


STUDY PROTOCOL

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Efficacy and safety of remimazolam for non-obese patients during anesthetic induction in cardiac surgery: study protocol for a multicenter randomized trial

Hong Yu^{1†}, Hong-Mei Liu^{1†}, Ping Li², Hai Yu¹, Bin Liu^{1*} and Peng Liang^{1,3*} 

Abstract

Background: Valvular heart disease remains common in both developed and developing countries, and it requires timely surgical treatment when necessary. However, the stability of hemodynamics during anesthesia induction in patients undergoing valve replacement surgery is difficult to maintain due to their impaired cardiac function. Remimazolam, a novel and ultrashort-acting intravenous sedative-hypnotic, may be beneficial to stable hemodynamics, but the evidence is limited. Therefore, this study aims to evaluate the effect of remimazolam induction on hemodynamics compared with midazolam and etomidate in patients undergoing valve replacement surgery.

Methods: This is a prospective, multicenter randomized controlled trial (RCT). Three hundred and sixty-three non-obese adult patients aged 45 to 80 years old undergoing valve surgery with cardiopulmonary bypass will be randomly allocated to receive remimazolam tosylate, midazolam, or etomidate during anesthetic induction. The primary outcome is the incidence of hypotension within 20 min after the administration of investigated drugs. The hypotension is defined as systolic blood pressure (SBP) < 90 mmHg or a 30% reduction in SBP from baseline or the application of vasoactive drugs. Secondary outcomes include incidence of successful sedation, time to successful sedation, incidence of delirium and postoperative low cardiac output syndrome within 7 days after surgery, hospital mortality, mechanical ventilation time, ICU length of stay, and hospital length of stay.

Discussion: To our knowledge, this is the first prospective RCT to investigate the efficacy and safety of remimazolam induction in adult cardiac surgery compared with midazolam and etomidate. This study will provide important information on the application of remimazolam in cardiac surgery in the future.

Trial registration: Chinese Clinical Trial Registry chictr.org.cn ChiCTR2100050122. Registered on August 16, 2021.

Keywords: Randomized controlled trial, Remimazolam tosylate, Midazolam, Etomidate, Cardiac surgery, Anesthetic induction

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Administrative information

Title {1}	Efficacy and safety of remimazolam for non-obese patients during anesthetic induction in cardiac surgery: study protocol for a multicenter randomized trial
Trial registration {2a and 2b}	Chinese Clinical Trial Registry ID: ChiCTR2100050122, August 16, 2021
Protocol version {3}	October 2020, version 1.1
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Role of sponsor {5c}	The trial sponsor has a regulatory role and will play a part in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication

Introduction

Background and rationale {6a}

Valvular heart disease (VHD) remains common in both developed and developing countries [1, 2], and it keeps a major contributor to physical dysfunction and decreased quality of life [3]. Timely surgical management can mitigate the deterioration to heart failure, disability, and death [4]. However, the stability of hemodynamics of patients with VHD is difficult to maintain due to their varieties of underlying cardiac dysfunction, especially during anesthesia induction when adrenergic tone acutely declines [5, 6].

Remimazolam is a novel and ultrashort-acting intravenous sedative-hypnotic, which mainly acts on the GABA-A receptor [7]. Unlike midazolam, remimazolam has the advantages of stable hemodynamics and mild respiratory inhibition [7–11], making it a potential drug for induction in cardiac surgery anesthesia [12–15]. Midazolam is one of the most frequently used sedatives in cardiac anesthesia. However, midazolam has been reported to be associated with a high incidence of hypotension in patients with cardiac disease and undergoing colonoscopy [16, 17]. Etomidate is another alternative sedative for patients with cardiovascular diseases due to its remarkably stable cardiorespiratory profile [18, 19]. However, etomidate can result in lower cortisol levels and higher adrenal insufficiency incidence compared with midazolam or propofol [18, 20]. So far, there is no evidence for the most appropriate sedative for cardiac surgery anesthesia.

Objectives {7}

Therefore, our study aims to evaluate the effect of remimazolam induction on hemodynamics compared with midazolam and etomidate in patients undergoing valve replacement surgery. We hypothesized the superiority of remimazolam in the incidence of hypotension compared with midazolam and its non-inferiority compared with etomidate during the induction of cardiac anesthesia.

Trial design {8}

This study is a prospective, parallel group, three-arm, multicenter randomized controlled trial (RCT). Patients will be allocated in a 1:1:1 ratio to one of the three groups: the remimazolam group (R group), the midazolam group (M group), or the etomidate group (E group).

