Trials

STUDY PROTOCOL

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Effects of opioid-free anesthesia combined with iliofascial nerve block on perioperative neurocognitive deficits in elderly patients undergoing hip fracture surgery: study protocol for a prospective, multicenter, parallel-group, randomized controlled trial

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Abstract

Background Perioperative neurocognitive dysfunction (PND), a prevalent complication affecting elderly surgical patients, poses substantial challenges to postoperative rehabilitation and long-term functional independence. Despite growing awareness of its clinical significance, current evidence regarding effective neuroprotective anesthetic strategies remains inconclusive. Where emerging evidence suggests opioid-free anesthesia (OFA) strategies could maintain analgesic efficacy while potentially attenuating opioid-associated neuroinflammatory mechanisms implicated in PND pathogenesis. This multicenter trial investigates the efficacy of OFA combined with ultrasound-guided iliofascial nerve block in mitigating PND among geriatric patients undergoing hip fracture surgery.

Methods This multicenter, randomized controlled trial will enroll 348 patients, who will be randomly assigned to receive either OFA combined with iliofascial nerve block or opioid-based anesthesia (OBA) combined with iliofascial nerve block. All patients will undergo hip fracture surgery under general anesthesia with tracheal intubation. The primary outcome will be the change in composite neurocognitive scores, assessed through a battery of neuropsychological tests from baseline to 3 months postoperatively. Secondary outcomes include alterations in serum protein and inflammatory markers, extubation time, postoperative pain incidence, intraoperative hemodynamic stability, and postoperative recovery parameters. The safety profile of OFA in hip surgery will also be assessed.

Discussion Effective prevention of PND is crucial for optimizing postoperative recovery and long-term functional outcomes in elderly patients. This trial aims to refine and optimize anesthesia management strategies to reduce the incidence of PND, improve postoperative quality of life, and ultimately enhance perioperative neurocognitive outcomes.

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Trial registration This trial protocol was registered with the China Clinical Trial Registry on December 14, 2023, under the registration number: ChiCTR2300078647.

Keywords Opioid-free anesthesia, Iliofascial nerve block, Perioperative neurocognitive disorders, Elderly patients, Hip fracture surgery

Introduction

Background and rationale {6a}

With the global aging population, the incidence of osteoporosis and associated fragility fractures continues to escalate, resulting in a rising number of geriatric patients requiring hospitalization. Hip fractures, representing one of the most debilitating osteoporotic fracture types, are particularly concerning due to their substantial surgical trauma and prolonged surgical duration, which collectively contribute to an elevated risk of perioperative neurocognitive disorders (PND) [1]. PND has emerged as the primary neurocognitive complication in geriatric surgical populations, requiring clear clinical differentiation from the classical construct of postoperative cognitive dysfunction (POCD) in both diagnostic criteria and temporal manifestation. Postoperative neurocognitive disorder (PND), an umbrella term encompassing both postoperative cognitive dysfunction (POCD) and postoperative delirium (POD), currently lacks a universally established gold standard for clinical diagnosis. The diagnostic process primarily relies on standardized neuropsychological scales administered through conventional assessment methods. Among the most commonly utilized cognitive screening instruments, the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) have emerged as predominant tools in both clinical practice and research settings, despite ongoing debates regarding their optimal application in postoperative evaluation. In recent years, there has been an increasing adoption of computer-based assessment methods. PND is a patient-centered outcome that encompasses symptom burden, functional impairment, prevalence, persistence, and societal impact [2]. Emerging epidemiological evidence reveals that 25% of geriatric patients undergoing major surgical procedures develop postoperative neurocognitive deficits, with 40–50% of these individuals progressing to irreversible cognitive deficits or dementia subtypes within 24 months postoperatively [3]. This neurocognitive deterioration substantially diminishes functional independence and life satisfaction while exponentially increasing caregiver burden. Given these clinical trajectories and their corresponding socioeconomic ramifications, PND requires urgent reconceptualization as a neurosurgical priority, necessitating coordinated multidisciplinary investigations to establish evidence-based preventive protocols and targeted neuroprotective interventions.

