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TITLE PAGE

Title

A randomized controlled trial of volatile anesthetics to reduce mortality in cardiac surgery (MYRIAD): rationale and design

Running head

Volatile anesthetics in cardiac surgery

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ABSTRACT

Objective: There is initial evidence that the use of volatile anesthetics can reduce the postoperative release of cardiac troponin I, the need for inotropic support, and the number of patients requiring prolonged hospitalization following coronary artery bypass graft (CABG) surgery. Nevertheless, other Randomized Controlled Trials have shown neutral results and whether volatile anesthetics improve the postoperative outcome of cardiac surgical patients is still a matter of debate. An adequately powered randomized controlled trial does not exist.

Design: Single blinded, international, multicenter randomized trial with 1:1 allocation ratio.

Setting: Tertiary care and University hospitals.

Interventions: Patients (n= 10,600) undergoing coronary artery bypass graft will be randomized to receive either volatile anesthetic as part of the anesthetic plan, or total intravenous anesthesia.

Measurements and main results: The primary end point of the study will be one-year mortality (any cause). Secondary endpoints will be 30-day death or non-fatal myocardial infarction (composite endpoint), cardiac mortality at 30 day and at one year, incidence of hospital re-admission during the one year follow-up period and duration of intensive care unit and hospital stay. The sample size is based on the hypothesis that volatile anesthetics will reduce 1-year unadjusted mortality from 3% to 2%, using a two-sided alpha error of 0.05, and power of 0.9.

Conclusions: The trial will determine whether the simple intervention of adding a volatile anesthetic, an intervention that can be implemented by all anesthesiologists, can improve one-year survival in patients undergoing coronary artery bypass graft surgery.

KEY WORDS:

Volatile anesthetics, Total intravenous anesthesia, Cardiac anesthesia, Cardiac surgery, Randomized trial, Intensive Care

INTRODUCTION

Coronary artery disease (CAD) remains one of the most common causes of death and significantly influences the use of health care resources. In the United States alone, it results in more than 397,000 Coronary Artery Bypass Grafting (CABG) surgeries per year.[1] There is initial evidence that the choice of anesthesia can influence survival in the specific setting of CABG. An international consensus conference considered volatile anesthetics among the few drugs, techniques or strategies that might reduce perioperative mortality in cardiac surgery and should be further studied.[2]

All volatile anesthetics have cardiac depressant effects with a beneficial role on the myocardial oxygen balance during ischemia.[3,4] Animal trials have shown that volatile anesthetics can provide protection against the ischemia-reperfusion injury that occurs during cardiac surgery via preservation of mitochondrial function and improved cell survival.[22] Furthermore volatile anesthetics reduce inflammatory response in acute lung injury,[5,6] and after brain,[7] liver[8] and kidney[9] ischemia with clinical benefits. The most recent and comprehensive meta-analysis[10] of 68 randomized controlled trials (RCTs) included 7,104 patients, compared volatile anesthetics versus total intra-venous anesthesia (TIVA) and showed that in cardiac surgery volatile anesthetics are associated with reduced overall mortality (OR 0.55, 95% CI 0.35–0.85, p=0.007), pulmonary complications (OR 0.71, 95% CI 0.52–0.98, p=0.038) and other complications (OR 0.74, 95% CI 0.58–0.95, p=0.020). Five RCTs that were analyzed for mortality outcome had one-year follow-up, including the largest multicenter study published so far on this topic by De Hert et al.[11] that randomized 414 participants undergoing on-pump CABG. In this study one-year mortality was a secondary outcome and was different among groups (12.3% in the TIVA group, 6.9% in the Desflurane group, and 3.3% in the Sevoflurane group; p=0.034). A further recently published RCT suggested a mortality reduction at 1 year in the sevoflurane group when compared to the TIVA group[12]. A previous large observational study[13] a long follow-up of a RCT[14] convincingly demonstrated that occurrence of complications in the postoperative period are independent

predictors of long-term survival, hypothesizing that perioperative organ protection and reduction in postoperative complications with volatile anesthetics could decrease long-term mortality.

