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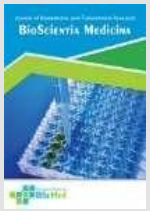

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Comparative Analysis of Early Postoperative Cognitive Decline Following Isoflurane versus Sevoflurane Anesthesia in Geriatric Patients: A Prospective Observational Study

Recky Antoni[1*], Nopian Hidayat[2], Dino Irawan[2]

[1]Specialized Residency Training Program, Anesthesiology and Intensive Therapy Study Program, Faculty of Medicine, Universitas Riau, Pekanbaru, Indonesia

[2]Department of Anesthesiology and Intensive Therapy, Arifin Achmad Regional General Hospital, Pekanbaru, Indonesia

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***Corresponding author:**
Recky Antoni

E-mail address:
reckyantoni19@gmail.com

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A B S T R A C T

Background: As the global geriatric population expands, postoperative cognitive dysfunction (POCD) has emerged as a critical perioperative complication. While volatile anesthetics are standard for maintenance, conflicting evidence exists regarding the comparative neurotoxicity of Isoflurane and Sevoflurane, particularly in resource-limited settings where cost influences agent choice. This study aimed to evaluate and compare the magnitude of early cognitive decline associated with these two agents in an Indonesian geriatric cohort. **Methods:** We conducted a prospective comparative observational study involving 40 geriatric patients (aged ≥60 years, ASA II-III) undergoing elective non-cardiac surgery at Arifin Achmad Regional General Hospital, Indonesia. Patients were recruited via consecutive sampling and allocated to receive maintenance anesthesia with either Sevoflurane (n=20) or Isoflurane (n=20) according to standard clinical protocols. Cognitive function was assessed preoperatively and at 72 hours postoperatively using the Montreal Cognitive Assessment-Indonesian Version (MoCA-INA). The primary outcome was the magnitude of cognitive change (Delta score) and the incidence of cognitive decline. **Results:** Baseline characteristics were homogenous ($p > 0.05$). The Sevoflurane group exhibited a non-significant trend toward decline (Pre: 26.85 ± 1.09 vs. Post: 26.45 ± 1.28; $p = 0.057$) with a mean delta of 0.40. Conversely, the Isoflurane group demonstrated a statistically significant deterioration (Pre: 26.90 ± 1.07 vs. Post: 25.90 ± 1.55; $p = 0.008$) with a mean delta of 1.00. The magnitude of decline was significantly greater in the Isoflurane group ($p = 0.026$). The incidence of early cognitive decline was 25% for Isoflurane versus 10% for Sevoflurane. **Conclusion:** Isoflurane anesthesia is associated with a greater magnitude of early postoperative cognitive decline compared to Sevoflurane in geriatric patients. While Sevoflurane is not devoid of cognitive impact, it appears to offer a superior safety profile for early neurocognitive recovery. These findings suggest Sevoflurane may be the preferable agent for geriatric anesthesia in settings where newer agents like Desflurane are unavailable.

1. Introduction

The demographic landscape of the 21st century is defined by a rapid and unprecedented expansion of the elderly population.[1] According to the World Health Organization (WHO), the proportion of the global population aged over 60 years is projected to nearly double from 12% to 22% between 2015 and 2050. This seismic demographic shift has precipitated a parallel surge in surgical volume; it is estimated that geriatric patients now account for a disproportionately large share of all surgical interventions globally.[2] With advancing age comes a reduction in physiological

reserve—a concept clinically recognized as frailty—which renders the geriatric brain uniquely susceptible to perioperative insults.

Among the myriad complications facing this demographic, postoperative cognitive dysfunction (POCD) has emerged as one of the most insidious, elusive, and debilitating sequelae.[3] Unlike postoperative delirium (POD), which is an acute, fluctuating state of confusion often observed in the immediate recovery period, POCD represents a more subtle deterioration in cognitive domains such as memory, executive function, attention, and information processing speed. The clinical implications of POCD are profound and far-reaching: it is strongly associated with prolonged hospital lengths of stay, increased healthcare expenditures, loss of functional independence, premature withdrawal from the workforce, and significantly elevated one-year mortality rates.[4]

The etiology of POCD is undeniably multifactorial, involving surgical stress, systemic inflammation, and patient-specific vulnerabilities.[5] However, the role of the anesthetic agent itself remains a subject of intense debate and investigation. Volatile anesthetics, the cornerstone of general anesthesia maintenance, work primarily by modulating Gamma-Aminobutyric Acid type A (GABA-A) and N-Methyl-D-Aspartate (NMDA) receptors. While effective for hypnosis, preclinical data suggests these agents may trigger neurotoxicity through pathways involving amyloid-beta (Aβ) oligomerization and calcium dysregulation.[6]

Isoflurane and Sevoflurane are two of the most ubiquitous halogenated ethers used in modern anesthetic practice.[7] In many advanced healthcare systems, Sevoflurane and Desflurane have largely supplanted older agents. However, in resource-stratified healthcare settings, including many hospitals in Indonesia, Isoflurane remains in frequent use due to its significantly lower acquisition cost compared to newer agents. This economic reality necessitates a rigorous evaluation of whether the cost-saving benefits of Isoflurane come at the expense of cognitive safety in vulnerable geriatric populations.[8]

The comparison between Isoflurane and Sevoflurane is not merely one of molecular neurotoxicity but also of pharmacokinetics.[9] Isoflurane has a blood-gas partition coefficient of 1.4, significantly higher than that of Sevoflurane (0.65). This physicochemical property means Isoflurane is more soluble in blood and, crucially, in lipid tissues. Geriatric patients typically possess higher adipose tissue ratios and reduced metabolic clearance (hepatic and renal). Consequently, Isoflurane predisposes elderly patients to prolonged emergence and washout periods. We hypothesize that the cognitive deficits observed in the early postoperative period may be driven as much by this pharmacological hangover or residual sedation as by direct neuronal injury.[10]

This study introduces distinct novelty by shifting the investigative lens to a specific Southeast Asian geriatric cohort, a demographic often underrepresented in global anesthetic literature. Unlike previous studies that utilized the Mini-Mental State Examination (MMSE), which suffers from ceiling effects and low sensitivity for mild dysfunction, this research utilizes the Montreal Cognitive Assessment-Indonesian Version (MoCA-INA). The MoCA-INA detects subtle executive and attention deficits that coarser tools miss, providing a more granular resolution of early postoperative cognitive trajectories. Furthermore, by isolating the specific comparison of Isoflurane and Sevoflurane in a resource-limited setting, this study directly addresses a pharmacoeconomic dilemma relevant to developing healthcare systems. The primary aim of this study was to conduct a prospective comparative analysis of the incidence and magnitude of early postoperative cognitive decline in geriatric patients receiving either Sevoflurane or Isoflurane anesthesia. The study specifically targeted the early postoperative window (Day 3) to quantify the acute neurocognitive impact, testing the hypothesis that Isoflurane induces a significantly greater magnitude of cognitive decline due to its distinct pharmacokinetic and neurotoxic profile compared to Sevoflurane.

