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Original Article

Anaesthesia Section

Effects of Isoflurane versus Propofol for Postoperative Neurocognitive Recovery in Patients Undergoing Surgery under General Anaesthesia: A Randomised Clinical Study

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ABSTRACT

Introduction: Propofol and isoflurane are commonly used in general anaesthesia. Both the drugs are neither neuroprotective nor neurotoxic. In clinical settings, inhaled anaesthetics like isoflurane are frequently used. But, it has been claimed that isoflurane anaesthesia would be a factor inducing cognitive impairment. Propofol is metabolised quickly, primarily in the liver, and its by products are inert. After the initial dose, the half-life of propofol is 2 to 8 minutes, and even with prolonged infusions, propofol promotes quick recovery.

Aim: To evaluate the effects of propofol and isoflurane on postoperative recovery patterns in patients receiving general anaesthesia and to determine how they affect cognitive function and memory.

Materials and Methods: A double-blinded randomised clinical study was conducted at the Department of Anaesthesia, RL Jalappa Hospital and Research Centre, Tamaka, Kolar, Karnataka, India, during the period from January 2022 to March 2022. In the present study, 60 patients of between age 50-90 years were included. Patients were split into two groups: group A received an intravenous infusion of propofol, and group B received isoflurane. Patients in both groups had their cognitive ability and memory tested before surgery. In the present study, baseline Mean Atrial Pressure (MAP), Heart Rate (HR), Pulse Oximetry (SpO_2) and Ramsay Sedation score were comparable in both groups. The novel variables, such as surgery types, duration, and medications were evaluated in both groups. Mini Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) were assessed one hour before and four hours after surgery. Comparison of a continuous variable across the groups was performed using the Student's t-test or Mann-Whitney U test, depending on the normality of the distribution. A comparison of categorical variables across the two study groups was made using the Chi-square test. A p-value of <0.05 was considered statistically significant.

Results: Age group of 50-60 years were more in both group A (66.7%), and group B (70%). In Group A, most participants were females (56.7%), and in group B, majority were males (60%). In group A, the postoperative assessment showed a mean MoCA score of 25.6±1.52; in group B postoperative assessment showed a mean MoCA score of 24.17±1.46 with a p-value of 0.001, which was statistically significant. The postoperative assessment showed a mean MMSE score of 26.3±1.58 in group A and in group B, the postoperative assessment showed a mean MMSE score of 24.9±1.4 with a p-value of 0.001, which was statistically significant.

Conclusion: The current results imply that postoperative delirium is more frequently present after isoflurane anaesthesia than after propofol anaesthesia.

Keywords: Cognitive assessment, Postoperative cognitive dysfunction, Postop recovery, Ramsay sedation score

INTRODUCTION

An important pathologic factor in postoperative cognitive impairment is neuroinflammation. Since, it is linked to negative outcomes, delayed neurocognitive recovery following surgery has become a prevalent worry. It is linked to a longer hospital stay, higher mortality, and higher healthcare costs [1]. By acting on different receptors in the brain, anaesthetics such as propofol, isoflurane, nitrous oxide, midazolam, and fentanyl contributed to the development of postoperative cognitive impairment [2]. Patients with Postoperative Cognitive Dysfunction (POCD) will have deficits in their ability to focus, pay attention, visuospatial ability, process information, and remember.

The first time Bedford mentioned POCD was in 1955, and he stated that "some of the elderly patients who were exposed to surgeries under general anaesthesia "never the same" afterwards" [3]. Although the exact cause of the isoflurane-induced cognitive impairment has not been determined, a growing body of research has supported the idea that cognitive impairment following surgeries and general anaesthesia is caused by overexpression of proinflammatory cytokines like Tumour Necrosis Factor (TNF) and Interleukin (IL)-1 [4]. The cognitive impairment brought on by isoflurane is probably a result of increased expression of inflammatory cytokines and decreased neuronal density in the hippocampus [5]. Oxidative stress-induced neuron cell death, may also play a role in the pathogenesis of POCD and the activated inflammatory response [6]. Anaesthesia and surgical trauma are considered major oxidative stressors which result in the development of POCD [7].