Contemporary therapeutic paradigms for PND encompass general supportive care, pharmacotherapy, physical rehabilitation, and psycho-behavioral therapy; however, these approaches collectively demonstrate limited clinical efficacy due to heterogeneous pathophysiological mechanisms. Despite comprehensive neuroanesthesia research spanning two decades, no pharmacological agent or technique has achieved robust evidence-based validation for PND risk reduction, with even promising candidates like dexmedetomidine showing inconsistent neuroprotective efficacy in this context. Current clinical guidelines emphasize a paradigm shift from post-onset management to preventive neurology, prioritizing preoperative cognitive optimization protocols and intraoperative cerebral oxygenation monitoring strategies [2, 4]. Notably, emerging pharmacogenomic studies have revealed that μ-opioid receptor polymorphisms mediate the neurocognitive effects of perioperative analgesics, particularly regarding their differential impacts on hippocampal neurogenesis and blood–brain barrier permeability. In recent years, increasing attention has been directed towards the effects of opioid analgesics on postoperative cognitive function, leading to a rise in research investigating their potential role in the development of PND.

Since their discovery, opioids have been a cornerstone of clinical anesthesia due to their dual sedative and analgesic properties, solidifying their role as an essential component of balanced anesthesia regimens. Nevertheless, their perioperative application is increasingly scrutinized due to a spectrum of dose-dependent complications, including but not limited to gastrointestinal dysmotility (postoperative ileus), immune system suppression, and neuropsychiatric manifestations such as cognitive dysfunction, delirium, and opioid-induced hyperalgesia. Particularly concerning is the growing body of evidence implicating opioids in the pathogenesis of perioperative neurocognitive disorders (PND), a complication associated with prolonged hospitalization, functional decline, and diminished postoperative quality of life. Opioid-free anesthesia (OFA) has emerged as a multimodal anesthetic strategy designed to minimize opioid-related complications and has been increasingly implemented across various surgical procedures [5]. This study aims to investigate the impact of opioid-based anesthesia on

the incidence of postoperative neurocognitive disorders (PND) by systematically evaluating the clinical outcomes associated with transitioning from conventional opioid-based anesthesia to an opioid-free anesthetic approach.

In recent years, OFA has emerged as a significant advancement in the field of anesthesiology, with its clinical applications becoming a focal point of contemporary research [6]. The Enhanced Recovery After Surgery (ERAS) protocols, supported by extensive studies, have established that multi-modal analgesic approaches—such as local infiltration analgesia and nerve blocks—can facilitate opioid-sparing or even opioid-free anesthesia in total hip arthroplasty, thereby enhancing postoperative recovery. Research has shown that iliac fascial nerve block offers postoperative analgesia efficacy comparable to that of subarachnoid block in total hip arthroplasty. However, sensory assessments at 24 h post-surgery indicate a slower regression of sensory blockade in the iliac fascial group. Nevertheless, iliac fascial nerve block remains a robust and dependable analgesic method. This study seeks to assess the impact of opioid-free anesthesia combined with iliac fascial nerve block on the incidence of PND in elderly patients undergoing hip fracture surgery. The ultimate objective is to refine anesthesia strategies to mitigate PND occurrence and improve postoperative quality of life.

Objectives {7}

As a prospective, randomized, double-blind trial, this study aims to investigate the impact of opioid analgesics on perioperative neurocognitive dysfunction and to develop evidence-based anesthesia strategies designed to minimize its incidence.

Trial design {8}

This study will be a randomized, multicenter, parallel-group controlled, prospective trial.

Methods: participants, interventions, and outcomes

Study setting {9}

This multicenter, randomized, controlled clinical trial will be conducted at the Affiliated Hospital of Jiaxing University, Jiaxing Hospital of Traditional Chinese Medicine, Zhejiang Provincial Rongjun Hospital, and The Third People's Hospital of Bengbu. The study has received approval from the Ethics Committee of the Affiliated Hospital of Jiaxing University and the respective institutional ethics committees and has been registered with the China Clinical Trial Center. The trial protocol adheres to the Consolidated Standards of Reporting Trials (CONSORT) guidelines (Ethics approval numbers: 2023-LY-317; 2023–055; 2023–018; 2024-K4). Participants will be randomly assigned to either the opioid-free anesthesia (OFA) combined with iliofascial nerve block group or the opioid-based anesthesia (OBA) combined with iliofascial nerve block group. The study design is outlined in the trial flowchart (Fig. 1), and the enrollment schedule is detailed in Table 1.

Eligibility criteria {10}

Inclusion criteria

1 Age 65–95 years old
2 Patients who intend to undergo hip fracture surgery
3 Voluntary signing of informed consent
4 No serious cardiopulmonary disease and liver and kidney dysfunction, no other compound injury
5 American College of Physicians ASA classification I-III cardiac function NHYA I-II

Exclusion criteria

1 Patients with a history of severe psychiatric illness before surgery
2 Patients with infection at the nerve block site
3 Patients allergic to local anesthetics
4 Patients abusing opioids
5 Those who are hearing impaired or otherwise unable to be assessed
6 Those with coagulation disorders or serious abnormalities in platelet count and function
7 Patients with pulmonary heart disease, uncontrollable hypertension, pulmonary arterial hypertension, hyperthyroidism, glaucoma, and intracranial hypertension

Consent or assent

Who will take informed consent? {26a}

Eligible participants are identified through a joint assessment by anesthesiologists and orthopedic surgeons, with written informed consent obtained from patients and their families prior to enrollment.