2. Methods

We conducted a Prospective Comparative Observational Study to evaluate the cognitive trajectories of geriatric patients. The research was executed at the Central Surgical Installation and Inpatient Wards of Arifin Achmad Regional General Hospital, a tertiary care center in Riau Province, Indonesia. The data collection period spanned from August to November 2025. The study protocol adhered to the principles of the Declaration of Helsinki and was reviewed and approved by the Health Research Ethics Committee of the Faculty of Medicine, Universitas Riau (Ethical Clearance No: 105/UN19.5.1.1.8/UEPKK/2025).

The population comprised geriatric patients aged 60 years or older scheduled for elective non-cardiac surgery under general anesthesia. Inclusion criteria: Age ≥ 60 years, American Society of Anesthesiologists (ASA) Physical Status II or III, Preoperative MoCA-INA score ≥ 26 (indicating normal baseline cognitive function), Minimum education level of Junior High School (SMP) to ensure the validity of neurocognitive testing. Exclusion Criteria: To minimize confounders, we excluded patients with pre-existing cognitive impairment (dementia, stroke), severe visual/auditory deficits, surgery duration > 4 hours, intraoperative adverse events (hypoxia/massive hemorrhage), or history of psychiatric disorders.

A consecutive sampling technique was employed. Eligible patients were recruited sequentially upon admission until the target sample size was reached. Patients were allocated into two groups based on the anesthetic agent determined by standard departmental protocols and clinical judgment, resulting in two comparison groups: Sevoflurane Group (n=20) and Isoflurane Group (n=20). Sample size calculation was based on the formula for comparative numeric analytical studies, using an estimated meaningful difference of 1.8 points on the cognitive scale and a standard deviation of 2.49. With a Type I error (α) of 5% and Power (1-β) of 95%, the minimum sample size required was 20 subjects per group.

To ensure the validity of the comparison, perioperative management followed a standardized institutional protocol. Anesthesia was induced with intravenous agents (Propofol/Fentanyl) titrated to the patient's hemodynamic status. Maintenance was achieved using the allocated volatile agent delivered in an oxygen/air mixture. The concentration was titrated to maintain a depth of anesthesia sufficient for surgical immobility. Specifically, the Sevoflurane group was maintained at approximately 2.0 vol% (~1 MAC), and the Isoflurane group at 1.2 vol% (~1 MAC). Standard ASA monitoring (ECG, NIBP, SpO_2, Capnography) was utilized. Hemodynamics were managed to stay within 20% of baseline values to prevent cerebral hypoperfusion.

The primary instrument was the Montreal Cognitive Assessment-Indonesian Version (MoCA-INA). This tool assesses seven cognitive domains: visuospatial/executive function, naming, memory (delayed recall), attention, language, abstraction, and orientation. The maximum score is 30. T0 (Baseline): Assessment performed 24 hours prior to surgery. T1 (Postoperative): Assessment performed at 72 hours (Day 3) after surgery. Definition of Decline: Early Cognitive Decline was clinically defined as a postoperative MoCA-INA score dropping below 26 or a statistically significant reduction in score from baseline.

Data were analyzed using SPSS version 26. The Shapiro-Wilk test was utilized (n<50). Key variables, including ASA status and cognitive scores, were found to be non-normally distributed ($p < 0.05$). Independent T-test (for normal numeric data like Age) and Chi-Square test (for categorical data). Wilcoxon Signed-Rank Test for Pre vs. Post scores. Mann-Whitney U Test for comparing Delta scores (magnitude of change). Chi-Square test for rates of POCD. Significance was set at $p < 0.05$.

3. Results

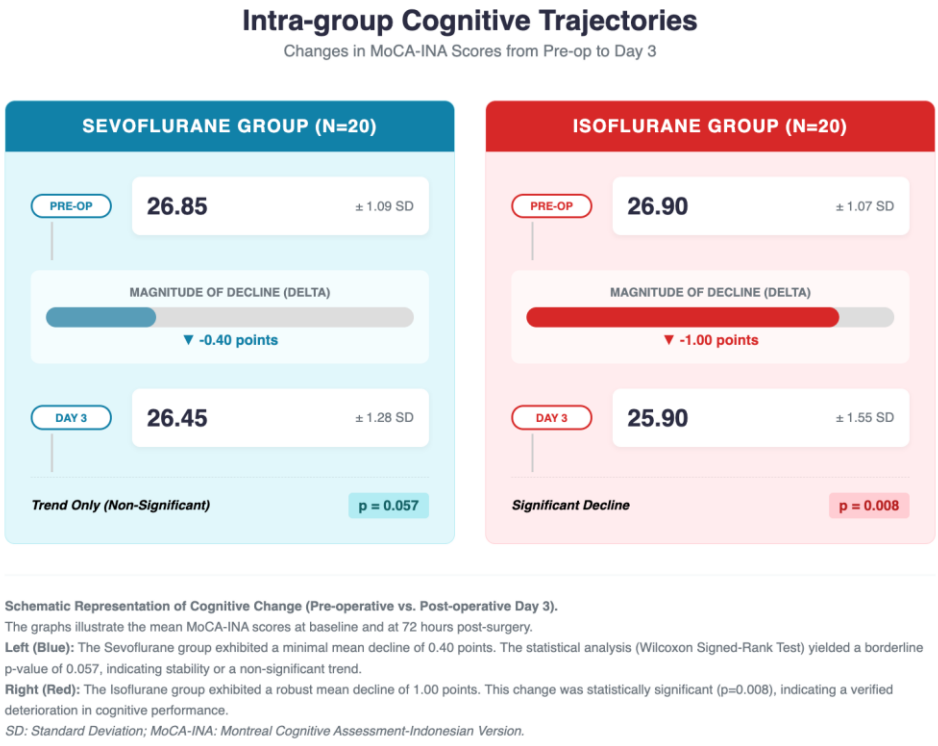
Figure 1 serves as the foundational bedrock of this prospective observational study, providing a comprehensive schematic visualization of the

