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Sevoflurane anesthesia did not affect postoperative cognitive dysfunction in patients undergoing coronary artery bypass graft surgery

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Abstract
Purpose. The purpose of this study was to retrospectively examine whether sevoflurane anesthesia had any ameliorative effects on postoperative cognitive dysfunction in patients undergoing coronary artery bypass graft (CABG) surgery.
Methods. One hundred and nine patients underwent elective CABG surgery at our institution from May 1999 to May 2001. From May 1999 to August 2000, the main anesthetic regime used included a propofol infusion with no volatile anesthetic being administered during the surgery. From September 2000 to May 2001, the main anesthetic regime used was 1.5%–2.0% sevoflurane from the postinduction period until the end of the surgery. All patients underwent a battery of neurological and neuropsychological tests 1 day before and 6 months after the operation.
Results. The use of sevoflurane did not have any significant effects on the postoperative levels of cognitive dysfunction. In contrast, multiple logistic analysis showed that age [odds ratio (OR), 1.3; $P = 0.047$], diabetes mellitus (OR, 2.5; $P = 0.03$), and atherosclerosis of the ascending aorta (OR, 1.4; $P = 0.047$) appeared to be predictive factors of postoperative cognitive dysfunction.
Conclusion. This retrospective study showed no relationship between postoperative cognitive dysfunction and the use of sevoflurane.

Key words Cognitive dysfunction · Coronary artery bypass graft · Preconditioning · Sevoflurane

Introduction

Central nervous system (CNS) complications are a major cause of morbidity and mortality after cardiac surgery [1–5]. In fact, neuropsychological dysfunction after cardiopulmonary bypass (CPB) has been reported in as many as 79% of patients during the early postoperative period [2–5].

Several proposed techniques have been considered for neuroprotection during surgery, including the use of beta-blockers to prevent postoperative atrial fibrillation [6], increasing the level of Immunoglobulin M (IgM) anti-endotoxin core antibody [7], avoiding CPB, and strictly controlling plasma glucose levels during the perioperative period [8].

Many animal studies have shown that volatile anesthetics, such as sevoflurane or isoflurane, have a preconditioning effect [9–13]. In addition, there have been several clinical studies regarding the effects of preadministration of volatile anesthetics, such as sevoflurane or isoflurane, on the heart during cardiac surgery. For example, De Hert et al. [10] reported that sevoflurane reduced the elevation of postoperative troponin concentration compared with that in the propofol group. In contrast, there have been no clinical studies regarding the effects of volatile anesthetics on neuroprotection during cardiac surgery. If volatile anesthetic agents prove to have neuroprotective effects, as suggested by studies in animal models, the use of volatile anesthetics for their specific antiischemic effect should be further explored. Numerous studies [9–12,14] providing evidence both of ischemic preconditioning in the brain and volatile anesthetic preconditioning of the heart led researchers to question whether volatile anesthetic agents might also have preconditioning effects on the brain and, hence, improve neurological outcome.

Thus, the purpose of this study was to retrospectively examine whether sevoflurane might have ameliorative effects on postoperative cognitive dysfunction after coronary artery bypass graft (CABG) surgery.

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Patients and methods

We retrospectively examined 109 patients who underwent elective CABG at our institution from May 1999 to May 2001. All protocols used in this study were approved by the Ethics Committee of our institution, and written informed consent was obtained from all patients.

Patients with cerebrovascular disease as determined by a history of ischemic cerebrovascular disease with symptomatic neurological disorders and confirmed by preoperative brain computed tomography and magnetic resonance imaging (MRI) were excluded because of suspension or incompletion of neurological and neurocognitive tests. All patients were examined for the presence of carotid artery disease; the presence of this disease resulted in their exclusion from the study.