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

During the preoperative visit on the day before surgery, the details of the opioid-free anesthesia regimen are thoroughly explained to the patient. Patients are informed of the necessity to actively participate in completing preoperative and postoperative assessment scales and are advised that a small blood sample will be collected intraoperatively for laboratory analysis, which will be safely disposed of after use.

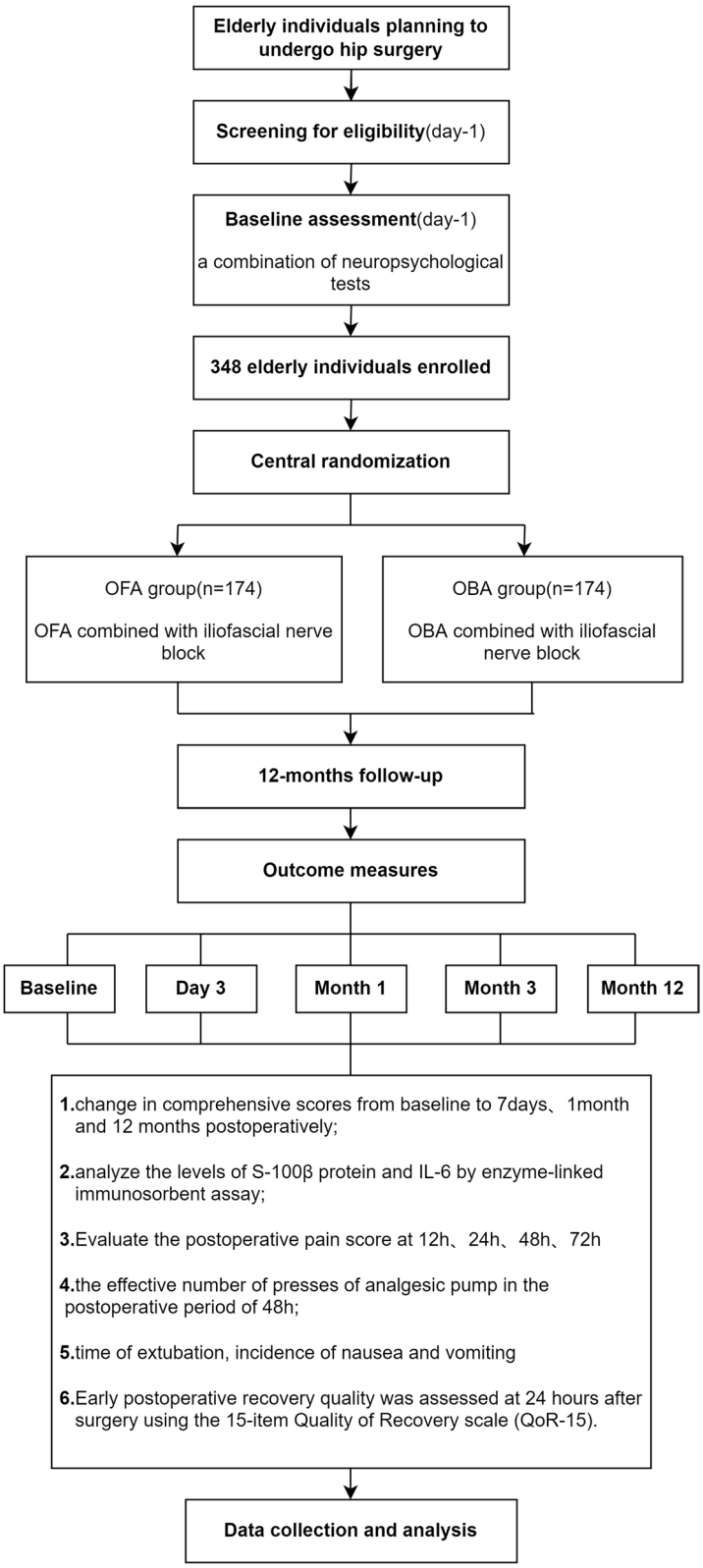

Fig. 1 Flowchart

Table 1 Schedule of recruitment, interventions, and assessments

Study period	Enrolment		Post-allocation			Follow-up			
Time point	Day − 1	Day 0	Day 1	Day 2	Day 3	Day 7	Day 30	Day 90	Month 12
Inclusion/exclusion criteria	√								
Sign informed consent	√								
Randomization	√								
Intervention									
Opioid-free anesthesia			√						
Opioid-base anesthesia			√						
Fascia iliaca compartment block			√						
Primary outcome									
The comprehension score		√				√	√	√	√
Secondary outcome									
S- 100β protein	√				√				
IL- 6	√				√				
Extubation time				√					
Pain incidence rate		√	√	√	√				
Intro-operation vital signs			√						
Post-operation recovery				√					

