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Effect of intraoperative intravenous esketamine on postoperative delirium in older patients undergoing hip fracture surgery: protocol for a randomised, double-blind, placebo-controlled trial

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ABSTRACT

Introduction Postoperative delirium (POD) is a common complication after hip fracture surgery in older patients. Esketamine may be beneficial in alleviating the occurrence of POD. Our trial aim is to investigate whether the intravenous administration of esketamine can improve POD in older patients undergoing surgery for hip fracture.

Methods and analysis This randomised controlled trial will be conducted at the Chengdu Integrated TCM & Western Medicine Hospital in Chengdu, China. A total of 260 older patients scheduled for hip fracture surgery under general anaesthesia will be randomly allocated to either an esketamine group (group E) or a control group (group C) at a 1:1 ratio (n=130 in each group). After tracheal intubation, group E will receive continuous infusion of esketamine at a rate of 0.3 mg/kg/h intraoperatively until the beginning of skin incision closure. Group C will receive equivalent volumes and rates of 0.9% normal saline; the injection methods are in accordance with those in group E. The primary outcome is the incidence of POD within 3 days after surgery, which will be evaluated using the confusion assessment method two times per day. Secondary outcomes are subtypes, duration of delirium, length of hospital stay, pain severity score within 3 days after surgery and 30-day all-cause mortality. Pain severity scores at rest will be evaluated using a numeric rating scale. Safety outcomes will include hallucination, dizziness, nightmares, nausea and vomiting. All analyses will be performed in line with the intention-to-treat principle.

Ethics and dissemination Ethics approval was obtained from the Medical Ethics Committee of Chengdu integrated TCM & Western Medicine Hospital (2024KT022). All patients will provide written informed consent before enrolment. The results of the trial will be published in an appropriate journal or an oral presentation at academic meetings.

Trial registration number Chinese Clinical Trial Registry (ChiCTR2400081681).

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is a double-blinded, randomised, placebo-controlled study focused on postoperative delirium in older patients undergoing hip fracture surgery.
⇒ Key confounding factors will be recorded, including age, sex, body mass index, American Society of Anesthesiologists physical status, haemoglobin, albumin, intraoperative mean arterial pressure and preoperative frailty score.
⇒ Given that this is a single-centre trial, further studies evaluating the association between esketamine and delirium are essential.
⇒ Esketamine may increase the bispectral index value, leading to blind weakening.

INTRODUCTION

Hip fracture in older individuals is a major public health concern, resulting in increased disability, morbidity and mortality. Postoperative delirium (POD) is a frequent and serious complication following surgery for hip fracture.[1] POD is an acute neuropsychiatric syndrome primarily characterised by disturbances of attention, awareness and cognition, with reported incidence varying between 16% and 70%.[2 3] POD is associated with poorer postoperative recovery, prolonged hospital stay, functional and cognitive decline, higher mortality and increased healthcare costs.[4] It has been suggested that increased age, intraoperative blood transfusion, intraoperative hypotension, frailty, sleep deprivation and non-relieved pain may play a role in the development of POD.[5–8] However, the pathophysiology of POD has not been fully studied and is not well understood.

Ketamine, a non-selective N-methyl-D-aspartate (NMDA) receptor antagonist, has been widely used and studied in the perioperative setting owing to its analgesic,[9] antihyperalgesic[10] and anti-inflammatory[11 12] effects. Delirium and depression seem to be caused by similar pathophysiological mechanisms,[13] and ketamine has been shown to exert rapid-acting antidepressant effects.[14] A randomised controlled trial (RCT) found that low-dose intraoperative ketamine significantly reduced the incidence of POD from 31% to 3% after cardiac surgery.[15] Contrarily, an international, multicentre clinical study demonstrated that the use of intraoperative ketamine did not decrease delirium and might increase postoperative hallucinations after major surgery.[16] Moreover, in a recently published multicentre RCT, a single dose of 0.5 mg/kg ketamine before surgery did not reduce the occurrence of delirium after major orthopaedic surgery.[17] Therefore, the association between intraoperative ketamine and delirium remains relatively unknown.

