Trials

STUDY PROTOCOL

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The use of remimazolam versus propofol for anesthesia induction in video-assisted thoracoscopic surgery: study protocol for a multicenter randomized controlled trial

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Abstract

Background Intraoperative hypotension may result in a higher incidence of postoperative myocardial injury, acute kidney injury, and stroke. Notably, more than half of intraoperative hypotension cases occur immediately after induction of general anesthesia. Although intraoperative hypotension has multiple causes, post-induction hypotension is primarily due to the effects of anesthetic drugs. Propofol is the most widely used agent for anesthesia induction. However, propofol can induce hemodynamic instability, potentially leading to adverse postoperative outcomes. Remimazolam, a novel ultra-short-acting intravenous sedative-hypnotic, may promote stable hemodynamics. Studies have reported that remimazolam is associated with less hypotension compared to propofol. Therefore, this study aims to compare the hemodynamic effects of remimazolam and propofol during anesthesia induction in patients undergoing video-assisted thoracoscopic surgery.

Methods This is a prospective, multicenter randomized controlled trial. A total of 172 patients aged 45 to 65 years undergoing video-assisted thoracoscopic surgery will be randomly allocated to receive remimazolam or propofol during anesthetic induction. The primary outcome is the incidence of hypotension occurring within 20 min after anesthesia induction. Hypotension is defined as systolic blood pressure (SBP) of less than 90 mmHg, or a reduction of more than 30% in SBP from baseline, or the administration of vasoactive medication. Secondary outcomes include the rate of successful sedation, time to successful sedation, coughing during the induction period, postoperative delirium within 7 days after surgery, and postoperative in-hospital mortality.

Discussion To date, remimazolam has rarely been used for anesthesia induction in video-assisted thoracoscopic surgery. This study will provide important information on hemodynamic stability and anesthesia efficacy of remimazolam in this surgical setting.

Trial registration Chinese Clinical Trial Registry ChiCTR2400085556. Registered on 12 th June 2024, http://www.chictr.org.cn/.

Keywords Remimazolam, Anesthetic induction, Video-assisted thoracoscopic surgery, Randomized controlled trial

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Administrative information

Title {1}	The use of remimazolam versus propofol for anesthesia induction in video-assisted thoracoscopic surgery: study protocol for a multicenter randomized controlled trial
Trial registration {2a and 2b}	www.chictr.org.cn identifier ChiCTR2400085556. Registered on 12 th June 2024, http://www.chictr.org.cn/
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Role of sponsor {5c}	The trial sponsor will participate in study design, data collection, management, analysis, interpretation, report writing, and the decision to submit the report for publication

Introduction

Background and rationale {6a}

After anesthesia induction, hypotension is a common occurrence in surgical patients, namely post-induction hypotension (PIH), which has been reported in 18–67% cases [1, 2]. This phenomenon occurs due to several factors, including the vasodilatory effects of anesthetic agents such as propofol and volatile anesthetics, which relax vascular smooth muscle and decrease systemic vascular resistance [3]. Additionally, anesthesia-induced suppression of sympathetic tone results in diminished compensatory responses to hypotension [4]. Similar to intraoperative hypotension, PIH is associated with organ hypoperfusion and adverse perioperative outcomes, such as myocardial injury, stroke, and acute kidney injury [5–7]. Propofol is the most commonly administered agent for the induction of general anesthesia. However, the administration of propofol induces hypotension, primarily due to reduced vascular resistance [8]. Approximately one-third of patients experience mean arterial pressures (MAP) <65 mmHg after propofol administration [9]. This highlights the need to explore alternative agents to reduce the occurrence of PIH.

