




BMJ Open Evaluation of volatile sedation in the postoperative intensive care of patients recovering from heart valve surgery: protocol for a randomised, controlled, monocentre trial

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ABSTRACT

Introduction Patients undergoing heart valve surgery are predominantly transferred postoperatively to the intensive care unit (ICU) under continuous sedation. Volatile anaesthetics are an increasingly used treatment alternative to intravenous substances in the ICU. As subject to inhalational uptake and elimination, the resulting pharmacological benefits have been repeatedly demonstrated. Therefore, volatile anaesthetics appear suitable to meet the growing demands of fast-track cardiac surgery. However, their use requires special preparation at the bedside and trained medical and nursing staff, which might limit the pharmacological benefits. The aim of our work is to assess whether the temporal advantages of recovery under volatile sedation outweigh the higher effort of special preparation.

Methods and analysis The study is designed to evaluate the differences between intravenous sedatives (n=48) and volatile sedatives (n=48) in continued intensive care sedation. This study will be conducted as a prospective, randomised, controlled, single-blinded, monocentre trial at a German university hospital in consenting adult patients undergoing heart valve surgery at a university hospital. This observational study will examine the necessary preparation time, staff consultation and overall feasibility of the chosen sedation method. For this purpose, the continuation of sedation in the ICU with volatile sedatives is considered as one study arm and with intravenous sedatives as the comparison group. Due to rapid elimination and quick awakening after the termination of sedation, closer consultation between the attending physician and the ICU nursing staff is required, in addition to a prolonged setup time. Study analysis will include the required setup time, time from admission to extubation as primary outcome and neurocognitive assessability. In addition, possible operation-specific (blood loss, complications), treatment parameters (catecholamine dosages, lung function) and laboratory results (acute kidney injury, acid base balance (lactataemia), liver failure) as influencing factors will be collected. The study-relevant data will be extracted from the continuous digital records of the patient data management system after the patient has been discharged from the ICU. For statistical

Strengths and limitations of this study

- Prospective randomised controlled trial of the real-time clinical benefit of the use of volatile sedation on nurse and physician workloads for time to patient awakening.
- Extend limited data on the short-term use of volatile sedatives in intensive care units in the setting of planned postoperative sedation.
- Application of volatile sedatives after cardiac valve surgery requiring heart-lung machine use with all authorised commercial anaesthetic conserving devices.
- Limited follow-up period covering up to hospital discharge.
- Limited by monocentric implementation at a university centre of cardiothoracic care and the associated intensive care unit.

evaluation, 95% CIs will be calculated for the median time to extubation and neurocognitive assessability, and the association will be assessed with a Cox regression model. In addition, secondary binary outcome measures will be evaluated using Fisher's exact tests. Further descriptive and exploratory statistical analyses are also planned.

Ethics and dissemination The study was approved by the Institutional Ethics Board of the University of Frankfurt, Germany (#20-1050). Informed consent of all individual patients will be obtained before randomisation. Results will be disseminated via publication in peer-reviewed journals.

Trial registration number Clinical trials registration (NCT04958668) was completed on 1 July 2021.

INTRODUCTION

Cardiac valve surgery remains a complex operative procedure under cardiopulmonary bypass (CPB), which is associated with a significant risk of postoperative complications such as bleeding, renal failure, arrhythmias or neurocognitive impairments.¹

Therefore, patients undergoing valve reconstruction or valve replacement are usually postoperatively transferred to the intensive care unit (ICU) under continuous sedation.² To maintain the required (analogue) sedation during ICU therapy, various substances are commonly used, such as volatile anaesthetics or intravenous sedatives combined with opioids.^{3,4}

Volatile anaesthetics have been indispensable for maintaining adequate sedation in the perioperative phase for many decades and can also be used successfully under CPB. Their ruinous usage in ICUs is limited due to technical reasons.^{5–8}