Esketamine (S-ketamine), the dextroisomer form of ketamine, has demonstrated double affinity for both opioid receptors and NMDA receptors, as compared with ketamine, and it has the characteristics of a higher clearance rate in vivo and lower incidence of adverse reactions like hallucinations. Animal experiments have shown that esketamine could remarkably mitigate neuroinflammation mediated by the brain-derived neurotrophic factor/tropomyosin receptor kinase B signalling pathway and nuclear factor κB pathway.[18] Additionally, a study reported that esketamine could reduce the incidence of delayed neurocognitive recovery and improve early postoperative cognitive function.[19] Furthermore, one recent RCT demonstrated that a single dose of esketamine (0.25 mg/kg) reduced the incidence of delirium after cardiac surgery.[20] As to older patients with hip fracture, one study (NCT05304559) aimed at determining the effect of esketamine and continuous iliac fascia space block on perioperative neurological cognitive impairment is ongoing. Thus, the optimal dosage and administration method of esketamine remains undetermined, and there is currently no published literature evaluating the impact of intraoperative esketamine infusion on POD in this specific patient population.

Given the potential of esketamine to improve patient outcomes, we will conduct a randomised, double-blind, placebo-controlled trial to determine whether intraoperative continuous infusion of esketamine is associated with a significantly lower incidence of POD in older patients undergoing hip fracture surgery. We hypothesised that the use of esketamine will reduce the incidence of POD in older patients undergoing hip fracture surgery.

Methods and analysis

Study objectives

The primary objective of the study is to investigate the impact of intraoperative continuous infusion of esketamine on the incidence of POD in older patients undergoing hip fracture surgery within the first 3 postoperative days. Secondary objectives of the study include assessment of the impact of intraoperative continuous esketamine infusion compared with no infusion on the duration and/or subtypes of delirium, pain score within the first 3 days after surgery, length of hospital stay and 30-day all-cause mortality after hip fracture surgery.

Trial design

This is a single-centre, randomised, double-blind, placebo-controlled trial among patients aged ≥65 years old undergoing hip fracture surgery. After obtaining their informed consent, participants will be allocated to either the esketamine group (group E) or the control group (group C) at a 1:1 ratio. This trial was approved by the Ethics Committee of Chengdu integrated TCM & Western Medicine Hospital (Ethical Committee No. 2024KT022) and was registered at the Chinese Clinical Trial Registry (ChiCTR2400081681). The trial design adheres to the standard protocol items in the Recommendations for Interventional Trials.[21] The study activities are expected to commence in March 2025 and will be completed in December 2026. The authors delayed recruitment to ensure that all amendments were finalised. The Consolidated Standards of Reporting Trials flow chart is shown in figure 1; the present study protocol is the second version, revised according to the reviewers' comments.

Study setting

This study will be conducted at the Chengdu Integrated TCM & Western Medicine Hospital (Chengdu, China).

Study population

Patients scheduled for hip fracture surgery under general anaesthesia aged 65 years or older will be recruited for this study.

After assessing patients' eligibility for inclusion, informed consent will be obtained 1 day before surgery. All participants will be informed about details of the study before signing the informed consent form; participants can withdraw at any time during the trial with no impact on their care.

Eligibility criteria

Inclusion criteria

The inclusion criteria are as follows: (1) patients must be aged 65 years or older and scheduled for surgery under general anaesthesia for hip fracture, including femoral neck, femoral head, intertrochanteric, or subtrochanteric fracture; (2) American Society of Anesthesiologists (ASA) grades I–III; (3) informed consent obtained from the patient or their legal representative.

Exclusion criteria

The exclusion criteria are the following: (1) patients with multiple injuries, multiple fractures and fracture types other than those listed in the inclusion criteria (pathological, pelvic and femoral fractures); (2) patients with neurological diseases or psychiatric disorders; (3)