After the release of propofol in the late 1980s intravenous anaesthesia is being widely utilised [8]. The injectable anaesthetic medication propofol is short-acting and is used to induce anaesthesia, sedate patients, and maintain anaesthesia. When propofol binds to the α-subunit of the Gamma-aminobutyric acid (GABA) receptor, it increases the GABA-induced chloride current, which is the primary mechanism by which it exerts its hypnotic effects. Hepatic metabolism of propofol is fast and its end products are inactive. With the starting dose propofol has a half-life of 2-8 minutes, even fast recovery is noticed with continuous infusions [9].

Dr. Ziad Nasreddine created the MoCA in Montreal, Canada, in 1995 to help medical professionals identify Mild Cognitive Impairment (MCI). The evaluation is a 30-point test that can be completed in 10

minutes. Normal range is considered to be 26 or higher. The MoCA evaluates various cognitive areas. These include executive (visual-spatial), naming, memory, attention, language, abstraction, delayed recall, and orientation (to time and place) [10]. Previous studies have considered MMSE for screening postoperative neurocognitive dysfunction [6,9]. Still, MoCA meets the criteria of screening tests in detecting cognitive impairment for patients aged 60 years and above than the MMSE [10].

In the present study, the incidence of delayed neurocognitive recovery in patients undergoing elective surgeries under general anaesthesia, which compared the effects of propofol and isoflurane. The primary objectives were to compare the effects of propofol vs isoflurane on the incidence of delayed neurocognitive recovery in patients undergoing elective surgeries under general anaesthesia. The secondary objectives were to monitor sedation scores, saturation till four hours postoperatively and haemodynamic status intraoperatively.

MATERIALS AND METHODS

A double-blinded randomised clinical study was conducted on patients undergoing surgery under general anaesthesia at the Department of Anaesthesia, RL Jalappa Hospital and Research Centre, Tamaka, Kolar, Karnataka, India, from January 2022 to March 2022. Institutional Ethical Committee (IEC) was approved no. SDUMC/KLR/IEC/573/2021-23.

Sample size calculation: Pandya MJ et al., reported the mean (SD) of the MMSE in the isoflurane group to be 27.65 (1.8) and in the propofol group to be 25.83 (1.82) [6].

Assuming an alpha error of 1% (99% Confidence limit),

Power of 90%, ratio of isoflurane: propofol group=1:1

The required sample size to identify the difference in the MMSE scores at 30 minutes was calculated to be 30 in each group, and a total sample size of 60 was included in the study.

Computerised random sampling was used to select the subjects. The sample size was derived from the following formula:

$$\text{Sample size (n)} = \frac{2S_p^2\,[Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}]^2}{\mu_d^2}; \quad S_p^2 = \frac{S_1^2 + S_2^2}{2}$$

Where, S_1: Standard deviation in the first group

S_2: Standard deviation in the second group

μ_d: Mean difference between the samples

α: Significance level

1-β: Power

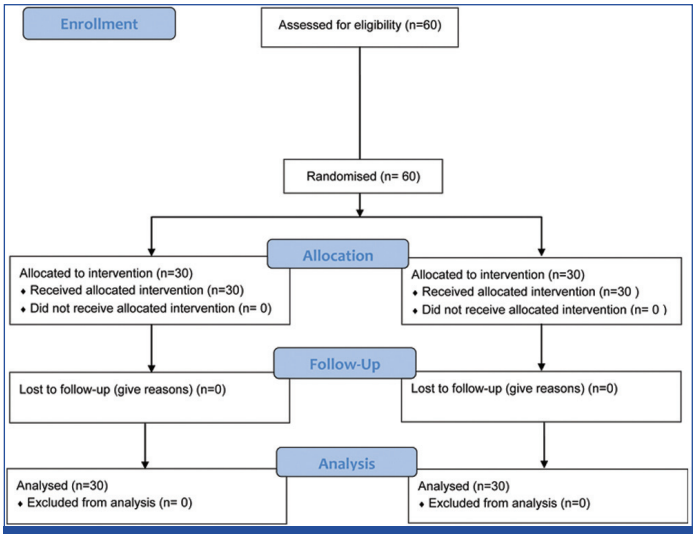
Inclusion criteria: Patients who fulfilled the following criteria were included in the study:

- Age ≥50 years and ≤90 years
- Surgery ≥2 hours to 4 hours
- American Society of Anesthesiologists (ASA) I and II

Exclusion criteria: Patients with the following medical conditions were excluded from the study:

- Preoperative history of schizophrenia, epilepsy, Parkinsonism, and myasthenia gravis.
- Communication difficulties before surgery due to coma, severe dementia, and language barriers. Patients taking antianxiety, anticonvulsant, and antipsychotic medications together.
- Critical illness (ASA III and IV), hepatic or renal dysfunction.
- Neurosurgery.
- Blind people.
- MMSE score <23 and MoCA score <24
- Surgery of more than 4 hours

Consolidated Standards of Reporting Trials (CONSORT) flowchart is shown in [Table/Fig-1].



