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MortalitY in caRdIAc surgery (MYRIAD): A randomizeD controlled trial of volatile anesthetics. Rationale and design

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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, small randomized controlled trials have failed to demonstrate a survival advantage. Thus, whether volatile anesthetics improve the postoperative outcome of cardiac surgical patients remains uncertain. An adequately powered randomized controlled trial appears desirable.
Design: Single blinded, international, multicenter randomized controlled trial with 1:1 allocation ratio.
Setting: Tertiary 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 mortality; 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 a 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.

1. Introduction

Coronary artery disease (CAD) remains one of the most common causes of death and significantly affects the use of health care resources. In the United States alone, it results in > 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 but also a beneficial effect 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 the inflammatory response seen in acute lung injury [5,6] and after brain [7], liver [8] and kidney [9] ischemia with associated clinical benefits. The most recent and comprehensive meta-analysis [10] of 68 randomized controlled trials (RCTs) included 7104 patients and compared volatile anesthetics with total intra-venous anesthesia (TIVA). It 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), reduced pulmonary complications (OR 0.71, 95% CI 0.52–0.98, p = 0.038) and a reduction in other complications (OR 0.74, 95% CI 0.58–0.95, p = 0.020). The largest multicenter study published so far on this topic by De Hert et al. [11] 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] and a long-term follow-up of a RCT [14] found that the occurrence of complications in the postoperative period was an independent predictors of long-term survival, supporting the notion that perioperative organ protection and reduction in postoperative complications with volatile anesthetics could decrease long-term mortality.

Therefore, we aim to carry out the MYRIAD trial (MortalitY in caRdIAc surgery. A randomizeD controlled trial of volatile anesthetics 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.

2. Materials and methods

2.1. Study design, approval, and registration

The planned study is 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.

2.2. 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).

2.3. Participants

We plan to enroll 10,600 participants with CAD undergoing elective CABG. Participants will be > 18 years and undergoing scheduled

isolated CABG (including multiple coronary artery bypass). The exclusion criteria are presented in Table 1.

2.4. 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 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 treatment, 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.

2.5. 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 min (this is the minimum concentration demonstrated to be cardioprotective in experimental studies); b) discontinuation of the volatile agent for at least 15 min 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 min, interspersed by wash-out periods of 10 min 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 infusions or manually controlled infusions 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. Accordingly, we have chosen not to require or define a strict anesthetic protocol. This allows all patients to be treated according to the best available treatment available in each center. We consider that this approach adds external validity to future findings.

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. Such treatment will include but not be limited to, invasive arterial pressure, electrocardiogram, central venous pressure, cardiac output, pulse oximetry, temperature, urine output, arterial blood gases and frequent routine laboratory examinations. No additional intervention or laboratory examination will be performed on participant

Data will be collected at the end of surgical intervention, at ICU discharge, and at hospital discharge. We will record data about dosage, timing 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 anesthetic use, we will collect 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). If available, we will be collecting the baseline creatinine value. In case of myocardial infarction we will be collecting the cardiac biomarker value. Follow-up at 30 days and at one year will focus on the adverse cardiac events, hospital readmissions and survival.

2.6. Outcomes

We hypothesize that volatile anesthetics will 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 and 30-day death (composite endpoint); 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 loss to follow-up by telephone, the following methods will be used to establish vital status at one year: contacting the patient's general practitioner, contacting the city municipality, and sending a letter to the home address of the patient.

2.7. 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-

Table 1
MYRIAD inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Age > 18 years	Planned: - Valve surgery - Surgery of the aorta
Scheduled procedure	Unstable/ongoing angina
Isolated coronary artery bypass graft	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)

