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Comparison of remimazolam total intravenous anesthesia versus sevoflurane inhalational anesthesia on emergence agitation in patients undergoing laparoscopic surgery for gastric or colorectal cancer: study protocol for a randomized controlled trial

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Study protocol

Keywords: Remimazolam, Sevoflurane, total intravenous anesthesia, inhalational anesthesia, emergence agitation, laparoscopic surgery, cancer

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Title {1a}

Comparison of remimazolam total intravenous anesthesia versus sevoflurane inhalational anesthesia on emergence agitation in patients undergoing laparoscopic surgery for gastric or colorectal cancer: study protocol for a randomized controlled trial

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Abstract

Background: Emergence agitation (EA) remains a common, potentially harmful complication after general anesthesia for prolonged laparoscopic oncologic surgery. Sevoflurane, a widely used inhalational anesthetic, is associated with higher EA risk. Remimazolam, an ultra-short-acting benzodiazepine, may reduce EA owing to favorable hemodynamic stability and a distinct recovery profile compared with sevoflurane. We aim to test whether remimazolam-based total intravenous anesthesia (RTIVA) decreases EA incidence versus sevoflurane-based inhalational anesthesia (SINH).

Methods: This single-center, assessor-blinded, randomized controlled trial will enroll 108 adults (≥18 years, ASA II–III) scheduled for elective laparoscopic radical resection of gastric or colorectal cancer with expected duration ≥2 hours. Participants will be randomized 1:1 to

RTIVA (remimazolam infusion + remifentanil) or SINH (sevoflurane + remifentanil). Perioperative management is standardized across groups. The primary outcome is incidence of EA in the post-anesthesia care unit (PACU), defined as Ricker sedation agitation scale (RSAS) ≥5, assessed by blinded observers from PACU arrival to discharge. Secondary outcomes include severe agitation (RSAS = 7), extubation time, time to BIS ≥80, time to full emergence, PACU length of stay, analgesic/antiemetic needs, use of flumazenil, postoperative nausea/vomiting within 24 h, postoperative delirium during hospitalization, QoR-15 on postoperative day 1, perioperative TNF-α and IL-6, intraoperative hemodynamics, hospital length of stay, and safety events (hypotension, bradycardia, resedation, hypoxemia, intraoperative awareness).

Discussion: This study will contribute to evaluating the efficacy and safety of remimazolam for preventing EA in patients undergoing laparoscopic radical resection for gastric or colorectal cancer. The results may provide preliminary clinical evidence informing evidence-based anesthetic practice for this high-risk patient group.

Trial registration: Chinese Clinical Trial Registry, ChiCTR2500095670. Registered on January 10, 2025, https://www.chictr.org.cn/showproj.html?proj=256625.

Keywords

Remimazolam, Sevoflurane, total intravenous anesthesia, inhalational anesthesia, emergence agitation, laparoscopic surgery, cancer

Structured summary {1b}

Item	Description
Primary Registry and Trial Identifying Number {4}	Chinese Clinical Trial Registry ID: ChiCTR2500095670, registered on January 10, 2025, https://www.chictr.org.cn/showproj.html?proj=256625.
Secondary Identifying Numbers	None
Source(s) of Monetary or Material Support	Project of Sichuan Medical Association (Grant No.:

	2024HR77)
Primary Sponsor and contact information {3b}	Huide Wang; E-mail: 1281520797@qq.com
Role of sponsor and funder {3c}	This is an investigator-initiated clinical trial. The sponsor is responsible for trial design and quality control and management, but is not involved in data collection or statistical analysis. The funder (Sichuan Medical Association) only provides financial support and has no role in trial design, conduct, data collection/analysis, or manuscript writing/publication.
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Contact for Scientific Queries	E-mail: 1281520797@qq.com
Public Title	Comparison of remimazolam versus sevoflurane anesthesia for emergence agitation in laparoscopic gastrointestinal cancer surgery
Scientific title	Comparison of remimazolam total intravenous anesthesia versus sevoflurane inhalational anesthesia on emergence agitation in patients undergoing laparoscopic surgery for gastric or colorectal cancer: study protocol for a randomized controlled trial
Countries of Recruitment	China
Health Condition(s) or Problem(s) Studied	Emergence agitation (EA) in adult patients undergoing elective laparoscopic radical resection of gastric or colorectal cancer under general anesthesia
Intervention(s)	Intervention group: Remimazolam-based total intravenous anesthesia (RTIVA) Control group: Sevoflurane-based inhalational anesthesia (SINH)
Key Inclusion and Exclusion Criteria	Inclusion criteria:

	1. Aged ≥ 18 years; 2. ASA physical status II-III; 3. Scheduled for elective laparoscopic radical surgery for gastric or colorectal cancer with expected duration ≥ 2 hours. Exclusion criteria: 1. Allergy to remimazolam, sevoflurane, or other study-related drugs; 2. Pre-existing cognitive impairment; 3. Severe hearing impairment; 4. History of mental illness or long-term use of sedatives or antidepressants; 5. Presence of severe organic diseases (e.g., liver or kidney dysfunction); 6. Body mass index (BMI) >35 kg/m^2; 7. Assessed as unsuitable for participation by the researchers.
Study Type	Single-center, prospective, assessor-blinded, parallel-group, superiority randomized controlled trial
Date of First Enrollment (planned)	March 2025
Sample Size	108
Primary outcome(s)	Incidence of EA in the Post-Anesthesia Care Unit (PACU), defined as Ricker Sedation-Agitation Scale (RSAS) score ≥ 5
Key Secondary outcome(s)	1. Incidence of severe agitation (RSAS=7); 2. Extubation time, time to BIS ≥80, PACU length of stay; 3. Incidence of postoperative nausea and vomiting (PONV) and postoperative delirium; 4. Quality of Recovery-15 (QoR-15) score on postoperative day 1; 5. Serum levels of TNF-α and IL-6; 6. Postoperative hospital length of stay; 7. Safety outcomes (hypotension, bradycardia, hypoxemia, etc.)
Ethics Review	Approved by the Institutional Review Board (IRB) of

	Jianyang People's Hospital (Approval No.: JYL2024128); Approval date: December 12, 2024
Individual Trial Participant Data sharing statement	De-identified individual participant data (IPD) will be shared upon reasonable request from the corresponding author after study completion. Data will be used only for non-commercial, scientific validation analyses.

