

Intravenous versus Perineural Esketamine for Brachial Plexus Block on Postoperative Rebound Pain in Patients undergoing Arthroscopic Shoulder Surgery: A study protocol for a Multi-centre, Prospective, Randomised, Controlled Trial

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1 **Title**

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30 **Administrative information**

31 Note: the numbers in curly brackets in this protocol refer to SPIRIT checklist item
32 numbers. The order of the items has been modified to group similar items (see
33 [http://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-s](http://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/)
34 [tandard-protocol-items-for-clinical-trials/](http://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/)).

Title {1}	Intravenous versus Perineural Esketamine for Brachial Plexus Block on Postoperative Rebound Pain in Patients undergoing Arthroscopic Shoulder Surgery: A study protocol for a Multi-centre, Prospective, Randomised, Controlled Trial
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Name and contact information for the trial sponsor {5b}	No sponsor
Role of sponsor {5c}	No sponsor

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Abstract

Background: Regional anaesthesia is widely favored in the multimodal analgesia strategies for orthopaedic surgery, yet rebound pain may undermine its advantages. The efficacy of esketamine in preventing rebound pain following peripheral nerve blocks remains unclear. The primary objective of this study is to compare the effects of intravenous versus perineural esketamine on postoperative rebound pain after shoulder arthroscopy.

Methods: A multi-centre, double-blind, prospective, randomised controlled trial will be conducted to primarily compare the incidence of postoperative rebound pain between the effects of intravenous and perineural esketamine with brachial plexus block. A total of 501 participants (n = 167 per centre) will be randomly assigned to one of three groups: the Control group (n=167), the Intravenous group (n=167), or the Perineural group (n=167). Each patient will receive general anaesthesia to complete the surgery and will receive their allocated intervention in the recovery room. The primary outcome will be the incidence of postoperative rebound pain when the perineural nerve block wears off. Additional variables, including the characteristics of rebound pain, postoperative pain scores, rescue opioid consumption, QoR-15 scale, the incidence of postoperative persistent pain and the adverse events of nerve blocks and esketamine, will be recorded as secondary outcomes.

Discussion: This protocol aims to compare the incidence of postoperative rebound pain in patients receiving intravenous esketamine versus those receiving esketamine as an adjuvant combined with brachial plexus block following arthroscopic shoulder surgery. The results may reveal whether esketamine can effectively mitigate the occurrence of rebound pain and provide evidence regarding which administration route is more efficacious in preventing rebound pain.

Trial registration

Chictr.org.cn, Registered on September 11, 2024, ChiCTR2400089564

Keywords: Esketamine, Brachial plexus block, Rebound pain, arthroscopic shoulder surgery, Randomised controlled trial

Background

The pain intensity experienced during arthroscopic shoulder surgery is among the most severe of all orthopedic surgical procedures, particularly for arthroscopic rotator cuff tear repair [1,2]. Ultrasound-guided peripheral nerve block (PNB) is considered one of the essential components of multimodal analgesia strategies following surgical procedures. However, a type of sudden and sharp pain may occur after the resolution of nerve block, particularly within the initial 24-48 hours post-surgery[3], and this phenomenon is recognized as rebound pain[4].

Bone surgery has been proven to one of the risk factors independently associated with rebound pain, which can diminish the effectiveness of nerve block[5]. Studies have shown that the incidence of rebound pain following shoulder surgery can be as high as 44.4% to 82.9% [6-10]. This can clearly lead to negative outcomes, such as reduced postoperative rehabilitation quality and patient satisfaction, increased opioid misuse and excessive medical expenses, persistent postoperative pain, and longer hospital stays[11]. As the peripheral nerve block technique is increasingly used in peri-orthopedic surgery, preventing the occurrence of rebound pain before the resolution of PNB presents a significant challenge.

Minimizing the incidence of rebound pain has become a clinical priority. Current prevention and treatment strategies include adding adjuvants to local anesthetics, employing continuous peripheral nerve blocks, and utilizing combined blocks at multiple nerve sites. The addition of adjuvants to local anesthetics is a commonly used modification intended to prolong the duration of motor and sensory nerve blocks while also reducing the cumulative dose of local anesthetics to decrease their neurotoxicity. Adjuvants such as α 2-adrenergic receptor agonists (e.g.,

dexmedetomidine), dexamethasone, and ketamine are frequently used in clinical practice[12]. However, ketamine is increasingly less favored due to its psychiatric side effects. The novel NMDA receptor modulator, esketamine, offers improved pharmacological properties compared to ketamine and demonstrates an optimized therapeutic profile with a reduced incidence of psychotomimetic reactions typically associated with traditional ketamine derivatives[13]. Several clinical studies have confirmed that the perioperative intravenous administration of esketamine in surgical patients of various ages undergoing different types of surgeries can alleviate the severity of postoperative acute pain, reduce the use of opioid drugs, enhance the quality of postoperative recovery, and mitigate negative emotions such as depression[14-18]. To our knowledge, there are few studies that involve esketamine as local anesthetic adjuvants for preventing rebound pain. Consequently, we designed this study to investigate the potential prophylactic impact of esketamine, whether administered intravenously or in combination with local anesthetics, on the phenomenon of rebound pain. This prospective, randomised, controlled trial aims to address a significant gap in current knowledge and provide new insights for tailored pain prevention and treatment strategies.

