Protective Effect of Low-dose Sevoflurane Inhalation and Propofol Anesthesia on the Myocardium after Carotid Endarterectomy: A Randomized Controlled Trial

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Abstract

Background: Myocardial infarction is an important cause of mortality after carotid endarterectomy (CEA). Sevoflurane provides myocardial protection to patients undergoing coronary surgery, but whether it also reduces the incidence of myocardial injury in CEA patients is unclear. In this study, we evaluated the cardioprotective effect of low-dose sevoflurane with propofol in patients undergoing CEA.

Methods: This was a single-center, prospective, randomized study conducted between November 2011 and December 2013. The study population of 122 patients who underwent CEA were randomly assigned to two groups. Group A (n = 62) received propofol for anesthetic maintenance, and Group B (n = 60) additionally received 0.8% end-tidal sevoflurane. The bispectral index was kept at 40–60. Myocardial injury, defined as cardiac troponin I (cTnI) levels >0.04 ng/ml, was the primary end-point. Levels of cTnI were measured before anesthesia, and at 4, 24, and 72 h after surgery. Perioperative hemodynamic parameters and adverse cardiovascular events after surgery were also recorded.

Results: Myocardial injury was detected in 18 patients in Group A and 7 in Group B. The difference was statistically significant (29.0% vs. 11.7%, \( P = 0.018 \)). The hemodynamic parameters were comparable between the groups, as were adverse cardiovascular events (\( P = 0.619 \)).

Conclusions: Low-dose sevoflurane inhalation along with propofol reduces the incidence of myocardial injury in symptomatic patients after CEA.

Key words: Carotid Endarterectomy; Myocardial Injury; Propofol; Sevoflurane

INTRODUCTION

Carotid endarterectomy (CEA) is an effective surgical procedure to reduce the risk of stroke in symptomatic patients with severe stenosis of the internal carotid artery.\(^1,^2\) Myocardial injury after noncardiac surgery is common\(^3\) and often associated with adverse cardiac events and mortality, both in the short- and long-term.\(^4,^5\) A recent study reported that the incidence of myocardial injury (cardiac troponin I [cTnI] > 0.04 ng/ml) shortly after CEA was as high as 42.5%,\(^6\) but there are few methods to reduce postoperative myocardial injury. Walsh et al.\(^7\) introduced remote ischemic preconditioning during CEA to reduce myocardial injury, but the sample size in their study was very small, and the procedure was very time-consuming. Sevoflurane exhibits cardioprotective effects during cardiac surgery\(^8\) and improves clinical as well as biochemical parameters during coronary artery bypass surgery.\(^9,^10\) Moreover, sevoflurane significantly reduces the number of cardiac complications in CEA,\(^11\) although the associated vasodilation may cause cerebral steal and thus cerebral ischemia.\(^12\) However, sevoflurane dilates cerebral vessels in a concentration-dependent manner, such that low-dose sevoflurane induces only mild vasodilation.\(^13\) In humans, sevoflurane at an end-tidal concentration of 0.5–1 vol% provides endothelial protection against ischemia/reperfusion injury.\(^14\) Based on these previous findings, we carried out a randomized controlled study to test the hypothesis that low-dose sevoflurane along with propofol decreases the incidence of myocardial injury in patients undergoing CEA.

METHODS

The study was conducted at Xuan Wu Hospital, Capital Medical University, China, between November 2011 and December 2013. The inclusion criteria were: Symptomatic patients with severe atherosclerotic stenosis of the internal carotid artery (≥70% of the luminal diameter diagnosed by Color Doppler) and a normal preoperative cTnI value (≤0.04 ng/ml). Patients were excluded if they had a history of acute myocardial infarction within 3 months,
All patients were transferred to the neurosurgical ward, stopped. The tracheal tube was removed when spontaneous of 35–45 mmHg. At the end of surgery, all anesthetics were removed. Volume-controlled ventilation and respiratory frequency and atropine, 0.25–0.5 mg i.v. for a heart rate <50 bpm. In MAP >30% above the ward baseline value; esmolol, 0.8% end-tidal sevoflurane combined with propofol the day before surgery. Randomization was based on a computer-generated randomization list, and the random number was sealed in an envelope until it was delivered to the patient. Patients, laboratory personnel, statisticians, and outcome assessors were blinded to the allocation. The study was approved by the ethics committee of our hospital. All patients provided written informed consent before entering the study.