Operative procedure

All patients received diazepam (10 mg orally) 1 h prior to anesthesia. Anesthesia was induced with 0.2 mg·kg^{-1} of midazolam, 10 μg·kg^{-1}, of fentanyl, and 0.2 mg·kg^{-1} of vecuronium, followed by tracheal intubation. After induction of anesthesia, a pulmonary arterial catheter (Vigilance, Swan-Ganz CCO thermodilution catheter, Baxter, Irvine, CA, USA) was inserted through the right internal jugular vein. For continuous monitoring of jugular venous oxygen saturation (Sjv_{O_2}), a 4-Fr fiberoptic oximetry oxygen saturation catheter (dual-lumen oximetry catheter, Baxter) was inserted into the right jugular bulb using a modified Seldinger technique.

The partial pressures of arterial and jugular venous blood gases were analyzed using a Stat Profile Ultima (NOVA Biomedical, Boston, MA, USA). All patients were ventilated with oxygen (50%) and nitrous oxide (50%). End-tidal CO_2 was monitored (Ultima, Datex, Helsinki, Finland) and were maintained between 35–40 mmHg. Following anesthetic induction, 5–10 mg·kg^{-1}·h^{-1} propofol was infused using a syringe pump, this being continued until the patients arrived in the intensive care unit. Muscular relaxation was achieved by intermittent administration of vecuronium. From May 1999 to August 2000, no volatile anesthetic was administered. From September 2000 to May 2001, instead of propofol infusion, we used 1.5%–2.0% sevoflurane after the induction of anesthesia until the end of the surgery. Sevoflurane dosage was determined by the hemodynamic stability of the patient. When sevoflurane was used during surgery, propofol was not used during the perioperative period. The tympanic temperature was continuously monitored by Mon-a-Therm (Mallinckrodt, St. Louis, MO, USA). Pa_{O_2} was maintained at 150–300 mmHg during the study.

The cardiopulmonary bypass (CPB) circuit was primed with a crystalloid, nonglucose-containing solution, and a nonpulsatile pump flow rate of 2.2–2.5 L·min^{-1}·m^{-2} was maintained. A membrane oxygenator and a 40-μm arterial line filter were used, and Pa_{CO_2}, uncorrected for temperature, was adjusted to normocapnic levels (35–40 mmHg) by varying the fresh gas flow to the membrane oxygenator (alpha-stat regulation). Target tympanic temperatures were 34.5°–36.0°C. The limit on maximal inflow temperature was set at 37.5°C. Hematocrit was maintained at greater than 20 during CPB using blood transfusions as necessary. Phenylephrine infusions were used during CPB to maintain mean arterial pressure (MAP) at 50–80 mmHg. Insulin infusions were used during CPB to maintain blood sugar at 100–200 mg·dl^{-1}. Distal and proximal coronary anastomoses were performed during a single aortic cross-clamp. During CPB, sevoflurane was added by a vaporizer connected to the CPB circuit. Propofol continued to be infused during CPB.

Hemodynamic parameters and arterial and jugular venous blood gases were measured at different times, as previously described in detail [15]. The presence or absence of carotid artery stenosis, defined as narrowing of greater than 50% [16], was confirmed by preoperative ultrasonography and MRI. The presence of atherosclerotic lesions in the ascending aorta was confirmed by intraoperative epiaortic ultrasonography. Atherosclerotic lesions in the ascending aorta were considered to be present if there were areas of 3.0 mm thickening or more with diffuse irregularities, large mobile or protruding atheromata, ulcerated plaques, and/or thrombi [16].

Neurological and neuropsychological assessments

All patients underwent a battery of neurological and neuropsychological tests on the day before the operation and at 6 months after surgery. These tests were administered by trained specialists, and intra- and interobserver validity was ensured. The neuropsychological portion of the study design followed the consensus statements on the assessment of central nervous system disorders after cardiac surgery [17]. Cognitive functioning was assessed using the following tests: Mini mental state examination, Rey auditory verbal learning test, trail-making test (part A), trail-making test (part B), digit span forward, and the grooved pegboard.