Methods

Study setting {9}

This study will take place in four tertiary hospitals in China including West China Hospital of Sichuan University, Henan Provincial Chest Hospital, Panzhihua Central

Hospital, and the Third People's Hospital of Chengdu upon obtaining ethical approval and written informed patient consent. This trial protocol was written following the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist (Additional file 1).

Eligibility criteria {10}

Inclusion criteria

Male and female non-obese patients aged 45 to 80 years are eligible to enter the study if they are scheduled to undergo selective valve surgery with cardiopulmonary bypass (CPB). In addition, they have an ASA physical status score of III or IV, with New York Heart Association (NYHA) class III–IV and a body mass index (BMI) of 18 to 30 kg/m². **Exclusion criteria.**

Patients meeting one or more criteria listed below will be excluded from this trial:

- (1) Coma, hypovolemia, or shock with vasoactive drug administration
- (2) General anesthesia combining with other anesthesia methods (such as epidural anesthesia or spinal anesthesia)
- (3) Acute heart failure, unstable angina pectoris, myocardial infarction in the last 6 months
- (4) Infectious heart diseases (such as myocarditis or endocarditis) or sepsis
- (5) Severe arrhythmia, such as HR \leq 50 bpm at rest, third-degree atrioventricular block, frequent ventricular premature beat, QTc: male \geq 450 ms, female \geq 470 ms
- (6) Uncontrolled hypertension with antihypertensive drugs [systolic blood pressure (SBP) \geq 160 mmHg when sitting and/or diastolic blood pressure (DBP) \geq 100 mmHg when sitting]
- (7) SBP \leq 90 mmHg when sitting
- (8) Abnormal coagulation function (PT, INR, or APTT \geq 1.5 \times upper limit of normal [ULN])
- (9) Anemia (hemoglobin \leq 90 g/L) or decreased platelet (platelet \leq 80 \times 10.⁹/L)
- (10) Abnormal hepatic function (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] \geq 2.5 \times ULN, or total bilirubin \geq 1.5 \times ULN)
- (11) Abnormal renal function (blood urea nitrogen \geq 1.5 \times ULN or serum creatine exceeds ULN)
- (12) Hyperglycemia (blood glucose \geq 11.1 mmol/L)
- (13) History of alcoholism or drug abuse in the last 2 years
- (14) Existing mental illness, taking psychotropic drugs for a long time, or cognitive dysfunction
- (15) Pregnant or lactating women
- (16) Known contraindication to benzodiazepines, opioids, propofol, muscle relaxants, or investigated drugs

- (17) Patients with anticipated difficult airway
- (18) Participation in other trials in the last 3 months
- (19) Patients with myasthenia gravis
- (20) Other circumstances deemed by the researchers as inappropriate to participate in this study

Who will take informed consent? {26a}

One of the trial members who have been trained for the study procedure will screen potential participants according to the inclusion and exclusion criteria, explain the purpose of the study thoroughly, and obtain informed consent (Additional file 2) on the day before the surgery.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

There is no plan for additional analyses using participant data or biological specimen.

Interventions

Explanation for the choice of comparators {6b}

Midazolam and etomidate are commonly used during cardiac anesthesia induction. And remimazolam is a novel intravenous sedative-hypnotic, and its effect on hemodynamics during cardiac surgery remains uncertain. Thus, we compare the effect of remimazolam with another two drugs on the incidence of hypotension during anesthesia induction.

Intervention description {11a}

Study drug administration

During anesthesia induction, patients in the R group will receive 0.2 mg/kg remimazolam tosylate within 3 min. If the BIS value cannot be \leq 60 in 3 min, then another 0.1 mg/kg remimazolam tosylate will be added in the following 2 min. Patients in the M group will receive 0.15 mg/kg midazolam within 3 min, and another 0.05 mg/kg midazolam will be employed if the BIS value cannot be \leq 60 in 3 min. Patients in the E group will receive 0.2 mg/kg etomidate within 3 min, and another 0.05 mg/kg etomidate will be administered if the BIS value cannot achieve \leq 60 in 3 min. At the same time, a total of 0.6–1.0 μ g/kg sufentanil will be administered in three groups. When the BIS value $<$ 70 or patients are unresponsive to mild prodding or shaking, cis-atracurium (0.2–0.3 mg/kg) or rocuronium (0.6–1 mg/kg) will be added. If the BIS value cannot achieve \leq 60 in 5 min after the beginning of the study drug administration, rescue sedative medications with no restriction will be administered. Endotracheal intubation will be accomplished when BIS maintains 45–55 and the TOF value equals to zero.

