Trials

STUDY PROTOCOL

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The EC90 of remifentanil for inhibiting endotracheal intubation responses under anesthesia induction with ciprofol: study protocol for a dose-finding trial with the biased-coin design

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Abstract

Background Tracheal intubation may cause significant hemodynamic responses. Many drugs have been shown to be effective in modifying these cardiovascular responses, including remifentanil, fentanyl, sufentanil, and alfentanil. However, the 90% effect-site concentration (EC90) of remifentanil required to control cardiovascular responses to tracheal intubation when combined with ciprofol remains unclear. The purpose of this study was to determine the EC90 of remifentanil inhibiting cardiovascular responses to tracheal intubation during anesthesia induction with ciprofol using biased-coin design up-and-down sequential method (BC-UDM).

Methods This is a prospective sequential allocation dose-finding study. American Society of Anesthesiologists physical status (ASA) I–II elective surgical patients receiving target-controlled infusion (TCI) of remifentanil effect-site concentration (Ce), followed by ciprofol and rocuronium for anesthesia, were enrolled. The cardiovascular response to tracheal intubation was defined as positive when mean arterial pressure (MAP) or heart rate (HR) is 15% higher than the baseline value. Using the BC-UDM, the Ce of remifentanil was determined based on the cardiovascular response to tracheal intubation of the previous patient. The EC90 and 90% confidence intervals (90% CIs) were estimated by R-Foundation centered isotonic regression and the pooled adjacent violators algorithm with bootstrapping.

Discussion The results of this study sought to demonstrate EC90 of remifentanil blunting sympathetic responses to tracheal intubation during anesthesia index (Ai)-guided ciprofol anesthesia using BCD-UDM. It may help to minimize the cardiovascular responses to tracheal intubation.

Trial registration Chinese Clinical Trial Registry ChiCTR2300078275. Registered on December 3, 2023.

Keywords 90% effective dose, Remifentanil, Ciprofol, Cardiovascular responses to tracheal intubation, Biased-coin design, Dose-finding trial

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Introduction

Tracheal intubation generally induces clinically relevant hemodynamic changes [1], and various pharmacological strategies have been suggested to prevent cardiovascular responses induced by these noxious stimuli [2–5]. In order to attenuate the hemodynamic changes during intubation, the inhibitory effect of opioids on intubation responses has been confirmed [5–7]. Remifentanil is a selective μ-opioid receptor agonist that has rapid onset, short latency, and short blood-effect-site equilibration time. Neither renal nor liver is affected by its metabolism, since it can be metabolized by nonspecific plasma and tissue esterase [8, 9]. Remifentanil is able to inhibit the activity of the sympathetic nervous system and enhance anesthesia depth [10]. The cardiovascular responses to tracheal intubation were blunted more effectively by remifentanil compared to fentanyl and sufentanil [10, 11].

Because of its unique pharmacokinetic and pharmacodynamic properties, remifentanil is ideally suited for continuous IV infusion [12, 13], whereas TCI has been demonstrated to be more effective in maintaining cardiovascular stability [14]. Remifentanil can inhibit the cardiovascular responses to tracheal intubation. However, little information is available in the literature on the effect-site concentration of remifentanil required to prevent cardiovascular responses to tracheal intubation during Ai-guided ciprofol anesthesia in 90% of patients.

In dose-finding studies, multiple effective concentration points are usually considered, such as median effective dose (ED50), 90% effective dose (ED90), and 95% effective dose (ED95). These parameters represent the concentrations at which the drug reaches its effect dose or concentration of 50%, 90%, and 95%, respectively. Recently, the determination of ED90 using an up-down sequential allocation with a biased-coin design has been widely applied in anesthesiology [15–21]. To date, the dose-finding studies of remifentanil in inhibiting cardiovascular responses to tracheal intubation mainly focus on ED50 [6–11, 22–26] and use ED50-finding up-and-down design to estimate the ED95. ED90 and ED95 are both concepts that reflect the dose-response. However, sample size requirements are the sharp increase when shifting the target from ED90 to ED95 [21]. Each dose decrease with biased-coin up-and-down design requires more than twice as many positive responses when targeting the ED95 as when targeting the ED90 [21]. In addition, compared to ED50 and ED95, ED90 can better reflect the safety and tolerability of drugs at higher doses [21].

Ciprofol is a novel intravenous anesthetic that has been used for anesthesia induction and maintenance for surgical patients and sedation in clinical practice [27, 28]. It has the advantage of rapid onset, minor side effect on the cardiovascular system and respiratory system as well as mild inhibition of sympathetic nervous activity than propofol [29, 30]. Nevertheless, the inhibitory effect of ciprofol on laryngopharyngeal reflex is insufficient. Consequently, hypertension and tachycardia are frequent after intubation with bolus ciprofol anesthesia [27, 28].

Ai is a newly developed technology for evaluating sedation level during general anesthesia and has similar characteristic of BIS as a monitor for the depth of anesthesia [31]. Based on sample entropy (SampEn), 95% spectral edge frequency (95%SEF), and burst suppression ratio (BSR), it is calculated with the algorithm based on decision tree and least square [31, 32].