Remimazolam is a new ultra-short-acting benzodiazepine that acts by enhancing the activity of Gamma-aminobutyric acid a (GABA) receptors, inducing hyperpolarization of the nerve cell membrane and inhibiting neuronal activity. It rapidly decomposes through serum esterase to produce CNS 7054, a metabolite with reduced affinity to the GABAa receptor [10]. A phase I dose-finding study compared remimazolam (0.01–0.30 mg/kg) with midazolam (0.075 mg/kg) and demonstrated that remimazolam has faster clearance (70.3 vs. 23.0 L/h), shorter residence time (0.51 vs. 3.62 h), a shorter half-life (0.75 vs. 4.29 h), and independent of body weight [11]. The context-sensitive half-time (CSHT) of remimazolam is shorter than that of midazolam (7.5 vs. 40 min after 3 h infusion) and similar to propofol, with CSHT remaining relatively stable regardless of infusion duration [12, 13]. Similar to other benzodiazepines, flumazenil can be used to reverse the sedative effects of remimazolam [14]. These properties make remimazolam particularly suitable for short surgical procedures or cases where rapid recovery is essential.

In a phase III trial, remimazolam achieved significantly higher procedural success rates for colonoscopy compared to midazolam, the gold-standard benzodiazepine [15]. Moreover, remimazolam demonstrated a lower risk of hypotension and respiratory depression compared to midazolam. When compared to propofol in patients undergoing upper gastrointestinal endoscopy, remimazolam showed comparable efficacy but exhibits a superior safety profile, with fewer cases of injection pain, hypoxia,

and respiratory depression [16, 17]. In addition to its advantages in procedural sedation, remimazolam is being investigated for its potential in general anesthesia. Clinical studies utilizing remimazolam for anesthesia induction (6 and 12 mg/kg/h) and maintenance (1 mg/kg/h) in American Society of Anesthesiologists (ASA) class I/II patients have found it to be non-inferior to propofol in terms of efficacy, while presenting a significantly lower incidence of hypotension and reduced vasopressor requirements [18]. For high-risk surgical patients, remimazolam (induction doses of 6–12 mg/kg/h and maintenance doses of 1–3 mg/kg/h) has been shown to provide stable hemodynamics with reduced norepinephrine requirements and fewer hypotensive events compared to propofol or propofol-sevoflurane regimens [19].

These beneficial properties, including rapid onset, short duration, availability of a reversal agent, and enhanced safety profile, make remimazolam a promising alternative to propofol for anesthesia induction, particularly in patients at risk of hemodynamic instability. Despite these advantages, the clinical application of remimazolam has been limited to a few volunteer studies and clinical investigations, especially in thoracic surgery. Therefore, this study aims to evaluate the efficacy and safety of remimazolam compared to propofol for anesthesia induction in patients undergoing video-assisted thoracoscopic surgery, with a focus on hemodynamic stability.

Objectives {7}

The primary objective of this study is to evaluate the hemodynamic effects of remimazolam compared to propofol during anesthesia induction in adult patients undergoing video-assisted thoracoscopic surgery. We hypothesize that remimazolam will result in a lower incidence of post-induction hypotension compared to propofol.

Trial design {8}

This study is designed as a prospective, parallel-group, two-arm, multicenter randomized controlled trial (RCT). Patients will be allocated in a 1:1 ratio to one of the two groups: the remimazolam group (R group), or the propofol group (P group). The study protocol is reported following the SPIRIT reporting guidelines [20].

Methods: participants, interventions, and outcomes

Study setting {9}

This study will be conducted at seventeen tertiary hospitals in China including West China Hospital of Sichuan University, Sichuan Provincial People's Hospital, Luzhou People's Hospital, the First People's Hospital Of Neijiang, the Fourth People's Hospital of Zigong, the Second People's Hospital of Yibin, Santai People's Hospital, Mianyang Central Hospital, Deyang People's Hospital, Guang'an People's Hospital, The First People's Hospital of Suining, The People's Hospital of the Linshui County, Guang'an City, Qionglai Medical Center Hospital, Dazhou Central Hospital, West China Tianfu Hospital of Sichuan University, Chengdu Shangjin Nanfu Hospital, Leshan People's Hospital, after obtaining ethical approval and written informed patient consent. This study has been registered in the Chinese Clinical Trial Registry (ChiCTR2400085556, Date of registration: June 12, 2024).

