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STUDY DESIGN

Sevoflurane vs propofol in high risk cardiac surgery: design of the randomized trial "Sevo-Aifa"

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ABSTRACT

Objective. Recent evidence indicates that volatile anesthetics improve post-ischemic recovery. In a meta-analysis of 22 randomized studies, the use of volatile anesthetics was associated with significant reduction in myocardial infarction and mortality. All the studies in this meta-analysis included low risk patients undergoing isolated procedures (mostly isolated coronary artery bypass grafting). We want to confirm the cardioprotective effects of volatile anesthetics, in cardiac surgery, as indicated by a reduced intensive care unit stay and/or death in a high risk population of patients, undergoing combined valvular and coronary procedures.

Methods. Four centres will randomize 200 patients to receive either total intravenous anesthesia with propofol or anesthesia with sevoflurane. All patients will receive a standard average dose of opiates. Perioperative management will be otherwise identical and standardized. Transfer out of the intensive care unit will follow standard criteria.

Results. Reduced cardiac damage will probably translate into better tissue perfusion and faster recovery, as documented by a reduced intensive care unit stay. The study is powered to detect a reduction in the composite end point of prolonged intensive care unit stay (>2days) and/or death from 60% to 40%.

Conclusions. This will be the first multicentre randomized controlled trial comparing the effects of volatile anesthetics and total intravenous anesthesia in high risk patients undergoing cardiac procedures. Our trial should help clarify whether or not volatile agents should be recommended in high risk patients undergoing cardiac surgery.

Key words: anesthetic gases, cardiac surgical procedures, myocardium protection, sevoflurane, cardiac anesthesia, intensive care, volatile agents

Introduction

Approximately one million cardiac surgery procedures are performed each year worldwide. These procedures are burdened by a significant risk of myocardial damage: this, in turn, can prolong intensive care unit stay as well as increase perioperative mortality rate.

The American College of Cardiology / American Heart Association Guidelines suggest considering, in the perioperative plan, anesthetic techniques and drugs that have known cardiac benefit. (1) The decision between different types of anesthesia is demanded to the anesthesia care team, because there is no proven myocardium protective anesthetic technique. (2,3) Up until now , no anesthetic drug or technique has been proven to reduce perioperative morbidity and mortality in cardiac surgery.

Volatile anesthetics improve postischemic recovery at the cellular level, in isolated hearts, and in animals, (4,5) both through a pharmacological preconditioning and postconditioning action. (6,7) Till recently there was no evidence that the cardioprotective effects of volatile anesthetics are applicable to clinical settings and are associated with improved cardiac function, ultimately resulting in a better outcome in patients undergoing cardiac surgery. (8,9)

A recent meta-analysis (10) summarized 22 randomized trials including 1922 patients (904 randomized to total intra-venous anesthesia (TIVA) and 1018 receiving desflurane or sevoflurane in their anesthesia plan). Significant reductions in myocardial infarctions (24/979 (2.4%) were found in the volatile anesthetics group vs 45/874 (5.1%) the control arm, odds ratio (OR) = 0.51 (0.32-0.84), p = 0.008, and p for heterogeneity = 0.77) and mortality (4/977 (0.4%) vs 14/872 (1.6%), OR = 0.31 (0.12-0.80), p = 0.02, and p for heterogeneity = 0.88). This was the first time that the choice of an anesthetic regimen seemed to have an impact on patients' outcome following cardiac surgery. All but one of the 22 randomized controlled studies included in the meta-analysis studied low risk patients undergoing isolated procedures (mostly coronary artery bypass grafting).

Studies performed on patients undergoing coronary artery bypass graft (CABG) surgery, either with cardiopulmonary bypass (CPB) (11-13) or on the beating heart, (14-16) showed lower postoperative values of cardiac troponin as a result of the cardioprotective effect of volatile anesthetics. At present, cardiac troponin is the most popular biomarker for myocardial damage, with nearly total myocardial tissue specificity and extreme sensitivity, reflecting even a very small amount of myocardial necrosis. (17)

Few and discordant results exist for valvular surgery. In Landoni et al. (18) myocardial damage measured by cardiac troponin release was not reduced by volatile anesthetics in patients undergoing mitral valve surgery. Cromheecke et al. (19) showed that an anesthetic plan with sevoflurane was associated with better preservation of cardiac function and lower cardiac troponin release peak in patients undergoing aortic valve replacement for aortic stenosis.

Large multicentre randomized controlled studies in high risk populations of patients are needed to evaluate the possible influence of different anesthetic regimens on patient outcomes after cardiac surgery. Clinical implication could be extended to patients with coronary disease undergoing non-cardiac surgery.

Materials and methods

Study population

Patients with concomitant valvular and coronary artery disease undergoing elective cardiac surgery in four teaching hospitals will be enrolled. All patients will be admitted to the main ward before the operation, will undergo cardiac surgery under general anesthesia (the randomization and administration of the study drugs will be performed in the operating theatre) and then transferred to the intensive care unit (ICU).