Based on previous studies, the purpose of this study was to determine the 90% effect-site concentration (EC90) of remifentanil required to prevent sympathetic responses to tracheal intubation during Ai-guided ciprofol anesthesia using BCD-UDM. This study will provide further evidence as to optimal dosage and dose-response relationship of remifentanil for preventing cardiovascular changes induced by tracheal intubation.

Methods

Ethics and registration

The protocol for this study is reported based on the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 Checklist [33]: defining standard protocol items for clinical trials (Additional file 1). The study has been approved by the Ethics Committee of Heping Hospital Affiliated to Changzhi Medical College (approval number 2023 No.029) and has been registered in the Chinese Clinical Trial Registry (ChiCTR) (registration number ChiCTR2300078275). This study is still ongoing.

Trial design

This study is a prospective dose-finding clinical trial using up-and-down method with biased-coin design (BCD) and determines the EC90 of remifentanil inhibiting cardiovascular responses to tracheal intubation during Ai-guided ciprofol anesthesia (Figs. 1 and 2). Based on previous study [21], a total of 60 patients scheduled to undergo elective surgery will be recruited in this study. Data analysis will be performed according to the superiority principle. The study will be carried out at Heping Hospital Affiliated to Changzhi Medical College and will be conducted according to the principles of the Helsinki Declaration (2000 edition, Edinburgh). Written informed consent will be obtained from each patient or, if the patient cannot provide informed consent, from the surrogate of the patient.

The study will continue for 12 months, and all the selected individuals will be from hospitalized elective surgery patients with tracheal intubation during general

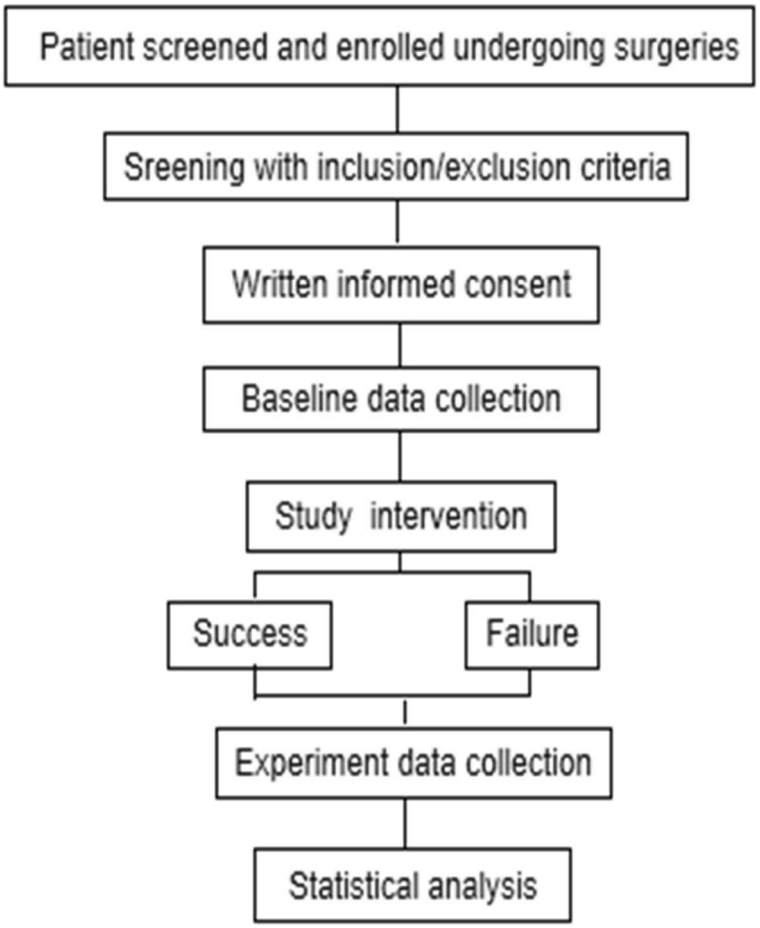

Fig. 1 Flow chart of the study design

anesthesia. The researchers will conduct screening in accordance with the established criteria. Data collection will start from the collection of basic data collection and continue until the end of follow-up (Fig. 2).

Randomization and implementation

This study is an adaptive dose-finding trial with biased-coin up-and-down sequential allocation design. In adaptive clinical trials with BC-UDM, randomization is often not used in the traditional sense. Instead of randomly assigning participants to different treatment groups, this design adapts the treatment allocation based on the outcomes observed during the trial. The next patient's treatment assignment may depend on the response of the previous patient, creating a sequence of adaptive treatment allocations. While this design is not based on randomization in the conventional sense, it still aims to minimize bias and ensure the validity of the study results by adjusting the treatment allocation based on observed responses.

The random walk rules for the sequential allocation of dose levels to patients in this trial were conducted using the BCD-UDM [21, 33–36]. Patients are sequentially assigned the next higher, same, or next lower dose level according to the probability distribution of BCD-UDM, which is determined by ethical considerations as well as the patient's binary endpoints [21].