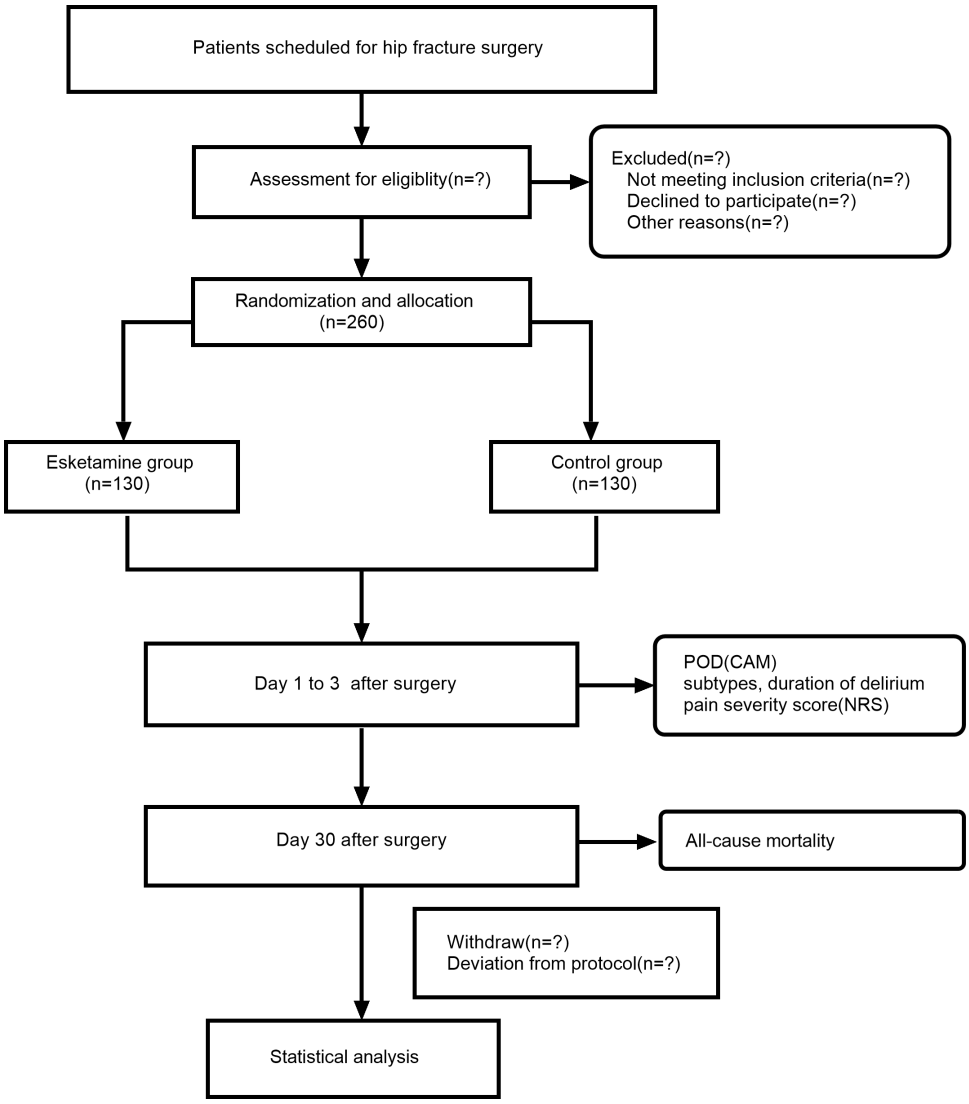

Figure 1 The flow chart of the trial procedure. POD, postoperative delirium; CAM, confusion assessment method; NRS, Numerical Rating Scale.

patients unable to communicate fluently, such as those with severe verbal, visual or auditory impairment; (4) contraindications or allergies to esketamine; (5) patients with severe heart, liver or kidney dysfunction; (6) history of alcohol or psychotropic drug abuse; (7) patients who are regarded as inappropriate by the investigators; and (8) Mini-Mental State Examination score <24.

Dropout criteria

The dropout criteria are as follows: (1) the patient and/or their legal representative wishes to withdraw their consent, (2) patients who are lost to follow-up, and (3) emergency unblinding.

Recruitment

All patients scheduled for hip fracture surgery will be screened and checked for eligibility on the day before surgery. The investigator will inform eligible patients or their legal representative about the study. We will provide verbal and written information to patients in easy-to-understand language, including the study objectives, procedures, benefits and risks. If the patient or their legal representative is willing to participate, informed consent will be obtained from the patient and/or their legal representative if the patient is unwilling or unable to provide informed consent owing to acute pain. Subsequently, we will address patient questions as soon as possible, guaranteeing that informed consent will be voluntarily obtained from patients or their legal representative. At any time during the study, patients or their legal representatives may refuse or withdraw consent without any reason.

Randomisation and blinding

Eligible patients will be randomly assigned at a 1:1 ratio to group E or group C according to a computer-generated random number list. Randomisation will be performed by an independent researcher (WH) using an online randomisation list. The results of randomisation will be

sealed in opaque envelopes. Nurses who are not involved in the management of anaesthesia will open the envelopes and prepare the esketamine or 0.9% normal saline in accordance with the allocated group. A total of 50 mg esketamine will be prepared with 48 mL saline solution. The same volume of saline solution will be used in group C, with syringes being identical in appearance. Anaesthetists, patients, follow-up personnel and statisticians will all be blinded to the group allocation.