Eligibility criteria {10}

Inclusion criteria

Male and female patients aged 45 to 65 years with a body mass index (BMI) between 18.5 and 28 kg/m^2, who are scheduled to undergo elective video-assisted thoracoscopic surgery and are classified as ASA class I to III, are eligible to participate in the study.

Exclusion criteria

Patients who meet one or more of the following criteria will be excluded from this trial:

1. Patients with severe heart, brain, liver, and kidney diseases.
2. Patients with mental disorders (schizophrenia, mania, bipolar disorders, insanity, etc.)
3. Long-term history of taking psychotropic drugs and cognitive impairment.
4. Patients who are allergic or contraindicated to benzodiazepines, opioids, propofol, muscle relaxants, and their drug components.
5. Patients with anticipated difficult airway
6. Participation in other trials in the last 3 months
7. Other situations were deemed by the researchers as inappropriate to participate in this study.

Who will take informed consent? {26a}

On the day before the surgery, the members of the research team will approach each patient for a brief screening evaluation. If the patient meets the inclusion criteria of this clinical trial, the research team members will explain the purpose, benefits, and risks to the patient in detail. Informed consent forms (see Additional file 1) will be signed by the patients and collected before the trial begins.

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

There are no plans for additional analyses using participant data or biological specimens.

Interventions

Explanation for the choice of comparators {6b}

Propofol has the advantages of rapid induction and recovery and is one of the most commonly used sedative drugs for pulmonary surgeries. Nevertheless, propofol has some unfavorable adverse effects, including pain noted on intravenous injection and dose-related cardiovascular depression. Remimazolam is a novel intravenous sedative-hypnotic, and its effects on hemodynamics during video-assisted thoracoscopic surgery remain uncertain. Thus, we will compare the effect of remimazolam with propofol on the incidence of hypotension during anesthesia induction.

The dosing of remimazolam (6 mg/kg/h) for anesthesia induction was selected based on previous clinical studies and pharmacokinetic data [18, 21, 22]. In the phase IIb/III trial of remimazolam, a dose of 6 mg/kg/h was shown to provide rapid and stable sedation with minimal hemodynamic instability in patients undergoing general anesthesia. Hyoungkyu Kim et al. reported that a dose of 6 mg/kg/h was associated with a lower incidence of hypotension compared to higher doses (12 mg/kg/h), making it suitable for patients with cardiovascular risk factors. Therefore, a dose of 6 mg/kg/h was selected to achieve the desired sedation depth while minimizing the risk of adverse effects.

Intervention description {11a}

Study drug administration

Anesthesia induction Patients in the R group will receive a continuous infusion with remimazolam at 6 mg/kg/h over 3 min, combined with a slow intravenous injection of sufentanil at 0.3–0.5 μg/kg. If the bispectral index (BIS) value falls below 60 at any time during the period, the infusion of remimazolam will be stopped. If the BIS value remains above 60 within 5 min after the start of the study drug administration, rescue sedative medications will be administered without restriction. Patients in the P group will receive propofol at 2 mg/kg within 3 min, combined with a slow intravenous injection of sufentanil at 0.3–0.5 μg/kg. If the BIS value remains above 60 in 3 min, propofol at 0.5 mg/kg was added. When the BIS value falls below 70, cisatracurium (0.2–0.3 mg/kg) or rocuronium (0.6–1 mg/kg) will be administered. Two min after the injection of muscle relaxant, laryngotracheal spraying with 2% lidocaine 2 ml is applied. Endotracheal intubation will be performed when BIS is maintained between 45 and 55 and the train-of-four (TOF) value equals zero (or based on the onset time of muscle relaxants). During the period, if SBP falls below 90 mmHg or decreases by more than 30% from baseline, vasoactive drugs will be administered as needed.

Anesthesia maintenance Anesthesia will be maintained by utilizing propofol (4–10 mg/kg/h) or volatile anesthetics (sevoflurane or desflurane,1.5–2.0 MAC) with remifentanil (0.1–0.2 μg/kg/min) to keep a BIS value between 40 and 60.

