

# Sevoflurane Versus Isoflurane for Postoperative Cognitive Dysfunction of Patients Undergoing Major Cardiac Surgeries: A Prospective Cohort Study

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## ABSTRACT

**Background:** Postoperative cognitive dysfunction is a complication associated with low quality of life in patients receiving major cardiac surgeries. Postoperative cognitive dysfunction due to inhaled anesthesia is not well established. The objective of the present study was to compare the incidence of postoperative cognitive dysfunction in patients undergoing major cardiac surgeries anesthetized with isoflurane or sevoflurane. **Materials and Methods:** The observational study conducted in a teaching hospital to compare the incidence of postoperative cognitive dysfunction as assessed by Mini-Mental State Examination (MMSE) in patients undergoing major cardiac surgery who received isoflurane or sevoflurane. MMSE was administered preoperatively (D0), postoperative day 1 (D1), postoperative day 3 (D3) and postoperative day 5 (D5) to assess cognitive performance. An MMSE score of < 24 or a difference greater than 3 as compared to preoperative score was considered as postoperative cognitive dysfunction. **Results:** A total of 254 patients (126 patients on isoflurane and 128 patients on sevoflurane) were included in the analysis. At D0, MMSE scores were not significantly different between patients who received sevoflurane and who received isoflurane ( $p=0.191$ ). The incidence of postoperative cognitive dysfunction was higher in the isoflurane group at all postoperative assessments compared to sevoflurane group ( $p<0.05$  for all). **Conclusion:** Sevoflurane has fewer chances of incidences of postoperative cognitive dysfunction than isoflurane.

**Key words:** Cardiac surgical procedures, Postoperative cognitive dysfunction, Isoflurane, Mini-Mental State Examination, Sevoflurane.

## INTRODUCTION

Postoperative cognitive dysfunction is cognitive impairment caused due to anesthesia after ambulatory or major surgery.<sup>1</sup> The incidence of postoperative cognitive dysfunction is up to 40 % in older adults.<sup>2</sup> This large difference in incidence rate is observed across studies due to the difference in study design, time point of postoperative cognitive dysfunction assessment,<sup>3</sup> type of surgeries,<sup>4</sup> type of anesthesia,<sup>5</sup> patient demographics,<sup>2</sup> apolipoprotein E4 status,<sup>6</sup> cerebral oxygenation<sup>7</sup> and the other clinical characters of patients. Although postoperative cognitive impairment is common in old adults, general anesthetic-induced postoperative cognitive dysfunction can also

occur in middle and younger-age.<sup>8</sup> Evidence showed that postoperative cognitive dysfunction causes both immediate and long-term burden on patients.<sup>4</sup> In cardiac surgical patients, early diagnosis and treatment might reduce the severity and duration of long-term postoperative cognitive dysfunction.<sup>7</sup>

Isoflurane<sup>8</sup> and sevoflurane<sup>1</sup> are two widely used general inhalation anesthetic agents used for induction and maintenance of general anesthesia. These anesthetic agents have low blood-gas partition coefficient, such that these agents allow rapid recovery than other

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commonly used volatile anesthetics.<sup>9</sup> Cell culture studies showed that concentrations of these fluorinated ethers can cause cytotoxicity to the brain due to the aggregation of amyloid peptides.<sup>10</sup> These agents can cause cognitive dysfunction due to residual effects that alter central nervous system activity.<sup>5</sup> Anesthetic agents with rapid recovery reduce the incidence of postoperative complications including delirium and respiratory distress.<sup>11</sup> In recent days, several studies are conducted and compared different anesthetic agents in terms of safety in the incidence of postoperative cognitive dysfunction in patients who took these agents but conflicting evidence exists on the safety of isoflurane and sevoflurane regarding postoperative cognitive dysfunction in patients undergoing major cardiac surgeries.<sup>1,9,12</sup> However, to date, there is no evidence exists to compare the safety of isoflurane against sevoflurane in the incidence of postoperative cognitive dysfunction in old adult patients undergoing cardiac surgery.

The objective of the present study was to compare the incidence of postoperative cognitive dysfunction in patients undergoing major cardiac surgeries anesthetized with isoflurane or sevoflurane.