Protocol version {2}

Version 2.0, November 10, 2024

Introduction

Background and rationale {9a}

Gastric and colorectal cancers are common gastrointestinal malignancies worldwide [1]. Due to its minimally invasive nature, laparoscopic surgery is currently the primary treatment method. However, emergence agitation (EA) remains a prevalent complication following these procedures, with reported incidences as high as 63.5% [2]. Characterized by cognitive impairment and behavioral abnormalities，including anxiety, restlessness, aggressive behavior during anesthesia emergence, EA arises from multiple factors, including indwelling urinary catheters and drainage tubes, neuroinflammatory responses to surgical trauma, emergence delirium, pain, and anxiety [3-6]. These manifestations can lead to severe consequences such as accidental extubation, wound dehiscence, prolonged hospital stays, increased healthcare costs, and elevated risk of postoperative delirium [7]. Therefore, effectively reducing EA risk is critical for enhancing postoperative recovery.

The pathogenesis of EA is complex, and anesthetic agents for general anaesthesia maintenance play a pivotal role [2,6]. Currently, general anaesthesia is most often maintained using either an inhaled volatile anaesthetic agent (e.g. sevoflurane) or intravenous infusions of anaesthetic drugs (e.g. propofol). These two techniques are widely used in clinical practice, each having their own advantages and limitations. Sevoflurane, a classic volatile inhalational anesthetic, is widely used clinically due to its favorable blood/gas partition coefficient and rapid,

controllable adjustment of anesthetic depth [8]. Additionally, inhalational anesthesia may suppress pro-inflammatory mediators, mitigating the systemic inflammatory response to surgical tissue injury [9,10]. However, accumulating evidence indicates that sevoflurane anesthesia is associated with a higher incidence of EA, particularly in prolonged surgeries [7]. This link is partially attributed to sevoflurane's direct excitation of neurons in the pontine locus coeruleus, which contributes to emergence delirium—a key correlate of EA [11,12]. As a common alternative, propofol-based total intravenous anesthesia (TIVA) has been shown to reduce EA rates effectively [13]. Propofol is also commonly used to manage EA due to its high clearance and redistribution properties [14]. Nevertheless, it has notable drawbacks such as injection pain and hypotension [15]. So far, clinical studies have not demonstrated any benefit of anaesthetic techniques in cancer outcomes following surgery [16]. However, in 3 systematic reviews TIVA is associated with faster recovery of consciousness, a reduced risk of nausea and vomiting and less pain immediately after surgery [17-19].

Remimazolam, a novel ultra-short-acting benzodiazepine intravenous anesthetic for induction and maintenance of general anesthesia, has gained increasing attention in recent years [20]. Studies have demonstrated that remimazolam achieves anesthetic efficacy comparable to propofol, with advantages including absence of injection pain, more stable hemodynamics [21,22], and even shorter emergence times when combined with flumazenil [23]. It also does not increase the risk of postoperative delirium [24,25]. Notably, a study in hip replacement surgery reported a significantly lower EA incidence in the remimazolam group than in the propofol group [26].

Additionally, studies in laparoscopic cholecystectomy, robotic gastrectomy, and cervical spine surgery have demonstrated that remimazolam outperforms sevoflurane in terms of hemodynamic stability, reduced PONV risk, and improved postoperative recovery quality [27-30]. Despite these promising findings, direct comparative studies on the effects of remimazolam and sevoflurane on EA following prolonged anesthesia for laparoscopic radical resection of gastric or colorectal cancer remain limited. It remains unclear whether the two anesthetic maintenance agents differ in this regard. Notably, patients undergoing these procedures are often older with multiple comorbidities, increasing their vulnerability to EA and related complications. Additionally, there is a distinct lack of data describing the safe

application of remimazolam-based TIVA in this high-risk population.

Explanation for the choice of comparators {9b}

Sevoflurane is a widely used volatile inhalational anesthetic for maintaining general anesthesia in clinic practice. The technique is safe and effective, with some side effect, for example, it may be associated with a higher incidence of postoperative EA.

Objectives {10}

The primary objective of this trial is to explore whether remimazolam-based total intravenous anesthesia (RTIVA) can reduce the incidence of EA in patients undergoing laparoscopic radical resection for gastric or colorectal cancer compared with sevoflurane-based inhalational anesthesia (SINH).

Methods: Patient and public involvement, and trial design

Patient and public involvement {11}

No patients or members of the public are involved in the design, conduct, reporting, or dissemination plans of this trial.

Trial design {12}

The study is an investigator-initiated single-center, prospective, assessor-blinded randomized controlled, superiority study. The protocol is designed in accordance with the CONSORT recommendations [31] and reported in compliance with the SPIRIT reporting guidelines [32]. The protocol was approved by the Institutional Review Board (IRB) of Jianyang People's Hospital (JYL2024128) on December 12, 2024 and registered with the Chinese Clinical Trial Registry (ChiCTR2500095670) on January 10, 2025. Patients will be randomly assigned in a 1:1 ratio to receive RTIVA or SINH. The specific flowchart is shown in **Fig. 1**.

