BMC Geriatrics

STUDY PROTOCOL Open Access

Effect of remimazolam tosilate for injection (HR7056) versus sevoflurane on the incidence of postoperative delirium in older patients undergoing total hip arthroplasty: study protocol for a prospective, multicentre, two-arm, parallel-group, randomised controlled trial

Lin-yu Wang[1,2], Meng-qing Zhang[2], Rui Sun[2], Liang Li[2] and Dong-liang Li[2*]

Abstract

Introduction Postoperative delirium (POD) is a common postoperative complication and is associated with numerous adverse outcomes. Advanced age and hip surgery are high risk factors for POD. Both remimazolam tosilate for injection and sevoflurane can be used as sedatives for the maintenance of general anesthesia, but the comparison of their impacts on the incidence of POD has not been reported. This study aims to compare the effect of remimazolam tosilate vernus sevoflurane on the incidence of POD in older patients undergoing total hip arthroplasty.

Methods and analysis This is a two-arm, parallel, prospective, multicenter, randomized controlled trial. A total of 456 older patients at six clinical trial centers in China will be randomly assigned in a 1:1 ratio to receive general anesthesia with remimazolam tosilate or sevoflurane as sedative. The primary outcome measure is the prevalence of POD during the first 4 postoperative days. Secondary outcomes include cognitive function [Mini-Mental State Examination (MMSE)], perioperative pain degree [Visual Analogue Scale (VAS)], postoperative nausea and vomiting (PONV) within 4 days after surgery, recovery time after drug withdrawal, the amount of vasoactive drugs used during operation, length of hospital stay, and in-hospital complications.

Ethics and dissemination The Research Ethics Committee of Qilu Hospital of Shandong University has approved the study protocol (REF: KYLL-202206-25), which is applicable to all research centers. Participant recruitment begins in August 2022. Written informed consent will be obtained from each patient before randomization. The findings will be published in an international peer-reviewed medical journal.

*Correspondence:
Dong-liang Li
ldl@sdu.edu.cn

Full list of author information is available at the end of the article

Trial registration The trial has been registered at the Chinese Clinical Trial Registry: ChiCTR2200062455; date of registration: 2022-08-08.

Keywords Postoperative delirium, Remimazolam tosilate, Hip arthroplasty, Sevoflurane, Older patients

Introduction

Postoperative delirium (POD) is an acute, fluctuating neurological syndrome characterized by decreased level of consciousness, attention disorders, and disorganized thinking [1]. It usually occurs within 24 ~ 72 h after surgery and is associated with prolonged hospital stay, poor functional recovery, long-term decline in cognitive function, and increased mortality [2, 3]. POD is one of the most common postoperative complications and its pathophysiological mechanism is still unclear, but previous studies have reported many risk factors [4–12] for POD, including age, level of education, preoperative cognitive function, the types of surgery, anesthesia methods, narcotic drugs, anemia, operation time, alcohol, physical function, intraoperative blood loss and pain stimulation, etc. The literature shows that the incidence of POD in patients undergoing orthopedic surgery is as high as 5–45% [13, 14]. The high incidence of POD in older patients undergoing hip surgery [15, 16] may be related to advanced age, preoperative cognitive impairment, and multiple comorbidities [17].

As a special group, older patients with hip arthroplasty are often accompanied by a variety of underlying diseases and have low body resistance, so they have high requirements for perioperative anesthesia and most of them prefer general anesthesia [18, 19]. Importantly, there is evidence that the same procedure under different anesthetics may have different incidences of postoperative neurocognitive impairment [20–23]. However, the effect of the type of anesthesia (e.g., inhalation versus intravenous anesthesia) on the incidence, duration, and severity of POD in patients remains largely unknown.

Sevoflurane is a common inhaled general anesthetic. In a clinical study of joint replacement surgery, the incidence of delirium after propofol anesthesia was 33.0% and that after sevoflurane anesthesia was 23.3% [24]. However, a study of delirium after laparoscopic cholecystectomy in older patients showed that sevoflurane and isoflurane significantly increased the incidence of POD compared with propofol [25]. These data suggest that the effect of sevoflurane inhalation anesthesia on POD requires further investigation.

Remimazolam tosilate, an analogue of midazolam, acts on $GABA_A$ receptors and is a short-acting sedative hypnotic that can be used for the maintenance of anesthesia. Remimazolam tosilate undergoes metabolism by plasma esterase in vivo into an inactive metabolite. Remimazolam tosilate has many advantages, including rapid onset and failure, short sedation recovery time, specific target, and controllable degree of cardiovascular and respiratory system depression [26–32]. However, as a newly marketed drug in China, its effect on POD has not been known yet, so it needs to be studied.