## MATERIALS AND METHODS

### Ethical Consideration and Consent to Participate

The study was conducted after approval from the Wuhan Puren Hospital medical ethics committee. A standard institute protocol (WP/CL/4/12 dated 4 December 2012) was followed for anesthesia and which was similar in both the isoflurane and sevoflurane group. The study had adhered to the Declaration of Helsinki (V2008), the Strengthening the reporting of Observational Studies in Epidemiology (STROBE) statement and the law of China. A written informed consent form had been signed by all participants or patients' caretaker regarding, anesthesia, surgery, pathology and publication of the study in all formats of the publication including patients' personal data.

### Inclusion Criteria

Patients had undergone major cardiac surgery, not having any history of use of general anesthesia in the last 3 months (to prevent prior anesthesia effect), receive either sevoflurane or isoflurane and able to provide a response to Mini-Mental State Examination (MMSE) were included in the study.

### Exclusion Criteria

Patients who had MMSE score less than 24 at the time of preoperative MMSE evaluation and missing data for

MMSE at any time point of assessment were excluded from the analysis.

## Study Design

It was a single center prospective observational study conducted in a teaching hospital to compare the incidence of postoperative cognitive dysfunction as assessed by MMSE in patients undergoing major cardiac surgery and receive isoflurane or sevoflurane. The sample size was estimated based on the incidence of postoperative cognitive dysfunction. Based on the literature, the sample size was estimated by assuming the incidence of postoperative cognitive dysfunction in patients undergoing cardiac surgery and receive sevoflurane as an anesthetic agent was assumed to be 30%. According to a sample size calculation determined by proportions sample size, 120 elderly patients per group were required ( $\alpha$  at 0.05; power (1- $\beta$ ) at 80%) to detect a 50% reduction in both groups. The study enrolled 132 patients in each group considering a 10% possibility of dropouts in each group.<sup>9</sup>

## Cognitive Impairment Assessment

MMSE is one of the most commonly used composite measures to assess dementia in general and postoperative cognitive dysfunction in the literature as it is reliable, extensively validated and it takes only 5–10 min to administer. Therefore, practically to use repeatedly and routinely in clinical practice and research.

MMSE contains 11 questions testing five areas of cognitive function, including temporal and spatial orientation, registration, attention and calculation, recall and language. A person could get a maximum score of 30 where a score of 23 or lower indicates cognitive impairment.<sup>13</sup> A study investigator who was unaware of anesthetic agent that patient received, administered MMSE preoperatively (D0), postoperative day 1 (D1), postoperative day 3 (D3) and postoperative day 5 (D5) to assess cognitive performance. It was considered that there was a significant change in cognitive performance on MMSE if there was a decline in MMSE score by at least 4 or more at postoperative assessment compared to preoperative assessment or if MMSE score is less than 24.

## Data Collection

Following data was collected from either medical records of the patients and in case of lack of information in medical records, patients were interviewed by the study personnel (Investigator different from the person who administered MMSE). No additional diagnostic tests or imaging tests were ordered for further informa-

**Table 1: Demographic, Clinical and Social Characteristics of Patients.**

Characteristics Isoflurane		Group		Comparison between group
		Isoflurane	Sevoflurane	
Medical records of patients reviewed		126	128	<i>p</i> -value*
Ethnicity	Han Chinese	114(90)	119(93)	0.754
	Mongolian	11(9)	8(6)	
	Tibetan	1(1)	1(1)	
Age (years)	Minimum	64	64	0.534
	Maximum	89	89	
	Mean ± SD	73.45±6.12	72.98±5.98	
Gender	Male	84(67)	83(65)	0.792
	Female	42(33)	45(35)	
Body mass index (kg/m <sup>2</sup> )		24.52±2.11	24.89±2.05	0.158
Duration of anesthesia (min)		273±46	281±49	0.181
Education status	Primary	45(36)	40(31)	0.746
	Below graduate	66(52)	71(56)	
	More than graduate	15(12)	17(13)	
History of hypertension		17(13)	15(12)	0.709
History of diabetes		15(12)	18(14)	0.71
Length of hospital stay (days)		10±5	9±4	0.079

Continuous and categorical data are summarized as mean (Standard deviation) or median (Interquartile range, 25–75 %) and frequency (Percentage) respectively. Continuous and categorical data between two groups were compared using the Mann-Whitney U test and Fischer exact test respectively. A *p* < 0.05 was considered significant.

tion. Information regarding diagnostic test and imaging test results were noted in patient case record form.