Anesthesia and CPB management

All patients will be monitored continuously with bispectral index (BIS) electrode, electrocardiogram, pulse oximetry, invasive arterial pressure with pulse index continuous cardiac output (PiCCO) system, central venous pressure (CVP), body temperature, end-tidal partial pressure of carbon dioxide, and train-of-four (TOF) simulation. Anesthesia induction will be conducted according to the group assignment. Anesthesia will be maintained by utilizing propofol or volatile anesthetics (sevoflurane or desflurane) with remifentanyl (0.1–0.2 $\mu\text{g}/\text{kg}/\text{min}$) to keep a BIS value between 40 and 60. All patients will receive standard CPB management and will be received standard ICU care after surgery.

Criteria for discontinuing or modifying allocated interventions {11b}

In the case where there is a withdrawal of consent to continue in this study or the patient is allergic to midazolam, etomidate, remimazolam, or other anesthetics during surgery, the patients will be dropped from this study.

Strategies to improve adherence to interventions {11c}

Not applicable. Interventions in this study will be completed during anesthesia and without the cooperation of patients.

Relevant concomitant care permitted or prohibited during the trial {11d}

There are no specific restrictions of concomitant care during this study.

Provisions for post-trial care {30}

Not applicable. Patients will be managed according to routine practice without other post-trial care.

Outcomes {12}**Primary outcome**

The primary outcome is the incidence of hypotension within 20 min after the investigated drug administration. The hypotension is defined as SBP < 90 mmHg or a 30% reduction in SBP from baseline or the application of vasoactive drugs.

Secondary outcomes

Secondary outcomes include the following: (1) incidence of successful sedation, defined as BIS value ≤ 60 within 5 min after the investigated drug administration, without needing rescue sedative medications [21]; (2) time to successful sedation, defined as the time from initial drug injection to BIS value ≤ 60 ; (3) postoperative delirium within 7 days after surgery; (4) hospital mortality, incidence of postoperative LCOS,

mechanical ventilation time, ICU LOS, and hospital LOS.

Participant timeline {13}

The schedule of trial enrollment, allocation, interventions, and assessments is shown in Table 1 and Fig. 1.

Sample size {14}

Based on previous studies, we estimated the incidence of hypotension during induction with remimazolam tosylate, etomidate, and midazolam as 16.7% [12], 13.3% [22], and 44.4% [16], respectively. We hypothesized that remimazolam tosylate was superior to midazolam with superiority marginal = 10% and non-inferior to etomidate with non-inferiority marginal = 10%. A total sample of 336 patients (112 in each group) was required to achieve a power ($1-\beta$) of 80% and type I α error of 0.025. A dropout of 10% was estimated; therefore, the total number of patients was increased to 369 (123 patients per group).

Recruitment {15}

All patients aged more than 18 with diagnosed VHD, planning for cardiac surgery, will be screened by the investigator in each center daily. Thereafter, verbal and written information regarding the trial will be provided if they meet all inclusion criteria and no exclusion criteria. The recruitment of patients is on-going. Since these four hospitals are high-volume centers, we will be able to identify eligible patients and recruit the required sample size.

Assignment of interventions: allocation Sequence generation {16a}

The randomization assignment will be generated by a statistician using a block randomization method with a block size of 3 and 6.

Concealment mechanism {16b}

Opaque, sealed envelopes generated according to the randomization schedule will be used.

Implementation {16c}

On the day of surgery, sequentially numbered opaque envelopes generated according to the randomization schedule will be provided to the attending anesthesiologists.

Assignment of interventions: blinding**Who will be blinded {17a}**

Patients, surgical team, anesthesia care providers after induction, care providers in the intensive care unit

Table 1 The SPIRIT figure of this trial

Time point	Study period										
	Enrollment	Allocation	Intervention	Post-intervention							
	Preoperative visit	Allocation	During induction until 20 min after induction	POD1	POD2	POD3	POD4	POD5	POD6	POD7	
Enrollment											
Eligibility screen	×										
Informed consent	×										
Demographic data	×										
Allocation		×									
Interventions											
Midazolam			×								
Etomidate			×								
Remimazolam			×								
Surgery and anesthesia date			×								
Assessments			×								
BIS			×								
SBP/DBP/MBP			×								
HR/CVP/CO/SVR											
RASS			×	×	×	×	×	×	×	×	×
CAM-ICU			×	×	×	×	×	×	×	×	×

POD postoperative day, BIS bispectral index, SBP systolic blood pressure, DBP diastolic blood pressure, MBP mean blood pressure, HR heart rate, CVP central venous pressure, CO cardiac output, SVR systematic vascular resistance, RASS Richmond Agitation-Sedation Scale, CAM-ICU Confusion Assessment Method in the intensive care unit