Jianing Guo generated the random allocation sequence, Luoyun Li and Zeru Zhang enrolled participants and assigned participants to interventions, and analysis was done by Fangsheng Xu who was blinded to the interventions.

Study participants and recruitment

We will recruit 60 patients scheduled to undergo elective surgery. These patients will be recruited from Heping Hospital Affiliated to Changzhi Medical College after they meet the eligibility criteria and sign their informed consent. We plan to enroll the first patient on July 1, 2024 and to end on December 31, 2024. All participants will

	Study period							
	ENROLLMENT ALLOCATION	POST ALLOCATION						
			Anesthesia induction					
Timepoints	Before surgery	Baseline	opioids Ce	intravenous anesthetics	Muscle relaxants	Baseline before intubation	30 seconds after laryngoscopy	3min after intubation
ENROLLMENT								
Informed consent	×							
Eligibility screen	×							
Allocation	×							
INTERVENTIONS								
Remifentanil			Ce →					
Ciprofol				0.4mg/kg				
Rocuronium					0.6mg/kg			
ASSESSMENTS								
Demographic characeristics	×							
Hemodynamic variable		×	×	×	×	×	×	×
MOAA/S			×	×				
Ai		×	×	×	×	×	×	×
Adverse effects			×	×	×	×	×	×
Rescue medicine consumption								×

Fig. 2 Standard Protocol Items: Recommendations for Interventional Trials (adapted from SPIRIT figure). MOAA/S, modified observer's assessment of alertness/sedation score; Ai, depth of anesthesia index

sign the informed consent form for participating in the clinical trials.

On the day before surgery (or Friday for patients undergoing surgery next Monday), researchers authorized by the chief investigator will examine the list of patients scheduled for surgery and their medical records to determine potential participants based on our inclusion and exclusion criteria. Then, they will visit these patients and formally invite them to participate. For patients who meet the inclusion/exclusion criteria and receive written informed consent, baseline data will be collected, including demographic data, preoperative diagnosis, medical history, medication history, and surgical history, as well as the main results of physical examinations and laboratory and instrument examinations.

Inclusion criteria

Inclusion criteria of participants in this trial is based on a previous study [22–26]. Inclusion criteria are as follows: (1) patients of general anesthesia for elective surgery; (2) age 18 to 64 years old; (3) ASA is graded I–II; and (4) body mass index (BMI) 18–28 kg/m^2.

Exclusion criteria

Exclusion criteria are as follows: (1) allergies or contraindications to opioids, ciprofol, propofol, and their components; (2) use of other sedatives such as ciprofol or propofol or midazolam within 24 h before surgery; (3) patients with severe central nervous system, respiratory or circulatory system diseases; respiratory diseases, difficult airway, liver dysfunction, renal dysfunction, mental disorders, long-term use of psychotropic drugs, and cognitive dysfunction, long-term use of psychotropic or sedative-hypnotic drugs, drug abuse and drinking; (4) patients with Allen test positive, hypertension, hemodynamic instability (systolic blood pressure [SBP] < 90 mmHg or > 180 mmHg, diastolic blood pressure [DBP] > 110 mmHg, peripheral blood oxygen saturation [SpO2] < 90%); (5) participation in other clinical studies within recent 1 month; and (6) patients with a

history of difficult endotracheal intubation or suspected difficult endotracheal intubation, defined as a Mallampati class IV airway; retrognathia; restricted neck movements; or more than two criteria among the following: Mallampati class III airway, mouth opening less than 35 mm, or thyromental distance less than 65 mm. All of these parameters were estimated by an experienced anesthesiologist.

Discharge criteria

The discharge criteria are as follows: (1) individuals are required to withdraw during the trial period; (2) violation of trial procedures; and (3) the occurrence of serious adverse events (AEs).

Intervention

In this study, we will investigate the EC90 of remifentanil blunting cardiovascular responses to tracheal intubation during Ai-guided ciprofol anesthesia using BC-UDM.

Definition of binary endpoint

The remifentanil during anesthesia induction with ciprofol inhibits cardiovascular responses to tracheal intubation and is simplified to a binary endpoint (i.e., positive/negative). Patients' systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), heart rate (HR), and Ai values were recorded before induction, at baseline (defined as the average of 3 and 1 min measured values before tracheal intubation), and 1 and 3 min after tracheal intubation. The increase in the MAP or HR was the difference between the average of the 1 and 3 min measured values after tracheal intubation and its baseline value. Based on previous study [22–26], if mean MAP or HR was elevated by 15% of the value compared with the baseline values before intubation, a positive response was defined, and a negative response was defined as unaltered or elevated mean MAP or HR by < 15%.

The probability of negative response must maintain the same direction of change (increasing or decreasing) with increasing dose. We assume that it is increasing and denote the relationship between dose and negative-response probabilities by the function $F(x)$, where x is the dose magnitude variable (Fig. 3).

