Volatile Agents for Cardiac Protection in Noncardiac Surgery: A Randomized Controlled Study

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Objective: **Volatile anesthetics reduce the risk of myocardial infarction and mortality in coronary artery surgery. Recently, the American College of Cardiology/American Heart Association Guidelines suggested the use of volatile anesthetic agents for the maintenance of general anesthesia during noncardiac surgery in patients at risk for perioperative myocardial ischemia, but no randomized experience to document the cardioprotective effects of these agents exists in this setting. Therefore, the authors performed a prospective, randomized, controlled trial to compare the effects of sevoflurane versus total intravenous anesthesia, in terms of postoperative cardiac troponin I release in patients undergoing noncardiac surgery.**

Design: **A randomized, controlled trial.**

Setting: **A teaching hospital.**

Participants: **Eighty-eight consecutive patients undergoing noncardiac surgery.**

Interventions: **Patients were allocated randomly to receive either volatile anesthetic (44 patients) as the main anesthetic agent or total intravenous anesthesia (TIVA) (44 patients).**

Measurements: **Postoperative cardiac troponin I release was measured as a marker of myocardial necrosis. Patients with detectable postoperative troponin I in the sevoflurane group (12/44, 27.3%) were similar to those in the propofol group (9/44, 20.5%; $p = 0.6$). There was no significant reduction of postoperative median peak cTnI release (0.16 ± 0.71 ng/mL in the sevoflurane group compared with the TIVA group, 0.03 ± 0.08 ng/mL; $p = 0.4$). Three patients died at the 1-year follow-up for noncardiac causes (2 in the TIVA group).**

Conclusions: **In the authors' experience, patients undergoing noncardiac surgery did not benefit from anesthesia based on halogenated anesthetics. Further studies are necessary to evaluate the cardioprotective effects of volatile agents in noncardiac surgery.**

KEY WORDS: halogenated anesthetics, volatile anesthetics, total intravenous anesthesia, noncardiac surgery, thoracic surgery, vascular surgery, cardiac troponin I, myocardial damage, anesthesia

CARDIAC DAMAGE IS one of the possible perioperative complications of cardiac and noncardiac surgery[1-4] and can lead to prolonged hospital stay as well as an increased perioperative morbidity and mortality rate. Cardiac troponin (cTn) is the most popular biomarker for myocardial damage, presenting with high myocardial tissue specificity and sensitivity, capable of detecting myocardial necrosis even at minimal amounts.[5] cTn predicts short- and long-term outcomes after cardiac[6] and noncardiac surgery.[7,8] The extent of cTn elevation is related directly with the magnitude of myocardial damage.[9]

Anesthetic strategies can directly affect the rate and entity of myocardial injury and subsequent patient outcomes. Volatile anesthetics, commonly used to induce and maintain hypnosis, analgesia, amnesia, and muscle relaxation, have shown the ability to improve postischemic recovery at the cellular level in isolated hearts and in animals, mainly through pharmacologic preconditioning.[10,11] There are 4 published articles suggesting a reduction in mortality in patients undergoing cardiac surgery and receiving volatile agents,[12-15] and a recent international consensus conference supported this point.[16,17] There is no published article suggesting a reduction in mortality in patients undergoing cardiac surgery with total intravenous anesthesia (TIVA).

Recent American College of Cardiology/American Heart Association Guidelines suggest that patients at high risk for myocardial ischemia undergoing noncardiac surgery who are hemodynamically stable could benefit from the use of volatile agents for the maintenance of anesthesia.[18] Whether such cardioprotective properties exist in noncardiac surgery settings is still unknown, and sufficient evidence is not available.[19] Recently, a meta-analysis of 79 randomized, controlled studies investigated whether the cardioprotective properties of desflurane and sevoflurane, widely shown in cardiosurgical patients, could possibly translate to a noncardiac surgery setting.[20] In contrast to the previously mentioned guidelines, the results of this meta-analysis could not support the hypothesis that the use of volatile anesthetics can reduce perioperative myocardial injury in noncardiac surgery.

Halogenated agents have cardioprotective properties and also mimic ischemic preconditioning, a powerful cardioprotec-

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tive phenomenon first described in 1986.[21,22] Myocardial cells exposed to brief sublethal episodes of ischemia show an adaptive response leading to an enhanced protection against subsequent lethal ischemia. A key question was whether the cardioprotective or the preconditioning effects of volatile anesthetics are clinically relevant, applicable, and associated with improved cardiac function, ultimately resulting in a better outcome in patients at high risk for myocardial infarction. Therefore, the authors performed a randomized trial to compare the cardioprotective effects of a volatile agent (sevoflurane) versus TIVA in patients undergoing noncardiac (thoracic and vascular) surgery. The hypothesis that volatile anesthetics would decrease perioperative myocardial damage as measured by cTnI release when compared with TIVA was tested.

MATERIALS AND METHODS

This prospective, randomized, single-blind, controlled study was performed according to Declaration of Helsinki principles. Ethical committee approval was obtained, and each patient signed a written informed consent. Consecutive patients with a Lee index ≥2 scheduled for elective lung surgery and major peripheral vascular surgery at a university hospital were assigned randomly to receive sevoflurane as the main anesthetic agent or a propofol-based TIVA. This article was written following the www.consort-statement.org checklist.

All subjects requiring one-lung ventilation for lung (using either thoracotomic or thoracoscopic approach) or peripheral revascularization surgery were eligible if they were over 18 years of age, signed the written informed consent, and planned for general anesthesia. Exclusion criteria were a previous unusual response to an anesthetic use of sulfonylurea, theophylline, or allopurinol.