Aims and objectives

Our objective is to compare the effectiveness of two methods, intravenous versus perineural esketamine, in preventing postoperative rebound pain following arthroscopic shoulder surgery. The primary outcome we are focusing on is the incidence of rebound pain. Secondary outcomes include the characteristics of rebound pain, postoperative pain scores, rescue opioid usage, QoR-15 scale, the incidence of persistent postoperative pain, and adverse events related to nerve blocks and esketamine. We aim to demonstrate that esketamine, whether administered intravenously or as an adjunct to local anesthetics, can decrease the incidence of rebound pain.

Methods: Participants, interventions, and outcomes

Study design

This is a protocol for a multicentre, double-blind, prospective, randomised, controlled trial. We will compare the effects of intravenous and perineural esketamine for brachial plexus block on the incidence of rebound pain after arthroscopic shoulder surgery.

This study was presented on the basis of the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT 2025 Guidelines). The study was registered on the <http://www.chictr.org.cn> (ChiCTR2400089564) on 11 September 2024. The final report of this trial will be written in accordance with the Consolidated Standards of Reporting Trials (CONSORT) statement. The flow chart for this trial is presented in Fig.1.

Before the study's commencement, a unified online training session was conducted for researchers from the three centres. The training encompassed the assessment of the scale, follow-up of postoperative rebound pain, and the specific procedures for implementing general anaesthesia and nerve block.

Study setting

This study will enroll 501 patients across three tertiary hospitals: Renji Hospital, Linyi City People's Hospital, and the Fourth Affiliated Hospital of Nanjing Medical University. The clinical trial has received approval and support from the ethics committees of Renji Hospital (LY-2024-178A), Linyi City People's Hospital (202410-H-020), and the Fourth Affiliated Hospital of Nanjing Medical University (20240825-K120).

Informed consent

Informed consent must be obtained in writing from each participant before their enrollment in the study. Upon a comprehensive understanding of the study protocol, which includes trial procedures, benefits, risks, potential adverse effects, and data management, interested participants will be evaluated against the inclusion and exclusion criteria by an independent investigator prior to surgery. Participants are entitled to withdraw from the trial at any point without the need to provide a reason. Similarly, the investigator has the authority to remove participants from the study if their safety is at risk. Additionally, a participant will be withdrawn if the nerve block procedure cannot be successfully completed to facilitate surgery. The grounds for withdrawal will be meticulously documented in the case report form.

Participants' eligibility criteria

Patients who are scheduled for unilateral arthroscopic shoulder surgery will be enrolled in this trial. An independent researcher will be responsible for recruitment and determining eligibility one day prior to surgery.

Inclusion criteria:

- Age 18-80 years
- ASA physical status I-III
- BMI 18-30 kg/m²
- Scheduled for unilateral arthroscopic shoulder surgery

Exclusion criteria:

- Contraindications for nerve block (including pre-existing neurological damage in the surgical area, symptoms of peripheral neuropathy associated with diabetes, bleeding or coagulation disorders, local or systemic infections)
- Prolonged administration of sedatives, analgesics, or steroid medications
- History of neurological, psychiatric, or neuromuscular disorders

- History of ipsilateral shoulder surgery
- Allergy to ropivacaine, esketamine or chronic pain medications
- History of diagnosed pulmonary diseases (including chronic bronchitis, chronic obstructive pulmonary disease, bullous lung disease, pulmonary embolism, lung cancer, etc.)

Randomization

Upon obtaining signed informed consent, participants will be randomly assigned to one of three groups in a 1:1:1 ratio: the Control group (n=167), the Intravenous group (n=167), or the Perineural group (n=167). Randomization is performed by a statistical expert, Jing Gao, using SAS 9.4 software. The sequence details, including assigned group, random numbers, and intervention specifics, will be concealed within identical opaque, sealed envelopes. All participants, surgeons, the researcher responsible for ultrasound performance, and the researcher assistant overseeing postoperative follow-ups will remain unaware of the group allocations.

