POST-OPERATIVE COGNITIVE FUNCTIONS AFTER GENERAL ANESTHESIA WITH SEVOFLURANE AND DESFLURANE IN SOUTH ASIAN ELDERLY

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Abstract

Background: The duration of the recovery of cognition after anesthesia and surgery is multifactorial and is dependent on the type of anesthesia used, the type of surgery, and the patient. The present study compared the speed of recovery in elderly patients undergoing general anesthesia with sevoflurane or desflurane and the incidence and duration of cognitive impairment in them.

Methods: The prospective study was conducted at a tertiary care centre in Bangalore from November 2008 to March 2010. Patients aged above 65 years with American Society of Anaesthesiology (ASA) physical status I, II, III undergoing surgeries under general anesthesia lasting from 45 min up to 3 hours were included in the study. The times from discontinuing nitrous oxide to eye opening, tracheal extubation, obeying commands, and the time to orientation to name and place were assessed at 30-60 s intervals. At 1, 3, 6 h after the end of anesthesia, the patient's cognitive functions were assessed by asking them to repeat the Mini Mental Score Examination.

Statistical analysis used: Student *t*-test, Chi-square test

Results: The time to eye opening, time until extubation, time to follow commands and orientation to time, place were significantly better with desflurane compared to sevoflurane ($p<.001$). Hundred percent of patients in the desflurane group and 97% in the sevoflurane group demonstrated completely normal cognitive function at 6 h postoperatively ($p=0.31$).

Conclusion: Desflurane was associated with a faster early recovery than sevoflurane in elderly patients. However, postoperative recovery of cognitive function was similar with both volatile anaesthetics.

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Key words: Desflurane, Sevoflurane, Cognition, Recovery, Elderly

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Introduction

Surgical intervention in the elderly population is associated with significant postoperative morbidity and mortality due to various reasons[1-5]. Brain function is usually altered post-anesthesia, with altered level of consciousness and impairment of attention, memory, and reaction time. The incidence of Post-Operative Cognition Dysfunction (POCD) has been reported to be between 1% and 60%, depending on the type of operation[6].

Few studies suggest that use of volatile anaesthetics that are rapidly eliminated with minimal metabolic breakdown may reduce postoperative delirium and cognitive dysfunction in elderly surgical patients by facilitating a faster recovery from general anesthesia[7]. Sevoflurane and desflurane have pharmacokinetic properties that favour rapid emergence from anesthesia. A lower blood:gas partition co-efficient (0.42 vs 0.65) and fat:blood partition coefficient (27 vs 48) of desflurane versus sevoflurane respectively, favour its more rapid elimination from the body and also provide shorter emergence times[8]. Cognitive decline after cardiac operations has been studied extensively but cognitive decline after non-cardiac operations is not as well studied. Chen *et al* compared POCD following sevoflurane and desflurane use in elderly patients mostly consisting of American Caucasians[1]. They reported that there was no difference in the total incidence of POCD between the desflurane and sevoflurane groups; however, desflurane was associated with a faster cognitive recovery than sevoflurane. A similar study done in European population by Rortgen and group also found the same results[9].

Miles and group demonstrated that the clinical and molecular aetiologies of dementia differ between ethnic groups[10]. Genetic factors and educational achievement together accounted for over half of variance in cognitive functioning of older men in a study done by Brandt and colleagues[11]. The Baltimore Memory Study had similar reports with regards to cognition and ethnicity[12]. While we are still not yet clear on the exact mechanism of producing loss of perception and or inducing unconsiousness of either sevoflurane and desflurane, we cannot rule out genetic influences on their mechanism of action. No previous studies compared the effects of the two anaesthetics in South Asian population.

We designed this study to investigate the speed of recovery in elderly patients undergoing general anesthesia with sevoflurane or desflurane and compared the incidence and duration of cognitive impairment in South Indian population. The level of cognitive impairment as measured by MMSE scale six hours post-operatively was defined as the primary outcome in the present study.