demographic, clinical, and psychometric profiles of the 40 geriatric patients enrolled. In any comparative study, particularly one that is observational rather than strictly randomized, establishing the comparability of the study groups at the outset (T0) is paramount to inferring that subsequent outcomes are attributable to the intervention—in this case, the specific volatile anesthetic agent—rather than preexisting disparities. This figure visually audits the success of our consecutive sampling and allocation protocols, rigorously demonstrating the homogeneity of the Sevoflurane (n=20) and Isoflurane (n=20) cohorts prior to surgical insult. Furthermore, it delineates the statistical distribution properties of the primary variables, which dictated the subsequent choice of parametric versus non-parametric analytical approaches. The figure is structured as a comparative duality, with the Sevoflurane cohort presented on the left (typically denoted in cool tones like teal in the associated schematic) and the Isoflurane cohort on the right (denoted in warmer tones like coral/red). The central axis presents the statistical adjudication (P-values) for each comparison. Starting with biological variables, the figure illustrates a remarkable similarity in Age structure. The mean age in the Sevoflurane group was 64.85 (± 3.80) years, nearly identical to the 64.80 (± 3.46) years in the Isoflurane group. The independent t-test confirms this balance with a highly non-significant p-value of 0.966. Given that age is the single most potent non-modifiable risk factor for cognitive decline, this parity is critical. Similarly, Gender distribution, visualized via proportional bar segments, shows a balanced mix of males and females across both groups (p=0.204), ruling out sex-based biological variables as confounders in this cohort. Moving to clinical indicators of frailty and surgical complexity, the figure highlights ASA Physical Status. The visualization—perhaps using stacked indicators—shows that both groups were predominantly composed of ASA II patients (90% vs. 85%) with a minority of ASA III patients, resulting in a non-significant Chi-square difference (p=0.633). This ensures that baseline physiological reserve and comorbidity burdens were matched. Furthermore, the Duration of Anesthesia, a proxy for the total dose of anesthetic exposure and the duration of surgical stress, was statistically indistinguishable between groups (2.35 vs. 2.40 hours; p=0.813). Crucially for a cognitive study, Education Level—a primary determinant of cognitive reserve and performance on psychometric tests—was balanced (p=0.573), with the majority in both groups having completed senior high school (SMA). Most importantly, the Baseline MoCA-INA Scores were virtually identical. The Sevoflurane group started with a mean of 26.85 (± 1.09), and the Isoflurane group with 26.90 (± 1.07). The Mann-Whitney U test yielded a p-value of 0.884, confirming that both groups entered the operating theater with equivalent cognitive functional baselines, all scoring above the impairment cutoff of 26. A critical feature of Figure 1 is the explicit presentation of normality testing results via Shapiro-Wilk analysis. The figure visually flags that while the variable of Age followed a normal Gaussian distribution ($p>0.05$), enabling parametric testing (T-test), other critical variables—specifically ASA Status, Duration of Anesthesia, and the cognitive scores themselves—did not meet the assumption of normality ($p<0.05$). This schematic declaration provides the necessary scientific justification for the widespread use of robust non-parametric statistical methods (Mann-Whitney U, Wilcoxon Signed-Rank) in the subsequent analyses of outcomes, ensuring the statistical validity of the study's conclusions. In summary, Figure 1 provides compelling visual evidence of a well-balanced study population, successfully isolating the anesthetic agent as the primary independent variable for the subsequent analyses.

Figure 1. Baseline characteristics.

Figure 2 shifts the analytical focus from baseline comparability to longitudinal change, offering a dynamic schematic representation of the intra-group cognitive trajectories. This figure is essential for understanding how cognitive function evolved over time—from the preoperative baseline (T0) to the critical postoperative Day 3 (T1) assessment—within each specific anesthetic cohort. By isolating each group, we can evaluate the specific biological impact of Sevoflurane and Isoflurane on the aging brain against its own baseline, independent of the other group. The figure is structured as two distinct panels or cards, designed to visualize the before and after state and quantify the statistical significance of the shift occurring during the perioperative window. The left panel, representing the Sevoflurane group (n=20), visualizes a trajectory characterized by relative preservation of cognitive function. At the Preoperative timepoint, the group exhibited a mean MoCA-INA score of 26.85 (± 1.09 SD), indicating healthy baseline cognition. Following the surgical intervention and maintenance anesthesia with Sevoflurane, the assessment at Postoperative Day 3 revealed a mean score of 26.45 (± 1.28 SD). Visually, this is represented as a minimal downward slope or a small negative displacement on a change gauge. The arithmetic mean difference is a modest decline of 0.40 points on the 30-point scale. The critical scientific insight lies in the

statistical adjudication using the Wilcoxon Signed-Rank Test for paired non-normal data. The resultant p-value is 0.057. In the rigorous binary landscape of hypothesis testing (where alpha = 0.05), this result is technically non-significant. However, a scholarly interpretation acknowledges that a p-value of 0.057 sits on the cusp of significance. This suggests that Sevoflurane is not physiologically inert; there is a discernible *trend* toward mild cognitive dampening in the early postoperative period. Yet, compared to the alternative, this trajectory represents a profile of relative stability where the cognitive insults of surgery and anesthesia did not result in a statistically verified deterioration for the group as a whole. Contrasting sharply with the stability of the Sevoflurane group, the right panel details the trajectory of the Isoflurane group (n=20). Starting from an equivalent baseline of 26.90 (± 1.07 SD), the postoperative assessment at Day 3 reveals a marked drop to a mean score of 25.90 (± 1.55 SD). Graphically, this is depicted as a steeper downward trajectory or a larger negative displacement, emphasizing a more profound cognitive hit. The arithmetic mean decline is 1.00 point—more than double the raw decline observed in the Sevoflurane group. Crucially, the Wilcoxon Signed-Rank Test confirms that this decline is highly statistically significant, with a p-value of 0.008. This signifies that it is highly improbable that this deterioration occurred by chance alone. It indicates a robust, systematic downward shift in cognitive performance across the Isoflurane cohort following exposure. Together, these side-by-side trajectories in Figure 2 provide the first definitive evidence of differential outcomes. The visual and statistical contrast reinforces the hypothesis: while patients receiving Sevoflurane largely maintained their cognitive footing, those receiving Isoflurane experienced a statistically verifiable and clinically potentially relevant deterioration in the acute recovery phase. This figure establishes that an injury did occur in the Isoflurane group, setting the stage for subsequent figures to quantify the magnitude of that injury relative to the comparator.



Schematic Representation of Cognitive Change (Pre-operative vs. Post-operative Day 3).
The graphs illustrate the mean MoCA-INA scores at baseline and at 72 hours post-surgery.
Left (Blue): The Sevoflurane group exhibited a minimal mean decline of 0.40 points. The statistical analysis (Wilcoxon Signed-Rank Test) yielded a borderline p-value of 0.057, indicating stability or a non-significant trend.
Right (Red): The Isoflurane group exhibited a robust mean decline of 1.00 points. This change was statistically significant (p=0.008), indicating a verified deterioration in cognitive performance.
SD: Standard Deviation; MoCA-INA: Montreal Cognitive Assessment-Indonesian Version.

Figure 2. Intra-group cognitive trajectories.

Figure 3 provides a direct, head-to-head statistical comparison of the magnitude of that decline between the two agents. This is arguably the most critical analytical figure for testing the primary hypothesis. It utilizes the Delta Score (Delta = Preoperative Score - Postoperative Score) as the primary metric. By focusing on the change score rather than absolute postoperative scores, we mathematically control for any minor individual variations at baseline, isolating the pure cognitive hit sustained during the perioperative period. The figure is schematically designed as a comparative bar graph or hanging bar visualization, where the length of the bar extending downward from a zero-change baseline represents the mean magnitude of cognitive loss. The visualization reveals a stark disparity in the magnitude of acute cognitive dysfunction at Day 3. The bar representing the Sevoflurane group is relatively short, indicating a mean decline of only 0.40 points (Standard Deviation ± 0.88). The range data presented alongside indicates that many patients in this group had a delta of 0 (stability) or even slightly improved (negative delta due to practice effect), with the maximum individual decline being limited to 2 points. This visually reinforces the profile of relative neurocognitive preservation. In sharp contrast, the bar representing the Isoflurane group is significantly longer, extending downwards to represent a mean decline of 1.00 point (Standard Deviation ± 1.59). The variance is also notably wider in this group, with the range indicating that at least one patient experienced a severe drop of 6 points on the MoCA-INA scale, a clinically devastating acute decline that would manifest as gross confusion or executive failure. The visual disparity between the short 0.40 bar and the long 1.00 bar immediately conveys the differential impact of the agents. The core scientific value of Figure 3 lies in the statistical comparison of these Delta scores. Because the Delta scores were not normally distributed, the non-parametric Mann-Whitney U Test was employed to determine if the difference between the mean rank of decline in the Isoflurane group versus the Sevoflurane group was statistically significant. Figure 3 prominently displays the result of this test: a p-value of 0.026. Being less than the alpha threshold of 0.05, this confirms that the magnitude of cognitive decline experienced by patients receiving Isoflurane was statistically significantly greater than that experienced by patients receiving Sevoflurane. This is not merely a difference in averages; it is a statistically robust finding indicating that Isoflurane anesthesia is associated with a steeper downward trajectory in early cognitive recovery. Figure 3 provides the quantitative evidence supporting the assertion that Isoflurane is less neuroprotective—or actively more neurotoxic/sedating—in the geriatric brain during the acute postoperative phase than Sevoflurane.