Despite these encouraging results, and in spite of the fact that there is no published evidence in favor of a survival benefit when using TIVA, the current evidence is inconclusive, as several small RCTs found no difference in cardiac biomarkers release, need of an inotropic support and length of intensive care unit (ICU) and in hospital stay when comparing volatile agents and TIVA.[12,14] The most recent meta-analysis on this topic confirmed that, overall, the use of volatile agents in cardiac anesthesia is associated with less complications and with a difference in mortality that was predominantly short-term.[10]

Therefore, we aim to carry out the MYRIAD trial (Volatile anesthetics to reduce **M**ortalit**Y** in ca**R**d**IA**c surgery. A randomize**D** controlled trial of volatile anesthetics to reduce mortality in cardiac surgery) a large multicenter RCT to identify whether a clinically important reduction in one-year mortality from 3% to 2% after CABG surgery can be achieved by including a volatile anesthetic as part of the overall anesthetic in patients receiving TIVA or volatile agents.

MATERIALS AND METHODS

Study design, approval, and registration

A parallel group, randomized controlled, single-blinded multicenter trial with 1:1 allocation ratio. The study has been approved by the Human Research Ethics Committee of all the participating centers and is registered on clinicaltrials.gov as NCT02105610.

Study aim

The aim of our study is to test the hypothesis that volatile anesthetics can reduce one-year mortality from 3% to 2% in participants undergoing CABG, either with or without cardiopulmonary bypass (CPB).

Participants

We will enroll 10,600 participants with CAD undergoing elective CABG. Participants will be >18 years undergoing scheduled isolated CABG (including multiple coronary artery bypass). Exclusion criteria are: pregnancy, planned combined intervention such as CABG plus valve surgery, surgery on the aorta, planned loco-regional anesthesia without general anesthesia, unstable or ongoing angina, recent (< one month) or ongoing acute myocardial infarction, medication with sulfonylureas, theophylline or allopurinol that cannot be discontinued within 24 hours of surgery, previous unusual response to an anesthetic agent, inclusion in other randomized controlled studies in the previous 30 days, any general anesthesia in the previous 30 days, a history of kidney or liver transplant, liver cirrhosis (Child-Pugh score B or C) (Table 1).

Inclusion criteria	Exclusion criteria
Age > 18 years	Planned
Written informed consent	-Valve surgery
Scheduled procedure	-Surgery of the aorta
Isolated coronary artery bypass graft	Unstable/ongoing angina
	Acute myocardial infarction (< 1 month)
	Use of:
	- sulfonylurea
	- theophylline
	- allopurinol
	Previous unusual response to an anesthetic agent
	Inclusion in other randomized controlled studies in the previous 30 days
	Any general anesthesia performed in the previous 30 days
	Emergency operation
	Kidney or liver transplant in medical history
	Liver cirrhosis (Child B or C).

Table 1: MYRIAD inclusion and exclusion criteria

Randomization, allocation and concealment

Subjects will be allocated according to a web-based centralized randomization service or by opening centrally provided sealed opaque envelopes with the use of a permuted-block design stratified according to center. We will use randomization blocks of 20. Patients will be unaware of the group assignments. Anesthesiologists will provide the trial treatment intervention and, as a consequence, will know patients' group allocation but will not be involved in postoperative medication prescription, data collection, data entry or data analysis. Investigators and clinical personnel caring for patients, including intensive care physicians, will be blinded to the study drug for the duration of the trial. Data will be collected by trained observers who will not participate in patient care and will be blinded to patient allocation.

Interventions

Participants will be randomized to receive either anesthesia which includes a volatile agent or TIVA alone (Fig.1).

The volatile group will receive Desflurane, Isoflurane or Sevoflurane to provide general anesthesia in addition to any intravenous agent (according to local protocols and expertise). The volatile agent will be administered for as long as possible (ideally from anesthesia induction to ICU sedation) and at the highest concentration permitted by local protocols and patient hemodynamics during at least one of the following time periods: anesthesia induction, pre-CPB, during CPB, after CPB in the surgical theatre, and in the ICU. Within the volatile group the following strategies are strongly suggested but not mandatory: a) at least 1 minimal alveolar concentration (MAC) for at least 30 minutes (this is the minimum concentration demonstrated to be cardioprotective in experimental studies); b) discontinuation of the volatile agent for at least 15 minutes before CPB (a wash-out period before ischemia seems to be a prerequisite for the preconditioning phenomenon); c) wash-in/wash-out periods, defined as: volatile administration (at least 0.5 MAC) for at least three periods of 10 minutes, interspersed by wash-out periods of 10 minutes or more.

