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Volatile compared with total intravenous anaesthesia in patients undergoing high-risk cardiac surgery: a randomized multicentre study

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Editor's key points

- Considerable preclinical and clinical evidence supports cardioprotection by volatile anaesthetics in cardiac surgery.
- This possibility was tested in high-risk cardiac surgery patients by comparing sevoflurane anaesthesia with propofol total i.v. anaesthesia.
- There was no significant difference between groups in the composite endpoint of intensive care unit stay and death at 30 days or 1 yr.

Background. The effect of anaesthesia on postoperative outcome is unclear. Cardioprotective properties of volatile anaesthetics have been demonstrated experimentally and in haemodynamically stable patients undergoing coronary artery bypass grafting. Their effects in patients undergoing high-risk cardiac surgery have not been reported.

Methods. We performed a multicentre, randomized, parallel group, controlled study among patients undergoing high-risk cardiac surgery (combined valvular and coronary surgery) in 2008–2011. One hundred subjects assigned to the treatment group received sevoflurane for anaesthesia maintenance, while 100 subjects assigned to the control group received propofol-based total i.v. anaesthesia. The primary outcome was a composite of death, prolonged intensive care unit (ICU) stay, or both. Thirty day and 1 yr follow-up, focused on mortality, was performed.

Results. All 200 subjects completed the follow-up and were included in efficacy analyses, conducted according to the intention-to-treat principle. Death, prolonged ICU stay, or both occurred in 36 out of 100 subjects (36%) in the propofol group and in 41 out of 100 subjects (41%) in the sevoflurane group; relative risk 1.14, 95% confidence interval 0.8–1.62; P=0.5. No difference was identified in postoperative cardiac troponin release [1.1 (0.7–2) compared with 1.2 (0.6–2.4) ng ml^{-1}, P=0.6], 1 yr all-cause mortality [11/100 (11%) compared with 11/100 (11%), P=0.9], re-hospitalizations [20/89 (22.5%) compared with 11/89 (12.4%), P=0.075], and adverse cardiac events [10/89 (11.2%) compared with 9/89 (10.1%), P=0.8].

Conclusions. There was no observed beneficial effect of sevoflurane on the composite endpoint of prolonged ICU stay, mortality, or both in patients undergoing high-risk cardiac surgery.

Clinical trial registration. ClinicalTrials.gov: identifier NCT00821262. Eudra CT (2008-001752-43).

Keywords: anaesthetics i.v., propofol; anaesthetics volatile, sevoflurane; cardiovascular anaesthesia; complications, death; heart, myocardial preservation technique

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Cardioprotective properties of volatile anaesthetics have been clearly demonstrated on a laboratory basis,[1–7] and translation of experimental evidence to clinical studies suggests a benefit in postoperative outcomes.[8–17] A recent international consensus conference indicated that volatile anaesthetics are among the few drugs/techniques/strategies that might be associated with mortality reduction.[18] They were recommended by the most recent American College of Cardiology/American Heart Association Guidelines in the setting of coronary artery bypass graft (CABG) surgery,[19] and during non-cardiac surgery to maintain general anaesthesia in patients haemodynamically stable at risk for myocardial ischaemia.[20]

Cardiac surgery has been the main arena for the comparison between volatile and total i.v. anaesthesia (TIVA) with regard to clinically relevant endpoints. Up to now, the main shortcomings of clinical trials were the small number of patients included, the predominance of single-centre studies, the low-risk isolated CABG surgery setting, the use of surrogate endpoints such as cardiac biomarkers, and short-term follow-up.[21 22] In a recent network meta-analysis, we confirmed that volatile agents might reduce mortality after cardiac surgery when compared with TIVA (mostly propofol-based TIVA) and that sevoflurane is the most studied volatile agent.[17] If we consider that at least 1 million cardiac operations are performed

annually, confirmation of the efficacy of this simple and low-cost treatment would have great clinical impact and significant implications for public health, especially for patients undergoing high-risk cardiac surgery.

The objective of this multicentre randomized controlled trial (RCT) was to study the effects of volatile agents in patients undergoing high-risk cardiac surgery with a long-term follow-up. Our *a priori* hypothesis was that sevoflurane reduces the composite endpoint of mortality, prolonged intensive care unit (ICU) stay, or both.