Intravenous sedatives, such as the frequently used substances propofol, clonidine and midazolam, undergo complex pharmacological metabolism and elimination mechanisms. In contrast, volatile anaesthetics are subject to inhalational uptake and elimination and, for example, in the case of isoflurane, are nearly eliminated without metabolism (0.2%).⁹ The use of both intravenous and inhaled anaesthetics has been proven to be a safe therapeutic standard for decades. The pharmacological advantages, in terms of the low context-sensitive half-life of volatile anaesthetics, have been repeatedly shown to be beneficial with respect to the recovery of postoperative patients. Accordingly, the use of volatile sedatives in ICUs has been included in sedation recommendations since 2015.^{10,11}

Technical advances over the last two decades have led to the development of technical devices that enable the use of volatile anaesthetics in ICUs. The development of reflector membranes was crucial.¹² These enabled counter financially viable use through anaesthetic gas recovery of up to 90%. Currently, two commercial systems are offered for this purpose: the AnaConDa system (Sedana Medical AB, Danderyd, Sweden) and the MIRUS system (TIM Medical, Koblenz, Germany).^{8,13,14}

The use of volatile sedatives in ICUs requires specific bedside preparation as well as trained medical and nursing staff. This includes, in particular, the preparation of the anaesthetic conserving device with an anaesthetic gas collection container, which results in increased time required for setting up the intensive care bed.

As surgical treatments have evolved, it has become easier to accomplish the same therapeutic goals with management options that do not require extended postoperative mechanical ventilation. Accordingly, the opportunity to reduce the morbidity associated with prolonged ventilation and shorten the length of stay in the ICU is being driven forward with the development of 'fast-track' cardiac surgery. The aim of the fast-track procedure is to extubate patients recovering from open heart surgery within the first 6 postoperative hours.^{4,15,16} To enable immediate neurological assessment and extubation after stabilisation of the patient's condition, a considerable interval for redistribution processes (especially with regard to the context-sensitive half-life time) and elimination of the substances must be taken into account,

depending on the duration of the preceding intravenous sedation.

The postoperative use of volatile anaesthetics in intensive care has already shown a significant acceleration of extubation for patients undergoing bypass surgery.³

Aims

While the use of volatile anaesthetics in ICUs is becoming an increasingly common clinical practice, there is a lack of prospective randomised trials on the extent to which known pharmacological advantages can be realised, despite the higher nursing and medical effort required. Our intended study would investigate the use of volatile anaesthetics as an established sedation option with regard to the wake-up behaviour of patients undergoing heart valve surgery. It will be investigated to what extent the already described positive effects can be realised, despite the necessity of differentiated intensive care and medical management. This primarily includes the necessity of workplace conversion to the previously described anaesthetic-conserving devices.

METHODS AND ANALYSIS

Study design

The study has been designed to assess the effect of continuing intensive care sedation with intravenous compared with volatile sedatives in patients after they receive heart valve surgical procedures. The study will be conducted as a prospective, randomised controlled, single-blinded, monocentric trial at a university hospital. The start of study recruitment is planned for 1 September 2021. The study is expected to enrol 48 patients per study arm over a period of up to 2 years. Block randomisation will be stratified according to single or combined surgical interventions and based on randomisation lists generated at the Institute of Biostatistics and Mathematical Modelling of Goethe University Frankfurt. The randomisation lists will be blinded to the study investigators before treatment arm allocation, and the block size will remain confidential during the study. Patients will be treated in a single-blinded approach (see [figure 1](#)).

Patient population

Patients presenting to the Department of Anaesthesiology, Intensive Care Medicine and Pain Therapy for preoperative evaluation prior to heart valve surgery in the Department of Cardiac and Vascular Surgery will be screened with regard to their suitability based on the following defined inclusion and exclusion criteria.

Inclusion criteria

- ▶ Adult (>18 years old) patients.
- ▶ Admission to the ICU after cardiac valve surgery.
- ▶ Informed consent of participant.

Exclusion criteria

- ▶ Age <18 years.