Unblinding

In the event of a serious adverse event, such as allergic shock, blindness or disturbance of consciousness, where it is necessary to disclose the type of medication the patient is taking, unblinding will be considered. The care team will treat these patients in a timely manner to ensure the patient's safety. The investigator must prepare detailed records using case report forms (CRFs) and report adverse events to the Institutional Review Board (IRB). The IRB will deliberate to decide whether the study should be discontinued or modified.

Intervention

Intervention description

After tracheal intubation, patients in group E will receive continuous infusion with esketamine at a rate of 0.3 mg/kg/h intraoperatively until the beginning of skin incision closure.[22 23] Patients in group C will receive the same volume of normal saline at the same infusion rate.

Interventions in this study will be conducted under general anaesthesia, and the attending anaesthesiologist will administer the intervention following the standard operating procedure. To enhance adherence, participants will be encouraged to contact our research team for any reason.

Anaesthesia protocol

On arrival in the operating room, standard monitoring will be established, including pulse oximetry, electrocardiography, non-invasive blood pressure, invasive radial artery blood pressure monitoring and bispectral index (BIS). Additionally, all participants will receive suprainguinal fascia iliaca compartment block under ultrasound guidance with 0.25% ropivacaine 40 mL before anaesthesia.

General endotracheal anaesthesia will be induced intravenously, with 0.2–0.3 mg/kg etomidate, 0.2–0.4 µg/kg sufentanil and 0.1–0.15 mg/kg cisatracurium. Anaesthesia will be maintained with an infusion of propofol (2–6 mg/kg/h) and remifentanil (0.1–0.2 µg/kg/min) and inhaled 0.4-0.9 minimum alveolar concentration of sevoflurane, with a target BIS of 50–60. Cisatracurium will be administered as required. Intraoperative mean arterial pressure (MAP) will be kept within 20% of baseline values using vasoactive drugs. Flurbiprofen ester (50 mg) and antiemetic drugs (such as ondansetron 4 mg) will be administered at the end of the surgery. Anaesthesiologic adjuvants, such as penehyclidine hydrochloride, atropine, dexmedetomidine and midazolam should be avoided. After the surgery, all patients will be transferred to the post-anaesthesia care unit for additional care and then moved back to the ward after 30 min of monitoring.

Following tracheal intubation, ventilator parameters will be adjusted to maintain end-tidal carbon dioxide partial tension at 35–45 mm Hg. Patients' core body temperature will be continuously monitored and will be kept above 36°C using warming blankets.

All patients will receive a patient-controlled intravenous analgesia device after surgery consisting of a mixture of sufentanil (1 µg/kg), ondansetron (8 mg) and normal saline at a total volume of 200 mL, with a basal infusion of 2 mL/hour, a bolus dose of 2 mL and a locking time of 20 min for 48 hours. If a patient's numeric rating scale (NRS) score is greater than 4, rescue analgesia with additional intravenous flurbiprofen ester (50 mg) will be administered.

Outcome measures

Primary outcomes

The primary outcome is the incidence of POD within 3 days after surgery, which will be evaluated during the 3 days following surgery by an investigator who is blinded to the patients' assignment. POD will be evaluated using the confusion assessment method (CAM) two times per day (8:00–10:00 and 15:00–17:00) during the first 3 postoperative days. The CAM defines delirium according to four characteristics: (1) acute onset and fluctuating course; (2) inattention; (3) disorganised thinking; and (4) altered level of consciousness. A patient showing both characteristics 1 and 2, together with either 3 or 4, will be diagnosed as having delirium.[24] Before study initiation, research fellows will undergo training in conducting delirium assessment. To prevent missed cases, two independent, trained research fellows will be responsible for the assessment of delirium.

Secondary outcomes

The secondary outcomes include subtypes, duration of delirium, length of hospital stay, pain severity score within 3 days after surgery and 30-day all-cause mortality. The subtype of delirium will be determined using the Richmond Agitation-Sedation Scale (RASS) score: hypoactive type, RASS score<0; hyperactive type, RASS score>0; and mixed type, hypoactive and hyperactive types occurring alternately. Pain severity scores are evaluated using the NRS score at rest after surgery. Postoperative pain intensity is quantified using an 11-point scale. The NRS scores range is from 0 to 10 (no pain=0 and worst pain imaginable=10).[25] The length of hospital stay will be defined as days from the date of discharge to the date of hospital admission, inclusive of the first and last dates. The 30-day all-cause mortality will be defined as mortality within 30 days, with the date of surgery defined as day 0.

