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The Effects of Isoflurane, Sevoflurane, and Desflurane Anesthesia on Neurocognitive Outcome after Cardiac Surgery: A Pilot Study

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ABSTRACT

Background. Inhalation anesthetics such as isoflurane, sevoflurane, and desflurane are widely used in clinical practice; however, there is no study for comparing these drugs in cardiac surgery with respect to postoperative cognitive outcome and S100 beta protein (S100 BP) levels. In this study, we evaluated the effect of sevoflurane, isoflurane, and desflurane anesthesia on neuropsychological outcome and S100 BP levels in patients undergoing coronary artery bypass grafting (CABG) surgery with cardiopulmonary bypass (CPB).

Materials and Methods. Forty-two male patients were prospectively randomized and classified into 3 groups according to the volatile agents used; isoflurane, sevoflurane, desflurane. All patients had a sufficient education level to participate in neuropsychological testing and a normal carotid Doppler ultrasonography. Blood samples for analysis of S100 BP were collected before anesthesia (T1), before heparinization (T2), 15 minutes into CPB (T3), following protamine administration (T4), postoperatively (T5), 24 hours after the operation (T6), postoperative day 3 (T7), and postoperative day 6 (T8). The neuropsychological tests, including Mini-Mental State Examination (MMSET) and visual-aural digit span test (VADST), were administered 1 day prior to surgery and on the third and sixth postoperative days.

Results. The postoperative third and sixth day MMSET scores and third day visual-written subtest scores in the sevoflurane group were significantly lower than in the isoflurane and desflurane groups ($P < .05$). S100 BP levels increased with the beginning of anesthesia in the sevoflurane and desflurane groups. Although S100 BP decreased to baseline levels on postoperative day 1 in the sevoflurane group, this was significantly higher on the third and sixth days postoperatively in the desflurane group ($P < .05$). In the isoflurane group, the S100 BP level was significantly higher than the baseline level only after CPB ($P < .05$).

Conclusion. Our study suggests that isoflurane is associated with better neurocognitive functions than desflurane or sevoflurane after on-pump CABG. Sevoflurane seems to be associated with the worst cognitive outcome as assessed by neuropsychologic tests, and prolonged brain injury as detected by high S100 BP levels was seen with desflurane.

INTRODUCTION

Cerebral and neurocognitive dysfunction has been proposed as a significant complication of on-pump coronary artery bypass graft (CABG) surgery [Ishida 2003]. Over the past decade, several refinements to the conduct of cardiopulmonary bypass (CPB) have reduced the incidence and severity of cognitive impairment [Dijk 2000; Missler 2003].

It has been reported that S100 beta protein (S100 BP) is an early marker for cerebral injury during cardiac operations. S100 BP subunits are present in glial and Schwann cells, and recently elevated levels have been detected after cardiac operations complicated by neurological injury [Jonsonn 1998; Westaby 2000]. The appearance of S100 BP in serum indicates both neuronal damage and increased permeability of the blood-brain barrier [Abdul-Khalig 2000].

The use of volatile anesthetics that are rapidly eliminated with minimal metabolic breakdown may reduce postoperative cognitive dysfunction by facilitating a faster recovery from general anesthesia [Chen 2001]. The availability of volatile anesthetics with low blood-gas partition coefficients such as sevoflurane and desflurane should also provide shorter emergence times compared with traditional inhaled anesthetics. Therefore, the use of shorter-acting anesthetics and analgesic drugs may contribute to less postoperative cognitive impairment and confusion [Frink 1992; Tsai 1992]. Inhalation anesthetics have different mechanisms for neuroprotection, and they appear to involve suppression of excitatory neurotransmission and potentiation of inhibitory activity. Activation of intracellular signaling cascades that lead to altered expression of protective genes may also be involved.