Methods

This prospective randomized study was conducted in a tertiary care medical teaching hospital from November 2008 to March 2010. The study was approved by the Institution's Ethical Committee. We designed the study in lines with the methodologies of studies done by chen *et al* and Rortgen *et al* to facilitate comparisons between the findings from the three studies[1,9]. Patients above 65 years of age with American Society of Anaesthesiology (ASA) physical status I, II, III undergoing surgeries under general anesthesia lasting from 45 min up to three hours were included in the study following a written informed consent. Patients who underwent general anesthesia within seven days prior to the procedure under study and those undergoing surgeries that required trendelenberg position were excluded from the study. Also, patients with history of neuropsychiatric disorders, alcohol consumption, BMI>30 were excluded from the study. Patients with clinically significant cardiovascular, respiratory, hepatic, renal, neurological, psychiatric and metabolic disease were also excluded from the study. Patients unable to read and write and with impaired hearing were excluded as they would not be able to comprehend the guidelines of the study.

In the preoperative holding area, the Mini-Mental State Examination (MMSE) test was conducted. The MMSE is a screening test that quantitatively assesses cognitive impairment by asking patients a variety of questions. The maximum MMSE score is 30 points, with scores of 23 or less being indicative of cognitive impairment[13]. Hence patients with pre-operative MMSE score <23 were excluded from the study. The

criterion used to define a decline in cognitive function in our study was a decrease of 2 or more points on the MMS test compared to the pre-operative value.

The present study was double-blinded where both patients and investigators were blinded to the group. Patients were randomized to two groups using a computer generated table. As soon as the patient arrived in the operating room, an intravenous infusion of ringer lactate was started at 100 ml/hr, and monitors such as Non-invasive blood pressure (NIBP), electrocardiogram (ECG), Pulse-oximeter were applied. All patients received midazolam 1 mg intravenously (IV) for preoperative medication.

Tracheal intubation was facilitated with vecuronium (0.1mg/kg IV) or atracurium (0.5mg/kg IV). Anesthesia was induced with fentanyl (1.0-2 mcg/kg IV) and propofol (1.0-2.0 mg/kg IV) until loss of response to oral commands. After loss of consciousness, patients received either desflurane 5% or sevoflurane 2% (volume percent) through the tec6 and tec7 vaporizer.

Anesthesia was maintained with desflurane 2-6% or sevoflurane 1-1.5% in combination with nitrous oxide 66% in oxygen which corresponded to 1-1.8 MAC (Age adjusted MAC)[14].

NIBP, heart rate and oxygen saturation were recorded before induction of anesthesia then, along with end-tidal carbon dioxide, every 2 min after induction of anesthesia for 15 min and then every 5 min until the end of surgery. Temperature was monitored and was maintained at 36^0 C.

Inspired volatile anaesthetic concentration was adjusted as necessary to maintain pulse and NIBP within 20% of pre-induction values. If acute increases occurred, the inspired concentration of desflurane/sevoflurane was increased by up to 50%. Supplemental doses of fentanyl, 0.5–1.0 mcg/kg IV (to maximum dose of 200 mcg), was used to control acute changes that did not respond to two consecutive 50% increases in the inspired concentration of desflurane/sevoflurane or if there were other signs of inadequate analgesia. Patients who required higher inspired inhalational agent concentration and patients who became haemodynamically unstable during the procedure were excluded from the study.

Atracurium/vecuronium was administered during the maintenance period. All patients received paracetamol infusion 15 mg/kg during intra-operative period. During the maintenance period, ventilation was controlled to maintain normocarbia using a semi closed circle system with a total fresh gas flow rate of 3 L/min.

Ten minutes before the estimated end of surgery the inhaled anaesthetics were reduced to 0.5 MAC. At the end of surgery, residual neuromuscular blockade was reversed using glycopyrrolate (0.01 mg/kg IV) and neostigmine (0.05 mg/kg IV). Sevoflurane or desflurane was discontinued at the start of skin closure, and nitrous oxide was discontinued at the end of surgery. The lungs were ventilated with 100% O_2 at a fresh gas flow rate of 8 L/min.

