Effect of propofol and sevoflurane on cognitive function among elderly patients undergoing elective surgery under anesthesia

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Abstract: The objective of present study was to compare the effect of propofol and sevoflurane on cognitive function among elderly patients undergoing elective surgery under anesthesia. Elderly patient who met eligibility criteria were randomized to receive Intravenous anesthetic (propofol) or Inhalation anesthetic (sevoflurane, Group II) in allocation ratio of 1:1. The following variables were assessed, 1) recovery time; 2) measurement of attention and psychomotor functions; 3) memory (verbal memory); 4) obvious memories during anesthesia assessed by remembrance (recall) and recognition tests. A total of 200 patients were completed study. Statistical analysis showed that the recovery time was significantly greater in patients who received sevoflurane when compared to patients who received propofol ($p<0.005$). Patients who had treated with sevoflurane had greater reaction time compared to the patients who had been treated with propofol after 30- minutes of anesthesia (immediate test) [$p<0.005$]. Similar trend of results was observed between both the groups after 120 minutes of anesthesia (delayed test). Moreover, the patients who were treated with propofol had better memory score as compared to patients treated with sevoflurane. The difference was statistically significant between both the treatment groups in both type of recognition test (immediate and delayed recognition test) [$p<0.005$].

Keywords: Propofol, sevoflurane, recognition test, recovery time, memory, elderly patient, elective surgery, anesthesia

INTRODUCTION

Surgical interventions with the use of anesthesia among elderly patients are gradually increasing worldwide, with an estimated prevalence of surgical interventions are 281 million cases per year worldwide (Weiser *et al*., 2008; Mandal *et al*., 2009). Surgery procedures including anesthesia have a noticeable effect on elderly patients undergoing elective surgery, this results in higher risk of cognitive decline among elderly patient. Post-operative complications include delayed hospital discharge and increased risk of morbidity and mortality. Several lines of clinical evidence showed direct effect of anesthetics agents on central nervous system and cardiovascular system (Ballard *et al*., 2012; Wang *et al*., 2015).

Confusion after surgical interventions is common among elderly individuals; mainly the elderly patients who underwent major non-elective surgery (Berggren *et al*., 1987). Berggren *et al* reported that approx. 44% of elderly individuals experienced confusion after major orthopedics surgery (Berggren *et al*., 1987). Memory defined as the attainment of new info, and its subsequent retrieval. There is two type of memory: 1) obvious memory which is the thoughtful remembrance of knowledge; 2) inherent memory (none declarative memory) (Bernstein *et al*., 1991; Andrade J, 2007; Ozkan *et al*., 2011; Sandin., 2006). Development of obvious memories during anesthesia is related with intra-operative responsiveness, which is assessed by remembrance and recognition tests (Deeprose *et al*., 2004). Cognitive decline after surgical interventions is defined as a failure to attain knowledge, resolve difficulties and to strategy for the forthcoming events after surgical interventions under anesthesia (Bowdle *et al*., 2006). Several lines of previous reports suggested that surgical interventions and anesthesia is a root cause postoperative cognitive dysfunction (POCD) in the elderly individuals (Russel, 1997; Nadstawek *et al*., 1990). Role of obvious memory during surgical intervention under anesthesia has been acknowledged recently. Since, no sensible recall of inherent memories, it can only be demonstrated by identification test after exposure to target resources. Briefing a list of verbal words during anesthesia procedure and its successive admin of a recognition test after occurrence from anesthesia is one of common method to test memory (Sneyd JR, 2004; Dobrunz *et al*., 2007; Mc Clintock *et al*., 1990).

Although, there is little known facts that anesthesia has a noticeable effect on elderly patients undergoing elective surgery, including cognitive decline. However, it is not known whether two different classes of anesthetic agents have different effect on memory among elderly patients undergoing elective surgery. Based on the facts, the present study was designed to understand the effects of two different classes of anesthetic agents on memory of elderly Chinese patients undergoing elective surgery. Thus, the present study compares the effect propofol and sevoflurane on memory impairment among elderly patients undergoing elective surgery.