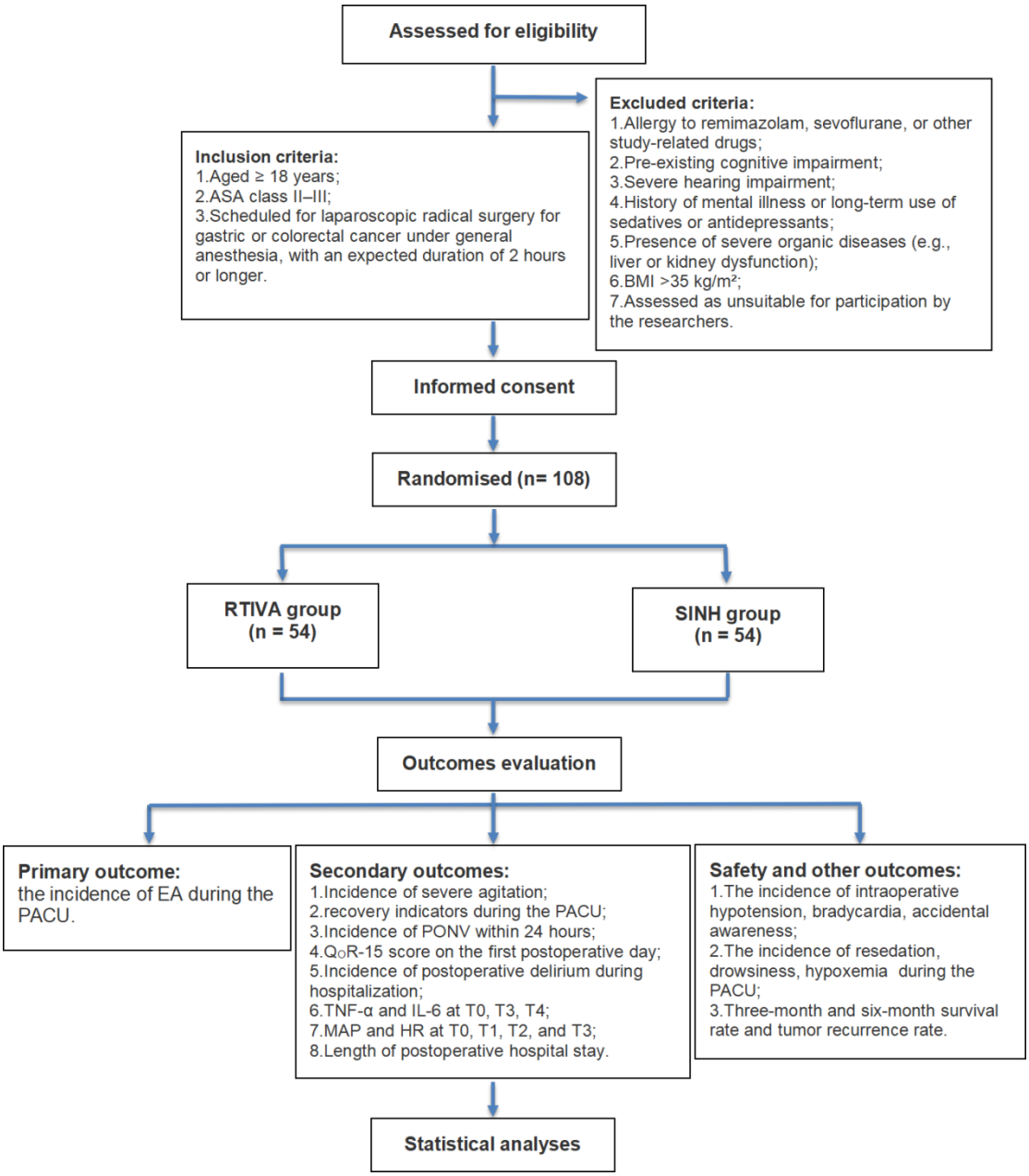


Fig. 1 CONSORT flowchart of the study. T0, before anesthesia induction; T1, 5 min after intubation; T2, 1 h after surgery initiation; T3, the end of surgery; T4, 24 h after surgery. BMI body mass index, ASA American Society of Anesthesiologists, RTIVA remimazolam-based total intravenous anaesthesia, SINH Sevoflurane-based inhalational anaesthesia, EA emergence agitation, PACU post-anesthesia care unit, PONV postoperative nausea and vomiting, QOR-15 15-item Quality of Recovery Questionnaire, TNF-α tumor necrosis factor-alpha, IL-6 interleukin-6, MAP mean arterial pressure, HR heart rate.

Methods：participants, interventions and outcomes

Trial setting {13}

The study will be performed in Jianyang People's Hospital, Chengdu, China. The hospital is a Grade-A tertiary general hospital. Recruitment to the trial will be based on screening of planned surgical schedules obtained the day before surgery. Patients will be recruited in the

surgical ward, including those scheduled for elective laparoscopic surgery for gastric or colorectal cancer. Patients are considered for inclusion if they meet the criteria as defined below.

Characteristics of the people who are needed for the trial

Characteristic	The people we would expect to see included
Age	Adult patients aged 18 years and older (predominantly middle-aged and elderly patients, consistent with the typical age distribution of gastric/colorectal cancer).
Sex	Male and female patients.
Gender	Men and women (documented as reported by patients or recorded in medical records).
Race, ethnicity and ancestry	Primarily Han Chinese (main ethnic group in Chengdu, Sichuan), other ethnic minorities in the local region are also eligible.
Socioeconomic status	Participants are local residents covered by either urban and rural resident basic medical insurance or employee medical insurance.
Geographic location	Patients living in Jianyang City and surrounding areas of Chengdu, Sichuan Province, China.
Other characteristics relevant to the trial	Comorbidities such as hypertension and diabetes mellitus; perioperative anxiety level; educational attainment, etc.

Eligibility criteria for participants {14a}

Inclusion criteria

Participants who meet the following criteria will be eligible for the study:

1. Aged ≥ 18 years.
2. American Society of Anesthesiologists (ASA) class II–III.

3. Scheduled for laparoscopic radical surgery for gastric or colorectal cancer under general anesthesia, with an expected duration of ≥ 2 hours.

Exclusion criteria

Participants will be excluded if they meet any of the following criteria:

1. Allergy to remimazolam, sevoflurane, or other study-related drugs.
2. Pre-existing cognitive impairment.
3. Severe hearing impairment.
4. History of mental illness or long-term use of sedatives or antidepressants.
5. Presence of severe organic diseases (e.g., liver or kidney dysfunction).
6. Body mass index (BMI) >35 kg/m².
7. Assessed as unsuitable for participation by the researchers.