Dose allocation and dose spacing

Remifentanil during anesthesia induction with ciprofol inhibits cardiovascular responses to tracheal intubation and must be ordered as a discrete set of increasing doses of the same treatment drug. Preferably, the allowed doses are uniformly spaced in an algebraic sequence.

In previous literature, there were differences in initial dose and dose spacing [22–26]. Based on previous study [22–26], the initial dose and dose spacing of remifentanil in this study were 3.5 ng/ml and 0.5 ng/ml, respectively. Remifentanil was administered at an effect-site concentration of 3.5 ng/ml to the first patient. The target effect-site concentration of remifentanil employs a dose range based on known clinical effectiveness and is split into 8 to 12 dose levels [21]. Dose range is 3.0 to 8.0 ng/ml, including 11 levels: 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, and 8.0 ng/ml.

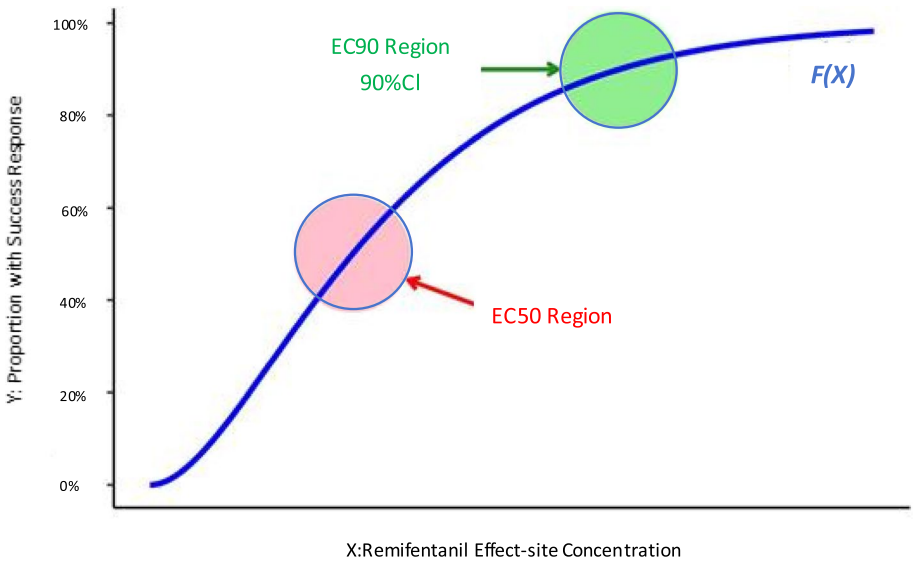

Fig. 3 Diagram of dose-response curve. EC90, 90% effective concentration; EC50, median effective concentration; 90% CI, 90% confidence intervals

Dose-transition and titration rules

The dose-transition rules are based on the doses and responses of the last patient or several patients rather than on all patient data going back to the beginning of the experiment. When EC90 was to be determined ($\tau = 0.9$), the following formula was used: probability (B) $= (1-\tau)/\tau = (1-0.9)/0.9 = 0.1/0.9 \approx 0.11$, where B is the target percentage [21, 37, 38].

Dose titration can be weighted on the probability of positive or negative response. If the cardiovascular response to tracheal intubation was a positive response, the effect-site concentration (Ce) of remifentanil would increase by 0.5 ng/ml. Conversely, if a patient was negative response based on cardiovascular responses to tracheal intubation, the next patients either received the same Ce (probability 1–11% = 89%) or a lower 0.5 ng/ml Ce (probability 11%), which was randomly decided using a computer-generated random list prepared by a statistician who was not involved in any other part of the study.

According to BC-UDM rules [21, 37, 38], doses are allocated to patients sequentially and only allow for increasing the dose by one level, decreasing by one level, or repeating the same dose. The dose-transition rules are based on the doses and responses of the last patient or several patients rather than on all patient data going back to the beginning of the trials. Furthermore, the rules do not use any estimated quantity that changes during the study.

Stopping rules

It is suggested in previous simulation study that including at least 50–60 patients will provide stable estimates of the target dose for EC90 [20, 21]. This trial will be recruiting 60 cases for evaluating EC90 of remifentanil blunting cardiovascular responses to tracheal intubation during Ai-guided ciprofol anesthesia using BC-UDM.

Anesthesia implementation and management

Preparation before general anesthesia

Prior to the surgery, all patients were routinely fasted of food and water without any premedication. A standard monitoring and anesthetic technique was applied to all patients in the operating room. After entering the operating room, one of the arms was inserted with a venous catheter of 20- or 22-gauge by a nurse, and a total of 10 ml/kg Ringer's solution was administered before anesthesia induction for fluid expansion. Patients with a negative Allen test were subjected to ultrasound-guided invasive arterial puncture and catheterization under local anesthesia by an anesthesiologist, along with real-time monitoring of arterial blood pressure.

During the perioperative period, electrocardiograms (ECG), pulse oximetry (SpO2), heart rate (HR), invasive blood pressure (IBP), and end-tidal carbon dioxide (PetCO2) were monitored (BeneVision M15 Monitor, Mindray, China), and Ai is also continuously monitored using a monitor for the depth of anesthesia (ConView YY-106; Pearlcare Medical Technology Company Limited, Zhejiang, China).