Study Intervention

All patients are required to fast for six hours prior to surgery. Vital sign monitoring, peripheral venous access, and invasive arterial pressure monitoring will be established during the surgical procedure. General anaesthesia will be induced using midazolam (0.05 mg/kg), propofol (target-controlled plasma concentration of 3-4 µg/ml in Marsh mode), sufentanil (0.1-0.2 µg/kg), and rocuronium (0.6 mg/kg) for endotracheal intubation. Anaesthesia will be maintained with propofol (target-controlled plasma concentration of 1-2 µg/ml in Marsh mode), remifentanyl (administered at a constant rate of 0.3-0.5 mg/h), and sevoflurane at a concentration of 1-2%. The depth of anaesthesia will be maintained within a BIS (bispectral index) range of 40-60. Surgery will be performed by two fixed senior-grade surgeons in each centre.

Flurbiprofen (50 mg) and ondansetron (5 mg) will be administered for postoperative analgesia and nausea before the completion of the surgery. Drugs with any adjuvant effects, such as corticosteroids, dexmedetomidine, and dexamethasone, are not allowed to be used throughout the entire procedure. Postoperative analgesia will be administered via patient-controlled intravenous analgesia (PCIA: 100 µg sufentanil and 10mg ondansetron with a bolus of 2 ml/h).

Before extubation in the recovery room, all patients are ensured to maintain a certain sedative depth, which is achieved through a single intravenous injection of propofol at a dosage of 1mg/kg before the nerve block operation. Additionally, two anesthesiologists with at least five years of experience in ultrasound-guided nerve block procedures are present at each centre to perform the ultrasound-guided interscalene brachial plexus nerve block. Utilizing a high-frequency linear array transducer under B-mode ultrasound localization, the C5-6 nerve roots and the middle scalene muscle are identified. The procedure employs an out-of-plane technique, with the needle inserted from the superficial to the deep side at the lateral aspect of the C5-6 nerve roots to inject a local anesthetic solution. The local anesthetic (or 0.9% saline) solution is prepared by an independent designated researcher.

1. **Control group (Saline group):** Under ultrasound guidance, the C5-6 nerve roots are located, and then 20ml of 0.25% ropivacaine is injected. Concurrently, a researcher blinded to the group allocation intravenously administers 10ml of 0.9% saline.
2. **Intravenous esketamine group:** The nerve block procedure and the injected solution are identical to those described above. The same researcher, who is unaware of the group allocation, intravenously administers 10ml of esketamine (0.3mg/kg).
3. **Perineural esketamine group:** The nerve block performance is the same as above, while a mixture solution consisting of 20ml of 0.25% ropivacaine and esketamine (0.3mg/kg) is injected as the local anaesthetic. The same

228 researcher, who is unaware of the group assignment, intravenously
229 administers 10ml of 0.9% saline.

230 Upon the patients' consciousness awakening in the recovery room, if a patient reports
231 significant pain (NRS>3), it can be considered a failure of the blockage. In such cases,
232 100mg of tramadol should be administered as a pain relief measure.

233

234 **Interventions, modifications, adherence and concomitant care**

235 The designated treatment will be halted solely if a participant chooses to withdraw.
236 Throughout the study, no adjustments to the treatment protocols are anticipated.
237 Compliance with the treatment primarily involves the participant's commitment to
238 self-management. Additionally, no other forms of care or treatments are allowed while
239 the trial is ongoing.

240

241 **Additional consent provisions for the collection and use of participant data and** 242 **biological specimens**

243 Participants will agree to the storage of data and publication of the results in the main
244 and ancillary studies. This trial does not involve collecting biological specimens for
245 storage.

246

247 **Outcome definitions and data collection**

248 **Primary outcome**

249 The primary outcome is the incidence of rebound pain following arthroscopic
250 shoulder surgery. Rebound pain is commonly characterized as a shift in pain intensity,
251 as measured by a numerical rating scale (NRS), from well-controlled ($\text{NRS} \leq 3$) to
252 severe ($\text{NRS} \geq 7$) [5].

Secondary outcomes

The secondary outcomes are as follows:

- The characteristics of rebound pain (onset time, duration, severity) and postoperative pain scores at rest and during movement
- Postoperative rescue opioid consumption in the recovery room and on the 1st, 3rd, 5th, and 7th days post-surgery
- Sensation and movement block duration
- DN4 scale (neuropathic pain assessment) scores pre-surgery
- QoR-15 (Quality of Recovery-15) Scale scores pre-surgery, on the 1st and 7th days post-surgery
- Incidence of persistent postoperative pain at 3 months post-surgery

Safety outcomes

- Adverse events of the nerve block (including accidental puncture of the common carotid, subclavian, dorsal scapular, or vertebral arteries, pneumothorax, hypotensive bradycardic event, epidural and intrathecal injections, local anesthetic systemic toxicity, neurologic complications, hiccups, Horner's syndrome, hoarseness and subjective dyspnea)
- Adverse events of esketamine (including vomiting and nausea, hypertension, somnolence, ocular nystagmus, psychiatric symptoms)