The inhalation anesthetics isoflurane, sevoflurane, and desflurane are widely used in clinical practice; however, there is no

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Table 1. Demographic and Surgical Variables (mean ± SD)

	Isoflurane Group, n = 14	Sevoflurane Group, n = 14	Desflurane Group, n = 14
Age, y	55.14 ± 13.34	63.21 ± 9.70	60.36 ± 8.13
Weight, kg	75.93 ± 7.71	73.64 ± 6.37	71.79 ± 10.50
Cross-clamp time, min	39.93 ± 11.84	43.64 ± 11.28	42.43 ± 12.57
Total bypass time, min	63.21 ± 13.81	77.71 ± 18.99	78.79 ± 24.96

study that compares these drugs in cardiac surgery with respect to postoperative cognitive outcome and S100 BP levels.

The goal of the present study was to investigate the effects of sevoflurane, isoflurane, and desflurane on neuropsychological outcomes using different neurocognitive tests for performance and by evaluating serum S100 BP levels in patients undergoing CABG.

MATERIALS AND METHODS

After obtaining University Ethical Committee approval and informed consent from the patients, we studied 42 male patients undergoing CABG surgery. Patients who were included in the study had a sufficient education level to participate in neuropsychological testing. No patient had major noncardiac impairment, such as renal, psychiatric, or neurological disease, that could interfere with recovery. All patients had a normal carotid Doppler ultrasonography.

Patients were excluded from the study if they had poor left ventricular function (ejection fraction <40%) and unstable angina, hepatic and renal insufficiency, additional valve disease, reoperation, preoperative insertion of an intra-aortic balloon pump, re-exploration for any reasons necessitating pharmacological support, or an intra-aortic balloon pump to wean from CPB.

All patients were premedicated with peroral diazepam 10 mg. Induction of anesthesia was performed with etomidate 0.2 mg/kg^{-1} and fentanyl 0.1 μg/kg^{-1}. Vecuronium bromide 0.1 mg/kg^{-1} was administered to facilitate endotracheal intubation. Oxygen and nitrous oxide were used (3-3 L/min^{-1}) during the maintenance of anesthesia in all patients. After induction, the 42 patients were divided into 3 groups of 14 patients. Isoflurane was used in group I at a concentration of 1% to 1.5% before and after CPB and 0.5% to 1% during CPB. Sevoflurane was used in group S at a concentration of 1.5% to 2% before and after CPB and 1% during CPB. Desflurane was administered to group D at a concentration of 7% to 8% before and after CPB and 4% to 5% during CPB. All the patients were monitored with the bispectral index, and the anesthetics were titrated to keep the bispectral index between 40 and 50.

Standard CPB management was performed in all patients with a roller pump, membrane oxygenator, a 40-micron arterial line filter, and nonpulsatile perfusion. Antegrade cold St. Thomas crystalloid cardioplegia and mild hypothermia (28°C) were applied. Hemodynamic management before and after CPB sought to keep mean arterial pressure above 60 mmHg by volume replacement, changes in anesthetic concentration, or administration of nitroglycerin and ephedrine. Distal coronary anastomoses were performed during a single period of aortic cross clamping. A tangential occluder replaced the cross clamp during the proximal anastomosis. Maximum care was exercised to remove particulate debris and air in the aorta before weaning from CPB.

All patients were transferred to the intensive care unit after the operation. For all patients, blood samples for analysis of S100 BP were collected before anesthesia (T1), before heparinization (T2), 15 minutes into CPB (T3), following protamine administration (T4), postoperatively (T5), 24 hours after the operation (T6), on postoperative day 3 (T7), and on postoperative day 6 (T8).

After centrifugation, the serum was kept at –20°C until analysis. The S100 BP was analyzed using a Liaison Sangtec 100 kit (DiaSorin, Saluggia, Italy) with a Liaison Sangtec analyzer (DiaSorin, Dietzenbach, Germany) for sandwich immunoluminometric assay. The sensitivity of the assay was 0.2 μg/L^{-1}. S100 BP levels in excess of 0.5 μg/L^{-1} were considered pathological. A neurologist who was blinded to anesthetic management examined all patients 1 day prior to surgery and on the third and sixth postoperative days. The neuropsychological tests were administered 1 day prior to surgery and on the third and sixth postoperative days.