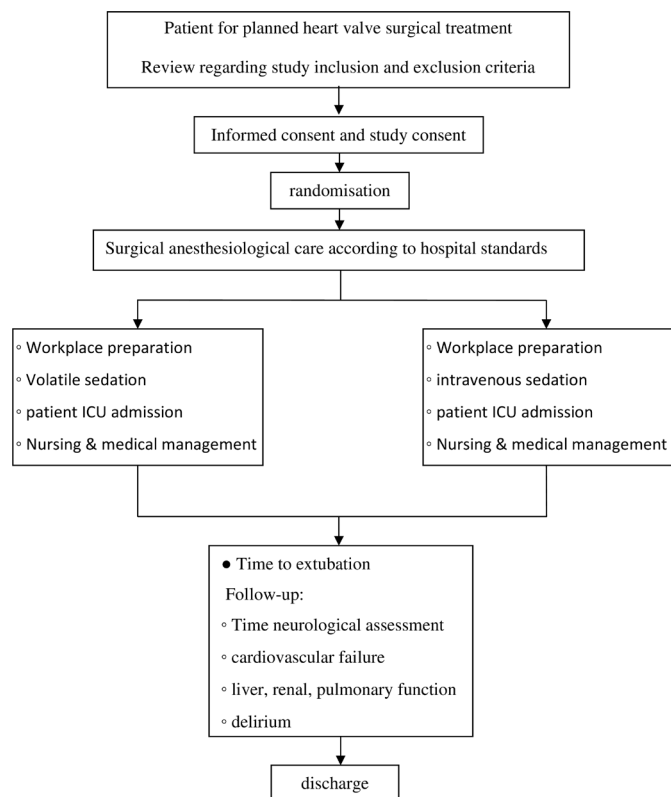


Figure 1 Flow chart of the study design for the evaluation of volatile sedation in postoperative intensive care in patients recovering from heart valve surgery. ICU, intensive care unit.

- ▶ Intolerance to volatile anaesthetics (eg, malignant hyperthermia).
- ▶ Severe obstructive pulmonary disease.
- ▶ Receiving extended aortic arch or ascending aorta surgeries.
- ▶ Withdrawal of prior consent.
- ▶ Unexpected serious intraoperative complications (eg, cardiac failure with the need for extracorporeal life support implantation).

To improve patient recruitment, in-clinic presentation events will be held, and patients will be interviewed and informed about their wish to participate in the study. If applicable, the patient will be informed by an experienced intensivist about the possibility of participating in the study and will be asked for his or her informed written consent (online supplemental I).

Within the context of study inclusion, a secondary medical anamnesis is carried out, in particular with regard to signs of contraindications, for example, anamnestic hints of malignant hyperthermia.

Types of intervention

In principle, both arms are observational without explicit medication advice within the two general sedation groups. Treatment will be given according to the current guidelines.¹⁰

The depth of sedation prior to planned awakening is assessed by performing the validated Richmond Agitation and Sedation Scale (RASS) at the bedside.¹⁷ The desired

depth of sedation is adjusted to a target value of RASS -3 (moderate sedation—any movement (but no eye contact) to voice) to -4 (deep sedation—no response to voice, but any movement to physical stimulation).

Intervention group—continuing intensive care sedation using volatile sedatives

In this intervention study group, the ICU workstation will be upgraded to allow volatile sedation to be performed after the announcement of the completed valve surgical procedure. For this purpose, an anaesthetic conserving device, an anaesthetic gas monitor and an exhaled gas absorber will be provided at the ICU workstation. After arrival of the patient in the ICU, sedation will be continued with volatile sedatives (eg, isoflurane, sevoflurane) until the scheduled wake-up 60 min after admission or immediately after the stabilisation of the patient's condition.

Due to the expected rapid elimination after the termination of the administration of volatile sedatives, close consultation between the attending physician and intensive care nurse regarding the time of termination with respect to the intended awakening with subsequent expected rapid extubation of the patient is required.