The times from discontinuing nitrous oxide to eye opening, tracheal extubation, obeying commands (e.g., squeeze the investigator's hand), as well as the time to orientation to name and place were assessed at 30-60 s intervals. The durations of anesthesia (from the start of induction to discontinuation of nitrous oxide) and surgery (from surgical incision to skin closure) were also recorded. At 1, 3, 6 h after the end of anesthesia, the patient's cognitive functions were assessed by asking them to repeat the MMSE. Adverse side effects like dizziness, headache, drowsiness, nausea, vomiting, anxiety and restlessness were recorded.

The primary and secondary outcome of the study was to compare the incidence of POCD in both groups and to determine the speed of recovery respectively.

Statistical Analysis

A sample size of 35 was determined by using power analysis based on an alpha error of 0.05, beta error of 0.2.and the assumptions that a) the incidence of postoperative cognitive impairment at one hour after anesthesia would be 50%; b) 70% reduction (eg: from 50% to 15%) would be of clinical significance.

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) for Windows 16.0 (SPSS Inc., Chicago, USA). The results for each parameter (numbers and percentages) for discrete data and average (mean $\pm$ standard deviation) for continuous data are presented in tables and figures using Microsoft office 2007 software package.

Student *t*-test was performed for continuous variables, and paired Student *t*-test was used to compare the intra-group differences in the MMSE scores at different assessment points with their baseline values. Categorical data were analyzed by chi-square test. A value of $P< 0.05$ was considered statistically significant.

Results

A total of 60 patients above 65 years of age who were undergoing elective surgical procedures under general anesthesia were included in the study. These patients were randomized to two groups of 30 each using a computer generated table.

The mean age in the sevoflurane and desflurane group were 69.47±4.42 years (range: 65-88 years) and 69.17±4.73 years (range: 65-84 years) respectively. The gender distribution is given in table 1. The various surgeries undergone by the study subjects in the two groups are given in table 2. Statistically, there was no significant difference with respect to age (p=.800), gender (p=.071), ASA grading (p=.371), BMI (p=.098), various surgeries undergone by the study subjects (p=.066), propofol (p=.9) and fentanyl (p=1.0) between the two groups.

The mean duration of anesthesia for sevoflurane and desflurane groups were 140.57±35.26 min and 145.33±40.77 min respectively (p=0.63). The average duration of surgery for sevoflurane and desflurane groups were 107.83±33.55 min and 119.17±36.34 min respectively (p=.21). The various recovery indices between the two groups are given in table 3. The time to eye opening, time until extubation, time to follow commands and orientation to time, place was significantly better with desflurane (p<.001).

Table 1

Gender distribution among the treatment groups

Treatment Group	Sevoflurane	Desflurane	Total
Male (%)	19 (63.3)	12 (40.0)	31 (51.7)
Female (%)	11 (36.7)	18 (60.0)	29 (48.3)
Total (%)	30 (100)	30 (100)	60 (100)

Table 2

Type of surgeries between the two treatment groups

Group	ENT (%)	OBG (%)	Orthopedics (%)	Surgery (%)	Urology (%)	Total (%)
Sevoflurane	0 (0.0)	1 (3.3)	11 (36.7)	11 (36.7)	7(23.3)	30 (100.0)
Desflurane	2 (6.7)	6 (20.0)	5 (16.7)	13 (43.3)	4 (13.3)	30 (100.0)
Total	2 (3.3)	7 (11.7)	16 (26.7)	24 (40.0)	11 (18.3)	60 (100.0)

ENT- Ear, Nose and Throat

OBG-Obstetrics and Gynaecology

Table 3

comparison of recovery indices between the treatment groups

Index	Group	N	Mean	Std. Dev	Minimum	Maximum	'p' value
Eye Opening (min)	Sevoflurane	30	7.93	1.530	5	12	<0.001
	Desflurane	30	5.37	.999	4	8	
Extubation (min)	Sevoflurane	30	10.10	1.583	7	14	<0.001
	Desflurane	30	7.17	.913	5	9	
Commands (min)	Sevoflurane	30	12.67	1.826	9	17	<0.001
	Desflurane	30	8.83	1.262	7	12	
Orientation (min)	Sevoflurane	30	13.80	1.789	9	17	<0.001
	Desflurane	30	9.63	1.377	8	13	