Postoperative pain is assessed using the Numerical Rating Scale (NRS), which ranges from 0 to 10. A score of 0 signifies no pain, 1-3 indicates mild pain, 4-6 represents moderate pain, and 7-10 denotes severe pain. This assessment is performed at rest and during movement, both before surgery and on the 1st, 3rd, 5th, 7th days, and three months post-surgery. On the first day following surgery, an independent researcher will closely monitor the patient for any signs of rebound pain. Should rebound pain occur, its characteristics, including onset time, duration, and severity, will be meticulously recorded. The severity of rebound pain, also referred to as the rebound pain score, is calculated as the difference between the lowest pain score within the

initial 12 hours before the PNB dissipates and the highest pain score within the first 12 hours following the dissipation of the PNB[19]. The Douleur Neuropathique 4 (DN4) scale is administered before surgery, and the Quality of Recovery-15 (QoR-15) Scale is assessed before surgery as well as on the 1st and 7th days post-surgery. Three months after surgery, persistent postoperative pain will be inquired about.

Participant timeline

Table 1 presents the schedule for enrolment, interventions, assessments and visits for participants.

Sample size calculation

The sample size calculation is based on the incidence of rebound pain. According to previous studies, the incidence of rebound pain following shoulder surgery is approximately 40%. It is anticipated that the incidence of rebound pain can be effectively reduced to 30% in the intravenous group and to 20% in the perineural group. The total sample size of 399 cases was calculated using a 1:1:1 randomization scheme by PASS 15 software, with a two-sided test at $\alpha = 0.05$ and $\beta = 0.9$. Accounting for a 20% loss to follow-up, at least 501 subjects are needed, meaning at least 167 subjects are required in each group.

Recruitment

The schedule of major study activities for each study visit is presented in Figure 1. This study enrolled older patients scheduled to undergo gastrointestinal endoscopy under propofol sedation. Patients (meeting the inclusion criteria ($18 \leq \text{age} \leq 80$ years)) were preliminary screened by investigators and recruited via distributing recruitment materials to patients and their families. Additionally, we posted

recruitment posters in the wards explaining the benefits of our trial. The esketamine used in this trial is provided free of charge, and participation in the trial offers benefits to participants. The entire process of participant recruitment and consent collection conducted by the research team members will comply with GCP.

Allocation

Sequence generation

In this trial, we will use a stratified blocked randomization method to design the central randomization system. Complete baseline data will be collected from participants, including name, gender, date of birth, etc. After assessing patient eligibility for inclusion, his/her informed consent will be obtained. We will randomly assign the participants in a ratio of 1:1:1 to the control group or the additional groups according to the allocation sequence generated by the randomization system. The block size of the random sequence is six.

Concealment mechanism

After obtaining signed informed consent, participants will be randomly assigned to either the standard group or the additional group via a central randomisation system. The randomisation results, random numbers, and their corresponding group assignments will be kept confidential from participants throughout the entire trial. Both groups will receive an equal-volume injection of identical-colored solution into the veins and around the nerves. Participants will remain unaware of their own and other participants' group assignments before, during, and after shoulder surgery.

Implementation

A designated researcher will generate the allocation sequence, enroll participants, and assign them to interventions.

Blinding

After the interventions are assigned, both the researcher and the trial participants will be blinded. The results in the central randomisation system will be kept confidential from the participants throughout the entire trial. Both the control group and the additional group will receive the same volume of solution with identical color. The researcher will ensure that participants are not aware of their own assignment or that of other participants.

Procedure for unblinding if needed

In the event of a medical emergency that requires identification of an individual patient's treatment, investigators will be permitted to open the corresponding emergency envelope. This action must be justified and documented in both the patient's medical record and the case report form (CRF). Serious adverse events will be collected and recorded for further analysis at the end of the trial, and investigators will assess the correlation between these events and patients' healthcare records.

Data collection and management

Plans for assessment and collection of outcomes

This study is an internal multi-centre clinical trial. All physicians involved in data collection will receive specialized training from study assessors. We will hold regular online meetings to share trial progress and discuss issues encountered during the project. In addition, we will conduct on-site visits to subcentres to perform quality control checks. We will also organize trial data on a regular basis to identify any missing data. To further improve data quality, we plan to implement supplementary verification measures and conduct follow-up calls with participants.

Plans to promote participant retention and complete follow-up

We plan to promote participant retention and complete follow-up through in-person inpatient follow-up one day after surgery and telephone follow-up after hospital discharge.

Data management

All patient data collected during this clinical trial will be entered into the corresponding patients' case report forms (CRFs). The study number, subject number, date of subject information collection, and informed consent documentation will be properly recorded in each patient's CRF. We will archive source data in accordance with GCP guidelines. The data manager will be responsible for data processing and conduct regular monitoring in accordance with the sponsor's standard operating procedures to ensure that all data are accurate, adequate, and complete. Source data locking will only be performed after all quality assurance procedures have been completed.