The test battery at pretest and follow-up consisted of the following:

- Mini Mental State Examination (MMSET), which includes a diagnostically valuable verbal retention test and tasks that assess basic orientation, short-term memory, ability to calculate, and visio-motor ability. The number of correct responses is the test score.
- Visual-Aural Digit Span Test (VADST), which assesses alertness, attention, concentration, and short-term memory. VADST mainly measures intersensory integration, sequencing, and recall. It consists of 4 subtests: aural-oral, visual-oral, aural-written, and visual-written. With regard to the statement of consensus [Murkin 1995] on the assessment of neurobehavioral outcomes after cardiac surgery, the neuropsychiatric test battery should have its sensitivity and reliability confirmed in specific populations. The sensitivity and

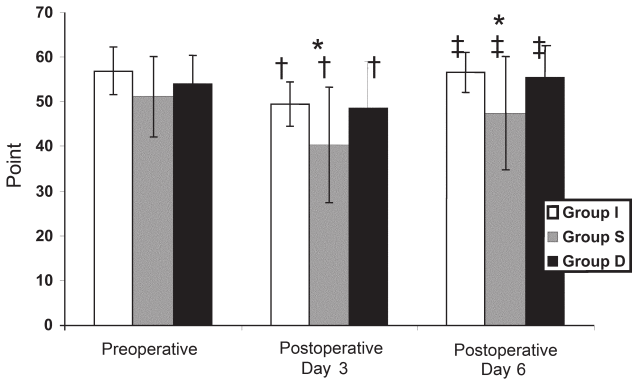

Figure 1. Mini-Mental State Examination scores of the groups (mean ± SD). *P < .05 between groups; †P < .05 compared to preoperative values; ‡P < .05 compared to postoperative day 3.

Table 2. Aural-Oral Subtest and Aural-Written Subtest Scores of Visual-Aural Digit Span Test (mean ± SD)

	Aural-Oral Subtest			Aural-Written Subtest		
	Preoperative	Postoperative Day 3	Postoperative Day 6	Preoperative	Postoperative Day 3	Postoperative Day 6
Isoflurane	5.93 ± 1	5 ± 0.8*	5.79 ± 1.2†	5.57 ± 1.2	4.64 ± 1*	5.43 ± 1.4†
Sevoflurane	5.29 ± 1.6	4 ± 1.4*	4.71 ± 1.6†	5.14 ± 1.8	3.43 ± 1.6*	4.36 ± 1.6†
Desflurane	5.86 ± 1.5	5.07 ± 1.7*	6 ± 1.6†	5.5 ± 1.7	4.86 ± 1.6*	5.57 ± 1.6†

*P < .05 compared to preoperative values.

†P < .05 compared to postoperative day 3.

reliability of the MMSET and VADST have been established in a Turkish population [Gungen 2002].

Statistical Analysis

Data were analyzed with SPSS 10.0.5 for Windows (SPSS, Chicago, IL, USA) software. One sample Kolmogorov Smirnov test was used for testing the distribution of data. Comparisons between the groups regarding age, weight, cross-clamp time, and total bypass time were done with 1-way analysis of variance. General linear model repeated measures analysis of variance was used for analyzing differences between groups and within time regarding the neuropsychological test results and S100 BP levels. The paired *t* test was used for analyzing the differences within groups compared to baseline values. Linear regression analyses including age, cross-clamp time, and grouping variables by setting the neurological test results as independent variables and the S100 BP levels as dependent variables were performed. Pearson correlation analysis was performed to assess the correlation between neuropsychological tests and the S100 BP levels. *P* values <.05 were considered significant, and Bonferroni correction was used when multiple comparisons were made.

RESULTS

Patient characteristics are described in Table 1. There were no differences in demographic characteristics and perioperative variables between the 3 groups. There was no difference between groups for MAP during CPB. No inotropic agent was used in any group. No overt incidence of neurological injury was detected in any of the patients. The neurological examinations of the patients on the third and sixth postoperative days revealed no pathological finding.

The MMSET scores of the 3 groups were significantly decreased on postoperative day 3 compared to preoperative scores. The postoperative day 3 and day 6 scores in the sevoflurane group were significantly lower than in the isoflurane and desflurane groups (Figure 1). Linear regression analyses including age, cross-clamp time, and grouping variable (the type of inhalation agent used) as the independent variables and the MMSET scores as the dependent variable were performed. The type of the inhalation agent did not reach statistical significance, but the effect of age was significant (β [95% confidence interval] for POD3 MMSET was –0.430; range, –0.717 to –0.142; P = .002).