In order to prevent intraoperative awareness, the modified observational alertness/sedation assessment (MOAA/S) score (qualitative evaluation) and Ai (quantitative evaluation) were used for sedation evaluation in this study. MOAA/S score is divided into 0–5 levels; each level score represents the different clinical levels of sedation [39] (Table 1). Ai is a better parameter to estimate alterations in consciousness. As a new monitoring index of anesthesia depth, Ai is based on the sample entropy of the electroencephalogram and then obtains a dimensionless value of 0–99 through certain calculation methods [31, 32]. As the optimal anesthesia depth in clinical practice, the Ai value is controlled between 40 and 60, and the MOAA/S is less than or equal to 1 (Table 1).

Anesthesia induction

The order of anesthesia induction is as follows: remifentanil-ciprofol-rocuronium bromide (Fig. 2). Before induction of intravenous anesthesia, preoxygenation of patients with 100% oxygen via facial masks for 3 min is applied. Anesthesia is performed using TCI for administering remifentanil, which starts at a predetermined target effect-site concentration and is administered through an infusion pump (Fresenius Kabi, France) according to the Minto model [40]. After reaching equilibrium

Table 1 Assessment of sedation level

Description of sedation level	MOAA/S	Description of sedation level	Ai
Responds readily to name spoken in normal tone	5	Awake	80–99
Lethargic response to name spoken in normal tone	4	Light/moderate sedation	60–80
Responds only after name is called loudly and/or repeatedly	3	General anesthesia	40–60
Responds only after mild prodding or shaking	2	Deep hypnotic state	0–40
Responds only after painful trapezius squeeze	1	Isoelectric EEG	0
No response after painful trapezius squeeze	0		

between remifentanil plasma and effect-site concentrations, an intravenous injection of ciprofol (0.4 mg/kg) [30] is administered within 30 s. When the patients is unconsciousness (MOAA/S scores ≤ 1 and Ai ≤ 60), rocuronium (0.6 mg/kg) was given within 30 s, and artificial ventilation was initiated.

A laryngoscopy and endotracheal intubation is performed 2 min after rocuronium injections, using a unified visual laryngoscope (TD-C-IV-3, Zhejiang Youyi Medical Equipment Co. Ltd, China) and an ordinary endotracheal tube (CGPO, TUORen, Henan Province, China); the diameter of the tube was individualized by the patient's height and gender.

All endotracheal intubations were performed by one experienced attending anesthesiologist; those patients whose endotracheal intubation was not successful at one time or whose intubation time was longer than 1 min were excluded from the study. General anesthesia was maintained using 0.8 MAC sevoflurane with oxygen (1 L/min), and end-tidal carbon dioxide concentrations were maintained at 35–45 mmHg using mechanical ventilation. Three minutes after endotracheal intubation, remifentanil's effect-site concentration remained unchanged.

During anesthesia induction, Ai and MOAA/S scores were also continuously monitored and recorded. MOAA/S score is assessed by the anesthesiologists every 10 s after administration of 0.4 mg/kg ciprofol until three consecutive MOAA/S scores ≤ 1 and Ai ≤ 60. Ai is quite the same as BIS does.

During data collection, excessive hemodynamic changes include systolic blood pressure < 80 or > 180 mmHg and HR < 50 bpm or > 120 bpm. Hypoxia is defined as $SpO_2 \leq 92\%$ for more than 10 s. If the patient experiences excessive hemodynamic changes, hypoxemia, severe muscle tremors, or persistent chest wall stiffness, we will handle it according to the emergency disposal plan, and the patient will withdraw from this study. The following cases will be treated with the same concentration of remifentanil.

Outcomes assessment

Primary outcome

The primary outcomes were Ce of remifentanil inhibiting cardiovascular responses to tracheal intubation during Ai-guided ciprofol anesthesia using BCD-UDM in 90% of the study population.

Secondary outcomes

Following the EC90 calculation, the data were further analyzed for secondary outcomes to compare those who were positive/negative response for tracheal intubation. Secondary outcomes of this study will include the following: (1) the changes of the hemodynamic indices (SBP or HR) and indices derived from Ai during tracheal intubation; (2) AEs related to remifentanil combined with ciprofol anesthesia, include great hemodynamic change, hypoxemia, muscle tremor, symptoms of chest wall rigidity, choking cough, and postoperative nausea and vomiting; and (3) the changes of MOAA/S score and Ai values during anesthesia induction.

Statistical analysis

Sample size estimation

A sample size of at least $n = 50$ to 60 for the EC90 was determined according to a statistical reference and previous recommendation [21, 37] and will provide stable estimates of the target dose for the most realistic scenarios. Therefore, 60 patients were enrolled in this study.

Data analyses

Statistical analysis was performed using SPSS version 25.0 software (IBM, Armonk, NY, USA). Normally distributed continuous variables are described as mean ± standard deviation (SD), while nonnormally distributed continuous variables are described as the median and interquartile range (IQR). Categorical variables are described as numbers (percentages).