### Statistical Analyses

Statistical analyses performed in R software version 3.3.3 (R-project, Vienna, Austria). Continuous and categorical data were summarized as mean (Standard deviation) or median (Interquartile range, 25–75 %) and frequency (Percentage) respectively. The incidence of postoperative cognitive dysfunction in each group at different time periods was represented as a percentage. Continuous and categorical data between two groups were compared using the Mann-Whitney *U* test and Fischer exact test respectively.<sup>9</sup> Multivariate logistic regression was performed to compare odds of incidence of postoperative cognitive dysfunction in patients receiving isoflurane compared to sevoflurane and expressed as Odds Ratios (OR) with 95 % confidence intervals (95 % CI). A *p*-value < 0.05 was considered statistically significant unless otherwise noted.<sup>14</sup>

## RESULTS

### Patient Characteristics

From 15 December 2012 to 1 January 2019, medical records of Wuhan Puren Hospital, China and the referring hospitals of 264 patients (132 patients who received

isoflurane and 132 patients who received sevoflurane) were reviewed. Three patients who received isoflurane and one patient who received sevoflurane were excluded as they had MMSE < 24 at D0 assessment. Three patients each in both the groups were excluded as these patients had not completed all postoperative MMSE assessments. A total of 254 patients (126 patients who received isoflurane and 128 patients who received sevoflurane) were included in the final analysis (Figure 1). Blood pressure and diabetes of patients were maintained before surgeries as per the guideline of the institute. No significant difference for demographic and clinical characteristics was observed between the two groups (*p*>0.05 for all, Table 1).

### Preoperative against Postoperative MMSE scores

At baseline (D0) MMSE scores were not significantly different between patients who received isoflurane and who received sevoflurane. In comparison to preoperative MMSE score, MMSE scores were reduced at D1, D3 and D5 in both the groups (*p*<0.05 for all). When MMSE scores were compared between isoflurane and sevoflurane group, MMSE scores were found to be significantly higher in the sevoflurane group than isoflurane group at all postoperative follow-up assessments (D1, D3 and D5, *p*<0.05 for all, Table 2).

### The Incidence of Postoperative Cognitive Dysfunction

The incidence of postoperative cognitive dysfunction (Defined as the change in MMSE score of > 3 at postoperative assessment regarding preoperative assessment or MMSE score < 24) depended upon age, gender, education status, baseline MMSE score, history of hypertension and/or diabetes and length of hospital stay.

#### Postoperative Cognitive Dysfunction defined as MMSE Score < 24

At all postoperative assessment periods, patients in the isoflurane group had significantly higher incidence of postoperative cognitive dysfunction (D1 (66 % vs. 48 %, p=0.015), D3 (49 % vs. 27 %, p=0.002) and D5 (36 % vs. 18 %, p=0.007), Figure 2).

#### Postoperative Cognitive Dysfunction defined as change in MMSE Score of > 3 at Postoperative Assessment

At all postoperative assessment periods, patients in the isoflurane group had a significantly higher incidence of postoperative cognitive dysfunction (D1 (100 % vs. 92%, p = 0.007), D3 (66 % vs. 45 %, p = 0.004) and D5 (53 % vs. 24 %, p < 0.0001), Figure 3).

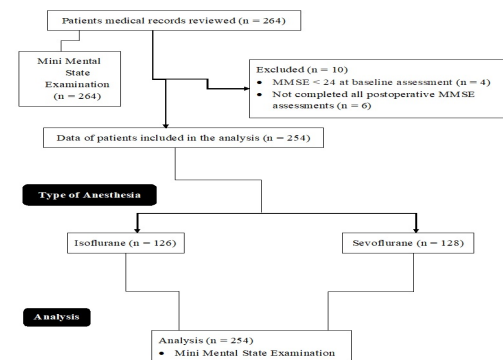


Figure 1: Flow Diagram of the Study.