The aim of these strategies is to enhance the cardio-protective properties of volatile agents[23,24] without significantly modifying the local protocols and without affecting patient safety.

The TIVA group will receive any intravenous agent and no volatile agent. Agents for TIVA will be administered as both target-controlled infusion and manually controlled infusion according to local protocols and expertise.

In case of repeated operation during the first hospitalization the patients will follow the study allocated anesthesia.

This is a pragmatic study so we avoided to define a strict anesthetic protocol. This allows all patients to be treated according to the best available treatment in each center. It also adds external generalization to our findings in case of positive results of the study.

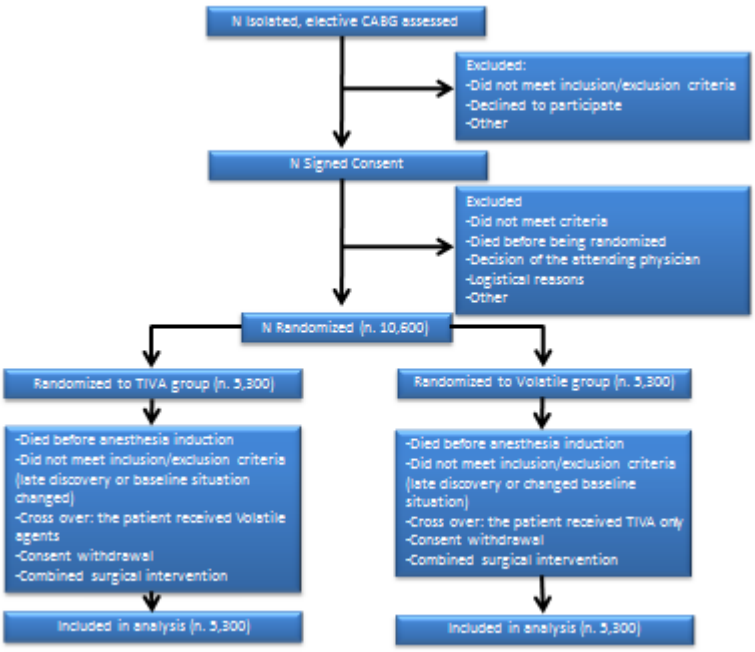

Figure 1: MYRIAD Flow chart.

All participants will receive perioperative intensive treatment according to their institutional practice, including general anesthesia, pacing, inotropic drugs, mechanical ventilation, postoperative sedation/analgesia, diuretics, intravenous fluids, antibiotics and invasive monitoring including, but not limited to, invasive arterial pressure, electrocardiogram, central venous pressure, pulse oximetry, temperature, urine output, arterial blood gases and frequent routine laboratory examinations. No additional intervention or laboratory examination will be performed on participants outside of institutional practice.

Data will be collected at the end of surgical intervention, at ICU discharge, and at hospital discharge. We will record the data about dosage, time and mode of administration of all drugs used for the anesthesia. Surgical characteristics including CPB and aortic cross-clamping duration will also be collected. With regards to volatile anaesthetic use, we will be collecting data on what agent was administered, what dose, for how long and at what time points (induction, before CPB or the start of the anastomosis, during CPB or anastomosis, after CPB or anastomosis, and in ICU). Follow-up at 30 days and at one year will focus on the adverse cardiac events, hospital readmissions and survival.

Outcomes

In the present study, we hypothesize that volatile anesthetics would reduce one-year mortality from any cause in participants undergoing CABG surgery.