Patients in the volatile anesthetics group received sevoflurane (Sevorane; Abbott, Queenborough, UK) 1% to 4% end-tidal concentration, corresponding to 0.5 to 2.0 end-tidal minimum alveolar concentration throughout the operation. Patients in the TIVA group received 4 to 6 mg/kg/h of propofol (Diprivan; Astra Zeneca, Brussel, Belgium) via target-controlled infusion.

Preoperative history, laboratory results, and an electrocardiogram were obtained, and an assessment of cardiac complications after noncardiac surgery risk was estimated through the Revised Cardiac Risk Index.[23] All preoperative medications were continued until the day of surgery except for aspirin, which was stopped 1 week before surgery; subcutaneous administration of heparin was started the evening before surgery. Preoperative β-blockers were continued postoperatively, if allowed by heart rate and blood pressure, to avoid withdrawal on the 1st postoperative day.

All patients were premedicated with diazepam (0.1 mg/kg intramuscularly). In patients undergoing thoracotomy, a thoracic epidural catheter was placed for postoperative pain control. Patients were monitored as follows: continuous electrocardiographic leads II and V_5 with ST-segment analysis, pulse oximetry, invasive radial artery blood pressure measurement, capnometry, and urine output. During anesthesia induction, each patient received an intravenous bolus of thiopental sodium (3-5 mg/kg), fentanyl (1-2 μg/kg), and atracurium besylate (0.5-0.6 mg/kg). Anesthesia was maintained with repeated doses of fentanyl (0.5 μg/kg), atracurium besylate, and with either volatile anesthetics or propofol as described previously. The authors recorded any of the following: use of inotropic or vasodilator drugs, intraoperative bleeding, blood product transfusion, intraoperative complication, and the need for postoperative intensive care. After surgery, muscle relaxation was reversed with atropine sulphate, 1 mg, and neostigmine, 2 mg; anesthesia was discontinued; and patients were extubated. Patients were transferred to the thoracic or vascular surgery unit when hemodynamically stable and conscious and with adequate pain control. Postoperative analgesic treatment consisted of tramadol + ketorolac or intravenous paracetamol and epidural administration of 4 to 6 mL/h of ropivacaine 0.2% (2 mg/mL) + sufentanyl (50 μg/mL) in patients with a thoracic epidural catheter.

The primary endpoint of the study was a dichotomous endpoint of detectable versus nondetectable postoperative cTnI. CTnI and an electrocardiogram were collected preoperatively and on the 1st and 2nd postoperative days. Data were collected by trained observers who did not participate in patient care and who were blinded to the anesthetic regimen used. Medical treatment and decision making in the ward were performed by physicians who were blinded to the anesthetic regimen used. Caregivers were interviewed daily for the occurrence of postoperative adverse events, and telephone interviews at 1 and 12 months after surgery were performed.

CTnI was used as a biomarker because it has myocardial tissue specificity and sensitivity and can detect microscopic zones of myocardial necrosis. An increased cTn measurement after surgery is an independent predictor of mortality.[24] Blood was collected in plastic tubes with a clot activator (Becton Dickinson Vacutainer Systems, Franklin Lakes, NJ) and was centrifuged (2,500*g* for 15 minutes) before analysis. CTnI was assayed with AIA 1800 (Tosoh, Tokyo, Japan) according to the manufacturer's instructions. The cTnI method is a 1-step enzyme immunoassay based on the sandwich principle. Sensitivity of the assay is 0.04 ng/mL.

On the basis of previous data investigating postoperative cTnI release,[25,26] the authors anticipated that the number of patients showing a detectable cTnI release would have been 40% and 10% in the TIVA and volatile anesthetics group, respectively. The authors calculated that a sample size of 38 patients per group would be needed. The authors planned to randomize 88 patients in order to account for possible protocol deviation. All patients were analyzed according to the intention-to-treat principle beginning immediately after randomization.

Randomization was conducted by a computer-generated list, and the details were contained in a set of sealed, opaque envelopes that were opened at the beginning of anesthesia. All study personnel, including those involved in cTnI measurement and participants, were blinded to treatment assignment for the duration of the study except the anesthesiologists who were not involved in data collection, data entry, or data analysis.

Data were stored electronically and analyzed by use of Epi Info 2002 software (CDC, Atlanta, GA) and SAS software, version 8 (SAS Institute, Cary, NC). All data analysis was performed according to a pre-established analysis plan. Dichotomous data were compared by using the 2-tailed chi-square test with the Yates correction or the Fisher exact test when appropriate. Continuous measures, including the primary outcome (cTnI), were compared by the Mann-Whitney *U* test. Two-sided significance tests were used throughout. Data are presented as median (25th and 75th percentiles) or as mean (± standard deviation) if not otherwise indicated.

RESULTS

In the study period, 88 consecutive qualifying and consenting patients were assigned randomly to receive either volatile anesthetics (44 patients) or TIVA (44 patients) (Fig 1). The baseline demographic and clinical characteristics of the 2 groups are summarized in Table 1; they showed no statistical difference and confirmed that the patients were at high risk (73% were American Society of Anesthesiologists ≥3, and all patients had a Lee score ≥2). Fentanyl administration did not differ between patients receiving volatile anesthetics (164 ± 57 μg) or TIVA (154 ± 68 μg; $p = 0.1$).

Twenty-one patients had detectable cTnI after surgery, with no differences between the volatile anesthetic group (12/44