So far there is no study about the effects of remimazolam tosilate and sevoflurane on the incidence of POD in hip replacement surgery, therefore, we design the multicenter, randomized controlled clinical trials to determine the effect of remimazolam tosilate versus sevoflurane on the incidence of POD in older patients undergoing total hip arthroplasty.

Methods and analysis

Trial design

This study is a prospective, multicenter, two-arm, parallel-group, randomized controlled trial, which will be conducted from August 2022 to June 2024. The design of the present study adheres to the Standard Protocol Items for Randomized Trials (SPIRIT) checklist (Supplementary Table 1). A total of 456 participants will be randomly assigned in a 1:1 ratio to either remimazolam tosilate or sevoflurane. We conduct simultaneous trials at six clinical trial centers in China until the target sample size is reached. The research pattern is shown in Fig. 1.

Objectives

Our primary objective is to determine whether remimazolam tosilate can reduce the incidence of delirium after hip arthroplasty in older patients compared with sevoflurane. Secondly, we will evaluate differences in cognitive function, pain scores, incidence of postoperative nausea and vomiting (PONV), recovery time, intraoperative hemodynamic fluctuations, length of hospital stay, and in-hospital complications between patients under remimazolam tosilate and sevoflurane anesthesia.

Recruitment and study setting

Patients scheduled for elective hip arthroplasty under general anesthesia will be enrolled by a member of the study team and screened based on inclusion and exclusion criteria. Eligible hip replacement patients will be visited preoperatively by another member of the study team, who will verbally express the written agreement and answer in detail any questions regarding the study (e.g., study objectives, procedures, timing, potential risks and benefits associated with the trial). Patients who agree to participate in the trial will be recruited to participate in the study after signing an informed consent form.