Secondary endpoints will include: 30-day all-cause mortality, 30-day non-fatal myocardial infarction, cardiac mortality at 30 days and at one year, hospital re-admission during the follow-up period, ICU and hospital stay. We also collect the number of adverse events: stroke, delirium, postoperative cognitive impairment, acute renal failure, surgical revision for bleeding, high dose inotropic drugs and the use of intra-aortic balloon pump or other mechanical circulatory support. Definitions of the outcomes are presented in the Supplementary material. To perform 30-days and one-year follow-up telephone contact (patient and relatives) will be used. In case of telephone follow-up loss, the following methods will be used: contact the patient's general practitioner, contact the city municipality, and send a letter to the home address of the patient.

Statistical analysis and sample size estimates

An epidemiologist with extensive experience in designing, conducting and analyzing clinical trials, not involved in patient management, and blinded to the assigned intervention will be responsible for the statistical analysis.

Data will be stored electronically via a web based CRF and analyzed using STATA (Stata Statistical Software: version 14, College Station, TX, USA). We will not apply any imputation for missing data. All data will be analyzed according to the intention-to-treat principle, beginning immediately after randomization.

Demographic and baseline disease characteristics will be summarized with the use of descriptive statistics. Categorical variables will be reported as absolute numbers and percentages. Unadjusted

univariate analyses, to compare the two treatment groups, will be based on Chi-square or Fisher's exact test. Relative risks and 95% confidence intervals will be calculated by means of the two-by-two table method with the use of log-normal approximation. Continuous variables will be reported as mean ± standard deviation (SD) or median and interquartile range (IQR). Normality will be evaluated using visual histogram evaluation and a Q-Q plot. Between-group differences will be evaluated using the T test or Wilcoxon signed rank test, in accordance with normality of the distribution. A logistic regression model using a stepwise selection will be used to estimate the treatment effect and predictors of mortality. The pre-randomization clinical data and center will be entered into the model if their univariate p value is less than 0.05. The treatment group (volatile anaesthetics or TIVA) will be forced into the multivariate model. If the outcome event proves to be rare a Poisson regression model will be used. A classic logistic regression will be performed with a consistent number of events and the number of covariates in the model will be decided based on the number of outcome events. Collinearity and overfitting will be assessed using a stepwise regression model and Pearson correlation test.

On the basis of the latest large RCTs comparing CABG versus percutaneous interventions[15,16,17,18] or comparing different CABG techniques,[19] we hypothesize a one-year mortality of 3% in the control (TIVA) group. Following the results of a recent meta-analysis[20] and one large retrospective observational study[21] demonstrating reduced mortality with the use of volatile anesthetics, we hypothesize a reduction in mortality from 3 to 2% in the volatile anesthetic group. Sample-size calculation is based on Pearson's Chi-square test with a two-sided alpha error of 0.05 and 90% power. We calculated that we would need a sample size of 5,300 participants per group using the continuity correction resulting in the total study population of 10,600 patients.

An independent safety committee will perform three interim analyses after recruitment of 25% (n=2,650), 50% (n=5,300) and 75% (n=7,950) of patients. Data evaluation at each interim analysis will be based on the alpha spending function concept, according to Lan and De Mets'[25], and will employ O'Brien-Fleming Z-test boundaries[26], which are very conservative early in the trial. For the

first interim analysis the efficacy stopping rule would require an extremely low P value (P< 0.000015). For the second interim analysis P< 0.003 will be taken as efficacy stopping rule. For the third interim analysis P< 0.02 will be taken as efficacy stopping rule. Investigators will be kept blind to the interim analysis results.

The independent safety committee will also perform conditional power analyses in order to evaluate potential futility issues in the trial. This analysis will be performed by assuming the outcomes will continue according to the observed trend, as the sample size included in the interim analyses is numerous. If the analysis will show futility, the trial will be interrupted for organizing reasons.

Moreover, if during the first interim analysis the independent safety committee will observe a similar direction and magnitude of the study technique effect on 30 day and 1 year mortality, they will be in the position to use 30-day mortality data to suggest study continuation or interruption in the following interim analyses.

All data analyses will be carried out according to a pre-established analysis plan. Because organ protection elicited by volatile anesthetics can be modulated by several clinical factors we prespecified subgroups analyses that are summarized in Table 2.