Criteria for discontinuing or modifying allocated interventions {11b}

The following conditions will lead to discontinuation or modification of the allocated intervention:

Withdrawal of consent: If participants withdraw their consent to continue in the study at any time, they will be withdrawn from the study.

Allergic reactions: If participants experience an allergic reaction to remimazolam, propofol, or any other anesthetics used during surgery, they will be withdrawn from the study, and appropriate medical management will be provided.

Strategies to improve adherence to interventions {11c}

Not applicable. Interventions in this study will be completed during anesthesia.

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

There are no specific restrictions on 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 administration of the investigated drug. Hypotension is defined as SBP of less than 90 mmHg, a reduction of more than 30% in SBP from baseline, or the administration of vasoactive medication.

Secondary outcome

Secondary outcomes include the following:

1. The rate of successful sedation, defined as BIS value ≤60 within 5 min after the administration of an

investigated drug, without the need for rescue sedative medications.
2. Time to successful sedation, defined as the time from initial drug injection to achieving a BIS value ≤60.
3. Coughing during the induction period, including the number, frequency, and severity of coughing.
4. Postoperative delirium within 7 days postoperatively.
5. Postoperative in-hospital mortality.

Participant timeline {13}

The schedule of trial enrollment, allocation, interventions, and assessments is shown in Figs. 1 and 2.

Sample size {14}

Based on previous studies [18, 23], we estimated the incidence of hypotension was 50% in the propofol group. We hypothesized that remimazolam is superior to propofol with a superiority margin of 10%. A total sample of 164 patients (82 in each group) was required to achieve a power (1-β) of 80% and a type I error (α) of 0.025. Considering a dropout rate of 5% in each group, the total number of patients was increased to 172 (86 in each group).