EC90 was calculated using centered isotonic regression with a bias-corrected Morris 90% confidence interval (CI) derived by bootstrapping using "dosefind" and "quickinverse" commands in the Centered Isotonic Regression R package (R's "cir" package authored and maintained by Dr. Oron) [21, 37]. Pooled-adjacent-violators algorithm (PAVA)-adjusted response rates were estimated using the weighted isotonic regression method [21].

Biased-coin up-and-down trials generate binary (positive/negative) response data. The proportion of negative responses at each dose is calculated and plotted by a dose-response plot. Targeting the EC90, from the dose-response observation pairs, isotonic regression methods are used to estimate the dose-response curve [21].

Data collection and monitoring

The statistical professionals are responsible for formulating the statistical analysis plan through consultation with the main researchers, establishing the database, and using the SPSS statistical analysis system for statistics. A comprehensive efficacy analysis was conducted in accordance with the program set, and the whole analysis set, demographic and other baseline characteristics, and other efficacy indicators were analyzed in accordance with the program set.

The Data Monitoring Committee (DMC) consists of a doctor in charge of data collection and sorting, a scientific research manager, and a statistician. The DMC will

meet three times a year throughout the entire research process. The DMC is responsible for safeguarding the interests of trial participants, evaluating the safety of intervention measures, and supervising the overall progress of the trial. Any deviation from the protocol will be recorded in the report. All major plan modifications will be communicated to relevant parties and updated in the trial register.

The project team designed and prepared the experiment and will announce the results. The group will hold monthly meetings to discuss the progress of the research. The doctor from the DMC will record the actual number of individuals enrolled, the cases of exclusion, demographic and other baseline characteristics, compliance analysis, safety analysis, incidence of complications and combined treatment, and comprehensive efficacy evaluation. The demographic characteristics, medical history, and treatment history of the patients will be described. The scientific research management committee will have access to the final trial dataset. At the end of the study, the original data and results will be submitted to the scientific research management committee; they will be disclosed to the public after the results are published.

Safety evaluation

AE refers to the appearance or progression of any discomfort, syndrome, or disease symptoms that occur during clinical trials, which can affect the patient's health. Any abnormalities in clinical trials indicating the presence of disease and/or organ toxicity, as well as severe abnormalities that require active treatment (such as discontinuation of medication, increased follow-up, and diagnostic studies), are considered AEs.

During clinical research, researchers should fill in the AE record form truthfully and in detail, recording the clinical manifestations, occurrence time, severity, duration, measures taken, and outcomes of AEs.

When an AE occurs, the observing doctor can decide whether to suspend observation based on the situation. All AEs should be tracked and recorded in detail until the patient's situation is properly resolved or the patient is in a stable state. If laboratory testing is abnormal and clinically significant, it should be traced back to the pretreatment levels.

Patient and public involvement

Patients with scheduled for elective surgery were involved during our previous pilot trial and reviewed project for the present study. At the protocol design stage, we gained opinions from participating medical center on the content of ethics and safety evaluation.

Dissemination plan

The results of this study will be presented at anesthesia conferences (local and international). The main investigation results will be reported at the trial registration office. The complete research report will be submitted for publication in anesthesia journals, preferably open-access journals.

Discussion

This study will determine the EC90 of remifentanil inhibiting cardiovascular responses to tracheal intubation during Ai-guided ciprofol anesthesia, using the BC-UDM for dose-finding. It will help optimize the combination of remifentanil and ciprofol and provide scientific and clinical evidence on the efficacy of controlling cardiovascular responses to tracheal intubation.

Cardiovascular responses to tracheal intubation is a sympathetic adrenergic response caused by the insertion of laryngoscopes and tracheal intubation during general anesthesia, often causing severe hemodynamic fluctuations and leading to complications such as hypertension, myocardial ischemia, and arrhythmia, even risk of causing cardiovascular and cerebrovascular events in surgical patients [1–3]. Tracheal intubation usually has no significant impact to patients with normal circulatory systems. However, they can be fatal for patients with coronary heart disease, aneurysms, hypertension, or other illnesses.

Ciprofol is a novel intravenous anesthetic that was recently developed and approved for the induction and maintenance of general anesthesia or procedural sedation. It is a new 2,6-disubstituted phenol derivative, which exhibits tighter binding to the γ-aminobutyric acid type A (GABAA) receptor than propofol. The PD results showed that the onset and recovery from ciprofol were rapid and produced good-quality clinical effects [29, 30]. It is recommended to use 0.4 mg/kg ciprofloxacin for deep sedation, with good tolerance, fast onset, and fast recovery [30]. Compared to propofol, ciprofol was a more stable hemodynamic profile during anesthesia induction in previous studies [29, 30].