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MATERIALS AND METHODS

In this comparative study clinical trial, elderly patient who met American Society of Anesthesiologists (ASA) I (healthy patient) and II (mild systemic disease) criteria and undergoing elective moderate orthopedic surgery were recruited at Department of Anesthesiology, the Second Hospital of Jiaxing, China. Exclusion criteria included history of drug abuse, antipsychotic medication treatment, head trauma, central nervous system disorders (e.g. epilepsy) or allergy to any of the study drugs (propofol/ sevoflurane/fentanyl/cis-atracurium). All elderly patients who were interested to participate in this study have provided their written inform consent document, and ethics committee approval was obtained from institutional ethics committee of Second Hospital of Jiaxing before initiation of this study or any study related procedure. Elderly patients with any neurological disorder or neuro-surgery in past were excluded. Patients with any central nervous system (CNS) disorder were also excluded from the study.

Subject who met eligibility criteria were randomized to receive Intravenous anesthetic (propofol, purchased from Jiabo Pharmaceutical Co., Ltd Qingyuan, China) or Inhalation anesthetic (sevoflurane, purchased from Abbott, China) in allocation ratio of 1:1. The elderly patients who receive Intravenous anesthetic (propofol) were named as Group I, whereas the elderly patients who receive Inhalation anesthetic (sevoflurane) were named as Group II. In Group I, anesthesia was induced and maintained by Intravenous anesthetic (propofol, 6–12 mg/kg h/1) followed by fentanyl (0.3ug/kg) and cis-atracurium (0.15 mg/kg). In Group II, anesthesia was induced and maintained by Inhalation anesthetic (sevoflurane, 1.5–2% tidal volume) followed by fentanyl (0.3 ug/kg) and cis-atracurium (0.15mg/kg). Mean duration of interventional procedure was 1–1.5 hour. Fentanyl was administered intravenously. The following variables were assessed, 1) recovery time; 2) measurement of attention and psychomotor functions; 3) memory (verbal memory); 4) obvious memories during anesthesia assessed by remembrance (recall) and recognition tests. Recovery time is well-defined as duration between stop of anesthetic agents and correct recall of memory. Attention and psychomotor functions was assessed using green/red light. Memory (verbal memory) was assessed by briefing a list of verbal words during anesthesia procedure (exposure phase) and its successive administration of a recognition test after occurrence from anesthesia. During exposure phase, five passionately bland words were presented to each enrolled patient via closed head phone for the duration of approx. 30 minutes. Also, patients were asked to remember/recall the words presented during surgical procedure (called free call test). Also, the distractors which were administered during presentation of those five passionately bland words, and patients were asked to recognize the distractors which were administered during presentation of those five words (called recognition test).

Since this study was designed as a pilot type of clinical study, thus there is no formal sample size calculation was executed for this study. Nevertheless, we have planned to include at least 200 elderly patients in this study (100 patients in each treatment group) who met ASA I and II criteria and undergoing elective surgery. Data/variables which fall under numerical data were analyzed using appropriate statistical test, namely unpaired t test (if data is normal) or Mann Whitney test (if data is non-normal). Demography and baseline characteristics were presented as descriptive statistics. The actual statistical test applied to find whether there was any statistical difference between both the treatment groups is mentioned in Footnote of table 2 to table 4. All the statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) statistical analysis software.

RESULTS

A total of 213 subjects were participated in the screening test. Out of this, 13 subjects were excluded during screening phase as not meeting eligibility criteria. Of subjects who met eligibility criteria, a total of 200 patients were enrolled (100 patients in each group), and randomized to receive Intravenous anesthetic (propofol) or Inhalation anesthetic (sevoflurane) in allocation ratio of 1:1. Patients of both the groups had similar demography and baseline characteristic, and presented in table 1. Gender distribution among both the groups was comparable. Also, mean age among both the groups was comparable.

Table 2 compare the recovery time after administration of propofol and sevoflurane among elderly patients. Statistical analysis showed that the duration between stop of anesthetic agents and correct recall of memory (recovery time) was significantly greater in patients who received sevoflurane when compared to patients who received propofol ($p<0.005$). In sevoflurane group, the mean (SD) recovery time was 18.34 minutes (1.2), whereas in propofol group, the mean recovery time was 11.01 (1.4) minutes. This indicates that the patients who had treated with propofol had faster recovery from anesthesia compared to the patients who had been treated with sevoflurane. The difference was statistically significant between both the treatment groups ($p<0.005$).