Table 4

Comparison of mean Mini Mental Scale Examination (MMSE) scores between the two groups

	Groups	N	Mean	Std. Deviation	Minimum	Maximum	'p' value
Pre op-MMSE	Sevoflurane	30	28.97	0.964	27	30	0.214
	Desflurane	30	28.60	1.276	25	30	
MMSE- 1h	Sevoflurane	30	27.17	1.234	25	29	0.109
	Desflurane	30	26.53	1.737	22	29	
MMSE- 3h	Sevoflurane	30	27.97	1.066	26	30	0.403
	Desflurane	30	27.70	1.368	24	29	
MMSE- 6h	Sevoflurane	30	28.67	0.959	27	30	0.321
	Desflurane	30	28.40	1.102	25	30	

Table 5

Comparison of percentage of patients having Post-Operative Cognitive Dysfunction (POCD)

Group	POCD at 1h	POCD at 3h	POCD at 6h
Sevoflurane	15 (50%)	4(13%)	1(3.3%)
Desflurane	18(60%)	5(16.7%)	0
p-value	0.44	0.71	0.31

The trend of MMSE scores at 1, 3 and 6 h post-operatively show that MMSE scores at 1 hr were significantly low in both groups (Table 4), but returned to the baseline by 6h. The incidence of POCD in the two study groups at various time-lines is gievn in table 5. There was statistically no difference between the two groups in the incidence of POCD. In addition, there were no significant differences in the amounts of postoperative analgesic and the incidence of side effects in the two study groups.

Discussion

Postoperative cognitive impairment is a condition characterized by impairment of memory and concentration, and the incidence has been reported to be extremely frequent in elderly patients. The aged brain is different from the younger brain in several important aspects, including size, distribution and type of neurotransmitters, metabolic function, and capacity for plasticity. For this reason, early POCD is more common in the elderly after major surgery, compared to middle-aged patients[15]. In the present study, we compared the speed of recovery in elderly patients undergoing general anesthesia with sevoflurane or desflurane and compared the incidence and duration of cognitive impairment in them.

The two anaesthetic groups were comparable with respect to age, gender, ASA grade, durations of anesthesia and surgery, BMI as well as doses of medications used for premedication, propofol induction dose and intra-operative analgesic requirement.

The emergence times from the end of anesthesia to eye opening, tracheal extubation, following verbal commands, and orientation were significantly shorter in the Desflurane (versus Sevoflurane) Group ($p<.001$) consistent with previous studies[16]. In the present study, there was no significant difference between desflurane and sevoflurane groups with respect to their MMSE score preoperatively and at 1h, 3h and 6h postoperatively. Chen *et al* and Rortgen *et al* also did not find any significant difference between desflurane and sevoflurane groups with respect to POCD, indicating that either of the agents are suitable for anesthetizing elderly patients without causing significant POCD[1,9].

The early recovery profiles (e.g., 0-4h) of

modern anaesthetics such as sevoflurane, desflurane and propofol have been well studied and recently reviewed. Most psychometric tests appear to show a return to baseline values between four and six hours after anesthesia[17,18]. A meta-analysis on post-operative recovery after general anesthesia reported that patients receiving desflurane followed commands, were extubated, and were oriented 1.0-1.2 minutes earlier than patients receiving sevoflurane[19]. However, Heavner and colleagues did not find any difference between desflurane and sevoflurane in the elderly after general anesthesia with respect to recovery time when they were assessed with the Digit–Symbol Substitution Test[20].

A smaller study group and use of single neurobehavioural assessment tool might have masked the subtle differences between the two compounds. A large scale study with multiple neurobehavioural assessment tools is needed to establish the present findings as facts.

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