The accurate and noninvasive assessment of the depth of anesthesia (DOA) is important for anesthesia induction, and there are several kinds of monitoring devices using electroencephalogram (EEG) signal to provide such information about DOA. Ai is a new index of DOA and has similar characteristic of BIS and revealed the advantage of SampEn for indicating conscious levels. Ai ranges from an isoelectric EEG (0) to a deep hypnotic state (40), general anesthesia (40–60), light/moderate sedation (60–80), and awake (80–99), which is quite the same as BIS does [31].

Remifentanil as an adjuvant anesthetic drug has been shown to effectively control the cardiovascular response to tracheal intubation when administered by bolus or infusion [41, 42]. The incidence of remifentanil-associated bradycardia and hypotension can be greatly reduced in the presence of a vagolytic agent [6]. Due to the side effects of bradycardia, and hypotension caused by a single high dose of remifentanil, many studies have evaluated the efficacy of TCI remifentanil with propofol on cardiovascular response to endotracheal intubation. The study show that effect-site concentrations of remifentanil of 5 ng/ml can effectively inhibit cardiovascular responses to endotracheal intubation in 50% of patients, when combining with target controlled infusion of propofol to maintain a BIS between 40 and 50 value [22]. Similarly, with TCI of propofol target effect-site concentration of 5.0 μg/ml, the EC(50) (± SD) values of remifentanil can provide acceptable conditions for orotracheal intubation was 5.58 ± 0.75 ng/ml [43]. Surgical Stress Index is a numeric index based on the normalized pulse beat interval and photoplethysmographic pulse wave amplitude and has been proposed for assessment of endotracheal intubation responses. Mustola and Toivonen confirmed mean (SD) effect-site concentrations of remifentanil attenuating endotracheal intubation responses in 50% of patients was 3.05 ± 0.27 ng/ml when anesthesia state entropy was maintained between 40 and 60 [44]. The EC50 of remifentanil for inhibiting responses to tracheal intubation was 3.20 ng/ml (95% CI, 3.13–3.27 ng/ml) [45]. When the optimal remifentanil effect-site concentration (EC50, 3.22 ng/ml) combined with propofol, nasotracheal intubation using a video laryngoscope can be successfully performed in a hemodynamically stable state [46]. In addition, remifentanil effect-site concentration of 7.73 ng/ml is effective in blunting sympathetic responses to tracheal intubation in 50% of patients when combined with etomidate anesthesia [25]. The EC50 of remifentanil required to blunt hemodynamic responses was 6.5 ng/ml (95% CI 5.6–6.7 ng/ml) during tracheal intubation when combined with a target-controlled infusion of propofol [24]. Based on the previous clinical studies, the initial effect-site concentration of remifentanil was chosen as 3.5 ng/ml.

The biased-coin up-and-down design is a nonmedian up-and-down design and is currently popular in anesthesiology study [16–19, 21, 47], possibly owing to its introduction by Pace and Stylianou [20]. The BCD is optimal among the up-and-down designs in the sense that the distribution of administered doses is most peaked around the target dose. A BCD study can be performed setting $\tau = 0.90$, permitting a direct estimation of EC90 and avoiding unverifiable extrapolations from the EC50 value. Under the biased-coin up-and-down design, increase the dose after a positive response. Upon a negative response, "toss a biased coin" (draw a random number) and then either: decrease the dose with probability inverse to the odds of negative response at the target. Otherwise, remain the same dose. For the EC90, take the ratio between 90% and the remainder from 100%, i.e., 10%, obtaining an odds of 9 [21]. Therefore, under a biased-coin up-and-down design targeting the EC90, the probability of dose decrease after a negative response will be 1/9 (the inverse of these odds). Since the "coin" probability is so small, the random walk will gravitate toward doses with high negative response rates. Due to the randomization, the number of consecutive negative responses before each dose decrease will vary randomly during the trials. The average will be 9 patients for targeting the EC90.

Given the biased-coin up-and-down design's typically modest amount of data concentrated at a few doses, previous studies have shown that isotonic regression estimate is simple to derive and to perform as well as or better than the other target dose estimators in terms of mean square error and average number of subjects needed for convergence in most scenarios studied. The centered isotonic regression estimate is the most viable general-purpose option in many regressions and a standard nonparametric method that assumes only that $F(x)$ is nondecreasing, making no further assumptions about its shape. Isotonic regression is a well-described variant of restricted least squares regression that constrains the point estimates to be either monotonic increasing (never decreasing) or monotonic decreasing (never increasing). Isotonic regression has favorable statistical properties [37, 38, 48]. It was shown to incur smaller estimation errors than the original isotonic regression. Regressions assume that the observed proportions plotted on the dose-response plane are unbiased estimates of the values of $F(x)$ at the assigned doses. However, all adaptive dose-finding designs (including up-and-down design) induce some bias on observed response proportions [49, 50]. This bias is minimal near the target and therefore has little effect on centered isotonic regression and isotonic regression target estimates. In addition, the R package (R's "cir" package authored and maintained by Dr. Oron) [21] implementing centered isotonic regression offers an empirical bias correction. It is recommended regarding up-and-down design CIs to provide 90% rather than 95% intervals [20]. Unless the sample size is far greater than those typically used in up-and-down designs, 90% is probably the highest level of confidence that the experiment can promise while remaining both reliable and informative.