Eligibility criteria for sites and those delivering interventions {14b}

The study will be conducted in two fixed standard operating rooms. Attending anesthesiologists responsible for providing interventions and intraoperative management will receive standardized training on the trial protocol.

Who will take informed consent? {32a}

Patients scheduled for elective laparoscopic radical surgery for gastric or colorectal cancer will be screened for eligibility to participate in this study. After identifying eligible patients, a specialized investigator will explain all details of the clinical trial, address any remaining questions, and obtain written informed consent on the day prior to surgery.

Additional consent provisions for collection and use of participant data and biological specimens {32b}

No additional informed consent form is required, all provisions are fully disclosed in the main written consent form, and participants' signature on the main form confirms their agreement: (1) Participants consent to the collection of their clinical data (demographics, preoperative history, intraoperative anesthesia records, postoperative recovery metrics, safety events) for this trial only. Data will be used exclusively to compare RTIVA vs. SINH and will not be shared with third parties or used for other research. (2) Participants agree to venous blood collection at pre-anesthesia, end of surgery, and 24 h post-surgery. Samples will be used solely for detecting TNF-α and IL-6 concentrations. No additional tests will be performed. Participants may withdraw consent at any time without impacting clinical care.

Intervention and comparator

Intervention and comparator description {15a}

Except for the different anesthesia maintenance strategies, all anesthesia techniques and surgical procedures will follow unified standards for both groups. All participants will be routinely fasted from food and water for 8 h preoperatively. On the day of surgery, patients will undergo ultrasound-guided radial artery puncture, central venous catheterization, and bilateral transversus abdominis plane (TAP) block (0.2% ropivacaine, 20 mL per side) in the pre-anesthesia holding area. Upon entering the operating room, heart rate (HR), pulse oximetry, invasive arterial blood pressure (ABP), and bispectral index (BIS) will be monitored. Patients will be preoxygenated 3 min using 100% fraction of inspired oxygen (FiO_2) before induction. Anesthesia induction will involve sufentanil (0.2–0.4 μg/kg), remimazolam (0.3 mg/kg), and cisatracurium (0.2 mg/kg) after loss of consciousness. After 3 minutes of positive pressure ventilation, tracheal intubation (size 7.0–7.5) will be performed using a video laryngoscope. Following intubation, lung-protective ventilation will be implemented in volume-controlled mode with a tidal volume of 8 mL/kg (predicted body weight), positive end-expiratory pressure (PEEP) of 5 cmH_2O, FiO_2 50% and regulate respiratory rate to maintain partial pressure of endexpiratory carbon dioxide ($P_{ET}CO_2$) between 35–45 mmHg.

During surgery, anesthesia will be maintained according to group allocation. A warming blanket will be used continuously for temperature maintenance. Additional cisatracurium 0.1 mg/kg will be administered as needed for muscle relaxation, with no additional doses given 30 minutes before the end of surgery. All patients will receive intravenous dexamethasone 5 mg and ramosetron 0.3 mg to prevent postoperative nausea and vomiting (PONV). The anesthesiologist will determine the fluid therapy regimen based on intraoperative conditions, and maintain mean arterial pressure (MAP) within 20% of the baseline value. Hypotension will be treated with metaraminol 0.2–0.3 mg, and bradycardia (HR < 50 beats/min) with atropine 0.3–0.5 mg. 5 minutes before the end of surgery, sufentanil 0.1 μg/kg and flumazenil 0.5 mg [33] will be administered, and all maintenance anesthetic drugs will be discontinued. Recruitment maneuvers (RM) will be performed after establishing the pneumoperitoneum-Trendelenburg position, after stopping the pneumoperitoneum and resuming the supine position, and at the end of the surgery. Patients will then be transferred to the post-anesthesia care unit (PACU) with a sufentanil-based patient-controlled intravenous analgesia (PCIA) pump (background infusion rate 0.04 μg/kg/h, bolus dose 0.01 μg/kg, lockout time 20 min).

PACU management and extubation timing will be performed by the same attending anesthesiologist. After the return of spontaneous breathing, neostigmine 30 μg/kg and atropine 10 μg/kg will be administered. Extubation will be performed when BIS > 80, tidal volume ≥ 5 mL/kg, spontaneous respiratory rate > 10 breaths/min, SpO_2 > 92%, and train-of-four (TOF) ratio ≥ 0.9, with the ability to follow verbal commands. If no signs of emergence are observed 15 minutes after anesthesia discontinuation or if resedation occurs

after extubation, additional flumazenil 0.2 mg/dose will be administered. Patients will be transferred from the PACU to the ward when their Aldrete score reaches 9.

Management of agitation in the PACU: pain will first be assessed using the Visual Analogue Scale (VAS), with a target pain score < 4. For patients with agitation and suspected severe pain (VAS ≥ 8), the PACU attending physician will administer sufentanil 2.5–5 μg/dose and propofol 0.05–0.1 mg/kg/dose. For VAS scores of 5–7, analgesia will be provided via the PCIA pump. Nausea and vomiting will be treated with intravenous ramosetron 0.3 mg.

Remimazolam-based total intravenous anaesthesia (RTIVA)

Participants randomised to the RTIVA group of the trial will be maintained with a continuous infusion of remimazolam (initial dose: 1 mg/kg/h after tracheal intubation, up to 3 mg/kg/h) combined with with an effect-site concentration of remifentanil 2–4 ng/ml (Minto model) to maintain a BIS of 40–60. Maintenance of general anaesthesia should be via RTIVA only. Clinicians should avoid any inhalational anaesthetic agent in this group.

Sevoflurane-based inhalational anaesthesia (SINH)

Participants randomised to the SINH group of the trial will be maintained with inhaled sevoflurane combined with an effect-site concentration of remifentanil 2–4 ng/ml (Minto model) to maintain a BIS of 40–60. Administration of SINH will not be protocolised and will be left to clinical discretion for management. Maintenance of general anaesthesia should be via inhalational route only. Clinicians should avoid intravenous anaesthetic agents in this group.