Major neurologic defects were defined as clinical evidence of any combination of focal cerebral infarction, including hemiparesis; visual or gait disturbances; mental status changes (confusion, agitation, inability to interact with others); or a combination of these.

Statistical analysis

All data are expressed as mean ± SD. The unpaired *t* test or Fisher exact test was used for analysis between the two groups. To obtain an indicator of overall outcome, significant impairment was defined as a decline from preoperative testing of more than 1 SD on more than 20% of test measures (at least 2 of 6). Multiple logistic regression was used to choose a best set of independent predictors of cognitive impairment 6 months after surgery. Variables entered into the initial logistic models were those with a univariate probability value of $P < 0.2$. The final model included all variables with an independent significant level of $P < 0.1$. The quality of the fit of the logistic and multiple models was tested with the Hosmer and Lemeshow goodness-of-fit test. After the study was completed, we evaluated the sample size. On the basis of our previous study, we considered a 20% reduction in cognitive dysfunction to be clinically important. The sample size provided 70% power to detect a 30% difference between patients receiving sevoflurane and those not receiving sevoflurane.

Statistical significance was set at $P < 0.05$. All calculations were performed on an Apple computer with SPSS (SPSS, Chicago, IL, USA) and StatView 5.0 software packages (Abacus Concepts, Berkeley, CA, USA).

Results

One patient (excluding a patient with major neurologic defects) had incomplete cognitive assessment data and one patient refused follow-up. One patient was diagnosed with major neurologic defects 2 days after surgery. Thus, a total of 106 patients completed the neuropsychological assessment and were included in the final analysis.

Demographic data from patients who did and did not undergo anesthesia with sevoflurane are summarized in Table 1. No significant differences in demographic data were observed between the two groups. Likewise, no significant differences in cognitive tests existed between the two groups in the preoperative period (data not shown).

The characteristics of patients with and without postoperative cognitive dysfunction at 6 months after the surgery are summarized in Tables 2 and 3. The incidence of postoperative cognitive dysfunction at 6 months in patients not receiving sevoflurane was 23% and that in patients receiving sevoflurane was 22%. There was no significant difference in the incidence of cognitive dysfunction at 6 months between the two groups.

The total incidence of cognitive decline at 6 months was 24/106 (23%). Increased age ($P = 0.02$), diabetes mellitus ($P = 0.01$), and atherosclerosis of the ascending aorta ($P = 0.02$) were significantly more frequent in patients with postoperative cognitive dysfunction at 6 months than in those without postoperative cognitive dysfunction (Tables 2 and 3).

Multiple logistic analysis showed that age [odds ratio (OR), 1.3; 95% confidence interval (CI), 1.0–1.7; $P = 0.047$], diabetes mellitus (OR, 2.5; 95%CI, 1.5–3.1; $P = 0.03$), and atherosclerosis of the ascending aorta (OR,

Table 1. Demographic data for patients who were or were not anesthetized with sevoflurane

Parameter	Without sevoflurane	With sevoflurane	*P* value
No. of patients	48	58	
Age (years)	62 ± 11	63 ± 10	0.98
Height (cm)	161 ± 14	160 ± 13	0.78
Weight (kg)	62 ± 11	63 ± 11	0.64
LVEF (%)	58 ± 12	60 ± 11	0.43
Hypertension	18/48 (38%)	27/58 (47%)	0.35
Beta-blocker	28/48 (58%)	28/58 (48%)	0.30
Male/female	20/48 (42%)	33/58 (57%)	0.12
Preoperative Hb ($g \cdot dl^{-1}$)	12.7 ± 1.1	12.9 ± 0.9	0.45
Total CPB time (min)	106 ± 22	112 ± 19	0.19
CPP (mmHg)	61 ± 11	60 ± 10	0.93
DeltaTT (°C)	1.1 ± 0.4	1.1 ± 0.5	0.80
Sjv_{O_2} 50% time (min)	24.3 ± 5.9	23.6 ± 5.6	0.37
Diabetes mellitus	13	12	0.44
Atherosclerosis of the aorta	7	5	0.33
Dosage of fentanyl (mg)	1.5 ± 1.1	0.9 ± 0.9	0.07