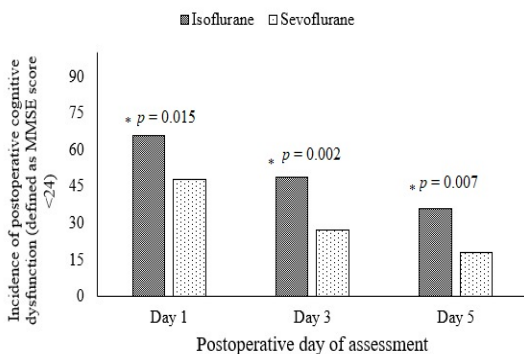


Figure 2: Incidence of Postoperative Cognitive Dysfunction (Defined as Mini Mental State Examination score < 24). \*Significantly higher incidence of postoperative cognitive dysfunction than sevoflurane.

Assessment day	Group	Group		Comparison between group
		Isoflurane	Sevoflurane	
Medical records of patients reviewed		126	128	p-value
D0		28.22±1.27	28.42±1.16	0.191
D1	Value	22.11±2.12	23.39±2.31*	<0.0001
	**p value	<0.0001	<0.0001	N/A
D3	Value	23.87±3.21	25.25±2.64*	<0.001
	**p value	<0.0001	<0.0001	N/A
D5	Value	24.51±2.64	26.46±2.71*	<0.001
	**p value	<0.0001	<0.0001	N/A

Data were summarized as mean ± standard deviation. Mann-Whitney U test was used for statistical analysis. \*\*Comparison respect to Do. A p < 0.05 was considered significant. \*Significantly higher compared to isoflurane group. N/A: Not applicable. Do: Preoperatively, D1: Postoperative day 1, D3: Postoperative day 3, D5: Postoperative day 5.

### Comparison of Risk of Postoperative Cognitive Dysfunction

Multivariate-adjusted logistic regression analysis showed that patients in the isoflurane group had significantly higher incidences of postoperative cognitive dysfunction compared to sevoflurane group at D1 (OR, 2.27 (95 % CI, 1.94–2.65)), D3 (OR, 1.55 (95 % CI, 1.40–1.72)) and D5 (OR, 1.72 (95 % CI, 1.64–1.83)) levels (Table 3).

### DISCUSSION

Patients undergoing general anesthesia during cardiac surgery reported postoperative cognitive dysfunction during the follow-up period. Studies showed that postoperative cognitive dysfunction was found to be prevalent in patients who received general anesthesia.<sup>1,9,12</sup> A prospective study showed that the risk of postoperative cognitive dysfunction was higher in older patients compared to younger patients undergoing general anesthesia.<sup>14</sup> General anesthesia involved in modern cardiac surgery found to have several adverse effects like delirium, respiratory depression and others that in conjunction with cognitive impairments cause short term and long-term effects on patients hampering the quality of life causing significant morbidity and mortality.<sup>4</sup> From past one and half decades, several *in vitro* studies in animals and observational and interventional studies in human beings are performed to assess the safety of general anesthesia in various surgical procedures. Different research groups proposed several mechanisms across the globe. These mechanisms include cytotoxicity in the brain due to a disturbance in calcium homeo-

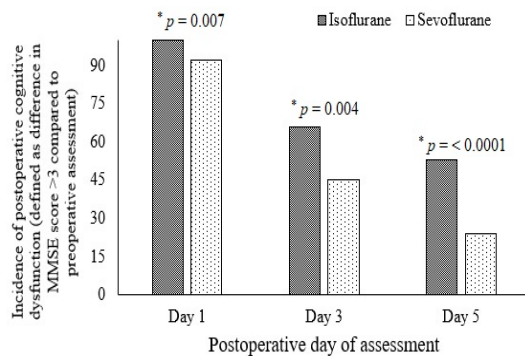


**Table 3: Odds of Postoperative Cognitive Dysfunction (Defined as Mini-Mental State Examination score < 24) in the isoflurane group versus sevoflurane group at different time points.**

Time point	Odds ratio (95% CI) of isoflurane versus sevoflurane*	p value#
D1	2.27 (1.94–2.65)	<0.0001
D3	1.55 (1.40–1.72)	0.0005
D5	1.72 (1.64–1.83)	0.001

\*At all time points, odds for sevoflurane group was 1.

