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Effects of S-ketamine on recovery quality in elderly patients with impaired intrinsic capacity after total knee arthroplasty: a single-centre, randomised, double-blind, placebo-controlled study protocol

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ABSTRACT

Introduction Elderly patients with impaired intrinsic capacity are at increased risk for delayed or suboptimal recovery from surgery. S-ketamine has been proven to improve postoperative recovery quality. However, limited trials are studying the postoperative recovery quality in elderly patients with impaired intrinsic capacity. Therefore, the objective of this study was to evaluate the impact of S-ketamine on the quality of recovery in elderly patients with impaired intrinsic capacity following total knee arthroplasty.

Methods and analysis This is a single-centre, randomised, double-blind, placebo-controlled trial. Participants undergoing total knee arthroplasty will be randomly assigned in a 1:1 ratio to either the S-ketamine group (n=80) or the placebo group (n=80). The S-ketamine group will undergo an intravenous infusion of S-ketamine administered at a dosage rate of 0.2 $mg \cdot kg^{-1} \cdot h^{-1}$ for 1 hour. The placebo group will receive an intravenous saline infusion at an identical rate and duration. Postoperatively, the S-ketamine group will continuously infuse S-ketamine for 48 hours using a patient-controlled intravenous device, with a fixed rate of 0.01 $mg \cdot kg^{-1} \cdot h^{-1}$, a bolus dose of 0.02 $mg \cdot kg^{-1}$, a lockout period of 10 min and a maximum infusion rate of 0.13 $mg \cdot kg^{-1} \cdot h^{-1}$. In contrast, the patient-controlled intravenous device for the placebo group will not contain S-ketamine. The primary outcome is the quality of recovery scores at 24 hours following total knee arthroplasty. Secondary outcomes encompass quality of recovery scores at 48 and 72 hours postoperatively, pain scores at rest and during movement, oral morphine equivalents, sleep quality assessments, depression scores, the Barthel Index and the time to meet discharge criteria.

Ethics and dissemination Approval for the trial was granted by the Medical Ethics Committee of The Affiliated Hospital of Qingdao University (QYFYEC2024-74). Written informed consent will be obtained from each patient before enrolment. The results of this trial will be presented at scientific conferences and in peer-reviewed scientific journals.

Trial registration number ChiCTR2400087028.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study employs a randomised controlled trial design, which effectively mitigates bias and enhances the reliability and validity of the findings.
⇒ The study focuses on older patients with intrinsic capacity impairments, thereby addressing existing research gaps for this specific population and offering more targeted guidance for clinical practice.
⇒ A multimodal approach is employed in the analysis of the primary outcome of this study to adjust for potential confounding variables and to ensure the validity of the trial results.
⇒ Due to the short follow-up period in the study, the long-term effects of S-ketamine could not be evaluated.

INTRODUCTION

Background and rationale

Healthy ageing and intrinsic capacity

The global elderly population is experiencing a notable increase, with the ageing trend becoming more pronounced in numerous countries. Data from the WHO indicate that by 2030, the worldwide population aged 60 and older is projected to reach 1.4 billion. In response to this trend, the WHO introduced the concept of 'Healthy Ageing' in the 2015 Global Report on Ageing and Health, which is characterised by the cultivation and preservation of functional ability to promote well-being in the elderly population.[1 2] The functional ability is influenced by intrinsic capacity (IC) and the external environment, as well as the dynamic interplay between the two. IC is characterised by the composite of physical and mental capacities that an individual can employ. IC encompasses five

essential domains: locomotion, vitality, cognition, psychological and sensory.[3] The five domains are interconnected and inseparable, and damage to any one domain may directly or indirectly affect the others.[4 5]

A cohort study revealed that a significant proportion of individuals aged 65 and above experience declines in one or more domains of IC.[6] A higher level of IC is associated with a decreased likelihood of experiencing frailty, falls, health decline, functional impairment and mortality among older adults.[7–9] Conversely, a lower level of IC may impede functional abilities in this population, resulting in various negative consequences including frailty, pneumonia, cognitive deficits, falls, disabilities, functional limitations, heightened mortality rates, depression and increased economic burdens.[10–14] In conclusion, the preservation of high and stable IC is crucial for maintaining functional abilities in the elderly population.[15]