Table 1 Schedule of process of trial

	Study period						
	Baseline	Treatment	Follow-up phase				
Time points	Day −1	Day 0	Day 1	Day 2	Day 3	Discharge	Day 30
Enrolment							
Demography	X						
Baseline data	X						
Eligibility screen	X						
Informed consent	X						
Randomisation		X					
Intervention							
Esketamine group		X					
Control group		X					
Assessments							
Intraoperative data		X					
MMSE scores	X						
CAM			X	X	X		
RASS scores			X	X	X		
NRS scores			X	X	X		
Adverse events		X	X	X	X	X	X
All-cause death		X	X	X	X	X	X

Day −1, preoperative visit before surgery; day 0, surgery day; day 1, 1 day after surgery.
NRS, numeric rating scale; RASS, Richmond Agitation-Sedation Scale; MMSE, Mini-Mental State Examination; CAM, confusion assessment method.

Safety outcomes

Patients will be closely monitored for adverse events throughout the study. Safety evaluations will be based on vital signs as well as the incidence and type of adverse events. During the operation, the occurrence of hypotension (a decrease in MAP >30% of the baseline value), hypertension (an increase in MAP >30% of the baseline value), bradycardia (heart rate (HR) <50 beats per min) and tachycardia (HR>100 beats per minute) will be recorded. After the surgery, episodes of nausea, vomiting, dizziness, nystagmus, daymares, hallucination and diplopia will be recorded. Adverse events will be treated on the basis of standard procedures.

Participant timeline

The trial schedule including enrolment, allocation, intervention, assessment and follow-up time points is illustrated in table 1.

Sample size calculation

The literature reports that the incidence of POD in older patients with hip fracture ranges from 15% to 61%.[26] We hypothesise that the incidence of POD is 30% in the control group.[27] According to experimental data reported by Xiong,[20] esketamine reduced the risk of delirium from 44.6% to 23.2%, with a decrease of 21.2%. Therefore, we considered a 15% decrease to be clinically relevant, that is, a POD rate of 15% in the esketamine group versus 30% in the control group. Thus, the sample size was calculated with a power of 0.80 and α=0.05, meaning that at least 118 patients are needed in each group. According to a 10% potential dropout rate, we plan to include 260 patients overall (130 patients in each group).

Data collection

Research team members will collect all perioperative data. Demographic data will be recorded, including sex, age, weight, ASA grade, body mass index (BMI), education level, comorbidities, frailty scale score, haemoglobin, albumin and preoperative medication use. Intraoperative data will include patients' vital signs, durations of anaesthesia and surgery, types and volumes of infused fluids, types and doses of vasoactive drugs, type of operation, blood loss, urine output and blood transfusion volume. Postoperative data, such as primary and secondary outcomes, will be carried out by blinded research team members. Additionally, research team members will regularly visit patients to ensure that follow-up assessments are completed. After discharge, the research team members will call all patients for follow-up at 30 days after surgery. All collected data for each patient will be recorded on paper CRFs.

Data management

The collected data will be converted into electronic data, with the data verification process conducted by two independent investigators. The data files will be password protected, with only research team members having access to the files. After all participants have been included, the

database will be closed, followed by data analysis and writing of the manuscript. All original records, including informed consent forms and CRFs, will be stored for 10 years in a locked cabinet in the research office. Any personally identifiable information will be anonymised for participant confidentiality purposes. The data monitoring committee, including two clinicians and one statistician who are independent from the sponsor and have no competing interests, will monitor the progress of the trial.

Statistical analysis

All analyses will be carried out according to the intention-to-treat principle and will be performed using IBM SPSS V.27.0 software (IBM Corp.). All statistical tests will be conducted using two-tailed testing, and a p value<0.05 will be considered statistically significant. Continuous variables will be presented as mean and SD or median and IQR. Categorical variables will be presented as frequencies and proportions.

For the primary outcome, the incidence of POD will be analysed using the χ^2 test. Regarding categorical secondary outcomes, such as subtypes of delirium, 30-day all-cause mortality will be assessed using the χ^2 test. Time-to-event results, including the duration of delirium and length of hospital stay, will be analysed using Kaplan-Meier survival analysis and log-rank tests.

Based on the type and distribution of each variable, parametric data will be compared using parametric *t* tests, the Wilcoxon rank-sum test, χ^2 test, or Fisher's exact tests, as appropriate.