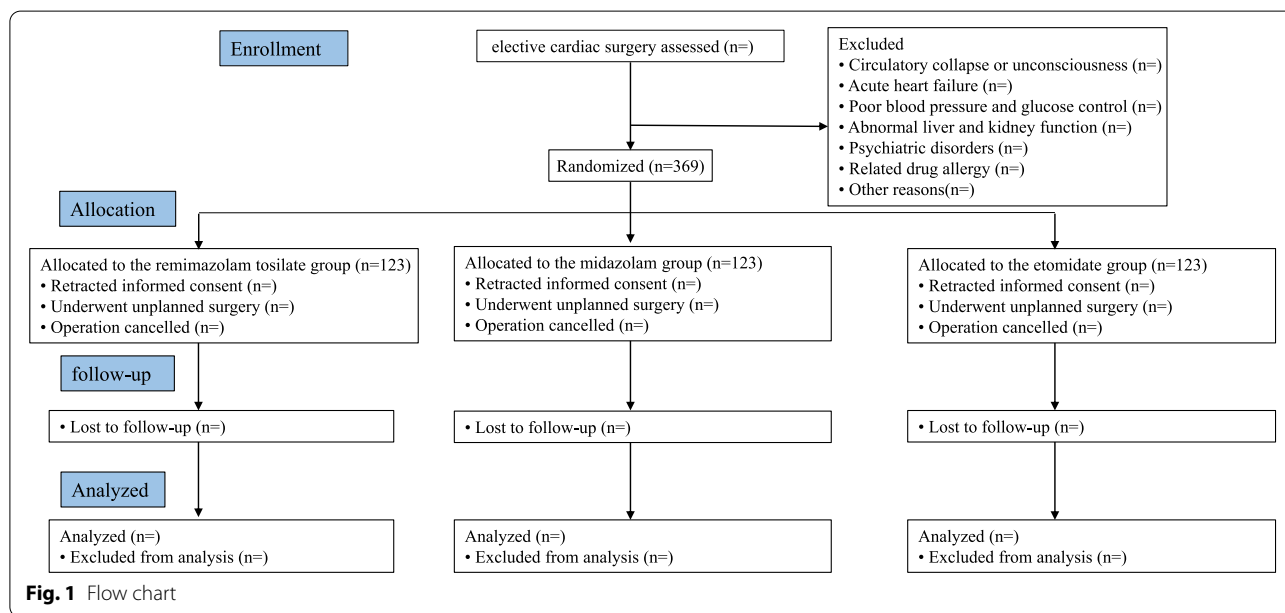


Fig. 1 Flow chart

and ward after surgery, and the investigators assessing outcomes and analyzing data will be blinded to the assignment.

Procedure for unblinding if needed [17b]

Not applicable. The attending anesthesiologists who give study drugs during induction will not be blinded to guarantee patients' safety.

Data collection and management

Plans for assessments and collection of outcomes {18a}

All data will be collected in the case report form (CRF) and the following data will be recorded.

Baseline characteristics of patients

Demographic data, ASA physical status score, preoperative NYHA grading, diabetes, hypertension, preoperative medication, arrhythmia, chronic obstructive pulmonary disease, dialysis, previous cerebral infarction, hypothyroidism, chronic heart failure, left ventricular ejection fraction (LVEF), cardiac surgery history, EuroScore II score, type of surgery, operation time, extracorporeal circulation time, aortic clamp time, the amount of blood product, and fluid balance will be recorded.

Evaluation during anesthesia induction

We will record the BIS value, the time from drug administration to the BIS value ≤ 60 , and the dosage of the sedative and sufentanil. Rescue sedative medications and the dosage used will also be recorded if the first sedation fails. The following hemodynamic data will be collected every 30 s for 20 min after the investigated drug administration: SBP, DBP, mean blood pressure, CVP, heart rate, cardiac output (CO), and systemic vascular resistance (SVR). The dosage of vasoactive drugs used within 20 min after induction will also be recorded. Bucking during induction will be recorded and scored as follows: no bucking, mild bucking (1–2 times), moderate bucking (3–4 times), and severe bucking (≥ 5 times).

Delirium evaluation and follow-up at discharge

Postoperative cognitive function will be evaluated daily (15:00–17:00) using the Richmond Agitation-Sedation Scale (RASS) score and Confusion Assessment Method in ICU (CAM-ICU) [23] within the first 7 postoperative days. And we also record hospital mortality, postoperative low CO syndrome (LCOS), mechanical ventilation time (from return to ICU after surgery to successful tracheal extubation), ICU length of stay (LOS), and hospital LOS.