[Table/Fig-1]: CONSORT flowchart.

Study Procedure

A thorough preoperative evaluation, general and systemic examination, and routine investigations were done. After the previous midnight of surgery, all the patients were kept nil by mouth. Informed consent was taken from the patients before the surgery. Cognitive functions were assessed one hour preoperatively using MMSE and MoCA [10,11].

In the operating room, baseline HR, Non Invasive Blood Pressure (NIBP) and SPO_2 were recorded in all patients. (As a part of routine investigations these tests were done, they were not specific for the aim and objective). All patients were given an injection of glycopyrrolate 0.005 mg/kg via the intravenous (i.v.) route. Injection fentanyl 2 µg/ kg i.v. was given to all patients before induction. In both groups, induction was done with the injection of propofol 2 mg/kg of body weight until initial loss of verbal contact. After checking for ventilation, injection vecuronium 0.08-0.1 mg/kg i.v. was administered. Endotracheal intubation was done after three minutess of intermittent positive pressure ventilation with an appropriate-sized cuffed endotracheal tube. Through computerised randomised sampling, the patients were allotted to one of the study groups (group A and group B).

In group A, patients were maintained on N_2O/O_2(60/40%) and propofol infusion at the rate of 50-100 µg/kg/min titrated to maintain adequate depth of anaesthesia. In group B, patients were maintained on N_2O/O_2 (60/40%) and isoflurane 0.2-1% to achieve adequate depth of anaesthesia. Depth of anaesthesia was monitored with Minimum Alveolar Concentration (MAC). In addition, 25-100 µg of fentanyl was given when the Mean Arterial Pressure (MAP) and HR are 20% higher than baseline.

At the end of the surgery, all patients received an injection of Paracetamol 1 gm i.v.. After confirming last suture from surgeons' anaesthetic agents were stopped and patients were administered with six litres of O_2 per minute. Injection of neostigmine 0.05 mg/kg i.v. and injection of glycopyrrolate 0.01 mg/kg i.v. was used to reverse neuromuscular blockade. Extubation was done after the return of spontaneous breathing and adequate motor recovery.

All patients were monitored intraoperatively for hemodynamic changes and documented. The Post Anaesthesia Care Unit (PACU) kept all patients under observation. The sedation score was assessed by using Ramsay sedation score after four hours [8]. Any drop in saturation was assessed for four hours and, if any drop in saturation was noted patients were supplemented with oxygen. Cognitive functions were reassessed after four hours postoperatively by MMSE and MoCA. In MMSE, a score less than 24 indicate MCI and a score less than 17 indicate severe cognitive impairment. In MoCA, a score of less than 25 indicate cognitive impairment.

STATISTICAL ANALYSIS

Data was entered using Microsoft Excel and analysed using the "Statistical Package for Social Science (SPSS)" standard version

20. All socio-demographic and clinical characteristics of the patient was summarised using Mean (SD) for continuous variables and proportions (%) for categorical variables. A constant variable (HR, O_2 saturation, MAP, MMSE score, MoCA score) across the groups (isoflurane vs propofol) was compared using the Student's t-test or Mann-Whitney U test depending on the normality of the distribution. Comparison of categorical variables across the two study groups was made using the Chi-square test. A p-value of <0.05 was considered statistically significant.

RESULTS

In group A, most participants were females (56.7%), and the rest were males (43.3%). Similarly, in group B, most participants were males (60%) compared to females (40%). There was no statistically significant difference found between two groups, with respect to age and with gender [Table/Fig-2].