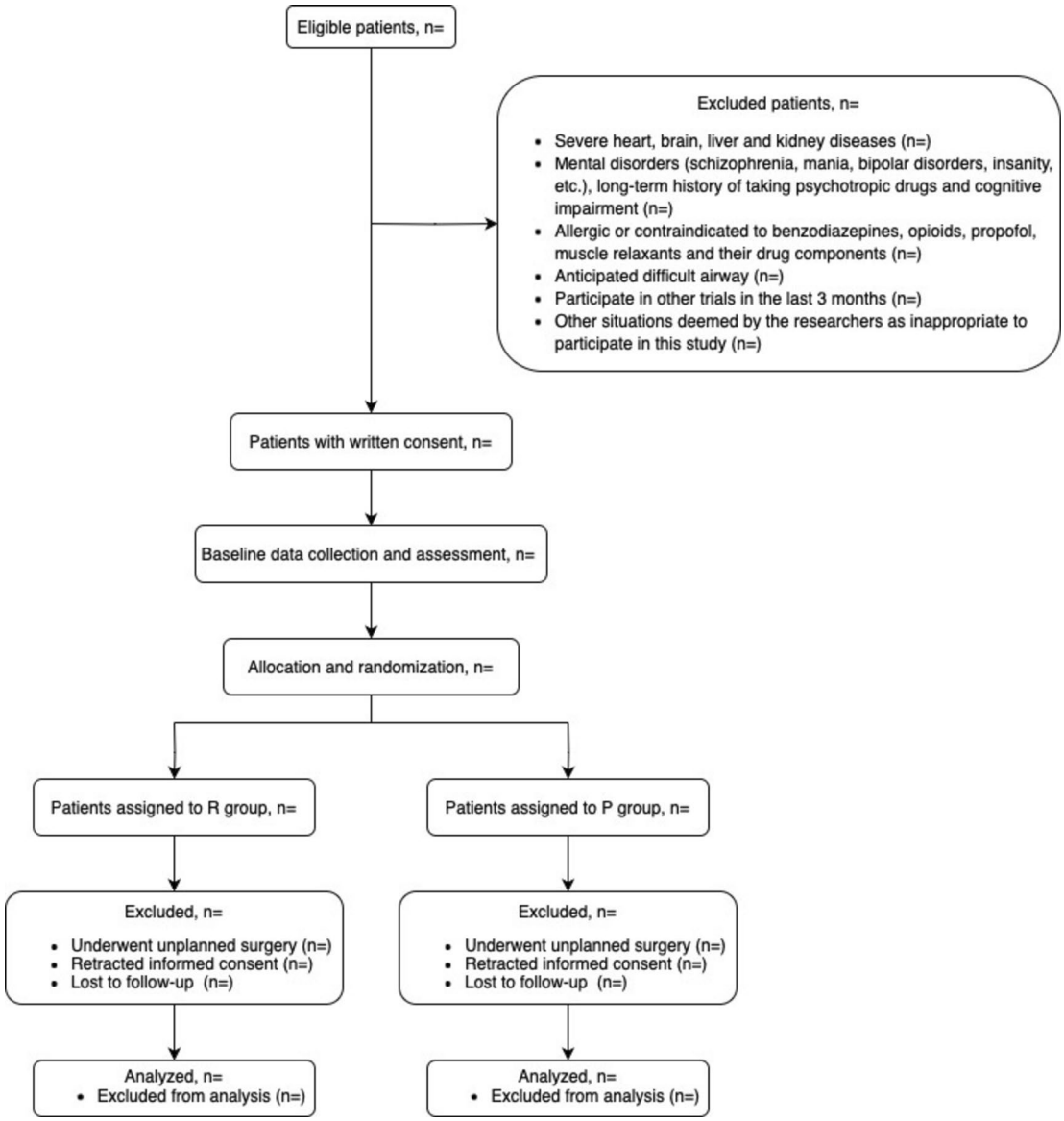

Fig. 1 Flow chart

	STUDY PERIOD						
	Enrolment	Allocation	Intervention	Follow up			
TIMEPOINT	*preoperative visit*	Allocation	*during induction until 20min after induction*	*POD0*	*POD1*	*POD3*	*POD7*
ENROLLMENT							
Eligibility screen	X						
Informed consent	X						
Demographic data	X						
Allocation		X					
INTERVENTION							
Remimazolam			X				
Propofol			X				
ASSESSMENTS							
BIS			X				
SBP/DBP/MBP/HR			X				
3D-CAM				X	X	X	X

Fig. 2 The SPIRIT figure of this trial. POD postoperative day, BIS bispectral index, SBP systolic blood pressure, DBP diastolic blood pressure, MBP mean blood pressure, HR heart rate, CAM Confusion Assessment Method

Recruitment {15}

All non-obesity (18.5 kg/m^2 < BMI < 28 kg/m^2) patients aged 45 to 65 years who are scheduled for video-assisted thoracoscopic surgery will be screened daily by investigators at each center. During the screening process, any situations deemed inappropriate for participation will be documented and excluded based on the predefined criteria. Thereafter, verbal and written information about the trial will be provided to patients who meet all inclusion criteria and none of the exclusion criteria. All exclusion reasons will be recorded in the trial documentation and reported in the final publication to ensure transparency. The recruitment of patients is ongoing. With seventeen hospitals participating in this trial, we anticipate being able to identify eligible patients and recruit the required sample size.

Assignment of interventions: allocation

Sequence generation {16a}

Randomization assignments will be generated using computer-generated block randomization with a block size of 6.

Concealment mechanism {16b}

Group allocations will be sealed in sequentially numbered opaque envelopes.

Implementation {16c}

After the patients enter the operating room, an independent study researcher who is not involved in anesthesia management or data collection will obtain the randomized allocation information and prepare the study agents for the anesthesiologists in charge.

Assignment of interventions: blinding

Who will be blinded {17a}

The anesthesiologist responsible for administering the study agent is a separate individual who prepares and administers the study drug (remimazolam or propofol) during the induction of anesthesia. This anesthesiologist is unblinded to the treatment group but is not involved in any other aspects of patient care, outcome assessment, or data analysis. Throughout the study, patients, all other anesthesia providers, surgical team members, and outcome assessors remain blinded to the treatment group.