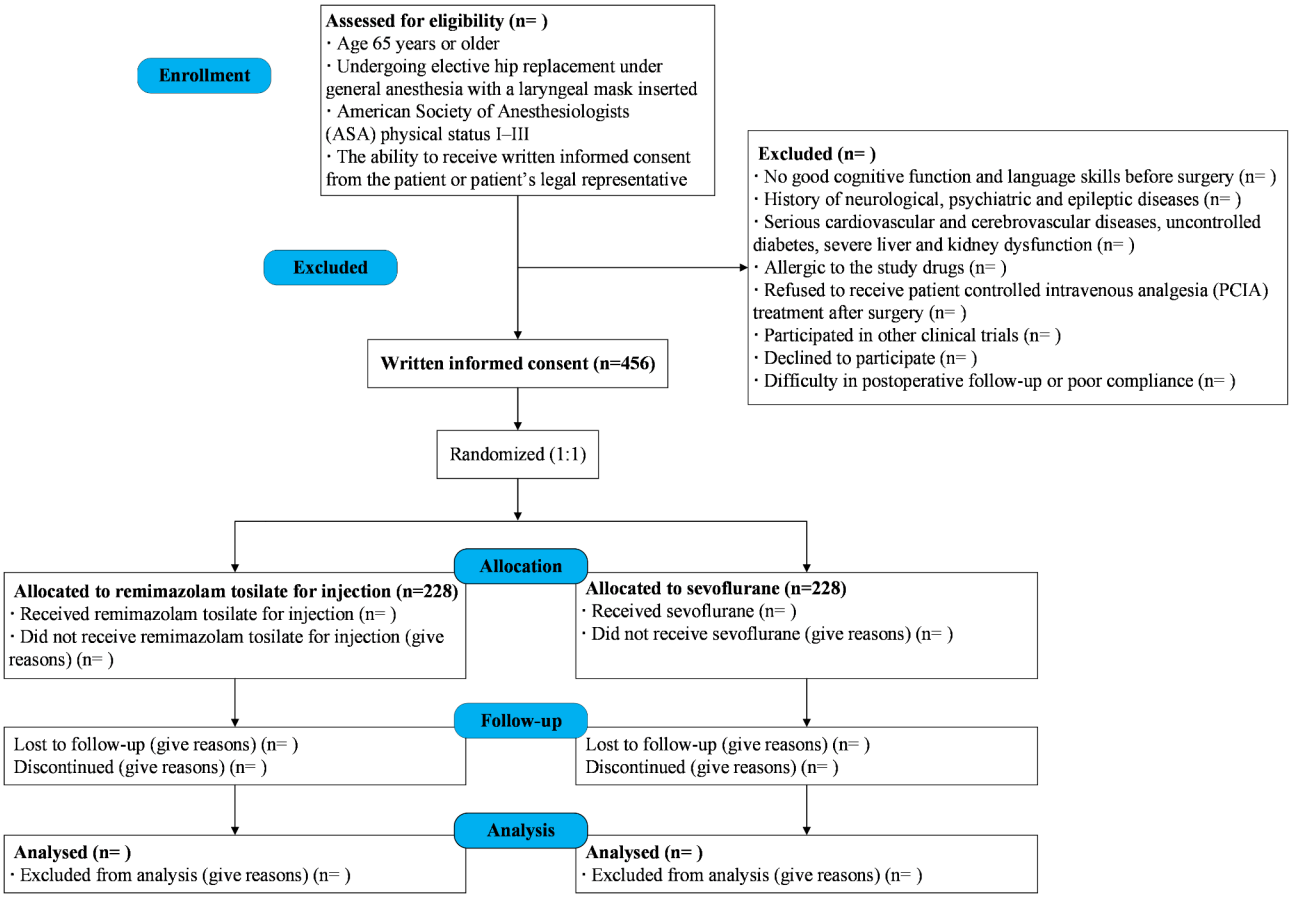

Fig. 1 Simplified schematic of the trial design

Inclusion criteria

Participants need to fulfil the following criteria:

- Age 65 years or older.
- Undergoing elective hip arthroplasty under general anesthesia with a laryngeal mask inserted.
- American Society of Anesthesiologists (ASA) physical status I–III.
- The ability to receive written informed consent from the patient or patient's legal representative.

Exclusion criteria

Patients with the following conditions will be excluded:

- No good cognitive function [Mini-Mental State Examination (MMSE) score, < 24 of 30 if the patient's education level is junior high school or higher or < 20 of 30 if the patient's education year is less than 6 years or < 17 if the patient is illiterate] and language skills before surgery.
- History of neurological, psychiatric and epileptic diseases.
- Serious cardiovascular and cerebrovascular diseases, uncontrolled diabetes, severe liver and kidney dysfunction.
- Allergic to the study drugs.
- Refuse to receive patient controlled intravenous analgesia (PCIA) treatment after surgery.
- Participate in other clinical trials.
- Decline to participate.
- Difficulty in postoperative follow-up or poor compliance.

Study centers

This trial is designed to include the following six investigational centers in China: Department of Anaesthesia, Qilu Hospital of Shandong University (primary centre); Department of Anaesthesia, Affiliated Hospital of Qingdao University (subcentre); Department of Anaesthesia, Qingdao Municipal Hospital (subcentre); Department of Anaesthesia, Jining First People's Hospital (subcentre); Department of Anaesthesia, Heze Municipal Hospital (subcentre); Department of Anaesthesia, 960th Hospital of PLA Zibo Medical District (subcentre).

Randomisation, allocation concealment and blinding

Stratified block randomization method is used in this study. The center is stratified, the length of the block is 4, and patients are enrolled in each hospital separately. SAS software is used to generate a random table. After written informed consent is obtained, participants are sequentially randomly assigned to one of two study groups (group R: remimazolam tosilate group; Or group S: sevoflurane group). Group assignments will be concealed in sequentially numbered opaque envelopes opened on the day of surgery. The envelopes will be placed in the patient's chart before the start of each procedure by a doctor of the research team. Subjects and researchers who interview patients before and after surgery and data analysts are blinded to the assignment of treatment.

General anaesthesia and postoperative analgesia protocol

On arrival at the operating room, all patients will be monitored by pulse oximetry, electrocardiogram and noninvasive blood pressure. Participants will be induced with etomidate (0.2 mg/kg), sufentanil (0.4ug/kg), and rocuronium (0.6 mg/kg) intravenously, and they will be inserted orally into a laryngeal mask after the muscle relaxant takes effect. Fascia iliaca nerve block (FINB) is comducted in both groups. Anesthesia will be maintained by intravenous continuous infusion of remimazolam tosilate (0.3 ~ 1.5 mg/kg/h) for patients in the group R. Anesthesia will be maintained with sevofurane inhalation (0.7 ~ 1.5MAC) for patients in the group S. For patients of both groups, intraoperative analgesia will be maintained with remifentanil (0.1 ~ 0.2 μg/kg/min) and neuromuscular block will be achieved by intermittent injections of rocuronium if necessary. The above maintenance drug dosage will be adjusted to maintain the BIS value between 40 and 60 to control the depth of anesthesia. Controlled ventilation will be performed using a volume regulation strategy with a tidal volume between 6 and 8 ml/kg, frequency between 10 and 16 per min, inspiratory/expiratory ratio of 1:2, and $PetCO_2$ between 35 and 45 mmHg. If excessive blood loss occurs during surgery, red blood cells will be replenished with blood transfusions if necessary to maintain hemoglobin levels within the target range of 7–10 g/dl. When necessary, vasoactive drugs will be administered to maintain systolic blood pressure fluctuations range within 20% of baseline. To prevent PONV, ondansetron (8 mg) and dexamethasone (5 mg) will be given intravenously 30 min before the end of operation. After the operation, the patient will be sent to the recovery room for observation. After the laryngeal mask is pulled out in the recovery room, all patients will be given PCIA treatment, which is established with sufentanil (1 μg/kg) and normal saline, programmed with a background infusion of 2 ml/h, a lockout interval of 15 min and duration of 2 days. If the outbreak pain cannot be relieved, flurbiprofen axetil (50 mg) by intravenous injection should be given temporarily.