Mechanisms and predisposing factors of intrinsic capacity decline

At present, there is a lack of comprehensive understanding regarding the mechanisms contributing to the decrease in IC. Studies indicate a strong correlation between chronic inflammation and the decline in IC.[16] Elevated levels of inflammation-related biomarkers in the elderly are linked to decreased baseline levels of IC and a more rapid deterioration of IC over time.[17] Tumour Necrosis Factor Receptor 1, interleukin-6 and C-reactive protein have been identified as potential biomarkers for the decline in IC among older adults.[16–19] Inflammatory factors have been shown to directly initiate muscle spasms and impede the action of growth factors in skeletal muscle, ultimately leading to a reduction in muscle strength and the development of mobility disorders.[20–23] Furthermore, mitochondrial dysfunction has been implicated in the decline of muscle function by promoting inflammation, cellular senescence, apoptosis and disturbances in energy metabolism.[24 25]

The decrease in an individual's IC is shaped by a variety of factors, including life course factors such as age-related physiological changes, health behaviours, the presence of illnesses and socioeconomic factors at various points in life.[26] A study conducted on a nationally representative sample of individuals in China revealed a significant correlation between adverse early life factors, including malnutrition, poor health, poverty and decreased IC in later life.[26] A research investigation on elderly individuals left behind in rural regions of China revealed that social isolation can have a direct impact on diminished physical activity, increased levels of anxiety and depression, as well as cognitive deterioration, ultimately leading to a decline in IC.[27]

Intrinsic capacity decline and delayed recovery

Physical resilience emphasises an individual's ability to effectively manage stress, with IC being a determinant factor of physical resilience.[28] Furthermore, IC serves as a comprehensive measure of physiological reserve, which is a fundamental determinant of an individual's ability to withstand stress.[28] Individuals with lower IC are more vulnerable to adverse environmental factors, increasing their likelihood of experiencing poor recovery outcomes or disability on exposure to stressors.[29] The process of recovery following surgery and anaesthesia is intricate and involves multiple facets.[30] Elderly patients with compromised IC are at an increased risk of experiencing delayed or suboptimal postoperative recovery when subjected to the stressors associated with surgery and anaesthesia (figure 1). Decreased quality of recovery is associated with heightened patient complications, diminished quality of life, reduced patient satisfaction and decreased utilisation of healthcare resources.[31 32]

The rationale of s-ketamine improving recovery quality in patients with decreased intrinsic capacity

S-ketamine is an N-methyl-D-aspartate receptors (NMDARs) antagonist that exhibits approximately twofold greater affinity for NMDARs in comparison to ketamine.[33] Two recent meta-analyses have demonstrated that S-ketamine can effectively alleviate early postoperative pain.[34 35] Therefore, in elderly patients with decreased IC, S-ketamine may have a positive impact on locomotion domains by reducing postoperative pain and promoting early mobility. S-ketamine demonstrates neuroprotective effects through a range of mechanisms, such as diminishing neuroinflammation,[36] enhancing hippocampal neuronal plasticity,[37] reducing oxidative stress and neuronal apoptosis,[38] and suppressing circulating branched-chain amino acid levels.[39] Prior research conducted by our team has demonstrated that S-ketamine effectively decreases the occurrence of postoperative delirium in elderly patients undergoing total knee replacement.[40] Therefore, S-ketamine may exert positive effects on the cognitive domain through neuroprotective effects in elderly patients with impaired IC.[41] S-ketamine, known for its rapid antidepressant effects, is linked to the facilitation of synaptic plasticity and the restoration of neurotransmitter equilibrium. This process can elevate dopamine levels in the ventral striatum and caudate nucleus, consequently activating limbic system regions and eliciting sensations of joy and contentment among individuals.[42 43] Therefore, S-ketamine may have a beneficial impact on the psychological domain of elderly patients with diminished IC through its antidepressant properties. In conclusion, S-ketamine has the potential to impact various domains in elderly patients with diminished IC for improvement in postoperative recovery quality.