Data are expressed as means ± SD
LVEF, left ventricular ejection fraction; Hb, hemoglobin; CPB, cardiopulmonary bypass; CPP, cerebral perfusion pressure; deltaTT, peak tympanic temperature during CPB minus the lowest TT during CPB; Sjv_{O_2} 50% time, time for which the jugular venous oxygen saturation was less than 50% during CPB

Table 2. Postoperative cognitive dysfunction at 6 months after surgery for the two groups

Parameter	Without sevoflurane	With sevoflurane	*P* value
Cognitive dysfunction at 6 months	11/48 (23%)	13/58 (22%)	0.94
Mini mental test	40.9 ± 4.3	40.5 ± 4.5	0.88
Rey learning test	25.1 ± 6.1	23.5 ± 6.0	0.51
Trail making A	44.1 ± 4.4	46.5 ± 5.3	0.47
Trail making B	187.1 ± 32.9	199.5 ± 41.7	0.34
Digit span forward	11.2 ± 3.4	12.9 ± 2.9	0.30
Grooved pegboard	21.9 ± 4.4	23.9 ± 5.1	0.32

Data are expressed as means ± SD
The Rey learning test is the Rey auditory verbal learning test

Table 3. Characteristics of patients with and without postoperative cognitive dysfunction at 6 months after surgery

Parameter	No cognitive dysfunction	Cognitive dysfunction	*P* value
No. of patients	82	24	
Age (years)	61 ± 11	67 ± 10	0.02
Height (cm)	163 ± 11	162 ± 9	0.53
Weight (kg)	61 ± 10	66 ± 14	0.06
LVEF (%)	59 ± 10	60 ± 12	0.73
Hypertension	34/82 (41%)	11/24 (46%)	0.70
Beta-blocker	43/82 (52%)	13/24 (54%)	0.90
Male	42/82 (51%)	11/24 (46%)	0.64
Preoperative Hb ($g \cdot dl^{-1}$)	12.8 ± 1.0	12.5 ± 1.0	0.22
Total CPB time (min)	108 ± 21	111 ± 17	0.61
CPP (mmHg)	61 ± 12	61 ± 10	0.98
deltaTT (°C)	1.1 ± 0.5	1.1 ± 0.6	0.90
Sjv_{O_2} 50% time (min)	24 ± 5	23 ± 9	0.82
Diabetes mellitus	12/82 (15%)	13/24 (54%)	0.01
Atherosclerosis of the aorta	6/82 (7%)	6/24 (25%)	0.03
Use of sevoflurane	46/82 (56%)	12/24 (50%)	0.60

Data are expressed as means ± SD

Table 4. Multiple logistic variables of cognitive dysfunction at 6 months after coronary artery bypass graft surgery

	Odds ratio	95%CI	*P* value
Age	1.3	1.0–1.7	0.047
Diabetes mellitus	2.5	1.5–3.1	0.03
Atherosclerosis of the aorta	1.4	1.1–2.0	0.047

CI, confidence interval

1.4; 95%CI, 1.1–2.0; $P = 0.047$), were predictors associated with cognitive impairment 6 months postoperatively (Table 4).

Discussion

We failed to demonstrate that administration of sevoflurane during surgery has ameliorative affects on postoperative cognitive dysfunction in patients undergoing CABG surgery.

Assessing the effects of volatile anesthetics on cerebral ischemia in animal studies, there is reasonable evidence to show that volatile anesthetics have preconditioning effects on the brain [12,18, 19]. In contrast to numerous studies showing the efficacy of volatile anesthetics on cardioprotection, there have been no clinical studies regarding the effects of volatile anesthetics on neuroprotection during cardiac surgery. If volatile anesthetic agents prove to have neuroprotective effects, as suggested by studies in animal models [9,14], the use of volatile anesthetics for their specific antiischemic effect should be further explored. However, our study showed no relationship between the use of sevoflurane and postoperative cognitive dysfunction after CABG surgery.