Age (in years)	Group A	Group B	p-value
50-60	20 (66.7%)	21 (70%)	0.906
61-70	7 (23.3%)	5 (16.7%)	
71-80	2 (6.7%)	3 (10%)	
>80	1 (3.3%)	1 (3.3%)	
Mean age (in years)	60+8.19	59+8.61	0.748
Females	17 (56.7%)	12 (40%)	0.196
Male	13 (43.3%)	18 (60%)	

[Table/Fig-2]: Distribution of subjects according to sex.

In group A, most participants underwent Functional Endoscopic Sinus Surgery (FESS) (29%), and in group B, most participants underwent spinal fusion with implant (13.8%) [Table/Fig-3].

Surgery	Group A	Group B	p-value
FESS	9 (29%)	3 (10.3%)	0.106
Spinal fusion with implant	2 (6.5%)	4 (13.8%)	0.670
Cortical mastoidectomy plus tympanoplasty	2 (6.5%)	3 (10.3%)	1.000
L3-L5 discectomy with fusion	1 (3.2%)	1 (3.4%)	1.000
L3-L5 decompression plus spinal implant fixation	0	2 (6.9%)	0.491
L4-L5 discectomy with fusion	0	2 (6.9%)	0.491
L4-L5 laminectomy and discectomy	2 (6.5%)	0	0.491
Laparoscopic cholecystectomy	1 (3.2%)	1 (3.4%)	1.000
Left cortical mastoidectomy plus tympanoplasty	0	2 (6.9%)	0.491
Modified radical mastoidectomy	2 (6.5%)	0	0.491
Hemi arthroplasty of left shoulder plus long pfn fixation for left femur	1 (3.2%)	0	1.000
L1 -L3 Laminectomy with foraminotomy with decompression	1 (3.2%)	0	1.000
L2- L4 Decompression with fusion	1 (3.2%)	0	1.000
L4-S1 Decompression with fusion	0	1 (3.4%)	1.000
L4- L5 Decompression with fusion	0	1 (3.4%)	1.000
L4-L5 Fusion with implant	1 (3.2%)	0	1.000
L4-L5 Laminectomy and discectomy with fusion	0	1 (3.4%)	1.000
L4-L5 Microscopic discectomy	0	1 (3.4%)	1.000
L4-L5 Spinal fusion with implant	0	1 (3.4%)	1.000
Left Hemi thyroidectomy	0	1 (3.4%)	1.000
Left mastoid exploration plus aural polypectomy	0	1 (3.4%)	1.000
Left PCNL plus right URSL plus bilateral DJ stenting	0	1 (3.4%)	1.000
Open renal CYST deroofing	1 (3.2%)	0	1.000
ORIF plus LCP fixation for left clavicle	1 (3.2%)	0	1.000
ORIF plus LCP fixation for right clavicle	1 (3.2%)	0	1.000
ORIF plus philos plating for right humerus-CRIF plus K-wire fixation for right radius fracture	0	1 (3.4%)	1.000
Partial nephrectomy of right kidney	1 (3.2%)	0	1.000
Right PCNL plus left URSL plus bilateral DJ stenting	1 (3.2%)	0	1.000
Right revision mastoid exploration	0	1 (3.4%)	1.000
Split skin grafting for right forearm	0	1 (3.4%)	1.000

[Table/Fig-3]: Intergroup comparison of the type of surgeries.
FESS: Functional endoscopic sinus surgery; L: lumbar; PFN: Proximal femoral nailing; PCNL: Percutaneous nephrolithotomy; URSL: Ureteroscopic lithotripsy; DJ: Double J; ORIF: Open reduction and internal fixation; LCP: Locking compression plate; CRIF: Closed reduction and internal fixation; K-wire: Kirschner wire; %: Percentage

Duration of Surgery (minutes)

Mean duration of surgery was similar in both the groups and the mean difference was non significant [Table/Fig-4].

Duration of surgery (minutes)	Group A	Group B	p-value
130-150	2 (6.7%)	4 (13.3%)	
151-200	22 (73.3%)	13 (43.3%)	0.062
>200	6 (20%)	13 (43.3%)	
Mean±SD	188.33±22.75	194.33±31.47	0.401

[Table/Fig-4]: Intergroup comparison of duration of surgery.
Values were expressed as frequency and percentage, mean and SD; the p-value was by student t-test. A p-value less than 0.05 was considered to be statistically significant

The two study groups did not show a significant difference in mean HRs at each interval [Table/Fig-5].