Intervention

Explanation for the choice of comparators {6b}

This study aims to evaluate the effect of opioid-free anesthesia (OFA) on perioperative cognitive function in elderly patients. The opioid-based anesthesia (OBA) group was chosen as the control, as opioid-based anesthesia remains a widely used clinical anesthetic regimen.

Intervention description {11a}

All patients will undergo ultrasound-guided iliofascial nerve block on the operative side prior to anesthesia induction, with 40 ml of 0.3% ropivacaine injected after proper needle placement. In OFA group, induction was primarily achieved using a combination of propofol (2–2.5 mg/kg, intravenously), lidocaine (1.5 mg/kg, intravenously), esketamine (0.25 mg/kg, intravenously), and rocuronium bromide (0.6–0.8 mg/kg, intravenously), with maintenance facilitated through continuous infusions of propofol (4–6 mg/kg/h), lidocaine (1–2 mg/kg/h), dexmedetomidine (0.4–1.4 μg/kg/h), and esketamine (0.2 mg/kg/h). In contrast, the opioid-based anesthesia (OBA) group received induction with propofol (2–2.5 mg/kg), sufentanil (0.3–0.5 μg/kg), and rocuronium bromide (0.6–0.8 mg/kg), followed by maintenance with propofol (4–6 mg/kg/h) and remifentanil (6–12 μg/kg/h) [7]. The infusion of ketamine and dexmedetomidine will be discontinued 30 min before the end of the surgery [8]. Anesthesia was sustained with sevoflurane at 0.8–1.0 MAC during the entire operation.

The iliac fascia is visualized using a probe placed along the long axis direction of the femoral region, displaying the iliac muscle on the lateral side. The deep iliac circumflex artery is identified at the proximal end of the inguinal ligament. By tilting the probe outward along the iliac fascia, better visualization of the iliac fascia can be achieved. The needle is inserted using a planar approach, from the distal to the proximal end. The critical step in this block is positioning the needle tip between the iliac fascia and the iliopsoas muscle, specifically at the distal end of the deep iliac circumflex artery. The needle is advanced through the deep aspect of the inguinal ligament, which crosses over the iliac muscle bulge, to administer the local anesthetic.

Criteria for discontinuing or modifying allocated interventions {11b}

The investigator will terminate the experiment for this participant if one of the following occurs during the experiment:

1 Those who have difficulty maintaining intraoperative blood pressure and heart rate and those who experience serious intraoperative complications (hemorrhagic and anaphylactic shock, cardiac arrest, etc.).
2 Patients who refuse neurological test scores after surgery.
3 Postoperative patients who have difficulty in tolerating pain using opioids.

4 The investigator may decide to end the trial due to other unforeseen reasons.

Strategies to improve adherence to interventions {11c}

The principal investigator (SPH) will conduct an anesthetic assessment and scale evaluation of the subject on the day before surgery, in accordance with the inclusion and exclusion criteria. During the informed consent process, the SPH will thoroughly explain the details of the study to the participant and their family, emphasizing the importance of their cooperation.

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

All participants will receive standard postoperative care, including monitoring and management in the operating room, post-anesthesia recovery room, and surgical care unit.

Ancillary and post-trial care {30}

At the conclusion of the procedure, the subject will be extubated and resuscitated in the post-anesthesia recovery room. If the patient's condition is unstable or if pain is unmanageable, appropriate interventions will be provided before transferring them back to the ward. In the event of any adverse events related to the surgery or anesthesia, our department and the hospital will ensure prompt and appropriate medical care is administered.

Outcomes {12}

The primary outcome measure of the study is the change in comprehensive scores derived from a combination of neuropsychological tests, comparing baseline to 3 months postoperatively. The neuropsychological tests included the Montreal Cognitive Assessment (MoCA), the Stroop Color Word Test (SCWT), the Digit Span Test (DST), the Symbol Digit Modalities Test (SDMT), and the Auditory Verbal Learning Test (AVLT) [9]. Follow-up testing will be primarily conducted through either on-site visits or video calls.