Several possible mechanisms should be considered for this lack of effect of administration of sevoflurane

during surgery on postoperative cognitive dysfunction. First, as has been reported by Rasmussen et al. [20], who reviewed studies that assess postoperative cognitive dysfunction, there are wide variations in several methodologies, including test batteries, the interval between sessions, the endpoints to be analyzed, the statistical methods, and the definition of neurocognitive deficits in these studies. Second, in this study, the sevoflurane dosage was determined by the patients' hemodynamic stability. The sevoflurane dosage was probably insufficient for neuroprotection. It is possible that the appropriate levels for volatile preconditioning effects might be different for the myocardium and the brain. There is, as yet, no agreement as to the appropriate anesthetic concentrations for volatile preconditioning [18]. In addition, Kawaguchi et al. [21] reviewed the neuroprotective effects of volatile anesthetics against ischemic insults and suggested that in the case of volatile agents and propofol, neuroprotection may be sustained if the ischemic insult is relatively mild. Thus, it is possible that the degree of ischemia during CABG may be different from those observed in animal studies. Finally, the anesthetic regime used may have had some effects on our result. De Hert et al. [10] showed that sevoflurane has differential protective effects on cardiac function. Further studies using standardized techniques would be of benefit to determine the relationship between postoperative cognitive dysfunction and the use of sevoflurane in patients undergoing CABG surgery.

The present study demonstrated that increased age, diabetes mellitus, and the presence of atherosclerosis in the ascending aorta were risk factors for the development of cognitive impairment at 6 months after CABG surgery with CPB. These findings are consistent with the observations of other studies [2–4,8]. Arrowsmith et al. [22] reviewed the etiology of postoperative neurological and neurocognitive dysfunction and showed that although this etiology is multifactorial, increased age, diabetes mellitus, and aortic atheromatous disease are important factors related to neurological and neurocognitive dysfunction.

Study limitations

In this study, we focused on the influence of the administration of sevoflurane on postoperative cognitive dysfunction. We did not examine the cardioprotective effects of the administration of sevoflurane. It is possible that improved cardiac function after surgery may be related to reduced postoperative cognitive dysfunction. Extensive studies are needed to clarify the mechanisms by which volatile anesthetics affect postoperative cognitive dysfunction after CABG surgery.

In this study, the sevoflurane concentration was determined by the patients' hemodynamic stability, resulting in different sevoflurane concentrations being given to each patient. Hence, we cannot rule out the possibility that neuroprotective effects might differ from patient to patient in the sevoflurane group due to different sevoflurane doses being administered.

We followed the recommendations for neuropsychological testing and the definition of postoperative cognitive dysfunction provided in the consensus statements on the assessment of central nervous system disorders [17]. The tests used in this study are widely accepted for evaluation of postoperative cognitive dysfunction. There have been many problems regarding definitions of postoperative cognitive dysfunction. Rasmussen et al. reported in a review of the literature that postoperative cognitive function has been extensively researched but is a difficult matter to evaluate [20].

This study was a retrospective evaluation, with the number of patients evaluated being too small to identify with certainty any clinical neuroprotective effects of sevoflurane on the brain during CABG surgery. Although perioperative factors such as surgical technique and surgical skills were almost identical during the examination period, we cannot rule out the possibility that other unknown factors may have affected our results.

In conclusion, the present study demonstrated that increased age, diabetes mellitus, and the presence of atherosclerosis of the ascending aorta are risk factors for the development of cognitive impairment 6 months after CABG surgery with CPB. In contrast, no relationship was found between the use of sevoflurane and postoperative cognitive dysfunction after CABG surgery. Further prospective studies are necessary to clarify any ameliorative effects of volatile anesthetics on postoperative cognitive dysfunction.

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