Heart rate in beats per minute	Group A	Group B	p-value
0 min	79.9±7.66	79.33±7.13	0.768
30 min	79.77±7.79	79.43±5.96	0.853
60 min	79.3±6.76	78.33±6.71	0.580
90 min	78.17±6.57	79.53±8.28	0.482
120 min	78.7±5.93	79.03±7.54	0.850
150 min	77.93±5.16	78±6.67	0.966
180 min	78.63±4.74	79.42±7.17	0.654
210 min	78.67±3.33	78.31±5.31	0.882

[Table/Fig-5]: Intergroup comparison of Heart Rate (HR).
Values were expressed as mean and SD; a p-value was by student t-test. A p-value less than 0.05 was considered to be statistically significant

The two study groups did not show a significant difference in MAP at each interval [Table/Fig-6].

Mean arterial pressure (MAP)	Group A	Group B	p-value
0 min	81.9±5.88	80.5±5.43	0.342
30 min	80.9±7.15	79.5±6.57	0.433
60 min	79.4±6.36	81.53±5.42	0.167
90 min	80.93±4.93	81.27±5.64	0.808
120 min	81.07±4.67	81.17±4.18	0.931
150 min	80±5.15	81.56±3.82	0.208
180 min	80.33±4.46	81.52±3.8	0.332
210 min	79.5±4.51	80.46±3.93	0.641

[Table/Fig-6]: Intergroup comparison of Mean Arterial Pressure (MAP).
Values were expressed as mean and SD; a p-value was by student t-test. A p-value less than 0.05 was considered to be statistically significant

The two study groups did not show a significant difference in SpO_2 at each interval and SPO_2 is 100±0 in both groups A and B. The association between group A, and B regarding Ramsay sedation score was non significant [Table/Fig-7]. Both MMSE and MoCA Score was reduced more in group B when compared with group A. Statistically significant difference was found between group A and group B with respect to MMSE and MoCA Score [Table/Fig-8]. On intragroup analysis within group, both groups had statistically significant difference between preoperative assessment and postoperative assessment with respect to MMSE and MoCA Score [Table/Fig-8].

Ramsay sedation score	Group A	Group B	p-value
1	14 (46.7%)	11 (36.7%)	0.432
2	16 (53.3%)	19 (63.3%)	
Total	30 (50%)	30 (50%)	

[Table/Fig-7]: Intergroup comparison of Ramsay sedation score.
Values are expressed as frequencies and percentages

Variables	Assessment	Group A Mean±SD	Group B Mean±SD	p-value
Mini-Mental State Examination (MMSE)	Preoperative assessment	27.6±1.13	27.2±1.19	0.187
	Postoperative assessment	26.3±1.58	24.9±1.4	<0.001**
	p-value	<0.001**	<0.001**	
Montreal Cognitive Assessment (MoCA) Score	Preoperative assessment	26.37±1.27	26.13±1.25	0.477
	Postoperative assessment	25.6±1.52	24.17±1.46	<0.001**
	p-value	<0.001**	<0.001**	

[Table/Fig-8]: Intergroup comparison of Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) score.
**=highly significant, SD=Standard deviation
Values are expressed as mean and SD; a p-value is by student t-test. A p-value less than 0.05 is considered to be statistically significant

DISCUSSION

An impairment of working memory, attention, cognitive flexibility, long-term memory, and information processing is a sign of postoperative neurocognitive dysfunction. Postoperative cognitive impairment is still a reasonably common consequence in surgical patients, despite technical advancement in anaesthesia and surgery over the past few decades [7].The MMSE is a popular dementia screening tool for evaluating mental function. However, reports claim that its inability to identify complex cognitive deficits rendered it ineffective at identifying MCI. Because it contains more difficult items like memory recall and executive function than the MMSE, the MoCA was developed to detect MCI in patients. When looking for patients with cognitive impairment, who are at a higher risk for dementia, the MoCA is a better alternative than the MMSE [12].