The results from the neuropsychological tests cannot be directly summed, so the raw scores are converted into *Z*-scores to derive a comprehensive score that reflects the subject's neuropsychological performance. To calculate the *Z*-score, the average (M) and standard deviation (SD) of the scores for each test are first determined. The *Z*-score for each patient is then calculated using the formula: $Z = (x - \mathrm{M})/\mathrm{SD}$, where x is the raw score for each neuropsychological test, and M and SD are the mean and standard deviation derived from the previous step. A positive *Z*-score indicates that the subject's score is above the mean of the combined sample, while a negative *Z*-score signifies a score below the average.

Secondary outcome indicators included (1) the change in comprehensive scores derived from a combination of neuropsychological tests at 7 days, 1 month, and 12 months postoperatively; (2) collection of 4 ml of blood from the elbow vein 1 day before surgery and 3 day after surgery for analysis of S- 100β protein and IL- 6 levels via enzyme-linked immunosorbent assay (ELISA); (3) evaluation of postoperative pain scores at 12, 24, 48, and 72 h using the visual analogue scale (VAS), with comparisons of VAS scores between different groups; (4) the effective number of analgesic pump presses in the first 48 h postoperatively; (5) postoperative outcomes including extubation time, incidence of nausea and vomiting, and duration of post-anesthesia care unit (PACU) stay; and (6) early postoperative recovery quality was assessed at 24 h after surgery using the 15-item Quality of Recovery scale (QoR- 15).

Participant timeline {13}

The participant timeline is shown in Fig. 1.

Sample size {14}

We conducted a pilot study comparing the effects of opioid-free anesthesia with opioid-based anesthesia on elderly people in Affiliated Hospital of Jiaxing University. Results from our pilot study revealed that: compared with the baseline, the change of the scores from the a combination of neuropsychological tests decreased by 6.28, with a standard deviation of 4.82, after the opioid-free anesthesia, and by 4.83 with a standard deviation of 2.16 after the opioid-based anesthesia. Consequently, we estimated that a sample size of 105 participants per group would provide 90% power to detect a difference in the combined neuropsychological test scores. The calculation is based on the assumption that measurements on the comprehension of the scores are normally distributed. This number has been increased to 126 per group (total of 252), to allow for a predicted dropout rate of 20%. As our pilot study had a small sample size and as we will undertake subgroup analysis, we expanded the sample size to 348 cases (174 cases in each group) to enhance the reliability of the study.

Recruitment {15}

Patients who met the inclusion criteria will be randomly assigned to either the opioid-free anesthesia (OFA) group or the control group using a central randomization system, with a 1:1 allocation ratio. Randomization will be stratified by the enrollment site and utilized a block size of 6. Both participants and outcome assessors will be blinded to treatment allocation. Enrolled

patients underwent routine preoperative examinations, including chest radiographs, abdominal ultrasound, cardiac color Doppler ultrasound, color Doppler ultrasound of the bilateral lower limbs, cardiopulmonary function assessments, complete blood counts (five categories), blood group determination, blood coagulation tests, liver and renal function tests, and electrolyte measurements. During the anesthesia consultation, patients and their families will be informed about potential postoperative complications, and informed consent will be obtained. To evaluate the success rate of subject blinding, two study centers will be randomly selected to analyze questionnaire responses (Fig. 2).

Assignment of interventions: allocation

Sequence generation {16a}

Randomization will be performed using a central stratified block randomization method across multiple centers. Eligible participants will be randomly assigned to either the opioid-free anesthesia (OFA) group or the control group in a 1:1 ratio, with stratification based on the enrolling center. The randomization process employed blocks and will be managed by the coordinating center using a central randomization system.

Concealment mechanism {16b}

A centralized randomization system is utilized for the allocation of subjects, thereby minimizing human intervention, enhancing transparency, and ensuring reproducibility of the allocation process. Blinding was maintained at both the subject and outcome assessor levels to ensure unbiased assessment of the outcomes.

Implementation {16c}

Subjects' anesthesia regimens will be determined according to the randomization process outlined above. Once group assignments are made, patients will be admitted to the operating room, where the investigator will inform the anesthesiologist of the subject's assigned group, ensuring appropriate preparation for the anesthesia protocol.

Assignment of interventions: blinding

Who will be blinded {17a}

Due to the use of a distinct anesthetic protocol, blinding of the anesthesiologist was not feasible. Therefore, this trial was conducted with blinding applied solely to the subjects and outcome assessors.