Outcomes

Primary outcome

The primary outcome is the incidence of POD during the first 4 days after surgery. The Confusion Assessment Method (CAM) is a screening tool for nonpsychiatrically trained clinicians designed to assess POD according to the DSM-5 criteria. Delirium can be diagnosed via interview using the CAM algorithm following four criteria: [1] acute onset or fluctuating course [2], inattention [3], disorganised thinking and [4] altered level of consciousness [33]. 3-minute diagnostic confusion assessment method (3D-CAM) scale includes 22 questions and is a further optimization of the CAM scale. The POD will be evaluated by 3D-CAM scale. If criteria 1 and 2 and either of 3 or 4 are present, delirium is diagnosed. The first time we screen POD is in the recovery room and then the following screening time is at 8 a.m, 2 p.m, and 8 p.m on the first 4 days after surgery.

Secondary outcomes

Occurrence of intraoperative complications, including:

- Intraoperative hypertension, hypotension, bradycardia and vasoactive drug dosage.
- Intraoperative myocardial infarction, myocardial ischemia, arrhythmias, anaphylaxis, hypoxemia, pulmonary embolism, massive hemorrhage, and hypothermia.
- Intraoperative fluid volume, blood loss, and hemoglobin at the end of operation.
- The dosage of remifentanil used and the dosage of rocuronium used.
- Occurrence of various complications during hospitalisation after surgery, including:
- Nausea, vomiting, respiratory depression, dizziness, headache, fever, hypotension, hypertension, pruritus, urinary retention, hypoxemia. [Nausea is seen as a subjective, unpleasant feeling associated with awareness of the urge to vomit. Vomiting is defned as the forceful expulsion of stomach contents from the mouth. If the patient has symptoms of nausea, the severity will be recorded using the following scale: 1, mild nausea; 2, moderate nausea; 3, severe nausea. If the patient had vomiting, the severity of the episode will be recorded using the following scale: 1, one episode; 2, two episodes; 3, three or more episodes [34].]

Cognitive function during the first 4 days after surgery assessed by MMSE.

Pain severity assessed with the visual analogue scale (VAS).

Operation time, anesthesia time, recovery time, length of postoperative hospital stay and length of total hospital stay.

Participant timeline

The participant timeline is demonstrated in Table 1.

Adverse events

In this study, the intervention drugs in both groups are anesthetic drugs that have been tested for safety and are currently used in clinical practice. Therefore, there is no additional risk to participants. However, some side effects such as low blood pressure, respiratory depression, and PONV may occur. Patient safety will be monitored. Serious adverse events should be reported to the sponsor immediately, and patients will get the corresponding compensation.

Data and safety monitoring

All evaluations will be performed by research team members without knowledge of treatment allocation. All researchers will receive standardized neurocognitive and delirium assessment training before the study begins. Missing intraoperative data will be obtained from the electronic medical record. Postoperative data will be obtained during the first 4 days after surgery through interviews and electronic medical records. The Research Ethics Committee of Qilu Hospital of Shandong University will complete the monitoring of research behavior and data quality. We don't expect this study to expose participants to any serious danger. All adverse events, whether related to the study drug or not, will be monitored and recorded. The anesthesiologist will decide whether to terminate the trial according to the severity of adverse events. All adverse events will be treated in a timely manner, and the reasons for temporary cessation of the trial will be recorded.

Sample size calculation

The sample size for the primary outcome (incidence of delirium after hip replacement surgery) is calculated based on a study investigating general versus spinal anesthesia in older patients undergoing hip surgery. Assuming the prevalence is 19.7% [35] in the sevoflurane group, and the prevalence in the remimazolam tosilate group based on the result of the preliminary experiment is 9.9%. The sample size is calculated using the formula $n = \frac{2\bar{p}\,\bar{q}(Z_\alpha + Z_\beta)^2}{(p_1 - p_2)^2}$. The parameters used include a two-sided α value of 0.05,95% confidence interval, 80% power, and 1:1 allocation. The minimum number of subjects required to qualify for statistical significance is determined to be 207 patients per group. Considering a 10% withdrawal or dropout, we aim to enroll 456 participants in this study, with 228 participants in each group.