Plans to promote participant retention and complete follow-up {18b}

During the preoperative visit, patients will be fully informed about the intraoperative procedure and postoperative follow-up. And the study investigators who are in charge of follow-up will visit patients daily within the first 7 postoperative days.

Data management {19}

Data recorded in CRFs will be entered into the Electronic Data Capture (EDC) system by trained nurses from each sub-center study team. Data accuracy will be supervised by the principal investigators (HY, HML, and PL). And all study members will receive protocol and device training (if necessary) before participating in the study to ensure protocol adherence. Data will be stored for at least 3 years after trial termination and publication of the final report.

Confidentiality {27}

All records of trial participants will be stored using identification numbers and initials in CRF and EDC system and remain confidential to the public.

Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

Not applicable. There exist no biological specimens to be collected in this study.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

Statistical analysis will be performed using SPSS 23.0 software. The continuous data will be described as the mean (SD) or median (interquartile range) and compared using the Student *t* test or the Mann–Whitney *U* test between groups, whereas categorical data will be described as frequencies (percentages) and compared using Pearson χ^2 test or Fisher exact tests. And we will conduct the analysis of variance for repeated measurements with Bonferroni correction to compare the hemodynamic effects between remimazolam and midazolam and between remimazolam and etomidate. To test the superiority of remimazolam to midazolam and the non-inferiority of remimazolam to etomidate, one-tailed tests will be performed, and other tests will utilize a two-tailed test. All tests will be conducted with 95% confidence intervals. A *P* value of less than 0.05 will be considered statistically significant.

Interim analyses {21b}

No interim analyses are planned for this study.

Methods for additional analyses (e.g., subgroup analyses) {20b}

No subgroup analyses are planned for this study.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

Primary analyses will be performed according to the intention-to-treat principle. Sensitivity analysis will be performed to handle protocol violation and deviation cases using the per-protocol principle. If the continuously collected data (e.g., SBP, DBP, BIS, RASS, CAM-ICU, et al.) is lost at one timepoint during the trial, the most recent data will be analyzed as if it were obtained at that time.

Plans to give access to the full protocol, participant-level data, and statistical code {31c}

The datasets analyzed during the current study and statistical code are available from the corresponding author on reasonable request, as is the full protocol.

Oversight and monitoring**Composition of the coordinating center and trial steering committee {5d}**

There are several tertiary hospitals in China participating in this study. The study team has a conference online weekly to discuss the problems in the conduct of the trial. There is no trial steering committee or stakeholder and public involvement group.

Composition of the data monitoring committee, its role, and reporting structure {21a}

Not applicable. There is no data monitoring committee in this study. Instead, the principal investigator will check the appropriateness of the data and conduction of the trial every 2 weeks.

Adverse event reporting and harms {22}

According to the drug instruction of remimazolam tosylate, the adverse events related to this drug include hypotension (2.65–6.45%), decreased neutrophil (6.45%), increased serum bilirubin (3.17%), increased serum unconjugated bilirubin, and dizziness (2.12%). But these adverse events will not result in severe consequences. Adverse events related to this study protocol include severe hypotension and failure in sedation. When hypotension occurs, vasoactive drugs will be utilized during anesthesia induction when SBP < 90 mmHg or a 30% reduction from baseline. And when study sedation fails, rescue sedative medications (including propofol, midazolam, or etomidate, etc.) will be used to accomplish anesthesia induction. Adverse events will be treated immediately and reported to the institutional review

board. The participants will also be followed up until it is completely resolved or therapy is terminated.

Frequency and plans for auditing trial conduct {23}

The department of research office and the ethics committee of each center will audit the study annually. And the principal investigator will check the appropriateness of the data and conduction of the trial every 2 weeks.

Plans for communicating important protocol amendments to relevant parties (e.g., trial participants, ethical committees) {25}

Any protocol amendments will be written into a formal substantial amendment reviewed by the institutional review board of the West China Hospital before application.

Dissemination plans {31a}

ALL patients will provide written informed consent before the start of any protocol-specified procedures or assessments. The results of the study will be presented at relevant conferences and submitted to international peer-reviewed journals.

Discussion

The current study will be the first prospective RCT assessing the efficacy and safety of employing remimazolam tosylate for anesthesia induction in patients undergoing cardiac surgery compared with midazolam and etomidate. Our results may show that the infusion of remimazolam tosylate titrated to a BIS value of 60 is superior to midazolam and non-inferior to etomidate on the incidence of hypotension during anesthesia induction.