Figure 4 translates these numerical averages into a concrete clinical reality: the incidence of patients crossing the diagnostic threshold for postoperative cognitive dysfunction (POCD). This schematic uses a patient matrix or dot-plot visualization to represent the entire study cohort of 40 geriatric patients. This approach is highly effective for small-to-medium sample sizes, as it allows the reader to visualize every individual subject as a data point, making the concept of clinical risk tangible and immediate. The figure categorizes outcomes based on the established clinical cutoff for the MoCA-INA, where a score below 26 indicates cognitive impairment. Figure 4 is divided into two panels representing the two anesthetic protocols. Each panel contains a matrix of 20 patient dots. On the left panel, representing the Sevoflurane group (n=20), the visualization shows a field predominantly composed of normal dots (typically colored neutral gray or white), indicating patients who maintained a score of 26 or higher at Day 3. Only 2 out of 20 dots are highlighted in the distinct color assigned to POCD cases (teal). This visually translates to a low incidence rate of 10%. The visual impression is one of general safety, with cognitive complications being rare outliers. On the right panel, representing the Isoflurane group (n=20), the visual landscape is markedly different. The matrix contains a noticeably higher density of highlighted POCD dots (red).

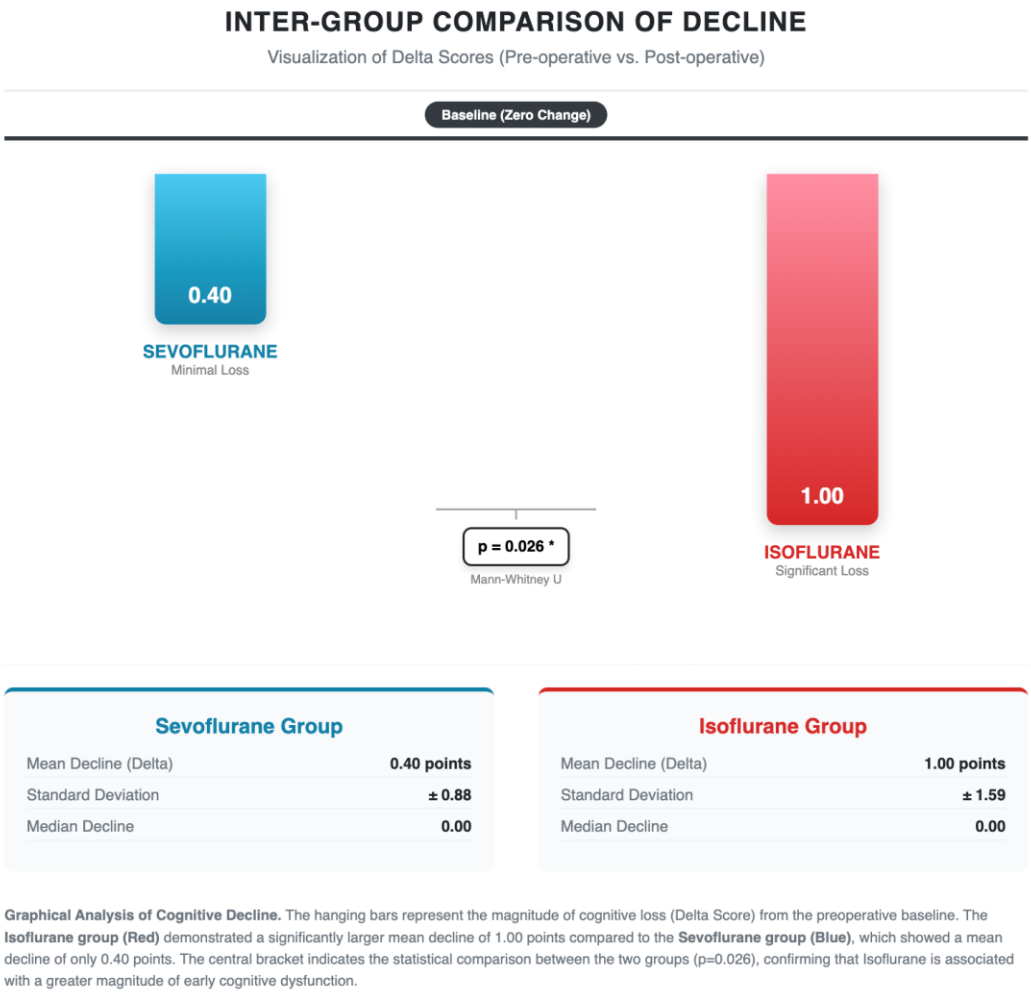


Figure 3. Inter-group comparison of decline.

A total of 5 out of 20 patients are shown to have dropped below the clinical threshold of 26. This translates to an incidence rate of 25%. Visually, the risk appears more than double that of the Sevoflurane group, a striking difference in a relatively small cohort. To determine if this observed difference in proportions (10% vs. 25%) was statistically significant, a Chi-Square Test was performed. The figure prominently displays the resultant p-value of 0.021. This indicates a statistically significant association between the anesthetic agent used and the likelihood of developing early POCD. From a scholarly and clinical perspective, Figure 4 is arguably the most impactful for changes in practice. A 25% incidence rate means that one in four geriatric patients receiving Isoflurane in this setting exhibited measurable cognitive impairment at Day 3, a state that complicates discharge instructions, increases the risk of in-hospital delirium, and predicts poorer long-term outcomes. The difference between 10% and 25% is not just statistical noise; it represents a substantial difference in clinical risk profile. Implicitly, these numbers suggest a relatively low number needed to harm (NNH) when choosing Isoflurane over Sevoflurane in this population, reinforcing the clinical imperative to adopt neuroprotective strategies for geriatric surgical patients.