Criteria for discontinuing or modifying allocated intervention/comparator {15b}

Theoretically, once a type of anesthesia technique was assigned according to the trial, there would be no interruption or change. The intervention (RTIVA or SINH) will be discontinued or modified under the following circumstances: 1) significant intraoperative instability requiring deviation from the planned anesthetic protocol; 2) clinical judgment of the attending anesthesiologist that continuing the intervention would not be in the participant's best interest. All modifications will be documented, and the participant will remain in the study for follow-up and analyzed per the intention-to-treat (ITT) principle.

Strategies to improve adherence to intervention/comparator {15c}

The anesthesia team responsible for intraoperative management will receive standardized training on the trial protocol, ensuring all members fully understand the details of anesthesia interventions (e.g., drug dosages for remimazolam/sevoflurane maintenance, BIS monitoring targets, and criteria for rescue medication use). Protocol deviations will be monitored throughout the trial by the trial management group and the data monitoring committee (DMC). In the event of a deviation, the root cause will be investigated promptly, and the findings will be

shared with the entire team via the designated group communication platform. Additional retraining and operational support will be provided to the team as needed to prevent recurrent deviations.

Concomitant care permitted or prohibited during the trial {15d}

Anesthesia will be administered by trained anesthetists, with management conducted in strict accordance with the "Anesthesia management" section. Preoperative anxiety will be assessed using the Anxiety subscale of the Hospital Anxiety and Depression Scale-Anxiety (HADS-A) [34] one day before surgery. All other perioperative care will be conducted as per routine clinical practice and information collected in trial case record forms (CRFs). No additional sedatives or analgesics beyond those specified in the protocol will be administered without documentation of the clinical rationale in the CRFs.

Ancillary and post-trial care {34}

Both RTIVA and SINH used in this trial are routine clinical anesthesia techniques. As such, no specialized continuing post-trial care will be provided beyond the standard local clinical practice for patients. However, for participants who experience intraoperative awareness and develop subsequent psychological harm (e.g., persistent anxiety, sleep disturbances, or post-traumatic stress symptoms), the research team will conduct extended follow-ups and provide targeted support. This support includes referrals to psychiatrists for psychological assessment and counseling, as well as coordination with the research team to ensure integrated care until the psychological symptoms resolve or stabilize. All costs related to psychological assessment and counseling for intraoperative awareness-induced harm will be covered by the trial funding.

Outcomes {16}

Primary outcome

The primary outcome is the incidence of EA during the patient's stay in the PACU, assessed from arrival until discharge therefrom. It will be diagnosed by two trained researchers using the Ricker Sedation-Agitation Scale (RSAS) and defined as a score ≥ 5 [35] (table 1).

table 1 Ricker sedation agitation scale（RSAS）

Score	Category	Description
7	Dangerous agitation	Pulling at endotracheal tube,trying to remove catheters, climbing over bedrail, striking at staff, thrashing side-to-side
6	Very agitated	Does not calm despite frequent verbal reminding of limits, Requires physical restraints, biting endotracheal tube
5	Agitated	Anxious or mildly agitated, attempting to sit up,calms down on verbal instructions

4	Calm, cooperative	Calm, easily arousable, follows commands
3	Sedated	Difficult to arouse, awakens to verbal stimuli or gentle shaking but drifts off again, follows simple commands
2	Very sedated	Arouses to physical stimuli but does not communicate or follow commands, may move spontaneously
1	Unarousable	Minimal or no response to noxious stimuli, does not communicate or follow commands

Secondary outcomes

A. Incidence of severe agitation (RSAS = 7).

B. Time to BIS recovery to 80.

C. Extubation time (from discontinuation of anesthesia to extubation).

D. Time to full emergence (Modified Observer's Assessment of Alertness/Sedation [MOAA/S] score = 5).

E. Length of stay in the PACU.

F. Dosages of sufentanil and propofol administered in the PACU.

G. The number of additional cases of flumazenil during PACU.

H. Incidence of PONV within 24 hours.

I. Incidence of postoperative delirium during hospitalization [36].

J. Quality of recovery (QoR-15) on the first postoperative day.

K. Serum levels of tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) at three time points: before anesthesia induction (T0), end of surgery (T3), and 24 h after surgery (T4). Blood samples will be collected via internal jugular vein and measured using chemiluminescence assay kit (Xieguang Biotechnology, China).

L. MAP and heart rate (HR) at four time points: before anesthesia induction (T0), 5 min after intubation (T1), 1 h after surgery initiation (T2), and end of surgery (T3).

M. Length of postoperative hospital stay.

Safety outcomes

A. The incidence of intraoperative hypotension, defined as systolic blood pressure (SBP) decreased by > 30% from baseline or SBP < 80 mmHg.

B. The incidence of intraoperative bradycardia, defined as HR < 50 beats/min.

C. The incidence of resedation, defined as a decrease of ≥ 1 point in the Richmond Agitation-Sedation Scale (RASS) score after extubation in the PACU.

D. The incidence of postoperative drowsiness, defined as persistent sleepiness during the PACU: arousable with response, but rapid return to sleep when stimulation is removed.

E. The incidence of hypoxemia (SpO_2 < 92%) after extubation in the PACU.

F. The incidence of intraoperative awareness (modified Brice questionnaire) [37].

Other outcomes

Three-month and six-month survival rate and tumor recurrence rate.

Harms {17}

This trial is considered low-risk as all trial interventions are already in routine clinical use. Expected post-operative complications (occurring from the end of surgery to the post-surgical hospital stay) will be collected as a trial outcome and will not be recorded separately as AEs. These events will be included as part of the safety analysis for the trial. Beyond these, other AEs will be recorded and reported by the investigators. When a serious adverse event (SAE) occurs, the investigator will immediately report it to the trial steering committee, the DMC, and the ethics committee. The investigators will record the symptoms, severity, duration, relevant medical measures taken, outcome, and correlation with the intervention (judged by the principal investigator) in the CRF and submit a complete SAE report form within 24 h. Investigators will follow up until the AE resolves or returns to the baseline level.