The study will start after Ethical Committee approval is received Consecutive patients who give written informed consent, aged 18 years or older, will be enrolled over a 2 year period.

Conversely, the following exclusion criteria will be applied: ongoing acute myocardial infarction, cardiac troponin >1 ng/ml, previous unusual response to an anesthetic, use of sulfonylurea, theophylline or allopurinol, thoracotomy.

Study procedure

In this randomized multicentre controlled study, the study group will receive sevoflurane (Sevorane, Abbott) 0.5-2 Minimal Alveolar Concentration (MAC) equal to 1-4% for a 4-6 hour period throughout the procedure (from anesthesia induction to transfer to the ICU). The control group will receive propofol (Diprivan, Astra Zeneca) 2-3 mg/kg/h for the same 4-6 hour period. This drug represents the standard hypnotic drug used in most cardiac anesthesia units. (20)

All pre-operative medications will routinely be omitted on the day of surgery. Pre-operative beta-blockers will be continued post-operatively if permitted based on heart rate, blood pressure and cardiac index evaluation. No other drugs will be continued routinely nor given for cardiac protection.

All patients will be premedicated with morphine 0.1 mg/kg and scopolamine 0.25 mg i.m. one hour before surgery. During anesthesia induction each patient will receive an intravenous bolus of hypnotics, opioids, and a muscle relaxant. Standard monitoring will include invasive radial artery blood pressure measurement, continuous ECG with ST segment monitoring, pulse oximetry, central venous pressure, capnometry and urine output. Transesophageal echocardiography will be used in all patients at CPB weaning and a pulmonary artery catheter will be used as indicated by the attending physician, but data will not be collected.

Anesthesia will be maintained with opioids, muscle relaxants and either sevoflurane or propofol for all the procedures, as described above, starting immediately after intubation.

All patients will receive an intraoperative infusion of tranexamic acid: 1g in 20 minutes followed by a 400 mg/h infusion.

CPB will be conducted at moderate hypothermia (32-34 °C) with myocardial protection during aortic cross clamping obtained by antegrade and/or retrograde cold blood cardioplegia. Acti-

vated clotting time will be maintained greater than 480 seconds for CPB, the effect of heparin (starting dose = 3 mg/kg) will be reversed with protamine sulphate in a 1 to 1 ratio. If the target mean arterial pressure of 65 mmHg is not achieved, despite volume loading to a central venous pressure of 10 cm H_2O after weaning from CPB, an infusion of dopamine (initial dose 5 μg/kg/min) will be started. Following surgery, patients will be transferred to the ICU, sedated with propofol for 4 hours and weaned from the ventilator as soon as hemodynamic stability- with no major bleeding, normothermia, and an adequate level of consciousness and pain control- is achieved. Postoperative pain relief will be provided to all patients by boluses of intravenous morphine. Blood pressure (systolic, mean and diastolic), heart rate and central venous pressure will be recorded at 7 time points: before induction of anesthesia, before and after cardiopulmonary bypass, upon ICU arrival and 4, 8 and 12 hours later. Myocardial infarction will be diagnosed on ECG, biochemical and echocardiographic findings.

Transfer out of the ICU will be performed with SpO_2 94% or greater at an FiO_2 of 0.5 or less by facemask, adequate cardiac stability with no hemodynamically significant arrhythmias, chest tube drainage less than 50 ml/h, urine output greater than 0.5 ml/kg/h, no intravenous inotropic or vasopressor therapy in excess of dopamine 5 μg/kg/min, and no seizure activity. Particular care will be taken to ensure that all patients will be actually discharged the moment they meet the criteria for discharge from the ICU. Times of fitness for discharge criteria will be noted and compared to the actual discharge times.

A register of the patients screened but not enrolled will be kept. Patients will sign the written informed consent the day before surgery but the envelopes with the randomization will be opened immediately before the beginning of anesthesia. Subjects will be allocated using a centralized randomization system derived from a computer-generated list of random numbers. Stratification per participating centre will be performed. All study personnel, including those involved in ICU management will be blinded to treatment assignment for the duration of the study, except for the cardiac anesthesiologists in the operating room who will not be involved in data collection, data entry or data analysis. To further reduce bias, data will be collected by trained observers who will not participate in patient care and who will be blinded to the anesthetic regimen. Data collection will end at ICU discharge. No interim analyses will be carried out during the course of this study.

Clinical end points and follow up

In the present study we will test the hypothesis that volatile anesthetics reduce cardiac damage and allow better tissue perfusion and faster recovery. The primary end point of the study will be a composite end point: death and/or reduction in prolonged intensive care unit stay (defined as > 2 days).