Perioperative management
Patients were managed according to standard protocols by the same neurosurgical and anesthesia teams. All patients were required to fast for 8 h before the operation and were premedicated with intramuscular injections of atropine (0.01 mg/kg) and phenobarbital sodium (2 mg/kg) 30 min before the induction of anesthesia. Medications for comorbidities were continued until the morning of surgery. Anesthetic monitors (five-lead electrocardiogram, pulse oximetry, noninvasive blood pressure, and temperature) were used for all patients. In each patient, the blood-pressure cuff was placed on the arm that had a higher blood pressure. If the blood pressure in the two arms was the same, the cuff was placed on the right arm. Blood pressure was measured continuously throughout surgery. A pulsed Transcranial Doppler (TCD) transducer (EMS-9PB, Delica Electronics, Shenzhen, China) was placed over the temporal bone to measure the middle cerebral artery velocity. Anesthesia was induced with etomidate (0.3 mg/kg), fentanyl (0.03 mg/kg), and rocuronium (0.6 mg/kg) through an intravenous (i.v.) line in the patient's hand, forearm, or arm. For anesthetic maintenance, patients in Group A received i.v. propofol (3–5 mg·kg⁻¹·h⁻¹) and remifentanil (0.1–0.15 µg·kg⁻¹·min⁻¹), and patients in Group B received 0.8% end-tidal sevoflurane, propofol (2–5 mg·kg⁻¹·h⁻¹), and remifentanil (0.1–0.15 µg·kg⁻¹·min⁻¹). The speed of propofol infusion was adjusted to maintain the bispectral index at 40–60. The following drugs were given to maintain stable hemodynamics during surgery: Phenylephrine, 25–50 µg i.v. for changes in mean arterial pressure (MAP) >30% compared to the ward baseline value; urapidil, 5–10 mg i.v. for changes in MAP >30% above the ward baseline value; esmolol, 20–40 mg i.v. for a heart rate >100 beats per minute (bpm); and atropine, 0.25–0.5 mg i.v. for a heart rate <50 bpm. Volume-controlled ventilation and respiratory frequency were adjusted to achieve a tidal volume of 8–10 ml/kg body weight and an intraoperative end-tidal carbon dioxide tension of 35–45 mmHg. At the end of surgery, all anesthetics were stopped. The tracheal tube was removed when spontaneous respiration returned, and the bispectral index exceeded 80. All patients were transferred to the neurosurgical ward, and five-end-electrocardiogram, blood pressure, heart rate, and pulse oximetry were continuously monitored for 24 h. TCD monitoring was used at intervals. For all patients, i.v. patient-controlled analgesia was provided using fentanyl and ondansetron. Adverse cardiac events were diagnosed by a cardiologist during the patient’s hospitalization. Patient data were obtained from the hospital information system.

Study endpoints
The primary end-point was the rate of myocardial injury, as measured by cTnI. In the healthy population, the 99 percentile value of cTnI is 0.04 ng/ml;[15] thus, the myocardial injury was defined as a cTnI > 0.04 ng/ml.[16] Blood samples (3 ml) were taken from the peripheral vein before anesthesia and at 4, 24, and 72 h after surgery. This protocol was similar to the one used in a previous study.[16] Samples were immediately centrifuged at 3000 r/min for 10 min, and the serum layer was aspirated and stored at −70°C until analysis. Serum cTnI concentrations were measured using an AxSYM troponin I analyzer (Abbott Laboratories, Longford, Ireland). The lower limit of detection was 0.02 ng/ml. The assays were performed by a technician who was blinded to the clinical data. Myocardial infarction was diagnosed if the cTnI value exceeded 1.5 ng/ml and myocardial ischemia if the cTnI value was between 0.5 ng/ml and 1.5 ng/ml.[17]

The secondary outcome was hemodynamic stability, which was determined by measuring blood pressure and heart rate before clamping, 10 min after clamping, and 10 min after declamping. Resting blood pressure and heart rate were measured at 4, 24, 48, and 72 h after surgery. Doses of vasoactive drugs administered intraoperatively and during the first 3 postoperative days were recorded.