In the present study, in group A, most participants were females (56.7%), and in group B, most participants were males (60%). There was no statistically significant difference found between two groups with respect to age and with gender. The mean age difference in between two groups is not statistically significant. Mean age in group A is 60±8.19 years and in group B is 59±8.61 years which was similar to study done by Zhang Y et al., in which mean age is 72.8±5.5 years in propofol group A and 72.4±5.6 years in Sevoflurane group [2]. Similarly in study done by Guo L et al., mean age is 69.0 years in all groups which did not show any statistical difference [9]. While most of the previous studies were done on elderly patients undergoing surgery, however, very few studies have been done in relatively younger age groups like the one by Goswami U et al., and Shrivastav P et al., [11,13].

In the current study, mean duration of surgery did not show any statistical difference which when compared to studies done by Guo L et al., (p-value=0.903) and Goswami U et al., (p=0.788) which did not show any difference statistically [9,11]. In the current study settings, the two groups did not show a significant difference in MAP and HR at each interval. Similarly, according to Pandya MJ et al., Guo L et al., Bindra TK., found no significant difference in MAP and HR in their studies [6,9,14]. Ramsay Sedation score did not show any significant difference in both groups. This was not comparable with other studies.

In the current study, preoperative assessment of mean MMSE score in both groups did not show any statistical significance (p-value=0.187), while the mean MMSE score postoperatively after four hours was significant statistically (p-value <0.001). In a study done by Shrivastav P et al., the preoperative mean MMSE score in Sevoflurane group was 26.7±1.17 and propofol group was 26.17±1.46 and this mean difference was statistically non significant. After 30 minutes of extubation, mean MMSE score in sevoflurane group was 19.43±2.27 and in propofol group was 17.10±2.23 and this mean difference was statistically significant. Few other studies, like the one by Pandya MJ et al., also used MMSE score for assessing cognitive functions along with other tests like California Verbal Learning Test (CVLT), Digit Span Test (DST), Rivermead Behavioural Memory Test (RBMT). Postoperative assessment was done at five minutes, 30 minutes followed by every hour till four hours. MMSE score showed statistical significance (p<0.001) till 30 minutes postoperatively and after 30 minutes, there was no cognitive impairment. Both the studies stated that Sevoflurane had less impact on cognitive function as compared to propofol upto 30 minutes postoperatively. Similarly in the present study, MMSE score was used to assess cognition along with MoCA but isoflurane was used as inhalational anaesthetic which was not similar to other studies. Both groups in present study showed cognitive impairment postoperatively but propofol based anaesthesia has shown better cognition compared to isoflurane based anaesthesia [6,13].

In the present study, preoperative assessment of mean MoCA score between both the groups was not significant whereas mean MoCA score postoperatively after 4 hours was statistically significant (p<0.001). Similarly in a study conducted by Sahoo AK et al., they performed numerous neuropsychological tests such as MoCA, Hopkin's verbal learning test, digit span test, controlled oral word association test, and inflammatory biomarkers such as S-100, IL-6, and TNF, which improved slightly on the fourth day of surgery, but were not statistically significant (p>0.5). Scores improved significantly when compared to baseline (p>0.5) in all three groups that received either sevoflurane, desflurane, or propofol in the delayed postoperative period, which was three months after surgery. They have concluded that there is no effect of anaesthetic agents on cognitive functions postoperatively in young and middle-aged persons. Similarly in a study by Qiao Y et al., both MMSE score and MoCA were used to assess cognitive dysfunction postoperatively and concluded that Sevoflurane plus Methylprednisolone showed better cognitive function postoperatively compared to Sevoflurane or propofol alone [15,16]. Similar studies by Geng YJ et al., and Zhang Y et al., have shown that incidence of delayed neurocognitive recovery is significantly lower in propofol based anaesthesia compared to sevoflurane-based anaesthesia. Both isoflurane and propofol based anaesthesia showed cognitive impairment postoperatively but propofol based anaesthesia had shown better cognition than isoflurane in present study results [2,17].

Limitation(s)

The practice effect on cognitive scores was another crucial factor that must be taken seriously. For patients to focus and cooperate during the test, which was not always possible, cognitive tests should be conducted in a serene and quiet environment.

CONCLUSION(S)

The study showed there was a significant difference between preoperative and postoperative evaluation of mean MMSE and MoCA score. As per the present study, both propofol and isoflurane groups produced cognitive dysfunction, but propofol is better when compared to isoflurane. The current results imply that postoperative delirium is more frequently and severely present after isoflurane anaesthesia than after propofol anaesthesia.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
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