Participant timeline {18}

Table 2 shows the participant timeline.

Table 2 Participant timeline

TIMEPOINT	Day - 1	Day 0	T0	T1	T2	T3	PACU	T4	Before discharge	POD 90	POD 180
ENROLLMENT:											
Eligibility screen	X										
Informed consent	X										
Randomization		X									
Allocation		X									
INTERVENTION/ COMPARATOR:											
RTIVA group: Remimazolam-based total intravenous anaesthesia				→	→	→					
SINH group: Sevoflurane-based inhalational anaesthesia				→	→	→					
ASSESSMENTS:											
Baseline characteristics	X										
Intraoperative			X	X	X	X					

hemodynamics											
TNF-α and IL-6			X			X		X			
Incidence of EA							X				
Recovery indicators							X				
Incidence of intraoperative awareness							X				
Incidence of PONV								X			
QOR-15 score								X			
Incidence of delirium								X	X		
Safety outcomes				X	X	X	X				
Survival rate and tumor recurrence rate										X	X

T0, before anesthesia induction; T1, 5 min after intubation; T2, 1 h after surgery initiation; T3, the end of surgery; T4, 24 h after surgery. PACU, post-anesthesia care unit; RTIVA, remimazolam-based total intravenous anaesthesia; SINH, Sevoflurane-based inhalational anaesthesia; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6; EA, emergence agitation; PONV, postoperative nausea and vomiting; QOR-15, 15-item Quality of Recovery Questionnaire.

Sample size {19}

The sample size calculation was based on the incidence of EA in patients with indwelling urinary catheters reported as 63.5% in a previous large-scale observational study [2]. With the assumption that RTIVA group would reduce the incidence of EA by 45%, a two-tailed significance level (α) of 0.05 and a power (1-β) of 0.8, 48 study participants per group were required, as calculated by PASS 15.0 software. Accounting for a 10% withdrawal or loss-to-follow-up rate, the final sample size will be 54 patients per group, totaling 108 patients.

Recruitment {20}

Patients will be recruited in the surgical ward of Jianyang People's Hospital. The hospital has mature surgical technology and large laparoscopic operation volume, which can meet the patient recruitment for this study.

Assignment of interventions: randomisation

Sequence generation: who will generate the sequence {21a}

An independent researcher will generate randomization codes using Statistical Package for Social Sciences (SPSS, version 24.0) random number generator software.

Sequence generation: type of randomisation {21b}

Block randomization will be employed to ensure balanced allocation between the two groups. Randomly varying block sizes of 2, 4, and 6 will be used to prevent selection bias and strengthen allocation concealment.

Allocation concealment mechanism {22}

The random allocation sequence will be concealed in sequentially numbered, opaque envelopes of identical shape and size. An independent investigator who is not involved in participant recruitment or outcome assessment will be responsible for preparing, storing, and dispensing the envelopes.

Implementation {23}

Participants will be assigned to RTIVA group or SINH group based on their enrollment order. On the day of surgery, upon the participant's entry into the operating room, the sealed opaque envelope containing the randomization code will be handed to the attending anesthesiologist, who will then proceed with the allocated anesthesia intervention (RTIVA or SINH). In cases where surgery is canceled at the last minute and rescheduled to a later date: 1) If the participant agrees to continue participating in the trial, they will receive their originally allocated anesthesia intervention at the new surgery date. Corresponding adjustments will be made to the data collection timepoints. 2) If surgery is canceled indefinitely or the participant no longer meets the eligibility criteria, the corresponding randomization code will be invalidated and not reused for other participants.

Assignment of interventions: blinding

Who will be blinded {24a}

The attending anesthesiologist will be aware of the group allocation but will not participate in subsequent research assessments or follow-up. Besides, outcome assessors, participants, data managers, and statisticians will be blinded.

How will be blinding be achieved {24b}

Participants will not be informed about the specific type of anesthesia maintenance (intravenous vs. inhalational), ensuring participant blinding. Outcome assessors responsible for evaluating emergence agitation, postoperative recovery, and follow-up will have no access to group allocation and will remain unaware of treatment assignments during all assessments. All data will be labeled with anonymous identification codes, and group allocations will be replaced with neutral codes (Group A / Group B) during data entry and statistical analysis. The true group assignments will remain concealed until the final statistical analysis is completed.

Procedure for unblinding if needed {24c}

Not applicable as no blinding was used in this trial.

Data collection and management

Plans for assessment and collection of outcomes {25a}

Data will be extracted from electronic patient records and documented using CRFs. Upon the participant's transfer to the PACU, two independent researchers blinded to group allocation will observe the entire recovery period, including the assessment of EA. The incidence of intraoperative awareness will be evaluated using the modified Brice questionnaire before leaving PACU. Postoperative delirium during hospitalization will be assessed twice daily (8:00–10:00 and 18:00–20:00) via the 3-Minute Diagnostic Interview for Confusion Assessment Method–defined delirium (3D-CAM). QoR-15 score on the first postoperative day will be assessed in the morning for participants who underwent morning surgery, and in the afternoon for those who underwent afternoon surgery. Laboratory tests are performed by the central diagnostic laboratory. Day 90 (+7 days) and 6 months post-surgery follow-up (±21 days) will be completed by telephone interview. Outcome assessors responsible for PACU, ward follow-up and scale evaluation will receive training and certification before the study initiation. The original data should to be stored in accordance with Good Clinical Practice (GCP) guidelines.

Plans to promote participant retention and complete follow-up {25b}

The research team will clarify how their participation supports anesthesia practice improvements. Each participant will receive a contact card with the phone number of the research team coordinator. The coordinator will respond to any question within 24 hours. Participants harmed by study anesthesia will get free medical care during hospitalization and follow-up. No additional financial compensation is planned.