The dosage and mode of anesthetic administration could be confounders in the trial. Therefore we will also separately analyze: centers using volatile agent also during CPB; centers that routinely do not use propofol as induction agent in the volatile group; centers with a high overall mortality; centers that use volatile anesthetic throughout all the procedure (before CPB, during CPB and after CPB); centers using TIVA as main anesthetic technique agent before study initiation; centers using volatile agent as main anesthetic technique before study initiation.

Planned subgroups analysis
Ejection Fraction < 40%
Males vs Females
Patients with diabetes mellitus
Age < 60 years
Previous:
-Myocardial infarction
-Vascular surgery
-Stroke or transient ischemic attack
Chronic kidney disease
Perioperative beta-blocker use
CPB-CABG
Bypass graft ≥ 4
Used as volatile agent:
-Desflurane
-Isoflurane
-Sevoflurane
Used as hypnotic agent:
-Propofol
-Midazolam
Used as opioid agent:
-Remifentanil
-Fentanyl
-Sufentanil
Volatile administration strategy:
-At least 1 MAC of volatile for 30 minutes
-15 minutes wash out period of volatile agent
-Planned wash in / wash out period of the volatile agent

Table 2: Planned subgroups analyses. Ejection Fraction will be measured by echocardiography.

Monitoring of the study

Auditors will verify adherence to required clinical trial procedures and will confirm accurate data collection according to 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.

Ethical aspects

This is a randomized trial on different anesthesiological strategies that have been used for decades on hundreds of millions of participants. The incidence of adverse events such as malignant hyperthermia, allergy and propofol syndrome is negligible, and unavoidable if the patient has to undergo general anesthesia. No additional risk for the study subjects is expected.

Data will be stored in an electronic database with no patient identifiers (a numeric code will be used).

Study initiation, timing, participating centers and source of funding

The study started after Ethical Committee approval from each contributing recruiting center. Consecutive participants who sign the written informed consent, aged 18 years or older will be enrolled. The study progress will be updated monthly. The first 4500 participants were randomized within April 2017 in 32 hospitals and 13 countries. The number of participating centers is continuously increasing, as no *a priori* limit to the number of participating centers was established.

The authors are solely responsible for the design and conduct of this study, all study analyses and drafting and editing of the paper.

This trial is funded by the Italian Ministry of Health (RF-2010-2318290).

DISCUSSION

The important innovation in this large multicenter RCT is that it potentially provides anesthesiologists with evidence for choosing anesthetics that will lead to the best clinical outcome for their patients. To the best of our knowledge it is the largest RCT ever performed on anesthetic drugs.

The inclusion of a volatile anesthetic for CABG is a simple technique that can be applied to all patients, as anesthesiologists worldwide are trained in both types of anesthesia delivery, and the equipment for both anesthesia techniques are readily available. If the hypotheses are proven and mortality is reduced, this simple intervention can save over 2,500 lives each year worldwide and contribute to reduced health care burden.

The design of the study is deliberately pragmatic rather than strictly controlled. By allowing a range of anesthesia drugs and techniques used by participating institutions, the feasibility and external validity is maximized. The inclusion of off-pump CABG is justified by preliminary randomized evidence on the efficacy of volatile agents in this group of patients.[26-29]

The tradeoff for a pragmatic design is to have a conservative estimate of mortality and power the study appropriately. This trial will be the largest study comparing anesthetic drugs ever conducted. Although an anesthetic intervention is studied, the outcome is highly relevant to cardiologists and cardiac surgeons, as survival after coronary intervention is the primary reason for performing the operation.

LIMITATIONS

A possible limitation, that, in our opinion, is also a strength of our study, is that we decided not to give a strict anesthetic protocol, including different opioids, induction agents, cardioplegia fluids, on- or off-pump procedures. This allows all patients to be treated according to the best available treatment in each center. It also adds external generalization to our findings in case of positive results of the study.

As the cardioprotective effect of volatile agents may be also mitigated by the lack of a strict volatile agent use protocol, we plan to collect data on the dose, length, and moment of administration of the various agents, in order to better understand how these parameters can influence the benefits of the volatile drugs.

CONCLUSIONS

The MYRIAD trial will be the first adequately powered RCT comparing the effects of volatile and total intravenous anesthetics on survival after CABG. If the predicted effect is proven, then approximately 2,500 lives could be saved each year worldwide.

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