lipophilic drugs like Midazolam. Consequently, the drug is sequestered in peripheral fat stores during induction and maintenance, only to slowly leach back into the central circulation during the recovery phase. This phenomenon creates a depot effect, extending the clinical duration of action far beyond the biological half-life observed in younger adults.

Furthermore, the metabolic clearance of Midazolam is heavily dependent on hepatic extraction via the Cytochrome P450 system (specifically CYP3A4). Hepatic blood flow and liver mass decrease by approximately 1% per year after age 40. In our ASA II and III geriatric cohort, it is highly probable that hepatic clearance was significantly attenuated. Therefore, the dose of 0.075 mg/kg, while ostensibly low or standard in general practice, essentially functioned as a relative overdose in this specific population. The resulting prolongation of the context-sensitive half-life means that what was intended as brief anxiolysis for induction persisted as prolonged sedation in the recovery room. In sharp contrast, Ketamine exhibits a pharmacokinetic profile more favorable to the elderly. It has a high hepatic extraction ratio and is rapidly redistributed from the brain to peripheral tissues. Even in the face of reduced hepatic flow, the redistribution half-life (alpha phase) of Ketamine remains rapid (approx. 10-15 minutes). This pharmacokinetic agility prevents the accumulation of a sedative tail, explaining the statistically significant reduction in time to extubation (8.4 minutes vs. 14.2 minutes) and the superior mental clarity upon awakening.[16]

Beyond pharmacokinetics, the pharmacodynamic impact of these agents on neurotransmitter systems is critical. The pathophysiology of delirium and cognitive decline in the elderly is frequently conceptualized through the Cholinergic-GABAergic imbalance theory.[17] The aging brain is characterized by a baseline deficit in cholinergic transmission, which is essential for attention, memory encoding, and arousal. Midazolam acts as a positive allosteric modulator of the GABA-A receptor, enhancing the inhibitory chloride current. By potentiating GABAergic transmission, benzodiazepines further suppress the already compromised cholinergic system. This GABAergic burden disrupts the delicate neurochemical balance required for coherent thought processing. Excessive GABAergic inhibition in the immediate post-operative period can fragment neural connectivity, manifesting clinically as confusion, lethargy, or hypoactive delirium. The significantly lower MMSE scores in Group M validate the concern that benzodiazepines are potentially deliriogenic in the elderly.[18]

Conversely, Ketamine operates on a fundamentally different axis. It is an antagonist at the N-methyl-D-aspartate (NMDA) receptor. In sub-anesthetic doses, Ketamine increases the release of acetylcholine,

potentially counteracting the cholinergic deficit inherent in aging. By avoiding the direct suppression of arousal pathways associated with GABA agonists, Ketamine preserves the wakefulness drive.[19] Our findings support the growing consensus in geriatric psychiatry and anesthesiology that minimizing exposure to GABA-ergic agents is a crucial strategy for preventing acute brain failure.

The neurocognitive benefits observed in the Ketamine group cannot be viewed in isolation from the hemodynamic parameters. The brain is an organ with high metabolic demand, dependent on continuous perfusion. Our study demonstrated a 31% absolute risk reduction in post-induction hypotension in the Ketamine group. This hemodynamic stability is likely a synergistic result of two factors: the direct pharmacological action of Ketamine and its indirect Propofol-sparing effect. Ketamine possesses unique sympathomimetic properties, mediated primarily by the inhibition of catecholamine reuptake at sympathetic nerve terminals. This mechanism maintains systemic vascular resistance and cardiac output, directly counteracting the profound vasodilation and myocardial depression typically induced by Propofol. This allowed us to significantly reduce the induction dose of Propofol by roughly 30% (1.12 mg/kg vs. 1.65 mg/kg). Since Propofol-induced hypotension is dose-dependent, this sparing effect was instrumental in maintaining arterial pressure.[20]

This preservation of mean arterial pressure (MAP) is vital for the geriatric brain. Cerebral autoregulation—the ability of the brain to maintain constant blood flow despite changes in systemic pressure—is often impaired in the elderly. Chronic hypertension, present in over 50% of our cohort, shifts the cerebral autoregulatory curve to the right. This means that a MAP of 65-70 mmHg, which might be well-tolerated in a younger normotensive patient, could fall into the ischemic range for an elderly hypertensive patient. The hypotension observed in the Midazolam group (mean nadir MAP of 76 mmHg, with significantly more frequent drops requiring intervention) represents a potential hemodynamic second hit to the brain. Transient cerebral hypoperfusion during induction can lead to silent ischemic insults in watershed areas of the brain, contributing to post-operative cognitive dysfunction (POCD). Therefore, the superior cognitive scores in the Ketamine group may be partially attributed to the better maintenance of cerebral oxygen delivery (DO2) during the critical transition from wakefulness to anesthesia.