Data analysis

All statistical analyses will be conducted using IBM SPSS Statistics V.25.0. We will use the Shapiro-Wilk test and q-q plots to assess the normal distribution of continuous data. Normally, normally distributed variables will be expressed as the mean (SD) and skewed distributed variables as the median (IQR). Categorical variables will be represented by numbers (proportions). All data will be analyzed using an intention-to-treat approach. Demographic information will be compared between the two groups of patients to ensure balance of data. The student's t-test will be used for quantitative variables such as age, body mass index (BMI), years of education, blood loss, operation time, anesthesia time, and awakening time. Chi-square test or fisher exact test will be used for categorical variables such as gender, ASA classification grade, prevalence of postoperative delirium, and incidence of complications such as PONV. Blood pressure, VAS pain score and MMSE score will be analyzed by repeated measures ANOVA. Logistic regression model will be used to evaluate the effect of different covariates on postoperative POD incidence. Logistic regression or ordinary multiple regression methods will also be used to assess the effect of covariates on secondary and other outcomes, depending on the type of dependent variable. A two-tailed P-value of less than 0.05 is considered statistically significant.

Data management and storage

All data will be recorded on the Case Report Form (CRF). After the data are recorded, the data is stored in a database that each participating center has password-protected access to and can be accessed by the research staff who sign the confidential disclosure agreements. The paper version of the data is locked in a specific cabinet. During the study, the personal information of the participants will be kept confidential and all data related to the trial will be kept confidential.Data without patient identification will be publicly accessible after the study.

Trial status

At the time of manuscript submission, the study is in the recruitment phase.

Discussion

This is a prospective, multicenter, randomized, parallel-group, controlled trial to compare the effect of remimazolam tosilate versus sevoflurane on the incidence of POD in older patients undergoing hip arthroplasty surgery. The current study will be the first to evaluate the

Table 1 Participant timeline

Study period									
Time point	**Enrolment**	**Allocation**	**Post-allocation**						
	Preoperative	**0 day**	**Surgery**	**Recovery room**	**D1**	**D2**	**D3**	**D4**	**Leave hospital**
Enrolment	×								
Eligibility screen	×								
Informed consent	×								
Random allocation		×							
Interventions									
Remimazolam tosilate infusion			×						
Sevoflurane inhalation			×						
Assessments									
Baseline data									
Age	×								
Gender	×								
Height	×								
Weight	×								
BMI	×								
ASA grade	×								
Diagnosis	×								
Time of medical history	×								
Past medical history	×								
Past medication	×								
History of smoking	×								
History of alcohol consumption	×								
Number of children	×								
Marital status	×								
Place of residence	×								
Education level	×								
Intraoperative data									
The dosage of remifentanil used			×						
The dosage of rocuronium used			×						
Intraoperative infusion volume			×						
Intraoperative blood loss			×						
Hemoglobin after surgery			×						
Time of operative			×						
Duration of anesthesia			×						
Awakening time			×						
Intraoperative complications									
Hypertension			×						
Hypotension			×						
bradycardia			×						
Myocardial infarction			×						
Myocardial ischemia			×						
Arrhythmias			×						
Anaphylaxis			×						
Hypoxemia			×						
Pulmonary embolism			×						
Massive hemorrhage			×						
Hypothermia			×						
Blood pressure	×	×		×	×	×	×	×	
Heart rate	×	×		×	×	×	×	×	
Pluse	×	×		×	×	×	×	×	
Respiratory rate	×	×		×	×	×	×	×	

Table 1 (continued)

Study period									
Time point	**Enrolment**	**Allocation**	**Post-allocation**						
	Preoperative	**0 day**	**Surgery**	**Recovery room**	**D1**	**D2**	**D3**	**D4**	**Leave hospital**
Body temperature	×	×		×	×	×	×	×	
POD (3D-CAM)	×			×	×	×	×	×	
MMSE assess	×			×	×	×	×	×	
VAS pain score	×			×	×	×	×	×	
PONV				×	×	×	×	×	
Other in-hospital complications									
Respiratory depression				×	×	×	×	×	
Dizziness				×	×	×	×	×	
Headache				×	×	×	×	×	
Fever				×	×	×	×	×	
Hypotension				×	×	×	×	×	
Hypertension				×	×	×	×	×	
Pruritus				×	×	×	×	×	
Urinary retention				×	×	×	×	×	
Hypoxemia				×	×	×	×	×	
Inspection result									
WBC	×				×				
RBC	×				×				
HGB	×				×				
HCT	×				×				
ESR	×				×				
HS-CRP	×				×				
DD-i	×				×				
Length of poostoperative hospital stay									×
Length of total hospital stay									×

POD, postoperative delirium; 3D-CAM, 3-minute diagnostic confusion assessment method; MMSE, Mini-Mental State Examination; VAS, Visual Analogue Scale; PONV, postoperative nausea and vomiting; WBC, white blood cell; RBC, red blood cell; HGB, haemoglobin; HCT, hematocrit; ESR, erythrocyte sedimentation rate; HS-CRF, hypersensitive C-reactive protein; DD-i, D-Dimer

impact of remimazolam tosilate and sevoflurane on the incidence of POD in older patients undergoing hip replacement surgery. Although several recent studies have compared the safety and sedative effects of remimazolam and propofol, and several studies have compared sevoflurane with propofol on delirium after hip arthroplasty, none has investigated remimazolam tosilate versus sevoflurane. In some but not all clinical studies, the use of sevoflurane has been associated with POD. Further studies are needed to elucidate the possible role of remimazolam tosilate in causing POD in the case of its use as a perioperative sedative.