There were significant decreases in postoperative day 3 scores and increases in day 6 scores in all of the VASDT subtests in the 3 groups. These changes were seen in all of the subtests of the VASDT (aural stimuli, verbal stimuli, intersensory integration score, and intrasensory integration score) (Table 2).

There was one significant difference between groups; the sevoflurane group visual-written subtest scores were significantly lower (P < .05) than in other groups at postoperative day 3 (Figures 2 and 3). Linear regression analysis including age, cross-clamping time, and grouping variable (the type of inhalation agent used) as the independent variables and the subtest scores as the dependent variable were performed; only age reached statistical significance in visual-oral and visual-written subtests.

S100 BP levels increased with the beginning of the CPB in the sevoflurane and desflurane groups. The patients in these groups reached the maximum levels at the end of CPB and returned to baseline levels 6 days postoperatively, except in the desflurane group. In the isoflurane group, there was a significant increase in S100 BP levels after CPB compared to preoperative levels (Figure 4). In the sevoflurane group, there was a significant increase at T2, T3, T4, T5, and T6 compared to preoperative values. There was a significant difference between groups only at T8 values. In the desflurane group, there were significant increases at all measurement

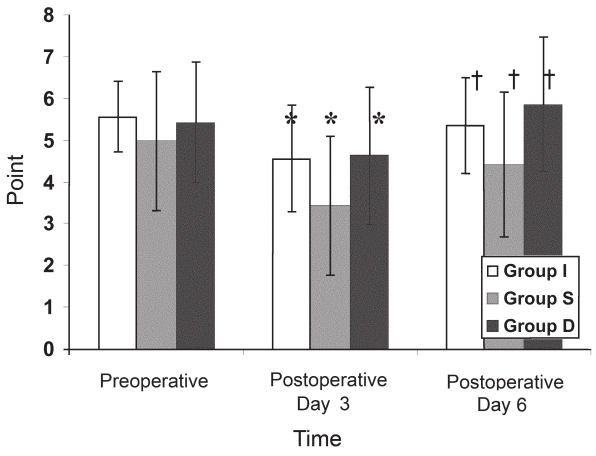

Figure 2. Visual-oral test scores (mean ± SD). *P < .05 compared to preoperative values; †P < .05 compared to postoperative day 3.

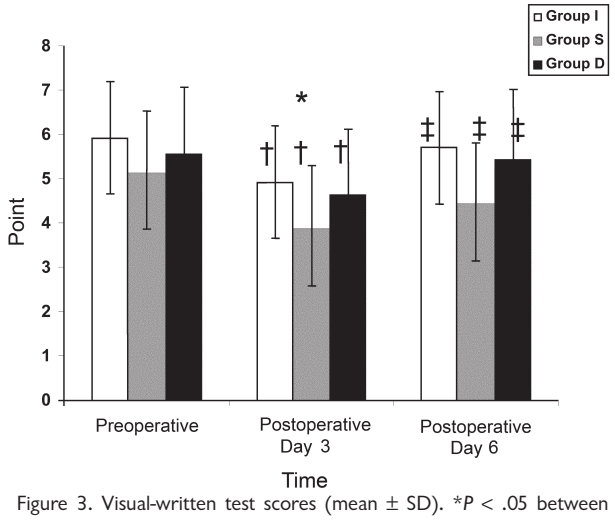

Figure 3. Visual-written test scores (mean ± SD). *P < .05 between groups; †P < .05 compared to preoperative values; ‡P < .05 compared to postoperative day 3.

time points (T2, T3, T4, T5, T6, T7, and T8) compared to preoperative values.