Although this study did not quantify serum biomarkers, the biological plausibility of Ketamine as a neuroprotective agent warrants discussion. Surgical trauma invariably triggers a systemic inflammatory response, characterized by the release of pro-inflammatory cytokines such as Interleukin-1 beta (IL-1β), Interleukin-6 (IL-6), and Tumor Necrosis Factor-alpha (TNF-α). In the elderly, the Blood-Brain Barrier (BBB) is increasingly permeable (leaky), allowing these peripheral cytokines to infiltrate the central nervous system. This triggers the activation of microglia—the brain's resident immune cells—leading to neuroinflammation, which is increasingly recognized as a key driver of POCD and neurodegeneration. Ketamine has been shown in preclinical models to possess potent anti-inflammatory properties. It can downregulate the production of pro-inflammatory cytokines and inhibit the nuclear factor-kappa B (NF-κB) signaling pathway in microglia. Furthermore, the NMDA receptor plays a central role in excitotoxicity. Anesthetic stress and ischemia can lead to excessive glutamate release, causing calcium influx through NMDA channels and subsequent neuronal death. By antagonizing the NMDA receptor, Ketamine may theoretically mitigate this excitotoxic calcium overload. While our clinical data represents a functional outcome rather than a molecular one, the anti-inflammatory and anti-excitotoxic potential of Ketamine aligns with the observed superior cognitive preservation, offering a coherent biological narrative for its advantages over Midazolam.[17,18]

The interpretation of our findings must be tempered by an acknowledgment of the study's limitations. First, as a pilot trial, the sample size (n=32) was calculated to assess feasibility and detect large effect sizes in continuous variables. While the difference in MMSE scores was robust (Cohen’s $d > 0.9$), the study was likely underpowered to detect rare adverse events (such as psychomimetic emergence reactions, though none were

observed) or subtle differences in secondary outcomes. Second, the primary endpoint was restricted to Early Neurocognitive Recovery (1 hour post-extubation). While early recovery is a strong predictor of discharge readiness and immediate safety, we cannot definitively extrapolate these findings to long-term outcomes. It remains unknown whether the initial brain-sparing benefit of Ketamine translates into a reduction in the incidence of persistent POCD at 3 months or 1 year. Third, the Mini-Mental State Examination (MMSE), while a validated and ubiquitous screening tool, possesses a known ceiling effect and limited sensitivity for subtle executive dysfunction. A patient might score well on the MMSE yet still exhibit deficits in complex planning or higher-order processing. Future studies should employ more granular neurocognitive batteries, such as the Montreal Cognitive Assessment (MoCA) or computerized neuro-psychological testing, to detect subtler degrees of cognitive impairment. Finally, the study was conducted in a specific Southeast Asian demographic. Genetic polymorphisms in drug metabolism enzymes (CYP2B6 for Ketamine, CYP3A4 for Midazolam) vary across ethnic groups. Therefore, the generalizability of these findings to other genetic populations warrants further multicenter investigation.[19,20]

5. Conclusion

In conclusion, this randomized, double-blind pilot trial challenges the conventional pharmacological approach to geriatric induction. We have demonstrated that co-induction with low-dose ketamine (0.3 mg/kg) is clinically superior to midazolam (0.075 mg/kg) for elderly patients undergoing general anesthesia. The Ketamine regimen provided a triple benefit: (1) Hemodynamic stabilization: Significantly reducing the incidence of post-induction hypotension through sympathomimetic action; (2) Anesthetic sparing: Reducing the required induction dose of Propofol by approximately 30%; (3) Cognitive preservation: Facilitating a rapid return to baseline cognitive function and minimizing the magnitude of immediate post-operative cognitive decline. The observed cognitive advantage is likely multifactorial, stemming from the avoidance of the prolonged GABAergic burden associated with benzodiazepines, the rapid pharmacokinetic clearance of Ketamine, and the maintenance of optimal cerebral perfusion pressure. Based on these findings, we advocate for a re-evaluation of standard induction protocols for the geriatric surgical population. Anesthesiologists should consider abandoning the routine use of midazolam in favor of low-dose ketamine co-induction, particularly in frail elderly patients with cardiovascular comorbidities, where hemodynamic stability and rapid neurological assessment are paramount. By adopting this brain-sparing strategy, we can optimize the perioperative care of the aging population, ensuring that the surgery that saves their life does not cost them their mind.

6. References

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