We also compared the adverse cardiac events, including acute coronary syndrome (ACS), myocardial infarction, heart failure, and new-onset arrhythmia, during the patients’ hospital stay after surgery. ACS was defined as resting angina, new-onset angina, and progressive angina with ST-segment depression or T-wave inversion. The incidence of severe neurological complications, such as stroke and cerebral hyperperfusion syndrome, was recorded as well.

Statistical analysis
The primary end-point was the rate of positive cTnI within the first 3 days after surgery. A previous study reported that the rate of myocardial injury was 42.5% in patients with propofol anesthesia after CEA.[16] Our pilot study in 20 patients administered 0.8% end-tidal sevoflurane combined with propofol showed that the rate of positive cTnI was 15%. With the (two-sided) α error set at 0.05 and the β error set at 0.1 (power of 90%), 54 patients per group were needed. Considering a 10% discontinuation rate, we recruited 60 patients per group.

Normally distributed data were presented as mean ± standard deviation. Means were compared using a one-way analysis of variance (ANOVA). Categorical variables are expressed as percentages. Proportions were compared using the fourfold
Results

From November 2011 to December 2013, 126 patients were randomly assigned to Group A (n = 65) or Group B (n = 61). Of these, 122 patients completed the study [Figure 1].

Baseline characteristics of the patients

Table 1 shows the baseline characteristics and demographic data of the patients. Baseline characteristics were balanced between the two treatment groups. Coronary artery disease was predefined as a history of myocardial infarction or coronary revascularization, or a >50% stenosis on coronary angiography, or myocardial ischemic induced by radionuclide or echocardiographic stress testing.\(^{[18]}\)

Cardiac troponin I outcomes

The cTnI values of all the patients were within the normal range (≤0.04 ng/ml) before surgery. During the first 3 postoperative days, 25 patients had a peak cTnI value >0.04 ng/ml, 18 (29.0%) from Group A and 7 (11.7%) from Group B; this result was statistically significant (P = 0.018). Most cTnI values (17/25) reached a peak on the 1st postoperative day, without a significant difference between the two groups (12/62 vs. 5/60, P = 0.079). Nine patients (14.5%) in Group A and 3 (5%) patients in Group B had peak cTnI values >0.5 ng/ml (P = 0.078). In all patients, the cTnI values were below the diagnostic cut-off for myocardial infarction (1.5 ng/ml; Figure 2).

The incidence of myocardial injury (cTnI >0.04 ng/ml) was compared in patients with a history of hypertension, coronary artery disease, ST-segment depression (>1 mm), cerebral ischemia, hyperlipidemia, or diabetes mellitus. In patients with hypertension, 14 (35.0%) in Group A and 6 (14.3%) in Group B had a peak cTnI value >0.04 ng/ml, P = 0.079. In patients with coronary artery disease, eight patients (80.0%) in Group A and four patients (33.3%) in Group B suffered myocardial injury (P = 0.043). In patients with ST-segment depression, 13 (65.0%) in Group A and 5 (22.7%) in Group B had a cTnI >0.04 ng/ml (P = 0.006). In patients with cerebral ischemia, 15 (38.5%) in Group A and 4 (10.8%) in Group B had a peak cTnI value >0.04 ng/ml (P = 0.016; Table 2).

Hemodynamic stability

There were no significant differences in any of the hemodynamic parameters either within or between Groups A and B [Table 3].

The percentage of patients who required atropine, esmolol, phenylephrine, or urapidil during the operation and the first 3 days postoperatively was not significantly different between the two groups (4.8% vs. 1.7%, 38.7% vs. 28.3%, 86.7% vs. 81.7%, and 58.1% vs. 61.7%, respectively; P = 0.635) [Table 4].

Adverse cardiovascular events

Adverse cardiovascular events in the hospital were comparable between Groups A and B (4.8% vs. 1.7%; P = 0.619). New-onset angina was reported in two patients in Group A, and one in Group B. Frequent ventricular extrasystole was reported in one patient in Group A. There were no severe neurological complications during hospitalization [Table 4].

Discussion

In our study, the incidence of myocardial injury, as detected by cTnI >0.04 ng/ml, after CEA was lower in patients who received low-dose sevoflurane combined with propofol than in patients who received propofol alone. In-hospital adverse cardiovascular events did not significantly differ between the two groups. However, the relatively low incidence of myocardial injury in Group B showed that, in patients undergoing CEA, low-dose sevoflurane had a protective effect on the myocardium that extended to the first 3 postoperative days.

