Rational Study Design is Important for Assessing Myocardial Protection of Anesthetics

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To the Editor: In a single-center, prospective randomized clinical study including 122 elderly patients undergoing the carotid endarterectomy (CEA), Wang *et al*.[1] showed that compared with propofol-based total intravenous anesthesia, low-dose sevoflurane inhalation along with propofol reduced the incidence of postoperative myocardial injury. Given the postoperative myocardial injury is a common cardiovascular adverse event and has been shown as an independent predictor of increased short-term mortality after noncardiac surgery, their findings have potential implications. We congratulate the authors for conducting this clinically useful research, but would like to ask some questions about their methodology.

First, the authors stated that patients were excluded if the fasting blood glucose was >7.0 mmol/L. However, the two study groups included 32 patients with diabetes mellitus. We would like to know what diagnostic standards of diabetes mellitus were used in this study.

Second, this study did not include perioperative hemoglobin levels of the patients. It has been shown that in patients undergoing vascular surgery, preoperative hemoglobin levels, postoperative hemoglobin levels, and intraoperative hemoglobin decreases are all related to an increased risk of 30-day postoperative cardiovascular adverse events and mortality, especially for postoperative hemoglobin levels.[2]

Third, the bispectral index (BIS) was used for monitoring of anesthetic levels and was maintained at a large range between 40 and 60 throughout the surgery. The authors did not specify whether the BIS values at all observed points were comparable between groups. This is an important prerequisite to rightly compare intraoperative consumptions of anesthetic and opioid drugs between groups. We noted that in this study, total dosages of fentanyl and remifentanil used in the two groups are comparable. Because sevoflurane has intrinsic analgesic property, whereas, propofol does not; it is difficult to homogenize anesthetic levels between groups, especially for the analgesic component. This may constitute a bias on the homogeneity between groups. Furthermore, only 0.8% end-tidal sevoflurane (about 0.5 minimum alveolar concentration [MAC]) was added to propofol-based total intravenous anesthesia in the treatment group. It has been reported that only when concentrations of sevoflurane are 1 MAC or more, pharmacological preconditioning by sevoflurane can produce a significant protection against myocardial ischemia-reperfusion injury in the rat heart *in vivo*.[3] Thus, we would argue that decrease incidence of postoperative myocardial injury in the treatment group may only be attributable to the improved anesthetic level, rather than the myocardial protection provided by sevoflurane.

Fourth, comparing means of intraoperative heart rate and mean arterial pressure between groups are barely meaningful. The authors should provide and compare the occurrence of intraoperative hemodynamic disorders in the two groups. In the patients undergoing noncardiac surgery, intraoperative hypotension, tachycardia, and hypertension have been associated independently with postoperative myocardial injury and adverse outcomes.[4,5] In fact, even short duration of an intraoperative mean arterial pressure <55 mmHg (1 mmHg = 0.133 KPa) can result in postoperative myocardial injury, with an independent graded relationship between duration of intraoperative hypotension and postoperative myocardial injury.[6]

Finally, it is somewhat surprising about the results of this study that incidence of postoperative myocardial injury is significantly higher in the treatment group than in the control group, but postoperative cardiovascular adverse events are not significantly different between groups. Besides a small sample size may not exclude a high-risk of α statistical error, a 3-day postoperative follow-up period also was too short to assess the clinically important variables, such as the duration of hospital stay, intensive care unit admission, medical costs, and in-hospital mortality, etc. Thus, an important question that remains unanswered in this study is whether the favorable effect of low-dose sevoflurane inhalation along with propofol on myocardial injury following CEA can be translated to clinical benefit. To address this issue, we believe that the large-scale clinical trials are still required, and these new studies should have enough power for clinically important endpoints, especially for postoperative cardiovascular adverse events and mortality.

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Authors' Reply

I'm glad to receive your letter about our article. Our answers to the questions are as follow.

First, the diagnosis of diabetes mellitus came from the patient's history medical record. Diabetes mellitus was diagnosed by the endocrinologist if any of the following criteria were met: (i) Fasting plasma glucose level ≥7.0 mmol/L, (ii) 75 g oral glucose tolerance test 2-h value ≥11.1 mmol/L, (iii) Casual plasma glucose level ≥11.1 mmol/L. The patient's glucose was well-controlled with insulin or other hypoglycemic agents before surgery. Hyperglycemia is a causal factor for increased levels of macrophage migration inhibitory factor which plays a role in the development of cardiomyopathy occurring in patients with type 2 diabetes.[7] We excluded the patients who had fasting glucose more than 7.0 mmol/L to reduce the interference of hyperglycemia on the results.

Second, patients were excluded if they had hemoglobin <90 g/L. Moreover, the amount of bleeding was small in both groups (57.6 ± 23.7 ml vs. 54.4 ± 24.9 ml). The differences of the amount of bleeding and the infusion volume between the two groups were not statistically significant.

Third, we introduced the methods for anesthetic maintenance in this article. The BIS was maintained at 40–60 in both groups. The range of BIS 40–60 was widely accepted in clinical practice. BIS is more reliable with propofol than with other anesthetics. Patients in Group B received low-dose sevoflurane and propofol, the level of BIS might not show the depth of anesthesia exactly.[8] Hence, it is very difficult to really homogenize anesthetic levels between the two groups. It is a pity that we did not compare the exact BIS values at different intraoperative time points, but we maintained the BIS values between 40 and 60, which is a widely accepted index to show adequate sedation level. The myocardial injury was defined as a cardiac troponin I >0.04 ng/ml. It's more sensitive to evaluate the effect of anesthetics on the myocardium than cardiac function and myocardial infarction. Only severe damage to the myocardium induced myocardial infarction and decreased cardiac function.

Fourth, in this article, we introduced the methods to maintain stable hemodynamics during surgery. Although the incidences of hypotension, tachycardia, and hypertension may be more direct to describe the hemodynamic disorders, we compared the percentage of patients who required atropine, esmolol, phenylephrine or urapidil in the two groups. These data showed us the intraoperative hemodynamic disorders as well. We usually supported the blood pressure during the internal carotid artery cross-clamping, decreased the blood pressure after the internal carotid artery declamped, and we monitored and controlled the blood pressure when the patients went back to the neurosurgical ward. Hemodynamic disorders were related to cardiac adverse events, so it was meaningful to compare the mean heart rate and mean arterial pressure between groups.

Finally, our results showed that 18 patients in Group A and 7 in Group B suffered a myocardial injury during the first 3 days after CEA. Most patients went back to the neurosurgical ward after CEA in our hospital. No patients went to intensive care unit in our study, and they left hospital at the 4th or 5th day after surgery. As we said in our article, there were several limitations, such as a long-term reduction in complications was not investigated in this study. Every clinical study had limitations. More clinical trials were needed to investigate the issue on the perioperative myocardial protection of CEA.

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Conflicts of interest

There are no conflicts of interest.

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