Confidentiality

Participant information will be kept confidential and managed in accordance with the Data Protection Act, NHS Caldecott Principles, the Research Governance Framework for Health and Social Care, and the conditions of Research Ethics Committee approval. The confidentiality of data collected during the research will be strictly maintained, and only members of the trial team (or authorized individuals from the sponsor organization or trial-relevant center sites) will be granted access to the data. All documents containing participant information are stored in a locked designated cabinet in the anesthesia department, with controlled key access for safekeeping. Removal of, or access to, the data requires explicit permission from the principal investigator. Participants will each be assigned a unique trial identification number, and their personal details will be stored in a secure database maintained by professional research staff, and only the principal investigator is granted access to the

full data set. Anonymised trial data will not be shared with external researchers.

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

Not applicable as no biological specimens were collected as part of this trial.

Statistical methods

Statistical analysis for primary and secondary outcomes

Statistical analysis will be conducted using SPSS 26.0 (IBM, Armonk, NY, USA), adhering to the principle of intention-to-treat analysis. Values of $P < 0.05$ are considered statistically significant. Missing values will be imputed using the last observation carried forward for longitudinal variables, the median of non-missing values for non-longitudinal continuous variables, and the mode of non-missing values for categorical variables. The Shapiro–Wilk test will be utilized to assess the normality of individual variables. Data will be presented as mean (standard deviation), median (interquartile range [min-max]), or absolute numbers (proportion), as appropriate. The One-way ANOVA will be employed to analyze patient characteristics across the three groups.

The primary outcome, the incidence of rebound pain, will be evaluated among the three groups using the $R \times C \chi^2$ test on the full analysis set (FAS), with the per-protocol (PP) set analysis results serving as supportive analysis. Secondary outcomes will be tested based on the FAS set for analysis. The characteristics of rebound pain, NRS scores, and postoperative opioid consumption will be analyzed using one-way ANOVA if normal distribution and homogeneity of variance are met; if these conditions are not met, the Kruskal-Wallis test will be applied. The results of the scale can be determined by comparing groups using ANOVA or the Kruskal-Wallis test.

416 Adverse events related to esketamine or nerve block will be assessed using the R*C
417 χ^2 test.

418

419 **Interim analyses**

420 No plans for formal interim analyses are included in this study.

421

422 **Methods for additional analyzes (e.g., subgroup analyzes)**

423 The association between the rebound pain and postoperative persistent pain incidence
424 was examined using univariable- and multivariable-adjusted logistic regression
425 models. The results were presented as the odds ratios and corresponding 95%
426 confidence intervals.

427

428 **Methods in the analysis to handle protocol nonadherence and any statistical** 429 **methods to handle missing data**

430 Statistical analysis was performed following the intention-to-treat principle. All
431 outcome analyses will be conducted regardless of whether participants adhered to the
432 study protocol. We will first screen the frequency and type of missing data for all
433 variables. If missingness exceeds 5% for any variable, we will use multiple
434 imputation. In the event of missing data following imputation, a complete case
435 analysis will be performed as a sensitivity analysis.

436

437 **Plans to provide access to the full protocol, participant-level data, and statistical** 438 **code**

439 Not applicable as we have no plans to provide access to the full protocol,
440 participant-level data, and statistical code.

441

Oversight and monitoring

Composition of the coordinating center and trial steering committee

Zhenling Huang, Fuyu Liu and Wenqing Cao are the members of the trial steering committee, and Zhenling Huang is responsible for preparing and revising the protocol and disseminating any changes. Yifen Qu and Zhenling Huang are responsible for overseeing the study design and protocol and interpreting the study findings. Ping Huang and Zhiwei Fu are responsible for coordinating data collection and analysis and writing the scientific manuscript. Ping Huang, Fuyu Liu, Wenqing Cao, Yuhang Zhang, Qiuyue Lian, Xiaoqiang Wang participated in performing the experiment and collection of data. Jing Gao and are responsible for overseeing any statistical analyses and ensuring that the study implementation on the floor follows the protocol.

Composition of the data monitoring committee, its role, and reporting structure

The Data Monitoring Committee (DMC), comprising two independent experts from outside the study at the Clinical Research centre of Renji Hospital, will provide recommendations on safety and possess the authority to terminate the trial. Clinical experts will have access to unblinded data, and the DMC will oversee the progress and safety of the study. The final trial dataset will be under the management of Renji Hospital and the Shanghai Jiaotong University School of Medicine. Access to the dataset will require written permission from the corresponding author.

Adverse event reporting and harms

All severe adverse events related to the study intervention will be documented in the study database and reported as necessary to the Ethics Commission of Renji Hospital, Shanghai Jiaotong University School of Medicine.

Provisions for post-trial care

Participants will receive free treatment in the event of injury or damage related to our clinical research work.

Frequency and plans for auditing trial conduct

The investigators shall maintain all study data according to GCP requirements. The original study data and information will be retained for at least 5 years following trial completion. Data security and monitoring reports will be submitted to the ethical committee every 3 months.