Our results are consistent with those of a previous study, in which the number of cardiac complications in CEA patients was significantly lower in those administered sevoflurane anesthesia than in those who received propofol.\(^{[11]}\)
Many studies have demonstrated the myocardial protective effect of sevoflurane in cardiac surgery, but its efficacy in noncardiac surgery is controversial. Some investigators found no difference between propofol and sevoflurane in myocardial protection in patients undergoing noncardiac surgery. A meta-analysis of 6219 noncardiac surgery patients from 79 randomized controlled studies was inconclusive. In that study, perioperative myocardial infarction and death served as the endpoints, but there were no cases of either one. However, myocardial infarction or ischemia may be clinically asymptomatic and thus evade detection unless more sensitive measure are used. Perioperative cTnl was shown to be sufficiently sensitive and specific to diagnose myocardial injury, and it is independent of ischemic symptoms. In their comparison of postoperative cTnl values in 88 noncardiac surgery patients, Zangrillo et al. found similar incidences of postoperative detectable cTnl and median peak cTnl values in the sevoflurane group versus the propofol group, but they did not identify the cut-off value of an abnormal cTnl or did they compare the incidence of myocardial injury.

In our study, the incidence of myocardial injury during the first 3 postoperative days was 29.0% in the propofol group, which was much lower than the 42.5% reported by Feng et al., perhaps reflecting the different study protocols. Moreover, in that study, the patients were administered ephedrine to elevate blood pressure. Ephedrine is a noncatecholamine sympathomimetic agent that stimulates α- and β-adrenergic receptors both directly and indirectly. However, because it increases heart rate and myocardial oxygen consumption, its use is contraindicated for myocardial protection. In this study, we used phenylephrine, an α-agonist that causes reflex bradycardia in response to an increase in peripheral vascular resistance. Unlike ephedrine, phenylephrine confers myocardial protection. Another reason for the different incidences of myocardial injury in the two studies may have been the differences in patient age, since in the study by Feng et al., 40% of the patients were older than 70 years of age compared to 29% in our study. Age ≥70 years was shown to be an independent risk factor for postoperative cardiac complications and mortality.

Mutch et al. reported that hemodynamic instability is associated with myocardial ischemia during CEA. In our patients, the MAP was maintained at 70–130% of the ward baseline value and heart rate at 50–100 bpm. Hemodynamic parameters did not significantly differ between the two groups and the doses of vasoactive drugs used both during the operation and during the first 3 postoperative days were comparable. Thus, differences in hemodynamics do not explain our findings.

This study had several limitations. First, we did not follow-up on the patients after hospital discharge. Several studies have shown that elevated cTnl values are associated with an increased frequency of delayed cardiac complications. Whether low-dose sevoflurane leads to

### Table 1: Baseline characteristics

| Items                        | Group A (n = 62) | Group B (n = 60) | P  |
|------------------------------|-----------------|-----------------|----|
| Age (years)                  | 65.8 ± 5.9      | 66.7 ± 6.4      | 0.410 |
| Males, n (%)                 | 54 (87.1)       | 56 (93.3)       | 0.248 |
| BMI (kg/m²)                  | 24.0 ± 3.0      | 24.1 ± 2.7      | 0.783 |
| Smoking habit, n (%)         | 32 (51.6)       | 29 (48.3)       | 0.717 |
| Hyperlipidemia, n (%)        | 10 (16.1)       | 10 (16.7)       | 0.936 |
| Diabetes mellitus, n (%)     | 18 (29.0)       | 14 (23.3)       | 0.474 |
| Cerebral ischemia, n (%)     | 39 (62.9)       | 37 (61.7)       | 0.888 |
| Hypertension, n (%)          | 40 (64.5)       | 42 (70.0)       | 0.519 |
| Coronary artery disease, n (%) | 10 (16.1)   | 12 (20.0)       | 0.578 |
| ST-segment depression, n (%) | 20 (32.3)       | 22 (36.7)       | 0.608 |
| Duration of operation (min)  | 196.1 ± 25.9    | 205.2 ± 94.3    | 0.515 |
| Infusion volume (ml)         | 1622.6 ± 371.7  | 1665.0 ± 348.3  | 0.517 |
| Amount of bleeding (ml)      | 57.6 ± 23.7     | 54.4 ± 24.9     | 0.474 |
| Urinary volume (ml)          | 508.1 ± 229.8   | 510.3 ± 237.3   | 0.957 |
| Fentanyl (mg)                | 0.3 ± 0.1       | 0.3 ± 0.1       | 0.754 |
| Remifentanil (mg)            | 1.6 ± 0.3       | 1.5 ± 0.4       | 0.222 |

*Significant at P<0.05. cTnl: Cardiac troponin I.