Table 3 compares the attention and psychomotor functions before and after administration of propofol and sevoflurane among elderly patients. Statistical analysis showed that attention and psychomotor functions were comparable before administration of propofol and sevoflurane among elderly patients. Before anesthesia, the

Table 1: Demography and baseline characteristic

Variables	Propofol group (N=100)	Sevoflurane group (N=100)
Age, years (Mean[SD])	66.34 (4.5)	67.9 (7.3)
Body weight, Kg (Mean[SD])	72.14 (3.2)	74.2 (4.9)
Sex (Male/Female), n	83/17	80/20
Lapsed Surgery time (min), (Mean[SD])	52.14 (3.4)	54.5 (6.4)
Heart rate per minute, (Mean[SD])	79.4 (7.2)	83.8 (5.3)
Blood pressure (SBP/DBP), (Mean)	115/85	125/90

Values are expressed as Mean (SD) for numerical data; n= number of patients in each category; N=Total number of patients in group.

Table 2: Comparison of recovery time among patients treated with propofol and sevoflurane

Variables	Propofol group (N=100)	Sevoflurane group (N=100)
Recovery time (in min), Mean (SD)*	11.01 (1.4)	18.34 (1.2))

Values are expressed as Mean (SD) for numerical data; N=Total number of patients in group. *p <0.005 between Propofol and Sevoflurane, and p value was calculated using Unpaired t test.

Table 3: Comparison of reaction time among patients treated with propofol and sevoflurane

Variables	Propofol group (N=100)	Sevoflurane group (N=100)
Before anesthesia, Mean (SD)	7.2 (1.3)	8.2 (1.9)
Post-operatively (30 min after surgical procedure), Mean (SD)*	74.23 (11.24)	89.12 (12.2)
Post-operatively (120 min after surgical procedure), Mean (SD)*	32.13 (5. 4)	45.17 (8.1)

Values are expressed as Mean (SD) for numerical data; N=Total number of patients in group.*p <0.005 between Propofol and Sevoflurane, and p value was calculated using Unpaired t test.

mean (SD) reaction time (s) was 7.2 (1.3), and 8.2 (1.9) in patients treated with propofol and sevoflurane, respectively. Post-operatively (after 30 minutes), in sevoflurane group after anesthesia, the mean (SD) reaction time was 89.12 (12.2) seconds, whereas in propofol group, the mean reaction time was 74.23 (11.24) seconds. This indicates that the patients who had treated with sevoflurane had greater reaction time compared to the patients who had been treated with propofol after 30-minutes of anesthesia (immediate trial). The difference was statistically significant between both the treatment groups (p<0.005). Similar trend of results was observed between both the groups after 120 minutes of anesthesia (delayed trial). The difference for delayed test results was also statistically significant between both the treatment groups (p<0.005).

Table 4 compares the cognitive functions after administration of propofol and sevoflurane among elderly patients. Statistical analysis showed that no patients from either group have given free recall test of the administered words after 30- min and 120 min of anesthesia. Regarding recognition test, it has been observed that few patients of both the groups answered questions correctly regarding administered/presented words after 30- min and 120 min of anesthesia. After 30 minutes of anesthesia (immediate trial), greater number of patients from propofol group have given correct answers of recognition test as compared to the sevoflurane. Similar trend of recognition test results was noted after 120 min of anesthesia, favoring propofol over sevoflurane. This indicates that the patients who were treated with propofol had better memory score as compared to patients treated with sevoflurane. The difference was statistically significant between both the treatment groups in both type of recognition test (immediate and delayed recognition test).

Safety was monitored throughout the study period for both the treatment groups. There was no serious or any significant adverse events occurred during study period. Both the study drugs were well tolerable and found safe among elderly patients who met ASA I and II criteria and underwent elective surgery.

DISCUSSION

In China, this was the first study designed to understand the effects of two different classes of anesthetic agents on memory among elderly Chinese patients undergoing elective surgery. Though, there are little known facts that anesthesia has an obvious effect on elderly patients undergoing elective surgery, including cognitive decline. Thus, the present study compares the effect propofol and sevoflurane on memory impairment among elderly

Table 4: Comparison of effect of propofol and sevoflurane on memory

Variables	Propofol group (N=100)	Sevoflurane group (N=100)
Free remembrance of words (free recall)		
Post-operatively (30 min after surgical procedure), n	0	0
Post-operatively (120 min after surgical procedure), Mean (SD)	0	0
Memory Recognition test		
Post-operatively (30 min after surgical procedure)*, Mean (SD)	30 (2.3)	12 (1.8)
Post-operatively (120 min after surgical procedure)*, Mean (SD)	42 (2.8)	23 (1.3)

Values are expressed as Mean (SD) for numerical data; N=Total number of patients in group. *p <0.005 between Propofol and Sevoflurane, and p value was calculated using Unpaired t test.

patients undergoing elective surgery. A total of 200 patients were enrolled (100 patients in each group), and randomized to receive Intravenous anesthetic (propofol) or Inhalation anesthetic (sevoflurane) in allocation ratio of 1:1. Patients of both the groups had similar demography and baseline characteristics.