#Model was adjusted for factors including age, gender, education status, baseline MMSE score, history of hypertension and diabetes and length of hospital stay (in days).



**Figure 3: Incidence of Postoperative Cognitive Dysfunction (defined as difference in Mini Mental State Examination score > 3 compared to preoperative assessment). \*Significantly higher incidence of postoperative cognitive dysfunction than sevoflurane.**

stasis and inflammation, anesthesia induced increased age-related suppression of neuronal stem cells and endogenous neurodegenerative processes.<sup>15,16</sup> Despite existing literature, the mechanism of postoperative cognitive dysfunction due to general anesthesia is not well established.

Patients who received sevoflurane found to have a lower incidence of postoperative cognitive dysfunction at all postoperative follow-up MMSE assessments (at postoperative day 1, day 3 and day 5) than patients who received isoflurane anesthesia during cardiac surgery. The studies suggest that apart from the patient characteristics, the incidence of postoperative cognitive dysfunction also depends on the type of general anesthesia that the patient receives.<sup>1,9,12</sup> Results of the present study were in line with randomized controlled clinical trial compared incidence of postoperative cognitive dysfunction in patients receiving propofol, sevoflurane and isoflurane in elderly patients undergoing laparoscopic cholecystectomy and reported that sevoflurane is safer than isoflurane in term of lower incidence of postoperative cognitive dysfunction.<sup>5</sup> Present study results were also backed by mechanistic studies which reported that sevo-

flurane is a less soluble agent than isoflurane. Therefore, sevoflurane enters and leaves the body more rapidly than isoflurane.<sup>17,18</sup> Isoflurane inhaled anesthesia could have effects on the mechanical activity of patients after operation.

The present study has certain limitations, for examples, patients were recruited from a single specialized hospital. Therefore, the results might not be generalizable. Although the study personnel who administered the MMSE was blinded to the anesthesia group, study personnel who collected and analyzed the data were not blinded. Therefore, the chances of bias were possible. Another limitation was the short postoperative MMSE assessment period (Last MMSE assessment at 5 days after surgery).

## CONCLUSION

Sevoflurane is safer than isoflurane in terms of causing a lesser incidence of postoperative cognitive dysfunction in patients undergoing general anesthesia.

## ACKNOWLEDGEMENT

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## CONFLICT OF INTEREST

Authors declare that they have no conflict of interest or any the other competitive interest regarding results and/or discussion reported in the research.

## ABBREVIATIONS

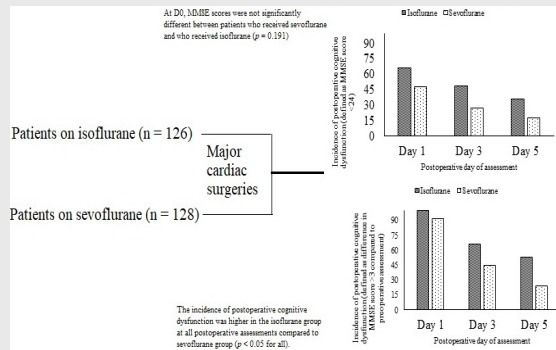
**STROBE:** The strengthening the reporting of observational studies in epidemiology; **MMSE:** Mini-Mental State Examination; **D0:** Preoperatively; **D1:** Postoperative day 1; **D3:** Postoperative day 3; **D5:** Postoperative day 5.

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### PICTORIAL ABSTRACT



### SUMMARY

Postoperative cognitive dysfunction is a major issue related to a low quality of life in patients receiving major cardiac surgeries. Isoflurane or sevoflurane was injected to the patients undergoing major cardiac surgery. Mini-Mental State Examination was administered preoperatively, postoperative day 1, postoperative day 3 and postoperative day 5 to assess cognitive performance. The incidence of postoperative cognitive dysfunction was higher in the patients who received isoflurane at all postoperative assessments compared to patients who received sevoflurane. Isoflurane inhaled anesthesia could have effects on the mechanical activity of patients after operation.

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