The primary advantages of remimazolam tosylate include rapid onset of action and minimal depression of cardiorespiratory function, allowing this drug favorable in sedation and general anesthesia. Several clinical cases found that remimazolam can be used to achieve the same appropriate anesthesia management as other existing anesthetics for patients undergoing cardiac surgery [13, 14, 24] or for the patient undergoing non-cardiac surgery with cardiac dysfunction [25]. And two RCTs [12, 15] suggested that remimazolam was safe and effective compared with propofol for induction in cardiac surgery with less hemodynamic fluctuations. However, propofol has a huge potential to cause hypotension, and its incidence could reach more than 70% during general anesthesia induction [26, 27]. It indicates that propofol may be inappropriate for patients with impaired cardiac function, consequently making the benefit of remimazolam on cardiovascular function less convincing when comparing with propofol. Clinical trials comparing remimazolam with sedatives other than propofol during cardiac

surgery are necessary and significant. Midazolam is the most frequently used sedative for anesthetic induction with mild adverse events [28], but there was scarce study investigating the hemodynamic change of midazolam in cardiac surgery so far. Besides, etomidate may be a better control drug as it has been proven to be associated with more stable hemodynamics for anesthetic induction in cardiac surgery [18] but with side effects of injection-site pain, myoclonus, and suppression of the adrenocortical axis [20]. Until now, the most optimal sedative for anesthesia induction in cardiac surgery was uncertain. Therefore, we design this study to evaluate the efficacy and safety profile of remimazolam tosylate during cardiac surgery by comparing with midazolam and etomidate. In summary, we anticipate the findings of this study will provide a high-quality evidence on the merit of stabilizing hemodynamics of remimazolam tosylate during anesthetic induction in cardiac surgery.

Strengths and limitations

This study is, to our knowledge, the first to evaluate the efficacy and safety of utilizing remimazolam tosylate in patients undergoing cardiac surgery. In addition, this is a multicenter trial involving several tertiary hospitals in China, making the results from this study generalizable. This prospective RCT has been carefully designed and will be meticulously implemented in each center. The major limitation of this study is that the definition of hypotension and the characteristics of participants varied in different studies, resulting in the potential difference between the estimated and the actual incidence of hypotension. In addition, we excluded obese patients with BMI > 30 in this study because obese patients often suffer from a combination of hypertension, dyslipidemia, and type 2 diabetes mellitus, also known as the “metabolic syndrome” [29]. Consequently, the pharmacokinetics of obese patients are different from patients with a normal range of BMI. Therefore, to control bias and also to guarantee patients’ safety, we will only recruit patients with BMI between 18 and 30.

Trial status

The current protocol is version 1.1 and was issued on 1 October 2020. At the time of manuscript submission, the study is in the phase of recruitment. Recruitment has been begun in April 2022 and is expected to be completed by June 2023.

Abbreviations

ALT: Alanine aminotransferase; APTT: Activated partial thromboplastin time; AST: Aspartate aminotransferase; BIS: Bispectral index; BMI: Body mass index; CAM-ICU: Confusion Assessment Method in the intensive care unit; CO: Cardiac output; CPB: Cardiopulmonary bypass; CVP: Central venous pressure; DBP: Diastolic blood pressure; GABA: Gamma-aminobutyric acid; ICU: Intensive care

unit; INR: International normalized ratio; LCOS: Low cardiac output syndrome; LOS: Length of stay; LVEF: Left ventricular ejection fraction; NYHA: New York Heart Association; PiCCO: Pulse index continuous cardiac output; PT: Prothrombin time; RASS: Richmond Agitation-Sedation Scale; RCT: Randomized controlled trial; RHD: Rheumatic heart disease; SBP: Systolic blood pressure; SD: Standard deviation; SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials; SVR: Systemic vascular resistance; TOF: Train of four; ULN: Upper limit of normal.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13063-022-06965-8>.

Additional file 1. The SPIRIT 2013 checklist of this trial.

Additional file 2. The model consent form.

Acknowledgements

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Author’s contributions {31b}

BL and Peng Liang (PL1) planned the study. Ping Li (PL2) performed the statistical design of the study. All authors contributed to the design and development of the trial. Hong Yu (HY1), HML, and PL2 drafted the manuscript. BL and Hai Yu (HY2) and PL2 critically revised the manuscript. The authors read and approved the final manuscript.

Funding {4}

None.

Availability of data and materials {29}

Any data required to support the protocol can be supplied on request.