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

This clinical trial will be conducted according to the ethical committee approval. Any problem or protocol modifications during the trial will be communicated to the ethical committees, trial participants, trial registries, journals, and regulators in a timely manner. The ethical committee's consent will be required to change the protocol.

Dissemination plans

The participants, healthcare professionals, the public, and other relevant groups in the form of articles will communicate the results of this trial.

Discussion

This pioneering study represents the first multi-centre, randomised controlled trial aimed at confirming the efficacy of esketamine administered intravenously, alone or in combination with local anaesthetics as adjuvants, in reducing the incidence of rebound pain among patients undergoing arthroscopic shoulder surgery. We anticipate that the intervention group will demonstrate a marked reduction in postoperative

rebound pain compared to the placebo group, and that the combination of esketamine with local anesthetics injected around the nerve will exhibit superior prophylactic efficacy against rebound pain.

To date, the mechanisms underlying rebound pain are not fully understood. Studies indicate that the occurrence of rebound pain ranges from 40% to 69.1% following the resolution of PNBs [20-22]. The average severity score of rebound pain after PNB resolution is 4.19 ± 2.0 , with 50.6% of patients experiencing severe pain [22]. This suggests that nearly half of the patients may face postoperative complications due to rebound pain, which clearly contradicts the concept of enhanced recovery after surgery (ERAS). The harm caused by rebound pain is evident, so the ultimate goal in addressing it should be the prevention of rebound pain [23].

In actual clinical practice, shoulder surgeries are predominantly conducted as day surgeries, and patients also require early postoperative functional recovery. Consequently, the anaesthesia method selected for shoulder arthroscopy is commonly a single-shot brachial plexus block, which, coincidentally, falls under the category of risk factors for rebound pain. Studies have indicated that single-shot peripheral nerve blocks have a higher probability of rebound pain compared to continuous peripheral nerve blocks [24], and rebound pain is more frequently observed in regions with relatively dense neural distribution (e.g., brachial plexus block, popliteal sciatic nerve block) [25,26]. Furthermore, prolonged exposure to high-volume, high-concentration local anesthetics may reduce blood flow in neural tissues [27], which might damage interfascicular vessels and lead to neural ischemia.

Recently, esketamine has been introduced as an adjuvant for nerve blocks, administered either by being combined with local anaesthetics or being injected intravenously, to exert analgesic effects and prolong the duration of the block. When

esketamine was combined with ropivacaine for ultrasound-guided sciatic and femoral nerve block in children with lower limb fractures, it could also effectively relieve postoperative pain and offered excellent anesthetic effects [28]. The question of whether NMDA-induced prolonged sensory blockade can lead to a reduced incidence of rebound pain remains a subject of debate. Touil et al. [8] investigated the efficacy of intravenous ketamine (0.3 mg/kg) in preventing rebound pain following peripheral nerve block, ultimately determining that it offered no advantage. In contrast, additional research has indicated that during anterior cruciate ligament reconstruction surgery, the combination of perineural ketamine with ropivacaine was more effective than intravenous ketamine alone in enhancing the analgesic effect of peripheral nerve block and diminishing rebound pain [29]. Compared to ketamine, esketamine is more favored in clinical settings because of its fewer mental symptoms such as fatigue, cognitive decline, attention impairment, and short-term memory disorders [13]. In terms of clinical research, the use of 0.5 mg/kg of esketamine combined with 0.375% ropivacaine at 0.3 ml/kg for ultrasound-guided sciatic nerve block and femoral nerve block in children with lower limb fractures can effectively reduce the incidence of complications and has good nerve block and anesthetic effects [28]. In elderly patients undergoing total hip replacement, a sub-anesthetic dose of esketamine (0.2mg/kg) administered intravenously combined with hip joint capsule block (PENG block) has good effects on intraoperative sedation and postoperative analgesia [30]. However, postoperative pain improvements are dissimilar between low and high esketamine doses. Given the potential adverse events associated with esketamine, a low dose may be more appropriate for postoperative pain control. This also served as the basis for the dose of esketamine (0.3mg/kg) utilized in this study.

This study will be the first to demonstrate the efficacy of intravenous or perineural esketamine in preventing postoperative rebound pain following arthroscopic shoulder surgery. The research highlights three primary strengths: First, it is the first systematic comparison of the effects of different administration routes of esketamine on rebound

pain. Second, as a pioneering multicenter trial with a large sample size, it significantly enhances the reliability and generalizability of the results. Third, the sub-anesthetic dose of esketamine (0.3mg/kg) is within clinically safe limits and has received international recognition, making it easily applicable in clinical settings. The results of this trial may provide high-quality evidence to guide clinical practice in preventing rebound pain after shoulder surgery, ultimately improving patient recovery outcomes and satisfaction.