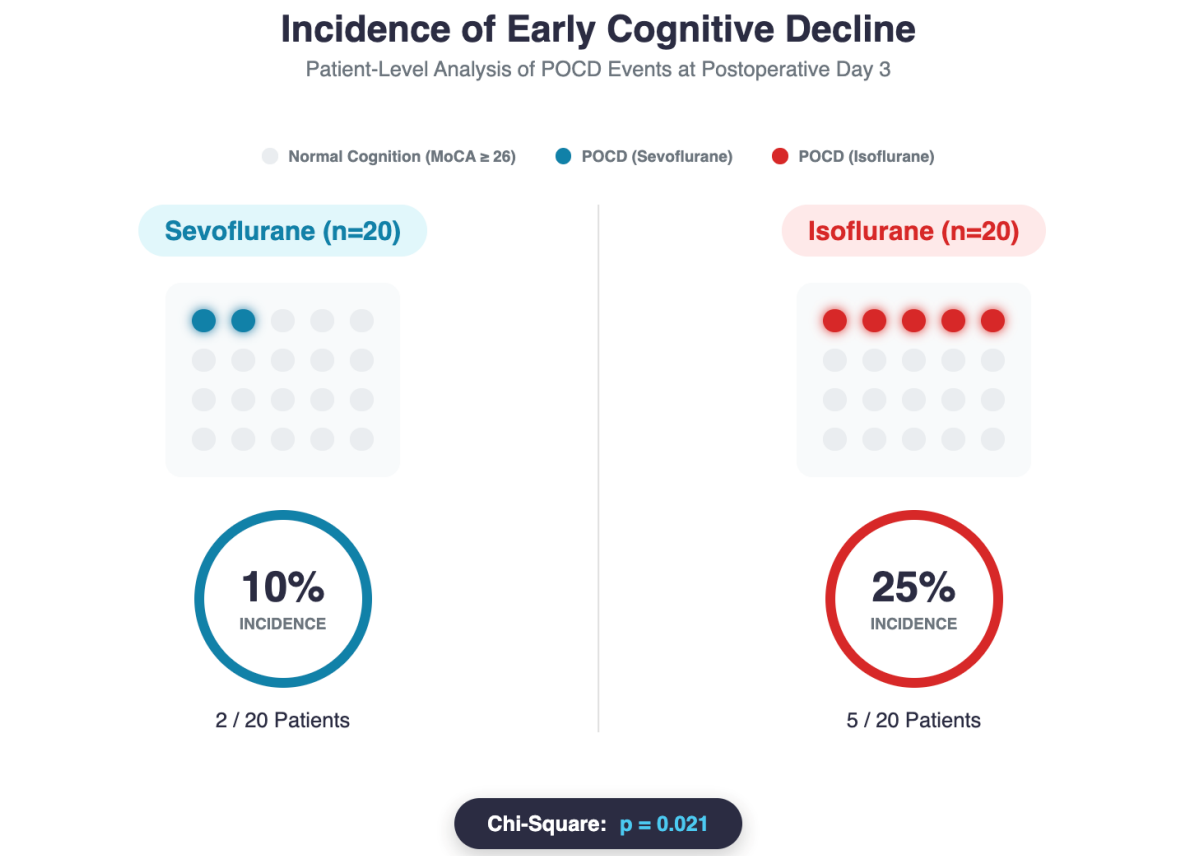


Figure 4. Incidence of early cognitive decline.

Figure 5 introduces a crucial nuance to the study's findings by stratifying the outcomes based on age. This schematic delves into the concept of cognitive reserve—the brain's resilience to insult—and how it interacts with the specific anesthetic agent. Geriatric patients are not a monolith; a 65-year-old often possesses significantly more physiological and cognitive reserve than an 80-year-old. This figure tests the hypothesis that different anesthetic agents have different thresholds of toxicity that overwhelm these varying levels of reserve. Figure 5 is organized as a split-panel comparison between the younger geriatric subgroup (aged 60-70 years) and the oldest old subgroup (aged 71-80 years). Panel A: The younger geriatric (60-70 Years) – Defining the Safety Margin. The left panel focuses on patients aged 60-70. These are typically patients with some remaining cognitive reserve, often still active in the community or workforce. The data visualization for Sevoflurane in this age bracket is striking: 0 out of 18 patients developed POCD. The incidence bar is completely empty (0%). This suggests that for relatively robust geriatric patients, the neurocognitive insult imposed by Sevoflurane anesthesia and moderate-duration surgery was insufficient to overwhelm their cognitive defenses. In sharp contrast, among patients aged 60-

70 receiving Isoflurane, 3 out of 15 patients (20%) developed POCD. This is a critical finding. It indicates that Isoflurane possesses a lower threshold for toxicity; it was potent enough to breach the cognitive reserve of these younger seniors, a demographic that remained completely stable under Sevoflurane. This visual evidence suggests Isoflurane is actively detrimental even before extreme frailty sets in. Panel B: The oldest old (71-80 Years) – The Limits of Reserve. The right panel examines the most vulnerable patients, those aged 71-80, whose cognitive reserve is assumed to be severely depleted. In this group, cognitive decline occurred regardless of the agent. 2 out of 2 patients in the Sevoflurane group and 2 out of 5 patients in the Isoflurane group developed POCD. While the sample sizes in this subgroup are too small for robust statistical inference, the pattern is highly informative from a scholarly perspective. It suggests that past a certain point of geriatric vulnerability (age >70 in this cohort), the combined stress of surgery, hospitalization, and any general anesthesia is sufficient to exhaust cognitive reserve and precipitate decline. Figure 5 provides a sophisticated, nuanced view of geriatric vulnerability. It visually demonstrates that Sevoflurane's safety profile is superior because its toxicity threshold appears to be higher—it only failed in the oldest, most vulnerable patients. Isoflurane's toxicity threshold appears lower, causing cognitive failure across a broader spectrum of geriatric ages, including those who might otherwise have had an uneventful recovery. This figure strongly argues for agent-specific selection based on patient age and presumed frailty.