POD is a serious and often underrecognized complication that can lead to worse outcomes in older adults [36, 37]. The occurrence of POD is associated with higher rates of postoperative stroke and mortality in older patients undergoing total hip arthroplasty. Due to the absence of effective treatment options, the focus of POD is on prevention [38]: reversible factors, including pain and anemia, should be minimized and appropriate treatment ought to be established.

There are some literatures demonstrate that RA may offer some advantages to GA, especially for pain control or postoperative dysfunction [39]. However, there are some studies that show spinal anesthesia for hip-fracture surgery in older adults was not superior to general anesthesia with respect to survival and recovery of ambulation at 60 days. The incidence of postoperative delirium was similar with the two types of anesthesia [35]. What's more, many patients undergoing total hip arthroplasty are not suitable for simple RA or peripheral nerve block due to various reasons, and can only be operated under general anesthesia. Therefore, this study compares the effect of two drugs used for general anesthesia on postoperative delirium. We implement FINB in both groups to reduce pain.

Sedation is an indispensable component of the maintenance of general anesthesia. Commonly used sedatives include intravenous drugs (e.g., propofol and benzodiazepines) and inhaled drugs (e.g., sevoflurane). Propofol has rapid onset and short metabolic time, but it has significant respiratory and circulatory inhibition. It is not

suitable for older patients with poor cardiac reserve function [40] and decreased lung function. Benzodiazepines, such as midazolam, are agonists of GABA receptors in the central nervous system with sedative, hypnotic, anxiolytic, and anticonvulsant properties. Sevoflurane is a halogen inhaled anesthetic with little respiratory irritation and no hepatorenal toxicity. It is easy to adjust the depth of anesthesia to maintain stable hemodynamics during operation by adjusting the inhalation concentration of sevoflurane. Sevoflurane produces better, dose-dependent sedation than midazolam, resulting in a rapid recovery from sedation. Although patients' acceptance and satisfaction with sevoflurane are high, the effect of sevoflurane on the incidence of POD still needs to be explored.

The main benefits of remimazolam tosilate, including short duration of action, non-transhepatic and renal metabolism, limited accumulation, minimal inhibition of respiration and circulation, and availability of reversal agents [26–32], have led to its widespread use as a sedative in general anesthesia. Remimazolam tosilate is an attractive alternative to general anesthesia surgery in older patients. However, its effect on POD has not been clarified. The aim of this study is to evaluate whether remimazolam tosilate, as compared with sevoflurane, reduces the incidence of POD in older patients undergoing hip arthroplasty surgery.

According to literature search, this is the first study to evaluate whether remimazolam tosilate reduces the incidence of POD after hip replacement surgery. The trial has been carefully designed with two related and widely used anesthetic agents, covering a large number of patients from multiple sites, and will be carefully conducted. Our results will contribute to the selection of better anesthesia for older hip replacement patients, which will have an important beneficial impact on patients and society.

However, our study has some limitations. Most notably, POD is assessed only on the first 4 days after surgery, which may have caused some patients to develop POD and recover after four postoperative days. Second, we don't monitor patients' long-term outcomes with different anesthetics. Therefore, we cannot draw conclusions about the effect of anesthetics on long-term outcomes in our participants. Finally, exclusion criteria may limit the generality of our findings to other patients.

Abbreviations

POD	Postoperative delirium
MMSR	Mini-Mental State Examination
VAS	Visual Analogue Scale
PONV	Postoperative nausea and vomiting
ASA	American Society of Anesthesiologists
PCIA	Patient controlled intravenous analgesia
FINB	Fascia iliaca nerve block
group R	Remimazolam tosilate group
group S	Sevoflurane group
CAM	Confusion Assessment Method
3D-CAM	3-minute diagnostic confusion assessment method
BMI	Body mass index
CRF	Case Report Form

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12877-025-05766-3.

Supplementary Material 1

Acknowledgements
Not applicable.

Author contributions
DLL planned and designed the study. LYW drafted the manuscript. DLL critically revised the manuscript. MQZ, RS and LL were responsible for calculating sample size and searching literature and put forward the new amendment opinion. All authors contributed to the design and development of the trial, read, and approved the final manuscript.