Procedure for unblinding if needed {17b}

Emergency unblinding will be conducted if it becomes necessary to identify the specific drug used for rescuing the subject or in the event of other medical emergencies during the trial, where knowing the specific drug is crucial for patient management.

Data collection and management

Plans for assessment and collection of outcomes {18a}

On the day prior to surgery, the evaluator will visit the ward to gather baseline patient data (including height, weight, education level) and conduct the scale evaluation, which will be documented in the CRF form. Anesthesia management and intraoperative data collection will be carried out by two anesthesiologists during the surgery, while postoperative follow-up will be conducted by evaluators who are blinded to the anesthesia regimen.

Blind Method Assessment Questionnaire

Name: Random Number: Date:

Please answer the following questions according to your lasted evaluate

1、How's your feel about your anesthesia plan(Including anesthesia medication level operations)?

2、Do you have anesthesia experience? Yes No

3、Do you have the experience of opioid-free anesthesia? Yes No

4、Are you sure you are receiving the opioid-free anesthesia? Yes No

Fig. 2 Blind method assessment questionnaire

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

This trial investigates changes in scores obtained from a combination of neuropsychological tests from baseline to 3 months postoperatively. Accordingly, outcomes will be assessed at 7 days, 1 month, 3 months, and 12 months postoperatively. After obtaining informed consent, the patient will be informed that each follow-up visit will involve a 30-min scale assessment, and their understanding and agreement will be confirmed.

Data management {19}

This study will handle the collected data in compliance with the Data Security Law of the People's Republic of China. Upon completion of each subject's visit, all participant data will be manually filled in the paper CRFs and then transcribed into Microsoft Excel by the researcher not involved in the implementation of the intervention. Raw data will be securely stored in a locked cabinet in the anesthesia department office, while electronic data will be kept on a computer protected by dual password authentication.

Confidentiality {27}

All researchers are dedicated to adhering to patient confidentiality regulations and maintaining ethical standards throughout the study. Personal data collected during the research will be treated with the utmost confidentiality and managed in compliance with relevant data protection laws. Confidential information will be securely processed and stored to ensure strict adherence to privacy regulations.

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

After obtaining the patient's consent, this trial will collect a small blood sample intraoperatively for protein analysis as a secondary outcome measure. The collected blood samples will be used solely for research purposes and will be destroyed following analysis.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

The main objective is to compare the change in the comprehensive scores derived from a combination of neuropsychological tests, at 3 months from the baseline between the treatment group and the control group. The null hypothesis is that the treatment group has the same change as the control group, while the alternative hypothesis is that the treatment group shows a fewer decrease.

All statistical analyses will adhere to the intention-to-treat (ITT) principle, defining the ITT analysis set as comprising all subjects randomized, regardless of their intervention assignment. Missing data, from subjects without any treatment after randomization, or without any valid data of evaluation although treated, will be analyzed by multiple imputation method under the missing at random assumption. Data processing and statistical analyses will be conducted using SPSS statistical software version 26.0 (IBM). Continuous variables will undergo normality testing via the Kolmogorov–Smirnov (K-S) method. Normally distributed data will be presented as mean ± standard deviation (SD), non-normally distributed data as median and interquartile range, and categorical data as counts (n) and percentages (%). For demographic and baseline characteristics, as well as intraoperative data, quantitative data comparisons between groups will be analyzed using the two-independent sample t-test or Mann–Whitney U test, while qualitative data will be analyzed using the chi-square test, continuous-corrected chi-square test, or Fisher's exact test. Demographics and baseline characteristics will serve as covariates in the logistic regression model. For comparison of two independent samples: if the residual are normally distributed, the analysis of covariance (ANOVA) will be used for the primary outcome and subgroup analysis stratified by age, a t-test for other continuous data, and a chi-square test for categorical data; if the residual are abnormally distributed, a non-parametric test will be used for both continuous and categorical date. In addition, the Bonferroni test is used for multiple comparisons of blood sample indicators (S- 100β and IL- 6).

Interim analyses {21b}

No interim analysis is planned for this trial.

Methods for additional analyses (e.g., subgroup analyses) {20b}

Subgroup analyses will be conducted based on age, with participants divided into three groups: namely 65 to 75 years, 75 to 85 years, and 85 to 95 years of age. The same statistical methods used for the primary and secondary outcome analyses will be applied to these subgroups.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

The study details will be thoroughly explained to the participants prior to enrollment, and informed consent will be obtained from both patients and their families. The dropout rate will be minimal, with very few patients non-compliant. To minimize the risk of data loss, we implemented strategies in line with our study protocol. However, in cases where missing data cannot be

disregarded, we applied the intention-to-treat principle for the primary outcome indicators. Missing data will be assumed to be missing at random, and multiple imputation methods were used to address any gaps in the primary data.