Methods

Trial design and participants

We undertook a multicentre, randomized, parallel group, controlled study to determine if sevoflurane has cardioprotective effects compared with propofol-based TIVA in a population of patients planned to undergo high-risk cardiac surgery, defined as combined valvular surgery and CABG. Short-term mortality for this kind of procedures is reported to be 5%.[23–25]

The study was conceived in accordance with the Declaration of Helsinki and its amendments. The study protocol was approved by Ethical Committees of the centres involved and registered with the identifier 2008-001752-43 on Eudra CT (https://www.clinicaltrialsregister.eu/ctr-search/trial/2008-001752-43/IT) and with the identifier NCT00821262 on ClinicalTrials.gov. No change to the methods was made after trial commencement. The study was performed at San Raffaele Scientific Institute and at Azienda Ospedaliero-Universitaria Pisana, in Italy, between September 2008 and June 2011, when the planned number of patients was enrolled. The 1 yr follow-up ended in September 2012. Our report follows the CONSORT 2010 statement guidelines.[26] The methods of the study were previously described.[27]

All patients aged 18 yr or more and undergoing combined valvular and coronary surgery were eligible and, if they provided written informed consent, were enrolled. Exclusion criteria were: ongoing acute myocardial infarction, elevated level of circulating cardiac troponin, previous unusual response to sevoflurane (malignant hyperthermia) or propofol (allergic reaction), thoracotomy, use of sulfonylurea, theophylline, or allopurinol.

Randomization and masking

Randomization sequence was stratified by site and generated by a computer by permuted block randomization with a 1:1 allocation and block size of 20. An independent epidemiologist prepared the allocation sequence and concealed it with opaque, sequentially numbered, sealed envelopes. After enrolment, subjects were randomly allocated to the placebo or intervention group by assigning them the envelope with the lowest number. Randomization was performed at the last available moment in the operating theatre. Envelopes were closed and sealed again before the end of surgery. No code break was reported.

Subjects and study personnel, including those involved in ICU management, were blinded to treatment for the duration of the study except for the cardiac anaesthesiologists performing the anaesthesia in the surgical theatre, who were not involved in collecting, entering, or analysing data. To reduce bias, data collection was made by trained observers not otherwise involved in patient care and blinded to the anaesthesia regimen.

Intervention

All subjects were admitted to the cardiac surgery ward before the operation, underwent cardiac surgery with general anaesthesia, and were transferred to the ICU after surgery. All preoperative medications were routinely omitted on the day of surgery. Preoperative β-blockers were continued after operation if permitted by heart rate, arterial pressure, and cardiac index. No other drug was continued routinely or given for cardiac protection.

Premedication was morphine 0.1 mg kg^{-1} subcutaneously and scopolamine 0.25 mg i.m. 1 h before surgery. During anaesthesia induction, subjects received i.v. midazolam (0.15–0.25 mg kg^{-1}) or thiopental (3–6 mg kg^{-1}), opioid (fentanyl 5–10 μg kg^{-1}), and neuromuscular blocking agent (rocuronium 0.6–1.2 mg kg^{-1}). Anaesthesia was maintained with opioid (fentanyl 3–5 μg kg^{-1} h^{-1} in repeated boluses), neuromuscular blocking agent (rocuronium 10 μg kg^{-1} min^{-1} continuous infusion), and either sevoflurane or propofol. The study group received sevoflurane (Sevorane, Abbott, Campoverde di Aprilia -LT-, Italy) at 0.5–2 minimum alveolar concentration (MAC), equal to 1–4 vol%, 4–6 h (from induction of anaesthesia to transport to ICU and including cardiopulmonary bypass—CPB). The control group received propofol (Diprivan, Astra Zeneca, Basiglio -MI-, Italy), at an infusion rate of 2–3 mg kg^{-1} h^{-1}, for the same 4–6 h period.

All subjects received an infusion of tranexamic acid: 1 g administered in 20 min followed by a 400 mg h^{-1} infusion. Moderate hypothermia (32–34°C) was maintained during CPB and myocardial perfusion during aortic cross-clamping was performed with antegrade, retrograde cold Custodiol or blood cardioplegia, or both. Activated clotting time was maintained >480 s for CPB, heparin (starting dose=3 mg kg^{-1}) was reversed with protamine in a 1:1 ratio. Target mean arterial pressure after CPB was 65 mm Hg.

After surgery, subjects were sedated with propofol and transferred to the ICU. After 4 h, weaning from mechanical ventilation began after achievement of haemodynamic stability with no major bleeding, normothermia, adequate level of consciousness and pain control. Postoperative pain relief was provided by morphine and paracetamol.

Transfer from the ICU was performed with the following criteria: peripheral oxygen haemoglobin saturation (Sp_{O_2}) ≥94% with an inspired fraction of oxygen ($F_{I_{O_2}}$) ≤0.5 with a facemask, cardiac stability and no haemodynamically significant arrhythmias, chest tube drainage <50 ml h^{-1}, urine output >0.5 ml kg^{-1} h^{-1}, no i.v. inotropics or vasopressors in excess of dopamine 5 μg kg^{-1} min^{-1}, and no seizures. Hospital discharge was performed with the following criteria: haemodynamic and cardiac rhythm stability, clean and dry incisions, apyrexia, normal bowel movement, and independent ambulation and feeding.