In summary, this is a dose-finding study using BCUDM. This study will determine the EC90 of remifentanil

to blunting cardiovascular responses to tracheal intubation during Ai-guided ciprofol anesthesia and will provide more useful clinical data in daily practice.

Trial status

This study was approved by the Institutional Review Board of the Ethics Committee of the Heping Hospital Affiliated to Changzhi Medical College (2023 No.029) on 12th September 2023 and registered at the Chinese Clinical Trial Registry (registration number: ChiCTR2300078275) on 3rd December 2023. The recruitment of participants started on 1st February 2024. The anticipated recruitment period is 11 months. This protocol is version 1.0 in September 2023.

Ethics and dissemination

Research ethics approval

The study protocol has received approval from the Ethics Committee of Heping Hospital Affiliated to Changzhi Medical College (2023 No.029) on 12th September 2023. The trial's protocol was registered at the Chinese Clinical Trial Registry (registration number: ChiCTR2300078275) on 3rd December 2023. Investigators will identify eligible participants according to the inclusion criteria. This study will be conducted in accordance with the ethical principles stated in the Declaration of Helsinki.

Eligible participants will receive written and oral information and will be included after investigators have obtained informed written consent. These materials are available from the corresponding author on request. Any changes to the protocol or severe adverse events will be reported to the Data Monitoring Committee. Confidentiality of the data and the results of monitoring will be protected.

Protocol amendments

Any significant modifications to the protocol will be promptly reported to the Ethics Committee of Heping Hospital Affiliated to Changzhi Medical College and updated on ChiCTR.gov.

Consent or assent

Eligibility screening for surgery patients will be conducted in preoperation. The researchers will provide participants with a detailed introduction to the trial situation, including the purpose, process, and requirements after qualification confirmation. All participants will voluntarily participate in the study and sign an informed consent.

Consent or assent: ancillary studies

There are no relevant plans.

Confidentiality

Each participant will be assigned a unique identifier after enrollment, replacing the need for personal names in the data collection process. This unique identifier will be meaningful only to the research team and be ensuring participant confidentiality. Accordance to research guidelines, the principal investigator will be responsible for securely storing and protecting these unique identifiers at end of the study. Any publications resulting from this study will not include any personally identifiable information and maintain participant privacy at all times.

Declaration of interests

The submitter declares that they have no competing interests.

Data access

This database will allow the application for Chunyu Li to access the final trial dataset.

Ancillary and post-trial care

If any harm related to this study occurs, participants can receive free treatment provided by Heping Hospital Affiliated to Changzhi Medical College, which will compensate in accordance with relevant laws and regulations.

Dissemination policy: trial results

The results of the study will be prepared for submission to international, peer-reviewed journals. This process involves assembling the data into a comprehensive manuscript that outlines the study's methodology, findings, and implications.

Dissemination policy: authorship

See the Authors' contributions section below.

Dissemination policy: reproducible research

The public can access the complete protocol through ChiCTR.gov website (ChiCTR2300078275), but it does not include the personal information of participants. This database will allow the reasonable application for corresponding author to access the final trial dataset.

Abbreviations

EC90	The 90% effect-site concentration
BC-UDM	Biased-coin design up-and-down sequential method
ASA	American Society of Anesthesiologists physical status
TCI	Target control infusion
Ce	Effect-site concentration
MAP	Mean arterial pressure
HR	Heart rate
90% CIs	90% Confidence intervals
Ai	Anesthesia index
ED50	Median effective dose
ED90	90% Effective dose
ED95	95% Effective dose
SampEn	Sample entropy

95%SEF	95% Spectral edge frequency
BCD	Biased-coin design
BSR	Burst suppression ratio
BMI	Body mass index
SBP	Systolic blood pressure
SpO_2	Peripheral blood oxygen saturation
AEs	Adverse events
DBP	Diastolic blood pressure
ECG	Electrocardiograms
IBP	Invasive blood pressure
$PetCO_2$	End-tidal carbon dioxide
MOAA/S	Modified observational alertness/sedation assessment score
IQR	Interquartile range
DMC	Data Monitoring Committee
DOA	Depth of anesthesia

Supplementary Information

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Additional file 1. SPIRIT 2013 Checklist: recommended items to address in a clinical trial protocol and related documents*.

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Authors' contributions
JG, FX, LL, ZZ, ZW and CL were involved in conception and study design. JG, FX, QF, ZW and CL were involved in drafting the article. FX, LL, BX, JG and CL made critical revision of the article for important intellectual content. All authors reviewed, read, and approved the final manuscript. All named authors adhere to the authorship guidelines of Trials; the authors have agreed to the publication and have contributed to the writing of the manuscript. No professional writer has been involved.

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Availability of data and materials
All data relevant to the study protocol is included as part of this manuscript. The prospective listing of the study on the Chinese Clinical Trial Registry can be found at https://www.chictr.org.cn/showproj.html?proj=212578.

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