Secondary end points will be represented by cardiac troponin release (ng/ml, either the peak value or the area under the curve); incidence of perioperative myocardial infarction (based on ECG, troponin values and clinical criteria); duration of mechanical ventilation (hours); postoperative hospital stay (days, in particular a prolonged hospital stay defined as > 7 days will be investigated).

Caregivers will be interviewed daily for the occurrence of postoperative adverse events. Clinical follow up will be performed before hospital discharge (length of hospital stay, major complications). Follow up by phone will be performed at 30 days and at 1 year and will focus on adverse cardiac events and hospital readmissions. We do not expect to lose any patients prior to hospital discharge. Default rate at 30 days and 1 year will be acknowledged in the paper.

Statistical analysis and sample size estimates

An independent clinical investigator with extensive experience in designing, conducting and analysing clinical trials, and who will not be involved in patient management, will be responsible for the statistical analysis. Data will be stored electronically and analysed using Epi Info 2002 (CDC), SPSS 11.0 (SPSS), and STATA 9.0 (STATA) softwares, where appropriate. All data analysis will be carried out according to a pre-established intention-to-treat analysis plan. Dichotomous data (including the primary outcome) will be compared by using a two-tailed c2 test with the Yates correction or Fisher's exact test when appropriate. Continuous measurements will be compared using the Mann-Whitney U test. Two-sided significance tests will be used throughout. Data will be presented as medians (25th and 75th percentiles) or as means ($\pm$ standard deviation –SD).

Sample-size calculation will be based on a two-sided alpha error of 0.05 and 80% power. On the basis of our experience investigating ICU stay and mortality after valvular surgery we anticipate 60% of patients with a composite end point of death and/or prolonged (>2days) ICU stay in the control group and 40% of patients in the treatment group. (18) We calculate that we will need a sample size of 97 patients per group. We plan to randomly select 200 patients in order to take into account possible protocol deviations. All 200 patients will be analysed according to the intention-to-treat principle, beginning immediately after randomization.

Monitoring of the study

Monitors will verify adherence to required clinical trial procedures and confirm accurate collection of data and will follow the Good Clinical Practice (GCP) guidelines. Study monitoring and follow-up, from the initial set-up to final reporting, will be fulfilled according to current National and International requirements.

Timing

The study will be concluded within 2 years after the first randomization.

Ethical aspects

Both anesthesia plans represent standard management for modern cardiac anesthesia. They have similar costs and result in the same haemodynamic

stability. They are both easily performed and all cardiac anesthesiologists can perform them. No risk for the study subjects is expected. Today there is still no evidence that high risk patients could benefit from volatile anesthetics.
No interference with subject privacy is planned. Data will be stored in an electronic database without indicating the name of the patients (a numeric code will be used).

Expected results

During the planned study we will test the hypothesis that volatile anesthetics could reduce cardiac damage and allow for better tissue perfusion and faster recovery. Our trial could help in determining whether these drugs, used in cardiac anesthesia, improve outcomes and reduce hospital costs. For this reason, high risk patients with planned combined valvular and coronary surgery will be enrolled in a multicentre controlled study and randomized to receive either total intravenous anesthesia with propofol or anesthesia with sevoflurane.

Discussion

Cardioprotection by anesthetic drugs is a topical matter in cardiac anesthesia. Many studies (11-16,18,19) and reviews (21-22) have appeared in the literature suggesting a cardioprotective effect provided by volatile anesthetics in patients undergoing cardiac procedures.
A recent survey (23) conducted in 64 Italian centres, encompassing a total of 34,310 patients undergoing coronary artery bypass graft surgery, showed that risk-adjusted mortality may be reduced by the use of volatile agents. Furthermore, a longer use of volatile anesthetics was associated with a significantly lower death rate.
Volatile anesthetics were considered among the few drugs that could reduce perioperative mortality in cardiac surgery and that deserve further studies by the first international consensus conference on mortality reduction in cardiac anesthesia and intensive care. (24)
However, data on high risk patients, such as those undergoing combined valvular and coronary surgery, are lacking. We will conduct a large multicentre randomized study in these patients, administering sevoflurane throughout the whole procedure to address the question whether the choice of anesthetic regimen might influence patients' outcome after cardiac surgery.
Clinical implications could be extended to patients with coronary disease undergoing non-cardiac surgery. To this day there is no evidence that volatile anesthetics could be cardioprotective in non-cardiac surgery. (25) On the contrary, a randomized study (26) showed that myocardial damage, measured by cardiac troponin release, was not reduced by the volatile anesthetic sevoflurane during interventional cardiology procedures.
This will be the first multicentre randomized controlled trial comparing the effects of volatile anesthetics and total intravenous anesthesia in high risk patients undergoing cardiac procedures. Evidence resulting from this study will be of primary importance in the anesthesiological management of high risk patients undergoing cardiac and non-cardiac procedures.

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