There was a significant difference between groups in S100 BP only in T8 values. The desflurane group had higher S100 BP levels at T8 (P < .005 between groups). The S100 BP levels at the fifteenth minute of CPB showed moderate correlations with the VASDT visual-oral subtest data from the third postoperative day (r^2 = 0.374; P = .018) and the 6 postoperative day (r^2 = 0.408; P = .009), with the VASDT visual-written subtest data from the third postoperative day (r^2 = 0.390; P = .013) and sixth postoperative day (r^2 = 0.405; P = .010), aortic cross-clamp time (r^2 = –0.342; P = .031), and age (r^2 = –0.342; P = .031).

The S100 BP levels on the third postoperative day showed moderate correlation with age (r^2 = –0.321; P = .043). The S100 BP levels on the sixth postoperative day showed moderate correlations with the VASDT aural-oral subtest on the third postoperative day (r^2 = 0.375; P = .017) and the VASDT visual-oral subtest on the sixth postoperative day (r^2 = 0.355; P = 0.024).

Linear regression analyses including age, cross-clamp time, and grouping variable (the type of the inhalation agent used) as the independent variables and S100 BP levels as the dependent variable were performed; none of the parameters reached statistical significance.

DISCUSSION

Neurological and/or cognitive impairment is one of the major complications of extracorporeal circulation after CABG procedures. The pathogenesis of postoperative cognitive dysfunction is unclear. We believe that this clinical state depends on many clinical factors, and patients' preoperative characteristics and surgical and anesthetic management play important roles. However, there is no report comparing the effects of volatile anesthetics on neurocognitive functions and S100 BP blood levels in CABG surgery patients after the operation. In this study, we examined the effects of anesthetics management on cerebral injury with neuropsychological tests and neurological examination in addition to evaluating S100 BP levels after CABG surgery.

A number of attempts have been made in the last few years to identify a serum marker of brain damage [Jonsson 1998; Westaby]. S100 BP is a promising chemical marker of perioperative neuronal damage associated with the use of extracorporeal bypass in cardiac surgery patients [Westaby 1996]. The timing of S100 BP sampling can affect its specificity. Jonsonn et al first made the distinction between the early and late release patterns of S100 BP [Jonsonn 1999]. It has been reported that there is a positive correlation between S100 BP levels and neurocognitive function in the late postoperative period after CPB [Kanbak 1999; Lardner 2004]. The early S100 BP release was significantly associated with age and bypass time but not with cerebral outcome, and S100 BP levels in the early phase after cardiac surgery are due to release not only from the brain but also from extracerebral tissue [Synder-Ramos 2004]. On the other hand, the late release of S100 BP (5-48 h after CPB) was significantly associated with cerebral complications [Jonsson 1999]. We had blood samples for S100 BP levels during CPB and 1 day, 3 days, and 6 days after CPB when the patients were examined for neuropsychological outcome. We evaluated the S100 BP level at a late phase after CPB as it is more valuable for determining cerebral damage. In the desflurane group, in the late phase, the S100 BP level was higher than in the isoflurane and sevoflurane groups.

Neuropsychological testing is accepted as one of the best methods for assessing changes in intellectual function after a cerebral incident and has identified persistent mild, moderate, or severe deterioration in 19% to 38% of patients who undergo CPB [Stump 1995]. In contrast to a previous study [Jonsonn 1999], we observed that patients in the sevoflurane

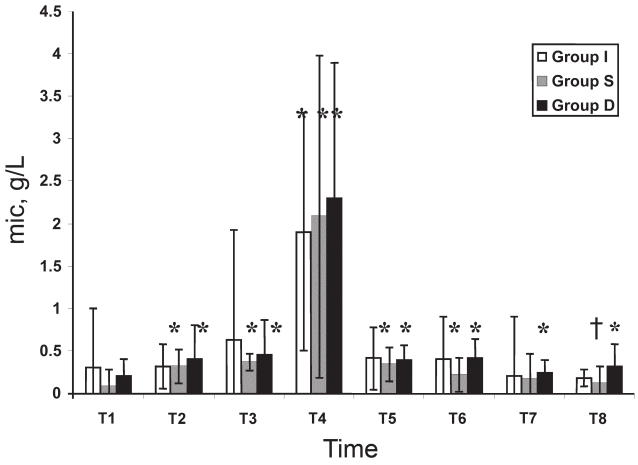

Figure 4. S100 B protein levels of the groups (mean ± SD). *P < .05 compared to preoperative values; †P < .05 between groups. T1 indicates before anesthesia; T2, before heparinization; T3, 15 minutes into cardiopulmonary bypass; T4, following protamine administration; T5, postoperatively; T6, 24 hours after the operation; T7, postoperative day 3; T8, postoperative day 6.