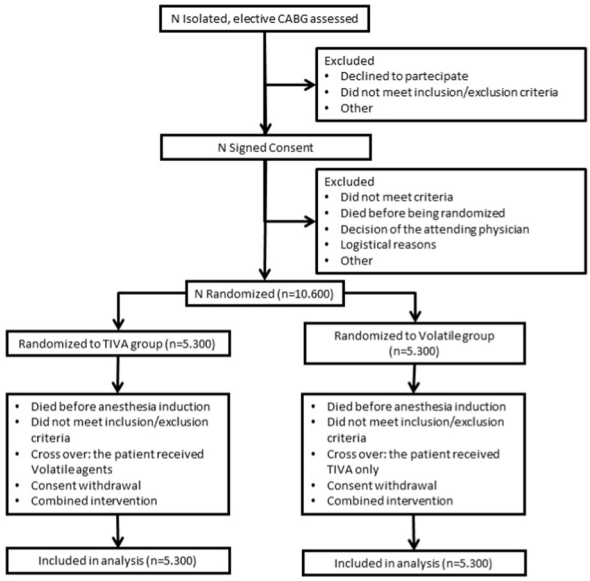

Fig. 1. MYRIAD Flow chart. CABG: Coronary artery bypass graft; TIVA: Total intravenous anesthesia.

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 < 0.1 and there is no correlation between them. Collinearity and overfitting will be assessed using a stepwise regression model and Pearson correlation test. The treatment group (volatile anesthetics 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.

On the basis of the latest large RCTs comparing CABG versus percutaneous interventions [15–18] 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 5300 participants per group using the continuity correction resulting in the total study population of 10,600 patients. Despite recent literature on sample size calculation in multicenter RCTs [25], we were unable to use this novel method in our competitive-enrolment trial as we did not know a priori the number of participating centers and the number of patients per center. We therefore used the conservative approach described above, which results in a greater sample size.

An independent safety committee will perform three interim analyses after recruitment of 25% (n = 2650), 50% (n = 5300) and 75% (n = 7950) of patients. Data evaluation at each interim analysis will be based on the alpha spending function concept, according to Lan and De Mets' [26], and will employ O'Brien-Fleming Z-test boundaries [27], 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.

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

Planned subgroup analyses
Ejection Fraction < 40%
Patients with diabetes mellitus
Age < 60 years
Previous:
- Myocardial infarction
- Vascular Surgery
- Stroke or transient ischemic attack
Chronic kidney disease
Perioperative beta-blocker use
On-pump CABG vs Off-pump CABG
Bypass grafts ≥ 4
Drug used as volatile agent:
- Desflurane
- Isoflurane
- Sevoflurane
Drug used as hypnotic agent:
- Propofol
- Midazolam
Drug used as opioid agent:
- Remifentanil
- Fentanyl
- Sufentanil
Volatile administration strategy:
- At least 1 MAC of volatile agent for 30 min
- 15 min wash-out period of volatile agent
- Planned wash-in/wash-out period of the volatile agent

CABG: Coronary artery bypass graft; MAC: Minimum alveolar concentration.

The independent safety committee will also perform conditional power analyses in order to evaluate potential interruption for futility issues in the trial. Conditional power will be calculated by assuming that the proportion of outcomes will follow the observed trend.

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 pre-specified 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.

2.8. 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 protocols, from the initial set-up to final reporting, will be fulfilled according to

current National and International requirements.

2.9. Ethical aspects

This is a randomized trial of 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. Subjects will not experience any tangible additional risk because of the trial.

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

2.10. 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 by 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 has been 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).

3. 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 this 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 hypothesis is proven correct and mortality is reduced, this simple intervention can save over 2500 lives each year worldwide and contribute to reduced health care cost.

The design of the study is deliberately pragmatic rather than strictly controlled. By allowing a range of anesthetic 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 [28–31], and differences between techniques will be explored in a subgroup analysis.

The tradeoff for a pragmatic design is to have a conservative estimate of mortality and power the study appropriately. Although we are studying an anesthetic intervention, 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 potentially a strength of our study, is that we decided not to mandate 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 practice in each center. It also adds external validity to our findings.

As the cardioprotective effect of volatile agents may also be diminished by the lack of a strict protocol to use volatile agents, we plan to collect data on the dose, length, and timing of administration of various volatile agents, in order to better understand how these variables might influence the potential benefits of volatile drugs.

4. 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, approximately 2500 lives could be saved each year worldwide.

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