This study results demonstrates that the patients who had treated with propofol had faster recovery from anesthesia compared to the patients who had been treated with sevoflurane. Statistical analysis revealed that the recovery time was significantly greater in patients who received sevoflurane when compared to patients who received propofol. The difference was statistically significant between both the treatment groups (p<0.005). Our study results were consistent with the published reports documented in Egypt population (Ahmed *et al*., 2015). The Egypt study showed that recovery time in patients treated with sevoflurane was significantly greater when compared to patients treated with propofol (P<0.001) (Ahmed *et al*., 2015). In Germany, Schwender *et al* have reported greater recovery time with enflurane and isoflurane as compared to intravenous anesthetic agents among German individuals; our study results were consistent with the reports of this German study (Schwender *et al*., 1993). Furthermore, Singh Y *et al.*, have shown that sevoflurane appears to be better anesthetic agents in terms of cost-effectiveness and recovery profile (Singh Y *et al*., 2015). Similarity in results was possibly because of no ethics difference in efficacy of sevoflurane across different ethnic population. Moreover, attention and psychomotor functions was assessed using reaction time to red/green light. The results of attention and psychomotor functions suggested that the mean reaction time (s) before anesthesia was comparable among the patients treated with propofol and sevoflurane, respectively. The patients who had treated with sevoflurane had greater reaction time compared to the patients who had been treated with propofol after 30-minutes of anesthesia (immediate trial). Similar trend of results was observed between both the groups after 120 minutes of anesthesia (delayed trial). The difference was statistically significant between both the treatment groups during immediate and delayed testing (p<0.005). Our study results were consistent with the published reports documented in Egypt (Ahmed *et al*., 2015) and German population (Schwender *et al*., 1993). The Egypt study showed that reaction time in patients treated with sevoflurane was significantly greater when compared to patients treated with propofol (P < 0.001) (Ahmed *et al*., 2015). Similar results were found in German study (Schwender *et al*., 1993). Our study results were consistent with the other several published reports which showed greater reaction time with inhalation anesthetic as compared to intravenous anesthetic agents (Schwender *et al*., 1993; Motsch *et al*., 1992; Flouda *et al*., 2013). Our study results were in consistent with several lines of clinical evidences which suggested that there are faster return of attention and psychomotor functions in patients treated with intravenous anesthetic as compared to inhalation anesthetics (Schwender *et al*., 1993; Motsch *et al*., 1992; Flouda *et al*., 2013). Moreover, the study results showed that no patients from either group have given free recall test of the administered words after immediate and delay testing. It has been noted that few patients of both the groups answered questions correctly regarding presented words after immediate and delay recognition testing. Statistical analysis revealed that greater number of patients from propofol group have given correct answers of recognition test as compared to the sevoflurane during immediate recognition testing. Similar trend of recognition test results was noted after delay recognition testing, favoring propofol over sevoflurane. The difference was statistically significant between both the treatment groups (p<0.005) for immediate and delay recognition testing. In contrast to our results, Egypt study showed no statistically significant between both the treatment groups (P>0.05) (Ahmed *et al*., 2015). Both the study drugs were well tolerable and found safe among elderly patients who met ASA I and II criteria and underwent elective surgery.

Subsequently the study was intended as preliminary study and was performed at single site (in China) only trial.

Thus, the current verdicts can't make straightforward conclusion to Chinese population. This study was implicated by designing large clinical trial in future to confirm the verdicts of this study.

CONCLUSION

The results of this clinical study demonstrated that the patients who were treated with sevoflurane had significantly greater recovery and reaction time when compared to the patients who were treated with propofol during immediate and delayed test. Moreover, greater number of patients from propofol group has given correct answers of recognition test as compared to the sevoflurane during immediate and delayed recognition test. Both the study drugs were well tolerable and found safe among elderly patients who met ASA I and II criteria and underwent elective surgery.

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