group had worse neurocognitive test scores in both MMSET and VADST visual-aural subtests than patients in the desflurane and isoflurane groups. Sevoflurane can cause agitation and delirium in the early postoperative period; therefore, this negative effect on neurocognitive outcome can be attributed to this side effect.

Studies that investigate the effect of volatile anesthetics on brain protection and neurocognition have increased in recent years. But these studies focus on traumatic brain injury rather than open heart surgery. In cardiac surgery, various techniques of neurological protection have been used during CPB, and some methods, such as pharmacological protection, remain controversial. Neuroprotection by anesthetic agents was first described more than 3 decades ago, when barbiturates were found to reduce neuronal energy consumption by reducing electrical activity. In recent studies, it has been reported that anesthetics produce changes in the patient's behavioral state by interacting with brain activity via at least 2 mechanisms, the dose-dependent global and regionally specific suppression of neuronal activity and disruption of functional interactivity within distributed neural networks. Isoflurane in particular was investigated for neuroprotective value, and its protection requires calcium release from intercellular stores and subsequent activation of MAP kinase and Akt signaling pathways and appears to be age related [Gray 2005]. Similar to isoflurane, sevoflurane treatment recently was shown to induce ischemia tolerance. The mechanism responsible is unclear, but may involve opening of ADP-dependent potassium channels [Payne 2005]. In our present study, when the 3 inhalation anesthetics were compared, isoflurane caused minimal change from baseline in the cognitive function after cardiac surgery. In our previous study, isoflurane was also better than propofol for cerebral protection during CPB as shown by the results of measuring S100 BP levels and a cognitive function test battery [Kanbak 2004]. Isoflurane may reduce excitotoxic damage by antagonistic action on NMDA-receptors, suppression of glutamate release, and potentiation of inhibitory activity, thereby decreasing immediate neuronal death [Koerner 2006].

Initially, anesthetics were believed to produce cerebral protection through a reduction in metabolism that provided greater tolerance to periods of cerebral ischemia or embolic insults [Kawaguchi 2004]. Volatile anesthetics have been shown to reduce or delay neuronal death induced by experimental ischemia. Indeed, halothane, isoflurane, and sevoflurane reduce infarct volume in focal cerebral ischemia in rats [Murkin 1995; Loepke 2002). Engelhard et al [1999] demonstrated that isoflurane and desflurane improved neurological outcome after incomplete cerebral ischemia in rats compared to fentanyl-nitrous oxide. They suggested that neurologic outcome was related to plasma concentrations of catecholamines [Engelhard 1999].

The choice of anesthetic drugs can affect postoperative cognition because residual levels of volatile anesthetics can produce changes in central system activity. Therefore, the use of anesthetics with rapid clearance and negligible metabolism may offer advantages in patients undergoing CPB. There is not yet a satisfactory study about the effect of volatile anesthetics on patients' cognition and CABG surgery. Chen et al has reported the only clinical study about the volatile agents' effects on cognitive outcome [Chen 2001]. They studied cognitive functions in elderly patients to compare the effects of desflurane and sevoflurane and reported that postoperative recovery of cognitive function was similar with both volatile anesthetics but added that only transient cognitive impairment occurred with these agents, even after anesthesia lasting 2 to 3 hours.

In conclusion, our prospective pilot study shows that isoflurane is associated with better neurocognitive outcomes after on-pump CABG procedure than sevoflurane and desflurane. The sevoflurane group had worse neurocognitive test results whereas desflurane is associated with prolonged S100 BP increase. It will be worth studying if isoflurane might be more advantageous than the other volatile anesthetics in cases with high risks of neurocognitive side effects due to extracorporeal circulation such as patients with a history of alcohol abuse, older patients, or patients with low baseline cognition.

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