Multivariable generalised linear regression analysis for the primary outcome will be performed to adjust for differences in demographic or intraoperative variables between groups, such as age, sex, BMI, ASA physical status, haemoglobin, albumin, intraoperative MAP and preoperative frailty score. Per-protocol analysis will also be performed in sensitivity analysis. Subgroup analyses will be performed based on regression models according to age, sex, BMI, ASA physical status, haemoglobin, albumin, intraoperative MAP and preoperative frailty score.

Interim analysis

Interim analysis will be performed when 40% of participants have completed follow-up. Interim analysis ensures that the study is feasible and safe during the study period. If there are severe adverse events, including death, disability, or severe allergic reactions, the study will be terminated. If the primary outcome is rapidly obtained before complete participant inclusion, the study will be stopped.

Patient and public involvement

Neither patients nor the public will be involved in the study design, enrolment, data analysis, or publication of the trial.

DISCUSSION

Hip fracture is the most common type of fracture in the older population and most patients are treated with surgical procedures. POD is a common postoperative complication in older patients with hip fracture. However, the pathophysiology of POD in this patient population has not been fully elucidated, and there are few effective pharmaceutical treatments to reduce the prevalence of POD. A recent clinical study in patients undergoing on-pump cardiac surgery showed that a single dose of esketamine (0.25 mg/kg) before anaesthesia induction significantly reduced delirium (23.2% in the esketamine group vs 44.6% in the placebo group).[20] In older patients after gastrointestinal surgery, esketamine (1 mg/kg) also decreased the prevalence of POD on days 1 and 3 postoperatively (13.3% in the experimental group vs 40% in the control group, p=0.041).[28] However, no clinical studies on hip fracture surgery have been reported. There is a paucity of data regarding the protective effects against delirium of esketamine in older patients with hip fracture. We therefore designed a randomised, controlled, double-blind trial assessing intraoperative intravenous esketamine to reduce POD in older patients undergoing surgery for hip fracture.

Animal studies have shown that esketamine improved cognitive impairment by mediating its neuroprotective effects.[29 30] Moreover, a recent RCT revealed that a single intraoperative injection of esketamine (0.5 mg/kg) could alleviate postoperative anxiety, depression and pain and could reduce levels of proinflammatory and brain injury-related factors in patients undergoing non-cardiac thoracic surgery.[31] A prior meta-analysis indicated that perioperative esketamine could improve postoperative subjective quality of recovery, pain and psychological symptoms without increasing adverse events.[32] Neuroinflammation is widely accepted as contributing to delirium. Thus, esketamine theoretically has potential value in the prevention of POD.

In the current study, the diagnosis of delirium remains mainly based on clinical characteristics. According to psychomotor behaviour, delirium is categorised into three subtypes: hyperactive delirium, hypoactive delirium and mixed delirium. Hypoactive delirium is the most frequent type, which is frequently undiagnosed and is linked to a worse prognosis. Studies show that the underdiagnosis rate of POD in older patients ranges from 60% to 84.6%.[33 34] Considering the characteristics of delirium, we suggest that researchers follow-up with patients twice, from postoperative day 1, to reduce the underdiagnosis rate of POD.

This study has several limitations. First, this is a single-centre study; further studies will be warranted to further clarify the role of esketamine administration in this surgical population. Second, no serum or biological samples will be collected, which could help elucidate the potential mechanisms underlying the beneficial effect of esketamine on POD.

In summary, the aim of this RCT is to determine the effects of esketamine administration on POD and postoperative pain in older patients with hip fracture. The results of this study will offer new insights into improving anaesthetic care for older patients undergoing surgical procedures for hip fracture.

Ethics and dissemination

This study has been approved by the Ethics Committee of Chengdu integrated TCM & Western Medicine Hospital (2024KT022) and was registered in the Chinese Clinical Trial Registry (ChiCTR2400081681). Written informed consent will be obtained from all study participants and recorded prior to enrolment. The results of the trial are to be disseminated in academic journals or presented at scientific conferences.

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Contributors CS and QH contributed equally to this work and are cofirst authors. SO and CS are involved in the design of the study. WH, DZ and QF will contribute to data acquisition. DZ and XT will conduct the follow-up. WH and YL are responsible for the data analysis. CS and QH wrote the manuscript. SO is responsible for the overall content as guarantor. All investigators have read this protocol and approved the manuscript.

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Competing interests The authors have declared that no competing interests exist.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained from parent(s)/guardian(s)

Provenance and peer review Not commissioned; externally peer reviewed.

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