Procedure for unblinding if needed {17b}

The anesthesiologists responsible for administering the study agents during induction will not be blinded to ensure patient safety.

Data collection and management

Plans for assessment and collection of outcomes {18a}

All data will be collected in the case report forms (CRFs) and the following data will be recorded.

1. Baseline characteristics of patients

Demographic data, ASA physical status score, history of diabetes, hypertension, preoperative medications, history of central nervous system disease, abnormal liver or kidney function indicators, hypothyroidism, type of surgery, anesthesia time, operation time, duration of one-lung ventilation, the lowest SpO_2, duration of $SpO_2 \leq$ 92%, amount of blood product administered, and fluid balance will be recorded.

2. 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 administration of the investigated drug: SBP, DBP, MAP, and HR. The dosage of vasoactive drugs used within 20 min after induction will also be recorded. Coughing during induction will be recorded and scored as follows: no coughing, mild coughing (1–2 times), moderate coughing (3–4 times), and severe coughing (≥ 5 times).

Baseline blood pressure (BP) was measured after the patient entered the operating room and before the administration of the investigated drug. During this period, patients remained in a stable supine position without any positional changes or external stimuli. Blood pressure monitoring was performed invasively, with measurements recorded starting at the time of drug administration, defined as "0 min." Subsequent BP measurements were recorded every 30 s for a total of 20 min. At each time point, BP values were recorded as the average of three consecutive measurements obtained from the monitor within a 30-s interval. Hemodynamic instability was defined as a sustained deviation from baseline BP over a 1-min period. The deviation from baseline BP was calculated as the difference between the baseline value and the BP values at each time point during the 20-min monitoring period.

3. Delirium evaluation and follow-up at discharge

Postoperative cognitive function will be evaluated using the 3D-CAM Chinese version (sensitivity: 84–99%, specificity: 90–97%) within the first 7 postoperative days (1 h after surgery, the first, third, and seventh postoperative day) [24]. The 3D-CAM resolves the four diagnostic features of delirium: acute onset and fluctuating course, inattention, disorganized thinking, and altered level of consciousness. A patient who displays both features 1 and 2, with either feature 3 or 4, will be diagnosed with delirium. We also record the length of stay after surgery, postoperative in-hospital mortality, and any unexpected events after surgery.

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

During the preoperative visit, patients will be fully informed about the intraoperative procedures and postoperative follow-up. 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 (ZL, LM, and ZL). 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 5 years after trial termination and the publication of the final report.

Confidentiality {27}

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

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

Not applicable. No biological specimens will 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. Continuous data will be expressed as mean ± standard deviation or median and interquartile range (IQR), and compared using the Student's *t*-test or the Mann–Whitney *U* test between groups. Categorical data will be described as frequencies (percentages) and

compared using the Pearson χ^2 test or Fisher's exact test. We will conduct repeated measures analysis of variance (ANOVA) with Bonferroni correction to compare the hemodynamic effects between remimazolam and propofol. To control the type I error rate due to multiple comparisons, the significance level (α) of 0.05 will be adjusted using the Bonferroni correction by dividing α by the number of comparisons. To test the superiority of remimazolam over propofol, one-tailed tests will be performed, while other tests will utilize a two-tailed test. All tests will be conducted with 95% confidence intervals. A *P*-value of less than the adjusted significance level will be considered statistically significant. Both intention-to-treat analysis and per-protocol analysis will be conducted in this study.

Interim analyses {21b}

No interim analyses are planned for this study. The primary outcome focuses on the hemodynamic changes within the first 20 min post-anesthesia induction, and secondary outcomes, including the CAM score and length of hospital stay, are assessed at 7 days post-surgery. Given the relatively short duration of data collection and the total sample size of 172 patients, we have not included an interim analysis in the study design.

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 analyses will be performed to handle protocol violations and deviation cases using the per-protocol principle. If the continuously collected data (e.g., SBP, DBP, BIS, 3D-CAM) are lost at one time-point during the trial, the most recent data will be analyzed as if they were obtained at that time.