Control group—continuing intensive care sedation using intravenous sedatives

The control group will be treated at a conventionally prepared intensive care workstation. This does not require any special preparation. Sedation will be continued under continuation of the existing total intravenous analgesia. This represents the international regular case of care sedation. Ending of continuous sedation will also be scheduled for 60 min after admission.

The slow elimination of intravenously administered sedatives, especially propofol with its known context sensitivity, leads to a delayed wake-up reaction and allows a less time-critical arrangement between the intensive care nurse and the attending physician regarding the termination and possible extubation capability, which can be expected to be delayed.

Outcome

Primary outcome

- ▶ Time from admission to the ICU after cardiac surgery until extubation.

Secondary outcomes

- ▶ The required setup time of the intensive care workplace and the time span from the end of narcosis to neurocognitive assessability (in terms of spatial, site, situational and person orientation) will be determined.
- ▶ For the classification of the required time span to awakening, the time of the intraoperative procedure including the heart–lung machine as well as intensive care application of sedatives and their dosages will be determined.
- ▶ Factors related to the course of intensive care, blood loss, cardiovascular medication, kidney function,

acid–base balance and lung function parameters will also be documented.

- ▶ Incidence of postoperative nausea and vomiting.

Safety outcomes

- ▶ Intra-hospital mortality.
- ▶ Liver failure.

Data extraction

Study-relevant data will be extracted from the continuous digital records of the patient data management system (PDMS; Metavision V.5.4, iMDsoft, Tel Aviv, Israel) after the discharge of the patient from the ICU.

Data that are not captured by the continuous recording of the PDMS system, such as the time intervals from the start of intensive care workstation preparation and testing, will be recorded using an Excel-based (Microsoft Office 365) Case Report Form.

Statistical analysis

The primary statistical objective is to evaluate the feasibility of assessing the separately determined time to extubation and neurocognitive accessibility in patients after valve surgery. For this purpose, 95% CIs of median time to extubation and neurocognitive assessability will be calculated, and the association will be assessed by a Cox regression model. A two-sided log-rank test ($\alpha=5\%$) will be used to compare the times until extubation of the two study groups. If the median length of time intervals can be reduced by 50% for the approach under the volatile sedation method, this can be demonstrated with a statistical power of 80% if at least 33 patients in each group can be analysed (assuming an exponential distribution). To compensate for missing values or deviations from the exponential distribution assumption, 48 patients should be included in each group.

The secondary test objectives will be evaluated descriptively and using appropriate statistical methods. In particular, Fisher's exact test is planned to be used for binary outcome measures (renal failure, liver failure, postoperative delirium). For a two-sided Fisher's exact test at the significance level of $\alpha=5\%$, an effect size of 0.75 with a case number of 48 patients in each group can demonstrate a power above 95%. In addition, further descriptive and exploratory statistical analyses are planned. Statistical data analysis will be supervised by experienced staff of the Institute of Biostatistics and Mathematical Modelling of the Department of Goethe University. Statistical analysis will be performed using the program SPSS V.26.0 or later (IBM Corp.) or R V.4.1.0 or later (R Foundation of Statistical Computing, Austria).

Patient and public involvement

There will be no patient or public involvement in the presented study.

Ethics and dissemination

This study is planned as a prospective randomised controlled trial at the University Hospital of Frankfurt. The

study was approved by the Institutional Ethics Board of the University of Frankfurt (#20-1050). The study has been registered on the clinical trials website (NCT04958668). Informed consent of individual patients will be obtained in accordance with the ethics committee's decision during the preoperative evaluation. This study will be conducted under the actual Declaration of Helsinki. Results of the study will be disseminated through publication in peer-reviewed journals.

Contributors ANF and EHA conceived and designed the study. ANF major contributed writing the manuscript. ANF, KZ, FJR, EHA worked on manuscript drafting and critical revision. ANF and EH performed statistic planning. All authors reviewed the manuscript for important intellectual content and approved the final version.

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