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

Access to the data and protocols of this trial is restricted to the trial leader. No individual is permitted to access participant data without prior approval from the principal investigator.

Oversight and monitoring

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

This study is a multicenter randomized controlled trial, with the steering committee based at the corresponding author's institution responsible for coordinating the allocation of tasks, ensuring full collaboration across all participating centers.

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

Not applicable. With an expected enrollment of 348 subjects and a trial duration of 2 years, the establishment of a data monitoring committee is not planned.

Adverse event reporting and harms {22}

Adverse events will be documented by the investigator on a case report form (CRF), including incidents of intraoperative hypertensive events, increased occurrence of adverse hemodynamic events, postoperative peritoneal emphysema, inguinal numbness of the thighs, and sensory abnormalities or delays. In the event of an adverse event, immediate protective measures will be taken to ensure the subject's safety. The incident will be reported to the principal investigator, who will assess the situation and determine whether the study should be terminated. Serious and unexpected adverse 9 events will be expeditiously reported to the Ethics Committee for review.

Frequency and plans for auditing trial conduct {23}

An independent reviewer, not involved in the trial, will be selected to assess the trial process. This reviewer conducted a thorough review of data collection and evaluated the informed consent forms at the form level every 2 weeks to ensure compliance with the study protocol and ethical standards. The reviewer conducts a visit every 6 months to check the existence and integrity of the investigation documents. In addition, 25% of patients were randomly selected for the following data: informed consent, inclusion and exclusion criteria, source data, and missing.

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

The trial protocol was reviewed and approved by the Ethics Committee of the Affiliated Hospital of Jiaxing University, as well as by the Ethics Committees of each participating sub-center. Any important protocol modifications will be reviewed by the principal investigator who will sign the amendment, which will be submitted to the ethics committee for approval later. For any planned protocol amendments, the sponsor and funder will be notified first, then the investigators at the sites will notify the sites, and a copy of the revised protocol will be sent to the PI for inclusion in the investigator's institute file. Any deviation from the protocol will be fully documented on the Violation Report Form and the protocol will be updated in the Clinical Trials Registry.

Dissemination plans {31a}

We will make every effort to publish the results of this trial in a peer-reviewed journal specializing in clinical anesthesiology and orthopedics.

Quality control, data management, and monitoring

Prior to the initiation of the study, researchers at each participating center will undergo rigorous training. This training will encompass a comprehensive overview of the study protocols, invasive procedures, and a meticulous data management plan. The latter will encompass data collection, entry, and monitoring procedures, as well as scale assessments. These measures are integral to ensuring the accuracy and reliability of the clinical trial. Anesthetists intending to participate in the study must possess a minimum of 5 years of clinical experience and be in possession of a valid license. Furthermore, they will receive standardized training in nerve block techniques prior to the commencement of the trial.

Discussion

Perioperative neurocognitive dysfunction (PND) has emerged as a pressing public health challenge, imposing substantial socioeconomic burdens through its detrimental impacts on patients' quality of life, sleep architecture, and psychosocial functioning [11]. The pathogenesis of PND involves multifactorial interactions, with established risk determinants spanning preoperative cognitive impairment, intraoperative physiological perturbations (including thermoregulatory instability, fluid/electrolyte imbalances, and neuroendocrine dysregulation), and postoperative pharmacological management involving

analgesics and anti-inflammatory agents [12]. Current evidence substantiates that surgical trauma and general anesthetic exposure synergistically impair neurocognitive homeostasis, with geriatric populations demonstrating heightened vulnerability to persistent PND manifestations that may compromise long-term functional recovery [13]. In addition, pain, opioid treatment, and inflammatory responses after surgery have been identified as potential risk factors for cognitive decline, as areas of the brain involved in pain perception and cognitive processes overlap. Despite concerted research efforts, current anesthetic protocols and pharmacologic interventions lack conclusive evidence for PND prevention or mitigation, though several neuroprotective strategies show preliminary efficacy in experimental models [15].

Emerging epidemiological evidence delineates the substantial clinical burden of perioperative neurocognitive dysfunction (PND), with meta-analyses indicating that 25% of geriatric patients undergoing major surgical procedures demonstrate measurable cognitive deterioration postoperatively. Notably, longitudinal studies reveal that over 50% of these cases progress to persistent neurocognitive impairment, frequently culminating in accelerated dementia progression and irreversible deterioration in activities of daily living [16]. This phenomenon exhibits particular clinical relevance in orthopedic populations: Systematic reviews report a 16–45% prevalence of postoperative neurocognitive impairment following arthroplasty, with hip replacement patients demonstrating acute PND incidence rates of 17–28% at 7-day postoperative evaluation—a critical window for neurocognitive monitoring [16, 17].