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

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

Oversight and monitoring

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

Coordinating Center: The coordinating center for this study comprises members from the Department of Anesthesiology, West China Hospital of Sichuan University, and is responsible for the overall management and coordination of the trial. This includes protocol development, regulatory compliance, data management, and ensuring adherence to the study timeline and objectives. The coordinating center also facilitates communication between all participating sites, monitors trial progress, and ensures the quality and integrity of the data collected.

Trial Steering Committee (TSC): The TSC is composed of the management team members and the ethics review committee of the Department of Anesthesiology, and is independent of the coordinating center. They are responsible for reviewing and approving the trial protocol and any amendments, monitoring trial progress, ensuring participant safety, and providing strategic advice on the conduct of the trial.

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

Given the low-risk nature of the intervention, a formal Data Monitoring Committee was deemed unnecessary. Instead, the Coordinating Center will check the data and trial conduct on a monthly basis.

Adverse event reporting and harms {22}

Adverse events related to this study protocol include severe hypotension and sedation failure. Severe hypotension is defined as SBP < 80 mmHg or a reduction > 40% from baseline, or any hypotensive event requiring prolonged use of vasoactive drugs. When hypotension occurs, vasoactive drugs will be administered. Sedation failure is defined as a BIS > 60 within 5 min after the administration of the study drug. If sedation fails, rescue sedative medications (propofol) will be administered to complete anesthesia induction. Adverse events will be treated immediately. Participants will also be followed up until the event is completely resolved or therapy is terminated.

Frequency and plans for auditing trial conduct {23}

To review and verify the progress of the study, the Coordinating Center will hold monthly meetings to review trial conduct. The Coordinating Center will assess participant recruitment, data collection, and any issues that may arise during the trial. The TSC will meet quarterly to provide oversight and strategic guidance.

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

Any protocol changes will be documented as formal substantial amendments, which must first be reviewed and approved by the Institutional Review Board at West China Hospital. Once approved, the Coordinating Center

will notify all study centers involved in the trial, and a revised version of the protocol will be provided.

Documentation of Deviations: Any protocol deviations will be thoroughly documented using a breach report form and submitted to the Coordinating Center for evaluation.

Clinical Trial Registry Updates: Any substantial amendments to the protocol will also be updated in the clinical trial registry to ensure transparency and compliance with regulatory requirements.

Dissemination plans {31a}

The database and related materials will be accessible to study staff and researchers. Results will be published in open-access peer-reviewed journals within 12 months of trial completion.

Discussion

Hypotension is a commonly seen phenomenon during anesthesia induction and is associated with adverse postoperative outcomes, including acute kidney injury, myocardial injury, and increased intensive care admission rates [1, 5, 25]. Given the significant impact of hemodynamic instability on patient outcomes, the choice of anesthetic agents for induction should prioritize both efficacy and safety. While propofol remains widely used due to its rapid onset and recovery, its association with hemodynamic instability, respiratory depression, and injection pain limits its use in high-risk patients [26]. In contrast, remimazolam, a novel ultra-short-acting benzodiazepine, has emerged as a promising alternative due to its favorable pharmacokinetic profile, including rapid metabolism by tissue esterases and a stable CSHT even after prolonged infusion [10–13]. Additionally, the availability of a specific antagonist (flumazenil) further enhances its safety profile [14].

Clinical studies comparing remimazolam and propofol for procedural sedation have demonstrated that remimazolam is non-inferior in terms of sedative efficacy while exhibiting a superior safety profile, with fewer adverse events such as injection pain, respiratory depression, and hypoxia [16, 17]. In the context of general anesthesia, remimazolam has shown comparable efficacy to propofol, with a lower incidence of hypotension and reduced vasopressor requirements during induction [18, 19]. Notably, remimazolam has also been successfully used in cardiac surgery, where it maintained hemodynamic stability during complex procedures such as transcatheter aortic valve implantation (TAVI) and off-pump coronary artery bypass grafting (OPCAB) [27, 28]. However, evidence regarding its use in pulmonary surgery remains limited, highlighting the need for further investigation.