Funding
This study was funded by Natural Science Foundation of Shandong Province (Role and mechanism of DNA receptor cGAS in cognitive deficits in developing rats induced by sevoflurane ZR2021MH102) and Medical Empowerment Public Welfare Special Fund of the Red Cross Foundation of China (CRCF-YXFN-202201035).

Data availability
The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
During the study, we will strictly follow the Declaration of Helsinki and China's good clinical practice guidelines to ensure that patients' rights are not violated. The study protocol has been approved by the Scientific Research Ethics Committee of Qilu Hospital of Shandong University (KYLL-202206-25). This study has been registered in the Chinese Clinical Trial Registry (ChiCTR2200062455) on 8 August 2022. Written informed consent will be obtained from each patient.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Anesthesiology, Shandong Provincial Hospital, Jinan, China
[2]Department of Anesthesiology, Qilu Hospital of Shandong University, 107 Wenhua West Road, Lixia District, Jinan City, Shandong Province, China

Received: 12 December 2022 / Accepted: 6 February 2025
Published online: 18 February 2025

References

1. Maldonado JR. Acute Brain failure: pathophysiology, diagnosis, management, and sequelae of Delirium. Crit Care Clin. 2017;33(3):461–519.
2. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. Lancet. 2014;383(9920):911–22.
3. Abelha FJ, Luís C, Veiga D, et al. Outcome and quality of life in patients with postoperative delirium during an ICU stay following major surgery. Crit Care. 2013;17(5):R257.