Trial status

Trial registration: Chictr.org.cn, ChiCTR2400089564. Registered on 11 September, 2024. The latest protocol version 3.0 (approved in Sep 2024) was uploaded on the website of trial registration. This study started in Oct 2024, and the recruitment phase is currently ongoing.

Abbreviations

ASA = American Society of Anesthesiologists; BMI = body mass index; BIS = bispectral index; CONSORT = Consolidated Standards of Reporting Trials; CRF = case report form; DN4 = Douleur Neuropathique 4; FAS = full analysis set; IQR = interquartile range; NRS = Numerical Rating Scale; NMDA = N-methyl-D-aspartate; PNB = peripheral nerve block; PACU = postanesthesia care unit; PCIA = patient-controlled intravenous analgesia; PP = per-protocol; QoR-15 = Quality of Recovery-15; SD = standard deviation; SPIRIT = Standard Protocol Items: Recommendations for Interventional Trials.

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contributions to this trial.

Authors' contributions

ZLH conceived the study idea. YFQ and ZLH led the proposal and design of the study and developed the protocol, the trial database and case report forms. PH and ZF shared first authorship and contributed to the final manuscript. FL, WC, JG, YZ, QL, XW participated in performing the experiment and collection of data. JG contributed to the sample size estimations and statistical design of the RCT. All authors have read and approved the final manuscript.

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Availability of data and materials

The participant-level dataset is not available for public access due to Chinese data protection laws and regulations. The statistical code can be provided upon request to the corresponding author.

Declarations

Ethics approval and consent to participate

This clinical trial was approved and supported by the Ethics Commission of Renji Hospital Shanghai Jiaotong University School of Medicine (LY-2024-178A), the Ethics Commission of Linyi City People's Hospital (202410-H-020) and the Ethics Commission of The Fourth Affiliated Hospital of Nanjing Medical University

(20240825-K120). All participants will provide written informed consent prior to enrolment.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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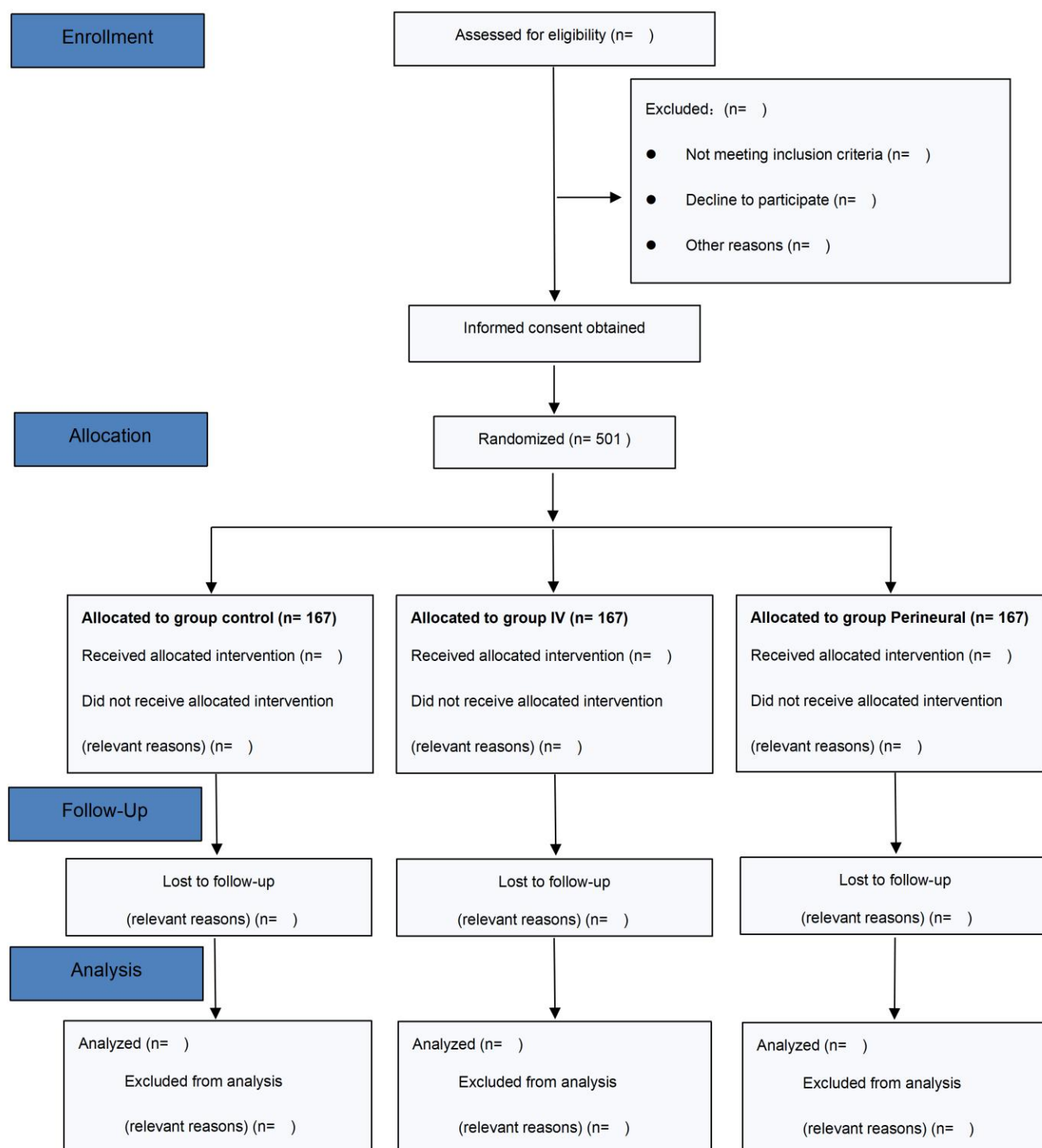
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718 Table 1. The standard protocol items of this study.