Declarations

Ethics approval and consent to participate {24}

The study protocol has been approved by the Ethics Committee of West China Hospital of Sichuan University [Ethics Committee No. 2021(225)] and registered at chictr.org.cn (ID: ChiCTR2100050122) on August 16, 2021. All patients will provide written informed consent before the start of any protocol-specified procedures or assessments. The patients can withdraw from the trial at any time. The results of the study will be presented at relevant conferences and submitted to international peer-reviewed journals.

Consent for publication {32}

Not applicable—no identifying images or other personal or clinical details of participants are presented here or will be presented in reports of the trial results. Informed consent materials are available from the corresponding author on request.

Competing interests {28}

The authors declare that they have no competing interests.

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References

- Huang X, Dhruva SS, Yuan X, Bai X, Lu Y, Yan X, et al. Characteristics, interventions and outcomes of patients with valvular heart disease hospitalised in China: a cross-sectional study. *BMJ Open*. 2021;11(11):e052946. <https://doi.org/10.1136/bmjopen-2021-052946>.
- lung B, Vahanian A. Epidemiology of valvular heart disease in the adult. *Nat Rev Cardiol*. 2011;8(3):162–72. <https://doi.org/10.1038/nrcardio.2010.202>.
- Coffey S, Roberts-Thomson R, Brown A, Carapetis J, Chen M, Enriquez-Sarano M, et al. Global epidemiology of valvular heart disease. *Nat Rev Cardiol*. 2021;18(12):853–64. <https://doi.org/10.1038/s41569-021-00570-z>.
- Kumar RK, Antunes MJ, Beaton A, Mirabel M, Nkomo VT, Okello E, et al. Contemporary diagnosis and management of rheumatic heart disease: implications for closing the gap: a scientific statement from the American Heart Association. *Circulation*. 2020;142(20):e337–57. <https://doi.org/10.1161/CIR.0000000000000921>.
- Watkins DA, Beaton AZ, Carapetis JR, Karthikeyan G, Mayosi BM, Wyber R, et al. Rheumatic heart disease worldwide: JACC Scientific Expert Panel. *J Am Coll Cardiol*. 2018;72(12):1397–416. <https://doi.org/10.1016/j.jacc.2018.06.063>.
- Nabzdok CGS, Read MD, Wieruszewski PM, Seelhammer TG. Proactive approach to peri-induction hemodynamic management in critically ill patients. *J Cardiothorac Vasc Anesth*. 2021;35(12):3489–92. <https://doi.org/10.1053/j.jvca.2021.06.015>.
- Lee A, Shirley M. Remimazolam: a review in procedural sedation. *Drugs*. 2021;81(10):1193–201. <https://doi.org/10.1007/s40265-021-01544-8>.
- Worthington MT, Antonik LJ, Goldwater DR, Lees JP, Wilhelm-Ogunbiyi K, Borkett KM, et al. A phase Ib, dose-finding study of multiple doses of remimazolam (CNS 7056) in volunteers undergoing colonoscopy. *Anesth Analg*. 2013;117(5):1093–100. <https://doi.org/10.1213/ANE.0b013e3182a705ae>.
- Wesolowski AM, Zaccagnino MP, Malapero RJ, Kaye AD, Urman RD. Remimazolam: pharmacologic considerations and clinical role in anesthesiology. *Pharmacotherapy*. 2016;36(9):1021–7. <https://doi.org/10.1002/phar.1806>.
- Keam SJ. Remimazolam: first approval. *Drugs*. 2020;80(6):625–33. <https://doi.org/10.1007/s40265-020-01299-8>.
- Freyer N, Knospel F, Damm G, Greuel S, Schneider C, Seehofer D, et al. Metabolism of remimazolam in primary human hepatocytes during continuous long-term infusion in a 3-D bioreactor system. *Drug Des Devel Ther*. 2019;13:1033–47. <https://doi.org/10.2147/DDDT.S186759>.
- Liu T, Lai T, Chen J, Lu Y, He F, Chen Y, et al. Effect of remimazolam induction on hemodynamics in patients undergoing valve replacement surgery: a randomized, double-blind, controlled trial. *Pharmacol Res Perspect*. 2021;9(5):e00851. <https://doi.org/10.1002/prp2.851>.
- Saito K, Ohno S, Maeda M, Hirata N, Yamakage M. Remimazolam anesthesia for cardiac surgery with cardiopulmonary bypass: a case report. *JA Clin Rep*. 2021;7(1):21. <https://doi.org/10.1186/s40981-021-00424-0>.