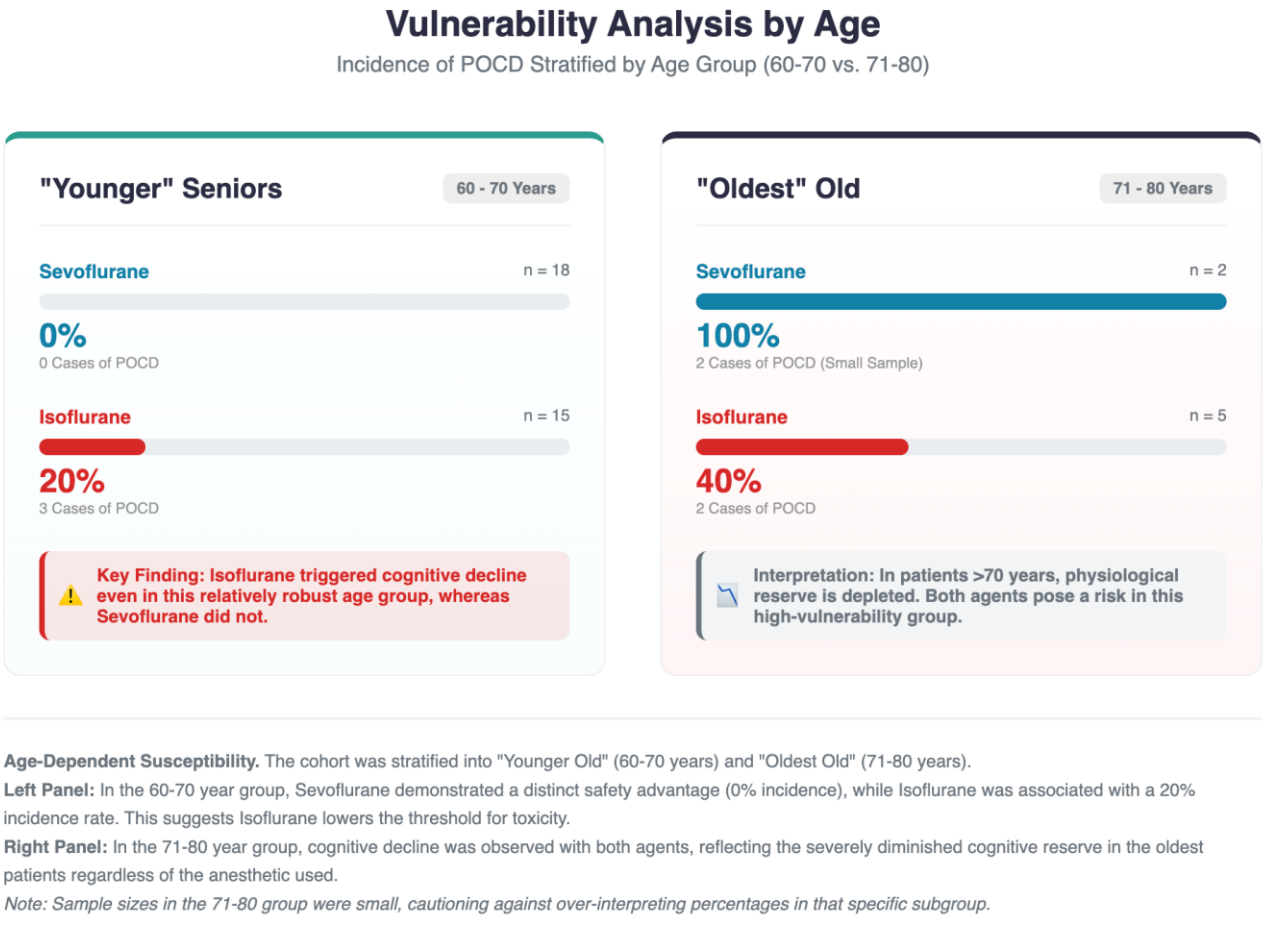


Figure 5. Vulnerability analysis by age.

4. Discussion

The results of this prospective study indicate that Isoflurane is associated with a significantly higher incidence and magnitude of early postoperative cognitive decline compared to Sevoflurane in an Indonesian geriatric cohort.[11] While patients receiving Sevoflurane maintained relatively stable cognitive trajectories (mean loss of 0.4 points), those receiving Isoflurane experienced a clinically relevant drop of 1.0 point on average, with 25% of the cohort falling into the range of cognitive impairment by Day 3. It is crucial to interpret the Sevoflurane finding (p=0.057) with scientific nuance. This borderline p-value suggests that Sevoflurane is not physiologically inert; rather, it appears to be less detrimental than Isoflurane. This aligns with the concept that general anesthesia constitutes a stress test for the aging brain, but the degree of insult varies by agent properties. Figure 6 serves as the intellectual culmination of the study, offering a schematic synthesis that connects the clinical results observed at Day 3 back to the fundamental pharmacological and molecular principles discussed in the introduction. It bridges the gap between bench (basic science theories) and bedside (clinical outcomes like MoCA scores). Figure 6 is designed as a dual-pathway flow chart, contrasting the proposed toxic/sedative pathway of Isoflurane on the left with the neuroprotective/rapid recovery pathway of Sevoflurane on the right. It integrates two major theoretical frameworks: pharmacokinetics and molecular neurotoxicity. The left side of the schematic begins with the inherent properties of the Isoflurane agent. It highlights its primary pharmacokinetic liability: High blood-gas solubility (coefficient 1.4). The diagram visually represents how this leads to significant sequestration of the anesthetic in the lipid-rich adipose tissues of geriatric patients, who are physiologically predisposed to reduced metabolic clearance. The resulting arrow points to prolonged washout/residual sedation at Day 3. This suggests that the deficits observed may not be permanent brain damage but rather a pharmacological hangover, where lingering sub-anesthetic concentrations continue to dampen executive function and attention. Simultaneously, a parallel branch outlines the molecular neurotoxicity mechanisms derived from preclinical literature. It details how Isoflurane is implicated in accelerating the amyloidogenic pathway (increasing BACE1 activity and Aβ oligomerization), disrupting intracellular calcium homeostasis (leading to mitochondrial dysfunction and apoptosis), and triggering robust neuroinflammation via the NF-κB pathway.[12] The schematic converges these pharmacokinetic and molecular insults to explain the observed Clinical Outcome: a significant cognitive decline, quantified by the 1.00-point drop and 25% POCD incidence documented in the study results. The right side of the schematic offers the contrasting narrative for Sevoflurane. It begins with its key advantageous property: Low blood-gas solubility (coefficient 0.65). The diagram shows this leading to minimal tissue accumulation and a rapid elimination/clean recovery. This implies that by Day 3, the patient's cognitive state is less likely to be clouded by residual drug effects. At the molecular level, the schematic indicates a profile of relative Neuroprotection. It suggests that at equipotent doses, Sevoflurane has a weaker interaction with amyloid pathways, better maintains calcium stability, and attenuates the pro-inflammatory response compared to Isoflurane. These distinct pharmacological behaviors converge to explain the observed clinical outcome for the Sevoflurane group: relative cognitive stability, characterized by a minimal 0.40-point change and a low 10% incidence of POCD.[13] Figure 6 provides a scientifically grounded, mechanistic framework for interpreting the statistical data. It proposes that the superior outcomes seen with Sevoflurane are likely due to a synergistic combination of faster pharmacokinetic clearance (reducing Day 3 sedation) and a less aggressive molecular neurotoxic profile. This schematic neatly summarizes the study's theoretical contribution to the field of geriatric anesthesiology.[14]