	STUDY PERIOD						
TIME POINT	1 Day before surgery-in the ward	Day of surgery-in the PACU	Within 24h post-surgery	POD 3	POD 5	POD 7	3 months after surgery
ENROLLMENT							
Eligibility screen	X						
Informed consent	X						
Demographic data collection	X						
DN4 scale	X						
Randomization	X						
Allocation	X						
INTERVENTIONS							
Control group		X					
Intravenous group		X					
Perineural group		X					
ASSESSMENT							
Rebound pain (including its characteristics)			X				
Block duration			X				
Adverse of nerve block			X				
Adverse of esketamine			X				
DN 4 scale			X			X	X
QoR-15 scale			X			X	
NRS score				X	X	X	X
Rescue opioid consumption				X	X	X	X
Postoperative persistent pain							X

719 Figure 1. The flowchart of this study.



720 The PRO EDI characteristics of included participants table

Item	Mandatory or depends on review?	Explanation
Age	Inclusion criteria: 18–80 years. No mean or median age is reported in the protocol.	Protocol section "Participants' eligibility criteria": Age 18–80 years.
Sex	Not explicitly reported as "sex" in the protocol, and both male and female patients are included in this study. The protocol mentions no specific inclusion/exclusion criteria based on sex.	Protocol does not report sex distribution. Corrected to "sex" by the review team — protocol uses general terms without specifying sex or gender.
Gender	Not reported. The protocol does not include any gender-related data collection or reporting.	Not applicable in this protocol.
Sexual identity	Not reported. The protocol does not include any sexual-related data collection or reporting.	Not applicable for this review (item: depends on review).
Race, ethnicity and ancestry	Not reported. The study is conducted in China (three tertiary hospitals in Shanghai, Shandong, and Jiangsu provinces). No race/ethnicity/ancestry data collection is described.	Protocol does not collect or report ethnicity data. Study location: China.
Socio-economic status (SES)	Not reported. No SES-related inclusion/exclusion criteria or data collection described.	Not reported in the protocol.
Level of education	Not reported. The any level of education-related data collection described.	Not applicable for this review (item: depends on review).
Disability	Exclusion criteria indirectly address some disability-related factors: pre-existing neurological damage in the surgical area, symptoms of peripheral neuropathy associated with diabetes, history of neurological/neuromuscular disorders, history of psychiatric disorders. ASA physical status I–III (i.e., no severe systemic disease that is a constant threat to life).	Protocol exclusion criteria and ASA I–III inclusion criteria. Not applicable for this review (item: depends on review).
Location (country/countries of data collection and site coordination)	Country of data collection: China. Recruitment sites (3 tertiary hospitals): 1. Renji Hospital, Shanghai Jiaotong University, Shanghai, China. 2. Linyi People's Hospital, Shandong Second Medical University, Shandong Province, China. 3. The Fourth Affiliated Hospital of Nanjing Medical University, Jiangsu Province, China. Study coordination site: Renji Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai, China. Urban setting (all three hospitals are located in urban areas; not explicitly stated	Protocol sections "Study setting" and "Author details".

	as "urban" but inferred from tertiary hospital status).	
Other factors relevant to the review	ASA physical status: I–III. BMI: 18–30 kg/m². Surgical procedure: Scheduled for unilateral arthroscopic shoulder surgery. Exclusion of patients with: contraindications for nerve block, prolonged administration of sedatives/analgesics/steroids, history of ipsilateral shoulder surgery, allergy to ropivacaine/esketamine/chronic pain medications, history of diagnosed pulmonary diseases. Sample size: 501 participants (167 per group, 3 groups: Control, Intravenous, Perineural group).	Protocol sections "Participants' eligibility criteria" and "Sample size calculation".

Supplementary Files

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- [Table1.Thestandardprotocolitemsofthisstudy.docx](#)