### Table 2: Incidence of myocardial injury in patients with comorbidities

| Comorbidities             | Group A | Group B | P  |
|---------------------------|---------|---------|----|
|                           | cTnl (+), n (%) | cTnl (+), n (%) |    |
| Hypertension              | 40 (14.3) | 6 (14.3) | 0.029* |
| Coronary artery disease   | 10 (33.3) | 4 (33.3) | 0.043* |
| ST-segment depression      | 20 (22)  | 15 (18.5) | 0.006* |
| Cerebral ischemia         | 39 (10.8) | 4 (10.8) | 0.016* |
| Hyperlipidemia            | 10 (60)  | 4 (48)  | 0.656 |
| Diabetes mellitus         | 18 (50)  | 7 (50)  | 1.000 |

### Table 3: Hemodynamic parameters

| Items (bpm) | Before clamping | 10 min after clamping | 10 min after declamping | 4 h after operation | 24 h | 48 h | 72 h | P  |
|-------------|-----------------|-----------------------|-------------------------|---------------------|------|------|------|----|
| HR (bpm)    | Group A         | 67.2 ± 8.4            | 68.0 ± 9.3              | 68.5 ± 8.5          | 68.6 ± 7.3 | 70.3 ± 7.8 | 70.5 ± 7.6 | 71.0 ± 7.6 | 0.068 |
|             | Group B         | 67.0 ± 10.0           | 68.6 ± 11.0             | 68.0 ± 11.0         | 68.7 ± 9.3 | 69.1 ± 9.6 | 69.6 ± 8.9 | 71.4 ± 7.9 | 0.298 |
| MAP (mmHg)  | Group A         | 83.3 ± 8.6            | 83.7 ± 9.3              | 81.0 ± 7.2          | 82.3 ± 5.9 | 84.1 ± 5.9 | 83.9 ± 6.2 | 83.6 ± 7.8 | 0.228 |
|             | Group B         | 83.6 ± 9.2            | 83.2 ± 8.3              | 81.3 ± 8.4          | 84.3 ± 8.2 | 84.2 ± 6.2 | 84.0 ± 6.0 | 81.3 ± 7.8 | 0.132 |

Data are reported as mean ± SD. HR: Heart rate; MAP: Mean arterial pressure; SD: Standard deviation.
Table 4: Proportion of patients who required vasoactive drugs and incidence of adverse cardiovascular events

| Items                                 | Group A (n = 62) | Group B (n = 60) | P   |
|---------------------------------------|-----------------|-----------------|-----|
| Vasoactive drugs                      |                 |                 |     |
| Atropine                              | 3 (4.8)         | 1 (1.7)         | 0.635|
| Esmolol                               | 24 (38.7)       | 17 (28.3)       | 0.225|
| Phenylephrine                         | 52 (86.7)       | 49 (81.7)       | 0.747|
| Urapidil                              | 36 (58.1)       | 37 (61.7)       | 0.685|
| Adverse cardiovascular events         |                 |                 |     |
| Acute coronary syndrome               | 2 (3.2)         | 1 (1.7)         | 1.000|
| Arrhythmia                            | 1 (1.6)         | 0 (0)           | 1.000|

a medium- to long-term reduction in cardiac complications was not investigated in this study. Second, the samples sizes of the patients with different comorbid conditions were too small to obtain statistically relevant results. Third, because it was difficult to blind the anesthesiologists during the therapeutic procedure, this may have been a source of bias in this study.

Nonetheless, our results support the use of low-dose sevoflurane combined with propofol for anesthetic maintenance in symptomatic patients undergoing CEA. Compared to propofol alone, the two drugs significantly reduced the incidence of myocardial injury during the first 3 postoperative days after CEA.

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