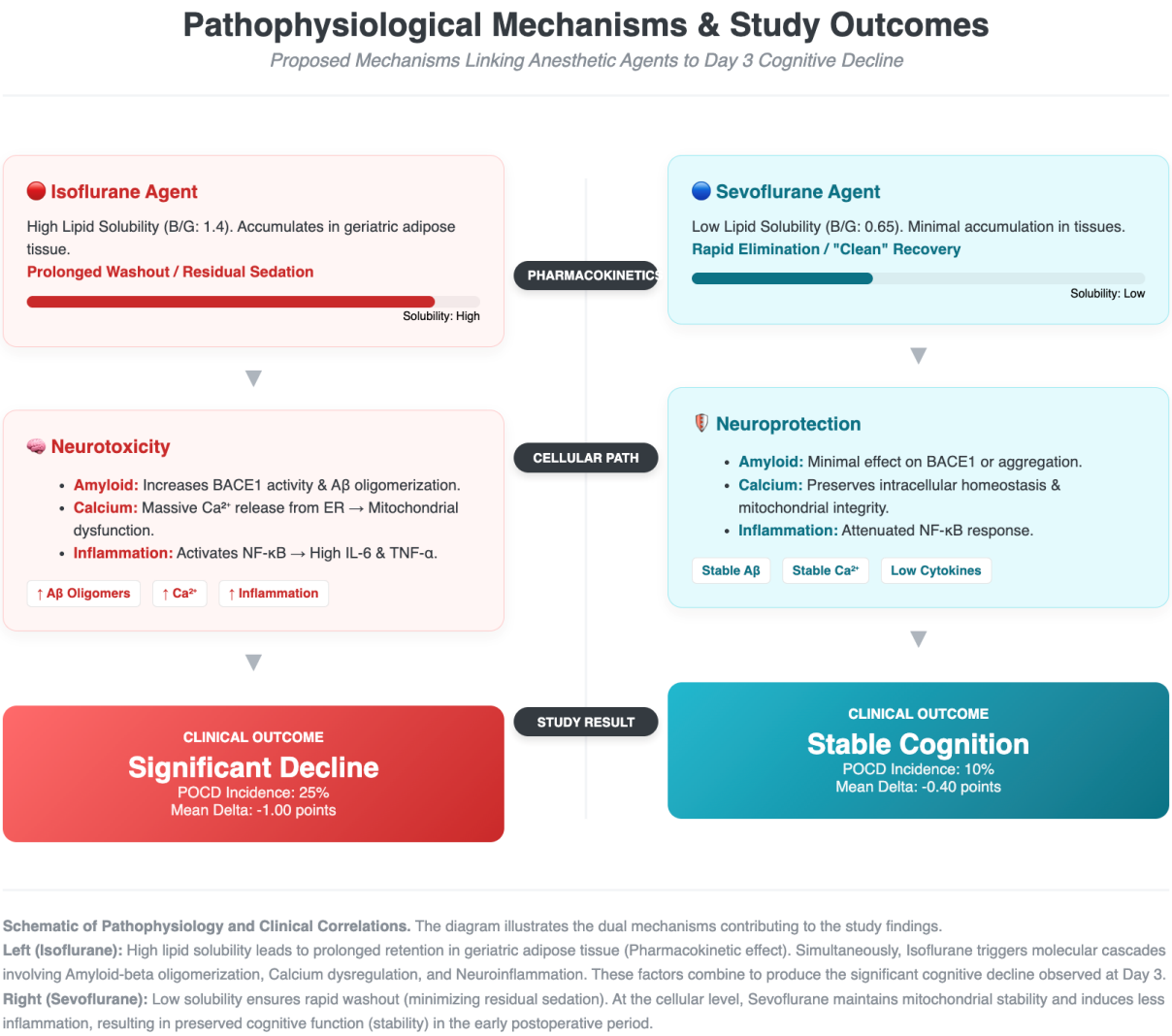


Figure 6. Pathophysiological mechanisms and study outcomes.

The divergent outcomes observed in our study can be deeply explained by the differential effects of these agents on amyloid pathology. The amyloid hypothesis posits that the accumulation of Amyloid-beta (Aβ) peptides leads to synaptic dysfunction and neuronal death. Preclinical studies utilizing nuclear magnetic resonance spectroscopy have demonstrated that Isoflurane, but notably less so Sevoflurane, interacts with the Aβ peptide to alter its conformation. Isoflurane has been shown to decrease the size of Aβ aggregates, effectively breaking down larger, less toxic plaques into smaller, highly soluble, and neurotoxic oligomers. These oligomers are potent inhibitors of Long-Term Potentiation (LTP), the cellular mechanism underlying memory formation.[15] Furthermore, Isoflurane has been implicated in upregulating the activity of beta-site amyloid precursor protein cleaving enzyme 1 (BACE1). BACE1 is the rate-limiting enzyme in the production of Aβ. By enhancing BACE1 activity, Isoflurane drives the amyloidogenic pathway, increasing the total load of Aβ in the brain.[16] In contrast, Sevoflurane, at equipotent clinical doses, has demonstrated a much weaker induction of BACE1 and Aβ oligomerization. This molecular disparity likely underpins the preserved cognitive scores observed in our Sevoflurane group, as their synaptic architecture

was spared from the acute oligomeric toxicity induced by Isoflurane.

Intracellular calcium homeostasis is fundamental to neuronal survival. Anesthetics can disrupt this balance by acting on ryanodine receptors (RyR) and Inositol 1,4,5-trisphosphate (IP3) receptors on the endoplasmic reticulum (ER). Isoflurane is a potent agonist of these receptors, causing a massive efflux of calcium from the ER into the cytosol. This cytosolic calcium overload triggers the opening of the Mitochondrial Permeability Transition Pore (mPTP).[17] The opening of the mPTP leads to mitochondrial swelling, loss of membrane potential, and the release of Cytochrome C into the cytoplasm. Cytochrome C release is the initiating step in the intrinsic apoptotic cascade, activating Caspase-9 and subsequently Caspase-3, the executioner enzyme that leads to programmed cell death. Our findings of greater cognitive decline in the Isoflurane group correlate with literature suggesting Isoflurane induces significantly higher levels of Caspase-3 activation in the hippocampus compared to Sevoflurane. Sevoflurane's milder effect on calcium release channels essentially preserves mitochondrial integrity, preventing the apoptotic cascade that results in the loss of neurons critical for memory and executive functions tested by the MoCA-INA.

While molecular theories regarding neurotoxicity are compelling, the timeline of our findings (Day 3) also points strongly toward pharmacokinetic mechanisms. Isoflurane has a blood-gas partition coefficient of 1.4, which is more than double that of Sevoflurane (0.65). This higher solubility indicates a greater affinity for fatty tissues.[18] Geriatric patients are physiologically characterized by an increased proportion of adipose tissue and reduced metabolic clearance rates (both hepatic and renal). During maintenance anesthesia, Isoflurane accumulates significantly in these lipid reservoirs. Upon cessation of anesthesia, the washout phase for Isoflurane is prolonged as the agent slowly leaches back from fat stores into the blood and subsequently the brain. It is highly plausible that the deficits observed at Day 3 in the Isoflurane group represent a pharmacological hangover or residual sedation. The lingering presence of sub-anesthetic concentrations of Isoflurane can subtly impair attention and executive function—domains heavily weighted in the MoCA-INA. Sevoflurane, with its rapid elimination profile due to low solubility, allows for a cleaner neurocognitive recovery, unmasking the patient's true baseline faster and resulting in higher postoperative scores.

The interplay between the anesthetic agent and the stress response involves neuroinflammation. Systemic inflammation from surgery can breach the blood-brain barrier, but the anesthetic agent can modulate the brain's intrinsic immune response.[19] Isoflurane has been shown to induce a robust pro-inflammatory response by activating the NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) pathway in microglia. Activation of NF-κB leads to the transcription and release of pro-inflammatory cytokines, specifically Interleukin-6 (IL-6), Tumor Necrosis Factor-alpha (TNF-α), and Interleukin-1β (IL-1β). Elevated levels of these cytokines in the hippocampus are directly neurotoxic and inhibit synaptic plasticity. Conversely, recent studies suggest Sevoflurane may attenuate part of this inflammatory response or induce it to a much lesser degree. The significantly higher incidence of POCD in the Isoflurane group (25%) may reflect an acute neuroinflammatory state that disrupts neural networks required for complex cognitive tasks assessed by the MoCA-INA.[20]

In repeated cognitive testing, a practice effect is expected—patients typically score higher on the second attempt because they are familiar with the test questions. In our Sevoflurane group, scores remained statistically stable (26.85 to 26.45), showing only a minimal numeric drop. In the context of the expected practice effect, this stability might actually mask a very mild decline (i.e., failure to improve as expected). However, in the Isoflurane group, scores dropped significantly despite the expected boost from the practice effect. This implies that the true magnitude of Isoflurane's deleterious effect might be even larger

than measured, as it had to overcome the natural tendency of patients to improve on re-testing. This study has limitations inherent to its design. Although groups were homogenous, the observational nature and consecutive sampling introduce potential selection bias compared to a randomized controlled trial. The sample size (n=40), while sufficient for the primary outcome, limits the power of detailed subgroup analyses. We did not measure serum biomarkers (S-100β or IL-6) or employ EEG monitoring (BIS) to control for depth of anesthesia, which are known independent predictors of cognitive decline. Finally, the assessment at Day 3 captures a mix of Early POCD, Postoperative Delirium, and residual sedation; long-term follow-up would be required to confirm permanent dysfunction.