Data management {26}

The trial will be conducted in accordance with the approved protocol, GCP guidelines and the trial data management plan. For all trial-specific documents (except the signed informed consent form), participants will be identified by a unique trial-specific number in any database.

Baseline characteristics collected include participant demographics, comorbidities, preoperative anxiety status (HADS-A), inclusion/exclusion criteria, documentation of informed consent and surgical type. Data captured following randomization will include administered anaesthetic techniques, duration of anesthesia, intraoperative condition, postoperative recovery quality and speed, AEs and long-term survival status. All data collected in accordance with the study protocol will be first manually completed in CRFs. Subsequently, the data will be transferred to an electronic database capture (EDC) system. Clinical data management should be performed in accordance with the data clean procedure. To avoid human error during data entry, two data entry personnel will be used to enter data

independently and synchronously, and then the system will compare the data to extract duplicates. After the trial is completed, the data in the EDC system will be locked and researchers will no longer have access to modify it. The collected original CRFs and signed informed consent forms will be stored in a locked office.

Confidentiality {33}

Any paper forms will be kept in a lockable cabinet in a restricted-access room. Only authorized trial staff can access them, and an access log (name, date, purpose) will be maintained. Electronic data will be stored in a password-protected, encrypted computer server and access permissions will be role-based. All databases containing identifiable information will be encrypted and stored separately in a secure place. No patient identification details will be reported in publications.

Statistical methods

Statistical methods for primary and secondary outcomes {27a}

For continuous variables, normality will first be tested using the Shapiro-Wilk test. Normally distributed data will be presented as mean ± standard deviation (SD), and between-group comparisons will be performed using the independent samples t-test. Non-normally distributed data will be presented as median (interquartile range [IQR]), and between-group comparisons will use the Wilcoxon rank-sum test. Categorical variables will be presented as frequencies and percentages, with between-group comparisons using the chi-square test or Fisher's exact test, relative risk (RR) and 95% confidence interval (CI) will be reported. TNF-α and IL-6 as repeated continuous variables will be compared within groups using the Friedman test and between groups using the Mann–Whitney U test. The survival rate will be presented using the Kaplan-Meier curve. A two-tailed P-value < 0.05 will be considered statistically significant. Statistical analyses will be performed using SPSS 24.0 software (IBM Corp, Armonk, NY, USA), and graphs will be generated using GraphPad Prism 9.0 (GraphPad Software, San Diego, CA, USA).

Who will be included in each analysis {27b}

The ITT principle will be applied for analysis, which includes all participants who have been randomized to study groups. An additional per-protocol (PP) analysis will also be conducted, including only participants who received their allocated intervention as specified in the protocol. Therefore, participants not receiving surgery or withdrawing consent for follow-up prior to surgery will be excluded.

How missing data will be handled in the analysis {27c}

Every effort will be made to collect full baseline, treatment and follow-up data on all trial participants, so missing data will be anticipated minimum. If the missing rate is ≥ 10% in the secondary outcomes, multiple imputation will be used.

Methods for additional analyses (e.g., subgroup analyses) {27d}

Exploratory subgroup analyses will be conducted based on the following predefined variables:age (< 65 vs. ≥ 65 y); sex; preoperative anxiety status (HADS-A score < 8 vs. HADS-A score ≥ 8); surgical type (gastric cancer surgery vs. colorectal cancer surgery). All subgroup analyses will be performed using a logistic regression model and results will be scrutinized graphically via forest plots.

Interim analyses {28b}

N/A. There are no interim analyses planned.

Protocol and statistical analysis plan {5}

The full trial protocol and statistical analysis plan are fully integrated into this study protocol submitted for publication and will also be available from the corresponding author upon reasonable request.

Oversight and monitoring

Composition of the coordinating centre and trial steering committee {3d}

The day-to-day running of the trial will be overseen by the Trial Management Team (TMT), whose members include the principal investigator, data managers, and study coordinators. They will assume the following responsibilities:

1. Monitor and supervise overall trial progress, and bear medical responsibility for participants' clinical safety during the trial.
2. Convene regular meetings (in-person or online) as needed, with a frequency of no less than once per month, to review trial progress, address emerging issues, and align on next steps.
3. Oversee trial data collection, conduct data verification and processing, and follow up on missing data to ensure data completeness.
4. Provide guidance and advice to trial site personnel on all aspects of trial implementation.
5. Coordinate participant study visits and prepare regular progress reports for the Trial Steering Committee.

Composition of the data monitoring committee, its role and reporting structure {28a}

The DMC consists of one ethics expert, one statistician, and one clinician with experience in clinical trials. All DMC members are independent of the study team and will be free of conflicts of interest related to the trial. The DMC's core role is to independently monitor the trial's safety, data quality, and scientific integrity. They will conduct monthly reviews of blinded trial data and the research progress, make recommendations to the trial steering committee regarding any ethical issues, check data integrity, ensure the confidentiality and security of all trial forms and data.

Frequency and plans for auditing trial conduct {29}

The study will be conducted and overseen by the ethics committee throughout its duration. The DMC will conduct monthly reviews to monitor trial progress across key phases, including the trial initiation phase, patient recruitment phase, and data analysis phase.

Protocol amendments {31}

Any proposed amendments to the protocol or the informed consent form will first be submitted to the IRB for review and approval. Upon receiving IRB approval, a copy of the revised protocol (marked with the amendment version number and approval date) will be distributed to all members of the research group. All team members will be required to review the amendments and sign a confirmation form acknowledging receipt and understanding—this form will be filed in the trial's regulatory documentation. For participants already enrolled in the trial: If the amendment affects their rights, safety, or willingness to continue participation (e.g., changes to follow-up frequency, addition of new assessments), the research team will provide a revised informed consent form. Participants will be given sufficient time to review the information, ask questions, and provide additional written informed consent if they agree to continue.

Dissemination policy {8}

Results of this research will be disclosed completely in international peer-reviewed journals. Both positive and negative results will be reported.