Emerging evidence suggests that opioid-free anesthesia (OFA) may reduce the incidence of perioperative neurocognitive disorders (PND). OFA employs a multimodal analgesic approach utilizing non-opioid pharmacological agents and techniques with complementary mechanisms of action to achieve optimal anesthetic quality. Ketamine, a versatile intravenous anesthetic, serves as a cornerstone in OFA protocols. Its N-methyl-D-aspartate (NMDA) receptor antagonism provides effective analgesia even at subanesthetic doses [18, 19]. Both bolus administration and continuous infusion regimens of ketamine demonstrate opioid-sparing effects while enhancing hemodynamic stability and postoperative pain control. Notably, ketamine's sustained antidepressant properties may confer additional benefits for cognitive recovery and pain modulation in the perioperative period [20].

To systematically evaluate OFA's potential advantages, we conducted a multicenter randomized controlled trial comparing PND incidence between conventional and OFA protocols. Both study arms received pre-induction iliofascial nerve blocks to standardize perioperative analgesia and maintain intraoperative hemodynamic stability. The experimental OFA protocol combined dexmedetomidine, esketamine, and lidocaine to achieve opioid minimization while mitigating typical opioid-related adverse effects [21].

Current clinical research increasingly supports the efficacy of OFA combined with multimodal analgesic techniques in achieving adequate pain control and reducing postoperative opioid requirements. However, significant heterogeneity persists in OFA implementation due to the absence of standardized definitions and variations in dosing regimens across institutions [22, 23]. This methodological inconsistency was highlighted in the 2018 *Chinese Journal of Anesthesiology* review "Urgent Solutions to the Ten Scientific Issues in Chinese Anesthesiology," which identified "The impact of general anesthetics and perioperative stress on aging brain function and long-term outcomes" as a critical research priority [24]. These findings emphasize the need for enhanced perioperative management through multicenter trials employing advanced PND detection methods and developing optimized anesthesia protocols to minimize PND risk.

Our understanding of OFA combined with iliofascial block in elderly hip fracture patients reveals established PND risk factors including baseline cognitive impairment, advanced age, and infectious complications. Nevertheless, a critical gap remains in identifying reliable biomarkers for PND prediction. Future investigations should prioritize developing comprehensive risk prediction models incorporating potential biomarkers and advanced neuroimaging modalities. Early identification of high-risk populations through such approaches could enable timely interventions to improve clinical outcomes and reduce PND incidence in this vulnerable demographic.

This study acknowledges several limitations. The fixed block randomization design carries inherent risks of allocation prediction bias. While conducted across multiple provincial centers, the sample size remains relatively constrained. Subsequent research should expand to interprovincial multicenter collaborations with larger cohorts to better elucidate OFA's impact on PND incidence and postoperative complications. Such efforts could significantly advance anesthetic strategy development for high-risk surgical populations, particularly geriatric patients.

Trial status

The trial has been registered with the Chinese Clinical Trial Registry (http://www.chictr.org.cn) under the registration number ChiCTR2300078647. The trial is scheduled to run from January 2024 to June 2026, with patient recruitment starting in February 2024 and expected to conclude by June 2025.

Abbreviations

PND	Perioperative neurocognitive disorder
OFA	Opioid-free anesthesia
OBA	Opioid-based anesthesia
POCD	Postoperative cognitive dysfunction
MoCA	The Montreal Cognitive Assessment
SCWT	The Stroop Color Word Test
VAS	Visual analogue scale
CRF	Case report form

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Authors' contributions {31b}
HN and MY, as principal investigators, completed the conception and design of the experiment and wrote the initial protocol, TZ and SW completed the first draft of the article, JK and SZ were responsible for the finalization of the article, and LC, DY, TG, LL, CX, and QZ were involved in the development of and made important revisions to the plan for the collection of the experimental data and statistical analysis. Authorship will be based on their contributions to this trial.

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Data availability {29}
All data during the study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate {24}
The study was approved by the Medical Ethics Committee of the Affiliated Hospital of Jiaxing University; the study strictly adhered to the legislative and institutional requirements and did not involve any disadvantaged groups; subjects participating in the study signed an informed consent form.

Consent for publication {32}
All investigators involved in this trial consented to publication.

Competing interests {28}
The authors declare that they have no competing interests.

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