5. Conclusion

This prospective comparative study provides evidence regarding the anesthetic management of geriatric patients in resource-limited settings. Patients receiving Isoflurane exhibited a statistically significant decline in cognitive scores and a higher incidence of POCD (25%) compared to those receiving Sevoflurane (10%). The Sevoflurane group maintained cognitive stability in the early postoperative period, with no statistically significant deterioration from baseline. Isoflurane appears to overwhelm cognitive reserves in younger geriatric patients (60-70 years), whereas Sevoflurane-associated decline was confined to the oldest patients (>70 years). Based on these findings, Sevoflurane should be considered the preferred volatile anesthetic agent for geriatric patients undergoing non-cardiac surgery to minimize the risk of early cognitive dysfunction and optimize neurocognitive recovery, particularly in settings where Desflurane is unavailable.

6. References

1. Liang L-Q, Jiao Y-Q, Guo S-L. Effects of sevoflurane inhalation anesthesia on cognitive and immune function in elderly patients after abdominal operation. Eur Rev Med Pharmacol Sci. 2018; 22(24): 8932–8.
2. Guo L, Lin F, Dai H, Du X, Yu M, Zhang J, et al. Impact of sevoflurane versus propofol anesthesia on post-operative cognitive dysfunction in elderly cancer patients: a double-blinded randomized controlled trial. Med Sci Monit. 2020; 26: e919293.
3. Yang L, Chen Z, Xiang D. Effects of intravenous anesthesia with sevoflurane combined with propofol on intraoperative hemodynamics, postoperative stress disorder and cognitive function in elderly patients undergoing laparoscopic surgery. Pak J Med Sci Q. 2022; 38(7): 1938–44.
4. Goettel N, Burkhart CS, Rossi A, Cabella BCT, Berres M, Monsch AU, et al. Associations between impaired cerebral blood flow autoregulation, cerebral oxygenation, and biomarkers of brain injury and postoperative cognitive dysfunction in elderly patients after major noncardiac surgery. Anesth Analg. 2017; 124(3): 934–42.
5. Geng Y-J, Wu Q-H, Zhang R-Q. Effect of propofol, sevoflurane, and isoflurane on postoperative cognitive dysfunction following laparoscopic cholecystectomy in elderly patients: a randomized controlled trial. J Clin Anesth. 2017; 38: 165–71.
6. Han Y, Han L, Dong M-M, Sun Q-C, Zhang Z-F, Ding K, et al. Preoperative salivary cortisol AM/PM ratio predicts early postoperative cognitive dysfunction after noncardiac surgery in elderly patients. Anesth Analg. 2019; 128(2): 349–57.
7. Langer T, Santini A, Zadek F, Chiodi M, Pugni P, Cordolcini V, et al. Intraoperative hypotension is not associated with postoperative cognitive dysfunction in elderly patients undergoing general anesthesia for surgery: results of a randomized controlled pilot trial. J Clin Anest. 2019; 52: 111–8.
8. Mao M, Gao D, Zhang L, Li B, Ji M, Yang J. Adverse postoperative outcomes in elderly

patients with preoperative cognitive impairment: a prospective cohort study. J Clin Anesth. 2020; 61(109588): 109588.

9. Tong C, Huang C, Wu J, Xu M, Cao H. The prevalence and impact of undiagnosed mild cognitive impairment in elderly patients undergoing thoracic surgery: a prospective cohort study. J Cardiothorac Vasc Anesth. 2020; 34(9): 2413–8.
10. Deng Y, Wang R, Li S, Zhu X, Wang T, Wu J, et al. Methylene blue reduces incidence of early postoperative cognitive disorders in elderly patients undergoing major non-cardiac surgery: An open-label randomized controlled clinical trial. J Clin Anesth. 2021; 68(110108): 110108.
11. Kang J, Zhu Z, Yuan Y, Li Y, Fang C, Yu Y, et al. Sedation efficacy of remimazolam besylate in elderly patients undergoing non-general anesthesia and effects on perioperative cognitive function: a clinical trial protocol. J Anesth Transl Med. 2022; 1(3): 6–10.
12. Mantovani L, Cimaglia P, Zannoni S, Tenti E, Sangiorgi D, Savini C, et al. A randomized comparison between two different CPB oxygenators in order to improve recovery from delirium and or cognitive decline in the elderly during cardiac surgery. J Cardiothorac Vasc Anesth. 2023; 37: 15–6.
13. Au E, Thangathurai G, Saripella A, Yan E, Englesakis M, Nagappa M, et al. Postoperative outcomes in elderly patients undergoing cardiac surgery with preoperative cognitive impairment: a systematic review and meta-analysis. Anesth Analg. 2023; 136(6): 1016–28.
14. Kılıç Y, Bilgeç MD, Sarıoğlan BT, Erdoğan Kayhan G, Güleç MS, Özer A. Impact of different regional anesthesia techniques on postoperative cognitive functions in geriatrics undergoing cataract surgery. ESMJ. 2021; 2(2): 111–7.
15. Ünal EA, Çömez MS, Demïrkiran H, Koyuncu O, Hakïmoğlu S, Urfali S. The effect of low-flow versus high-flow anesthesia on postoperative cognitive functions in geriatric patients undergoing TUR-P surgery. Turk Geriatri Derg. 2024; 27(1): 42–51.
16. Argun G, Has Selmi N, Sahin H. Effects of intraoperative body temperature, blood pressure, cerebral tissue oxygenation, and anesthesia type on postoperative cognitive functions in geriatric arthroplasty surgery for hip fracture. Jt Dis Relat Surg. 2024; 35(3): 662–73.
17. Hameed S, Bhatti AH, Feroz SH, Butt NT, Kenan Anwar khan, Cheema NI. Effects of Post-Operative Cognitive Dysfunction after spinal anesthesia between geriatric and middle-aged patients. Pak Armed Force Med J. 2024; 74(4): 1058–61.
18. Yao J, Gao Z, Qu W, Li J. Propofol total intravenous anesthesia vs. sevoflurane inhalation anesthesia: Effects on post-operative cognitive dysfunction and inflammation in geriatric patients undergoing laparoscopic surgery. Exp Ther Med. 2024; 28(3): 343.
19. Yu X, Zhang F, Shi J. Sevoflurane anesthesia impairs metabotropic glutamate receptor-dependent long-term depression and cognitive functions in senile mice. Geriatr Gerontol Int. 2019; 19(4): 357–62.
20. Fang J, Liang H, Chen M, Zhao Y, Wei L. Association of preoperative cognitive frailty with postoperative complications in older patients under general anesthesia: a prospective cohort study. BMC Geriatr. 2024; 24(1): 851.