This study aims to address this gap by evaluating the hemodynamic effects of remimazolam during anesthesia induction in patients undergoing video-assisted thoracoscopic surgery. Our findings are expected to provide high-quality evidence on the potential benefits of remimazolam in stabilizing hemodynamics during anesthesia induction, particularly in the context of pulmonary surgery. To minimize confounding factors, we focused on middle-aged patients with a BMI between 18.5 and 28 kg/m^2, This decision was based on evidence that interindividual variability in physiological responses increases with age [29], and the 95% effective dose (ED95) of remimazolam for anesthesia induction varies significantly across age groups [30]. Additionally, obesity-related physiological changes can alter the pharmacokinetics and pharmacodynamics of anesthetics, narrowing their therapeutic window [31]. By excluding patients with BMI >28 kg/m^2 and those at high surgical risk, we aimed to ensure patient safety and enhance the internal validity of our results.

Strengths and limitations

This multicenter RCT involved seventeen tertiary hospitals in China. The rigorous study design and standardized implementation across centers further strengthen the validity of our results. However, several limitations should be acknowledged. First, we utilized BIS monitoring as a tool to assess the depth of anesthesia during the induction and maintenance phases. While BIS is a widely adopted in clinical practice and provides a standardized measure of anesthesia depth, it has not been specifically validated for remimazolam [32]. Despite this limitation, we chose to employ BIS for several reasons: (1) it offers an objective and consistent method for monitoring anesthesia depth, which is critical for patient safety and study consistency; and (2) its widespread use facilitates comparison with existing literature [10]. Future studies should aim to validate BIS specifically for remimazolam-based anesthesia and explore alternative monitoring methods that may better capture its unique pharmacodynamic profile. Second, the strict inclusion and exclusion criteria may limit the applicability of our findings. By focusing on middle-aged patients with a BMI between 18.5 and 28 kg/m^2 and excluding high-risk populations, we ensured internal validity but potentially restricted the generalizability of our results. Future research should investigate the efficacy and safety of remimazolam in special populations, including the elderly, obese, and high-risk surgical patients, to provide a more comprehensive understanding of its clinical utility.

Patient and Public Involvement (PPI)

Due to the specific nature of this study, which focuses on anesthesia induction, direct involvement of patients or the public in the design of the protocol is not feasible. The study requires highly specialized knowledge and expertise in anesthesia, which limits the opportunity for PPI at this stage.

Despite the lack of formal PPI in the protocol, we ensure that all patients are fully informed about the study details prior to enrollment, and written consent was obtained in accordance with ethical guidelines. We recognize the importance of patient perspectives in clinical research and will incorporate patient feedback in future studies where appropriate.

Trial status

The current protocol is version 1.1 and was issued on 15 October 2023. At the time of manuscript submission, the study is in the phase of recruitment. Recruitment has been begun in June 2024 and is expected to be completed by December 2026.

Abbreviations

ASA	American Society of Anesthesiologists
BIS	Bispectral index
BMI	Body mass index
BP	Blood pressure
CAM	Confusion assessment method
CRFs	Case report forms
DBP	Diastolic blood pressure
EDC	Electronic Data Capture
GABA	Gamma-aminobutyric acid
HR	Heart rate
IQR	Interquartile range
PIH	Post-induction hypotension
POD	Postoperative day
PPI	Patient and public involvement
RCT	Randomized controlled trial
SBP	Systolic blood pressure
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
TOF	Train-of-four
TSC	Trial steering committee

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Authors' contributions {31b}

BL and Leng Zhou planned the study. HY performed the statistical design of the study. All authors contributed to the design and development of the trial. Lu Zhang and Juan Yang drafted the manuscript. BL and Leng Zhou revised the manuscript. The authors read and approved the final manuscript.

Funding {4}

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Data availability {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. 2023(2258)) and registered at chictr.org.cn (ID: ChiCTR2400085556) on June 12, 2024. 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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