- Satoh T, Nishihara N, Sawashita Y, Ohno S, Hirata N, Yamakage M. Remimazolam anesthesia for MitraClip implantation in a patient with advanced heart failure. *Case Rep Anesthesiol*. 2021;2021:5536442. <https://doi.org/10.1155/2021/5536442>.
- Tang F, Yi JM, Gong HY, Lu ZY, Chen J, Fang B, et al. Remimazolam benzenesulfonate anesthesia effectiveness in cardiac surgery patients under general anesthesia. *World J Clin Cases*. 2021;9(34):10595–603. <https://doi.org/10.12998/wjcc.v9.i34.10595>.
- Zuin M, Rigatelli G, Dell'Avvocata F, Faggian G, Conte L, Giatti S, et al. Ketamine and midazolam differently impact post-intubation hemodynamic profile when used as induction agents during emergency airway management in hemodynamically stable patients with ST elevation myocardial infarction. *Heart Vessels*. 2018;33(3):213–25. <https://doi.org/10.1007/s00380-017-1049-5>.
- Rex DK, Bhandari R, Desta T, DeMicco MP, Schaeffer C, Etkorn K, et al. A phase III study evaluating the efficacy and safety of remimazolam (CNS 7056) compared with placebo and midazolam in patients undergoing colonoscopy. *Gastrointest Endosc*. 2018;88(3):427–37.e6. <https://doi.org/10.1016/j.gie.2018.04.2351>.
- Yao YT, He LX, Fang NX, Ma J. Anesthetic induction with etomidate in cardiac surgical patients: a PRISMA-compliant systematic review and meta-analysis. *J Cardiothorac Vasc Anesth*. 2021;35(4):1073–85. <https://doi.org/10.1053/j.jvca.2020.11.068>.
- Wagner CE, Bick JS, Johnson D, Ahmad R, Han X, Ehrenfeld JM, et al. Etomidate use and postoperative outcomes among cardiac surgery patients. *Anesthesiology*. 2014;120(3):579–89. <https://doi.org/10.1097/ALN.0000000000000087>.
- Valk BI, Struys M. Etomidate and its analogs: a review of pharmacokinetics and pharmacodynamics. *Clin Pharmacokinet*. 2021;60(10):1253–69. <https://doi.org/10.1007/s40262-021-01038-6>.
- Punjasawadwong Y, Boonjeungmonkol N, Phongchiewboon A. Bispectral index for improving anaesthetic delivery and postoperative recovery. *Cochrane Database Syst Rev*. 2007;4:Cd003843. <https://doi.org/10.1002/14651858.CD003843.pub2>.
- Hannam JA, Mitchell SJ, Cumin D, Frampton C, Merry AF, Moore MR, et al. Haemodynamic profiles of etomidate vs propofol for induction of anaesthesia: a randomised controlled trial in patients undergoing cardiac surgery. *Br J Anaesth*. 2019;122(2):198–205. <https://doi.org/10.1016/j.bja.2018.09.027>.
- Ely EW, Inouye SK, Bernard GR, Gordon S, Francis J, May L, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA*. 2001;286(21):2703–10. <https://doi.org/10.1001/jama.286.21.2703>.
- Kitaura A, Kosumi R, Iwamoto T, Nakao S. Remimazolam anesthesia for transcatheter mitral valve repair in a patient with mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome: a case report. *JA Clin Rep*. 2022;8(1):38. <https://doi.org/10.1186/s40981-022-00528-1>.
- Furuta M, Ito H, Yamazaki M. Anaesthetic management using remimazolam in a patient with severe aortic stenosis: a case report. *BMC Anesthesiol*. 2021;21(1):202. <https://doi.org/10.1186/s12871-021-01422-6>.
- Chen L, Lu K, Luo T, Liang H, Gui Y, Jin S. Observer's Assessment of Alertness/Sedation-based titration reduces propofol consumption and incidence of hypotension during general anesthesia induction: a randomized controlled trial. *Sci Prog*. 2021;104(4):368504211052354. <https://doi.org/10.1177/00368504211052354>.
- Thirunelli RK, Nanjundaswamy NH. A Prospective observational study of plethysmograph variability index and perfusion index in predicting hypotension with propofol induction in noncardiac surgeries. *Anesth Essays Res*. 2021;15(2):167–73. https://doi.org/10.4103/aer.aer_81_21.
- Conway A, Rolley J, Sutherland JR. Midazolam for sedation before procedures. *Cochrane Database Syst Rev*. 2016;5:CD009491. <https://doi.org/10.1002/14651858.CD009491.pub2>.
- Pouwels S, Buise MP, Twardowski P, Stepaniak PS, Proczko M. Obesity surgery and anesthesiology risks: a review of key concepts and related physiology. *Obes Surg*. 2019;29(8):2670–7. <https://doi.org/10.1007/s11695-019-03952-y>.

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