Discussion

This protocol is a prospective, assessor-blinded randomized controlled trial designed to determine whether remimazolam-based TIVA reduces the incidence of EA in patients undergoing laparoscopic radical resection for gastric or colorectal cancer. The trial will also evaluate the anesthetic efficacy of remimazolam in surgeries expected to last longer than 3 hours.

The selection of anesthetic techniques in clinical practice is influenced by a complex interplay of factors, including clinical environment constraints, equipment availability, anesthesiologists' personal preferences, and considerations regarding potential impacts on

cancer recurrence. Notably, recent decades have witnessed a striking shift in anesthetic practice patterns: in the United Kingdom, for example, the proportion of general anesthetics using total intravenous anesthesia (TIVA) with propofol as the maintenance agent increased from 8% in 2013 to 26% in 2023 [38]. The drivers behind this significant shift remain poorly understood, highlighting the need for further research to clarify how emerging anesthetic agents fit into evolving clinical paradigms.

Existing evidence supports remimazolam's potential to mitigate EA compared to traditional anesthetics. In hip replacement surgery, remimazolam was associated with a lower EA incidence than propofol [26]; similarly, in nasal surgery, it outperformed desflurane in reducing EA [39]. However, published data comparing remimazolam directly to sevoflurane (one of the most widely used inhalational anesthetics in general anesthesia) remain scarce. Therefore, building on previous similar studies, the present trial will not only compare clinical outcomes but also incorporate objective inflammatory biomarkers (serum TNF-α and IL-6 concentrations) to provide potential mechanistic insights into any observed differences in EA or recovery quality.

It is well known that patients undergoing gastric or colorectal cancer surgery are increasingly elderly and present with more comorbidities. These factors elevate their risk of perioperative complications and make anesthetic management more demanding. Importantly, the review [20] and multiple studies [21,22,26-30] have demonstrated that remimazolam offers advantages over propofol or sevoflurane, including more stable intraoperative hemodynamics, a lower risk of PONV, and improved postoperative recovery quality. These attributes suggest that RTIVA could be a potentially effective anesthetic strategy for elderly and frail patients. This study will further observe and report postoperative changes in outcomes such as QoR-15 score, PONV, and delirium.

This study protocol has several limitations. First, it is a single-center trial, and there may be geographical differences in the baseline characteristics of patients. Therefore, caution should be exercised when generalizing the conclusions to other regions or different surgical populations. Second, the sample size of this study is based on an earlier observational study. Currently, advances in anesthetic techniques such as TAP block may reduce the actual incidence of emergence agitation, which may lead to inadequate sample size. We will objectively verify the actual statistical power when reporting the study conclusions. Third, due to the obvious differences in the administration routes (intravenous vs. inhalational) of the two anesthetics, the anesthesiologists cannot be blinded. This may result in biases in concomitant treatments such as intraoperative fluid management and vasopressor use; although biases are reduced through standardized operating procedures, they cannot be completely eliminated.

In conclusion, this study will contribute to evaluating the efficacy and safety of remimazolam-based total intravenous anesthesia for preventing EA in patients undergoing laparoscopic radical resection for gastric or colorectal cancer compared with

sevoflurane-based inhalational anesthesia. The results may provide preliminary clinical evidence informing evidence-based anesthetic practice for this high-risk patient group.

Trial status

Recruitment started in March 2025. Recruitment is estimated to be completed in October 2026.

Abbreviations

ABP	Arterial blood pressure
AE	Adverse event
ASA	American Society of Anesthesiologists
BIS	Bispectral index
BMI	Body mass index
3D-CAM	3-Minute Diagnostic Interview for Confusion Assessment Method
CI	Confidence interval
CRF	Case Report Form
DMC	Data monitoring committee
EDC	Electronic data capture
FiO_2	Fraction of inspired oxygen
GCP	Good Clinical Practice
HADS-A	Hospital Anxiety and Depression Scale-Anxiety
HR	Heart rate
IQR	Interquartile range
IL-6	Interleukin-6
MAP	Mean arterial pressure
MOAA/S	Modified Observer's Assessment of Alertness/Sedation
PACU	Post-anesthesia care unit
PBW	Predicted body weight
PEEP	Positive end-expiratory pressure
$P_{ET}CO_2$	Partial pressure of end-expiratory carbon dioxide
PONV	Postoperative nausea and vomiting
QoR-15	Quality of Recovery-15
RASS	Richmond Agitation-Sedation Scale
RM	Recruitment maneuvers
RR	Relative risk
RSAS	Ricker Sedation Agitation Scale
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Standard deviation
SINH	Sevoflurane-based inhalational anaesthesia
SpO_2	Pulse oxygen saturation
TAP	Transversus abdominis plane
TNF-α	Tumor necrosis factor-alpha
TOF	Train-of-four stimulation
RTIVA	Remimazolam-based total intravenous anaesthesia
VAS	Visual Analogue Scale

Declarations

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Authors' contributions {3a}

HD W: chief investigator, conceived the study, protocol development and trial management. WJ M: co-chief investigator, protocol development, drafted the manuscript. BB Y: protocol development. F H: revised and edited the manuscript. C C: study within a trial lead, protocol development. SY L: trial management, protocol development. All authors read and approved the final manuscript.

Sources of funding and other support {7a}

This trial is funded by the Project of Sichuan Medical Association, funder's reference 2024HR77. The funding institution does not have a role in research design, data collection, statistical analysis, manuscript writing, or article publication.

Availability of data and materials {6}

The datasets used and analyzed during the current study will be made available from the corresponding author upon reasonable request.

Ethics approval and consent to participate {30}

This trial has been approved by the IRB of Jianyang People's Hospital (JYL2024128) on December 12, 2024. Written informed consent will be obtained from all participating patients before the start of any protocol-specified procedures or assessments. We have submitted the informed consent form in the attachment.

Consent for publication

Not applicable, no identifying images or other personal or clinical details of participants are presented in the study protocol.

Competing interests {7b}

The authors declare that they have no competing interests.

Supplementary Information

Additional file 1 (RASS, MOAA/S).

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