4. Ma J, Li C, Zhang W, et al. Preoperative anxiety predicted the incidence of postoperative delirium in patients undergoing total hip arthroplasty: a prospective cohort study. BMC Anesthesiol. 2021;21(1):48. Published 2021 Feb 12.
5. Marcantonio ER. Delirium in hospitalized older adults. N Engl J Med. 2017;377(15):1456–66.
6. Hempenius L, Slaets JP, van Asselt DZ, et al. Interventions to prevent postoperative delirium in elderly cancer patients should be targeted at those undergoing nonsuperficial surgery with special attention to the cognitive impaired patients. Eur J Surg Oncol. 2015;41(1):28–33.
7. Shah S, Weed HG, He X, et al. Alcohol-related predictors of delirium after major head and neck cancer surgery. Arch Otolaryngol Head Neck Surg. 2012;138(3):266–71.
8. van Meenen LC, van Meenen DM, de Rooij SE, et al. Risk prediction models for postoperative delirium: a systematic review and meta-analysis. J Am Geriatr Soc. 2014;62(12):2383–90.
9. Kalisvaart KJ, Vreeswijk R, de Jonghe JF, et al. Risk factors and prediction of postoperative delirium in elderly hip-surgery patients: implementation and validation of a medical risk factor model. J Am Geriatr Soc. 2006;54(5):817–22.
10. Smith PJ, Attix DK, Weldon BC, et al. Executive function and depression as independent risk factors for postoperative delirium. Anesthesiology. 2009;110(4):781–7.
11. Serafim RB, Dutra MF, Saddy F, et al. Delirium in postoperative nonventilated intensive care patients: risk factors and outcomes. Ann Intensive Care. 2012;2(1):51. Published 2012 Dec 31.
12. van der Zanden V, Beishuizen SJ, Scholtens RM, et al. The effects of blood transfusion on Delirium Incidence. J Am Med Dir Assoc. 2016;17(8):748–53.
13. Yang Y, Zhao X, Gao L, et al. Incidence and associated factors of delirium after orthopedic surgery in elderly patients: a systematic review and meta-analysis. Aging Clin Exp Res. 2021;33(6):1493–506.
14. Williams-Russo P, Urquhart BL, Sharrock NE, et al. Post-operative delirium: predictors and prognosis in elderly orthopedic patients. J Am Geriatr Soc. 1992;40(8):759–67.
15. Poeran J, Cozowicz C, Zubizarreta N, et al. Modifiable factors associated with postoperative delirium after hip fracture repair: an age-stratified retrospective cohort study. Eur J Anaesthesiol. 2020;37(8):649–58.
16. Halaas NB, Blennow K, Idland AV, et al. Neurofilament light in serum and cerebrospinal fluid of hip fracture patients with Delirium. Dement Geriatr Cogn Disord. 2018;46(5–6):346–57.
17. Yang Y, Zhao X, Dong T, et al. Risk factors for postoperative delirium following hip fracture repair in elderly patients: a systematic review and meta-analysis. Aging Clin Exp Res. 2017;29(2):115–26.
18. Bantie M, Mola S, Girma T, et al. Comparing Analgesic Effect of Intravenous Fentanyl, femoral nerve Block and Fascia Iliaca Block during spinal anesthesia positioning in Elective Adult patients undergoing femoral fracture surgery: a Randomized Controlled Trial. J Pain Res. 2020;13:3139–46.
19. Pu X, Sun JM. General anesthesia vs spinal anesthesia for patients undergoing total-hip arthroplasty: a meta-analysis. Med (Baltim). 2019;98(16):e14925.
20. Fodale V, Tripodi VF, Penna O, et al. An update on anesthetics and impact on the brain. Expert Opin Drug Saf. 2017;16(9):997–1008.
21. Miller D, Lewis SR, Pritchard MW, et al. Intravenous versus inhalational maintenance of anaesthesia for postoperative cognitive outcomes in elderly people undergoing non-cardiac surgery. Cochrane Database Syst Rev. 2018;8(8):CD012317.
22. Zhang Y, Shan GJ, Zhang YX, et al. Propofol compared with sevoflurane general anaesthesia is associated with decreased delayed neurocognitive recovery in older adults. Br J Anaesth. 2018;121(3):595–604.
23. Tang N, Ou C, Liu Y, et al. Effect of inhalational anaesthetic on postoperative cognitive dysfunction following radical rectal resection in elderly patients with mild cognitive impairment. J Int Med Res. 2014;42(6):1252–61.
24. Mei X, Zheng HL, Li C, et al. The effects of Propofol and Sevoflurane on postoperative delirium in older patients: a Randomized Clinical Trial Study. J Alzheimers Dis. 2020;76(4):1627–36.
25. Geng YJ, Wu QH, Zhang RQ. Effect of propofol, sevoflurane, and isoflurane on postoperative cognitive dysfunction following laparoscopic cholecystectomy in elderly patients: a randomized controlled trial. J Clin Anesth. 2017;38:165–71.
26. Song X, Wang F, Dong R, et al. Efficacy and safety of Remimazolam Tosilate Combined with Esketamine for Analgesic Sedation in mechanically ventilated ICU patients: a single-arm clinical study protocol. Front Med (Lausanne). 2022;9:832105.
27. Remimazolam for Sedation in ICU Patients Undergoing Mechanical Ventilation. Available online at: https://ClinicalTrials.gov/show/ NCT04815265 (accessed March 24, 2021).
28. Jiangsu HengRui Medicine. Co. L. *A trial of Effifffifficacy and Safety of remimazolam Tosilate for Injection in local anesthesia assisted Sedation*. (2021). Available online at: https://ClinicalTrials.gov/show/NCT05015361
29. Hospital R, Hospital SE, Hopital JPPs UTSAHJ. *Effifffifficacy and Safety of remimazolam Tosilate for Sedation in Gastroscopy*. (2021). Available online at: https://ClinicalTrials.gov/show/NCT04727034
30. Jiangsu HengRui Medicine Co. L. Study of remimazolam Tosilate in Patients Undergoing Colonoscopy. (2018). Available online at: https://ClinicalTrials.gov/show/NCT03779061
31. Jiangsu HengRui Medicine Co. L. A Clinical Study of remimazolam Tosilate in Patients Undergoing Bronchoscopy. (2020). Available online at:https://ClinicalTrials.gov/show/NCT04400201
32. Hospital TN. *Effifffifficacy and Safety Profifile of remimazolam-alfentanil Combination for ERCP Sedation*. (2020). Available online at: https://ClinicalTrials.gov/show/NCT04658173
33. Inouye SK, van Dyck CH, Alessi CA, et al. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. Ann Intern Med. 1990;113(12):941–8.
34. Won YJ, Yoo JY, Chae YJ, et al. The incidence of postoperative nausea and vomiting after thyroidectomy using three anaesthetic techniques. J Int Med Res. 2011;39(5):1834–42.
35. Neuman MD, Feng R, Carson JL, et al. Spinal anesthesia or General Anesthesia for hip surgery in older adults. N Engl J Med. 2021;385(22):2025–35.
36. Leslie DL, Zhang Y, Holford TR, et al. Premature death associated with delirium at 1-year follow-up. Arch Intern Med. 2005;165(14):1657–62.
37. Martin BJ, Buth KJ, Arora RC, et al. Delirium: a cause for concern beyond the immediate postoperative period. Ann Thorac Surg. 2012;93(4):1114–20.
38. Banerjee A, Girard TD, Pandharipande P. The complex interplay between delirium, sedation, and early mobility during critical illness: applications in the trauma unit. Curr Opin Anaesthesiol. 2011;24(2):195–201.
39. Lim EJ, Koh WU, Kim H, et al. Regional nerve Block decreases the incidence of postoperative delirium in Elderly Hip fracture. J Clin Med. 2021;10(16):3586.
40. Claeys MA, Gepts E, Camu F. Haemodynamic changes during anaesthesia induced and maintained with propofol. Br J Anaesth. 1988;60(1):3–9.

Publisher's note