Objectives

Numerous studies have indicated that the intraoperative administration of low-dose S-ketamine can enhance the postoperative recovery quality in patients.[44 45] However, there is a lack of research in evaluating the impact of S-ketamine on postoperative recovery quality in elderly patients with diminished IC. This study hypothesises that the administration of S-ketamine may enhance the

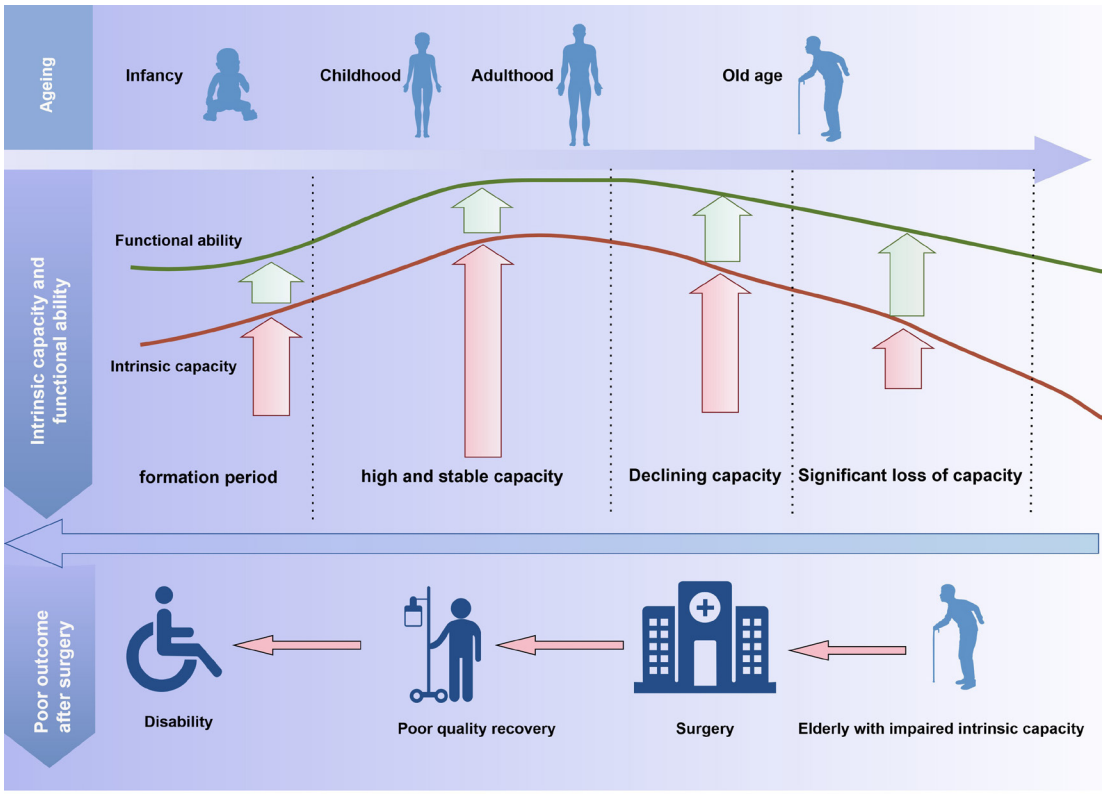

Figure 1 Intrinsic capacity and functional ability are not static but tend to diminish with advancing age, primarily due to underlying pathological conditions and the natural ageing process. Elderly patients with diminished intrinsic capacity may encounter delayed or suboptimal recovery following surgical procedures, potentially resulting in subsequent disability.

postoperative recovery quality in elderly patients with impaired IC.

METHODS

Trial design and study setting

This study is a single-centre, prospective, double-blind, randomised, placebo-controlled trial that is scheduled to take place at The Affiliated Hospital of Qingdao University. Participants meeting the eligibility criteria will be randomly allocated to either the S-ketamine or placebo group in a 1:1 ratio (figure 2). We report this study protocol according to the Standard Protocol Items: Recommendations for Interventional Trial guidelines.

Eligibility criteria

Inclusion criteria

(1) Age is greater than or equal to 60 years; (2) American Society of Anesthesiologists (ASA) classes I–III; (3) elective total knee arthroplasty (TKA) under intraspinal anesthesia; (4) patients with impaired IC, as indicated by a comprehensive IC score of 8 points or less.

Exclusion criteria

(1) Intraspinal anaesthesia failed; (2) past surgeries on the same knee; (3) severe cardiocerebrovascular disease, such as grade III hypertension, significant valvular disease, chronic heart failure, severe arrhythmia, ischaemic heart disease and stroke; (4) severe liver or kidney disease, such as a Child-Pugh score of C or a creatinine clearance rate below 30 $mL \cdot min^{-1}$; (5) contraindications for the administration of S-ketamine include refractory hypertension, pulmonary heart disease, hyperthyroidism, epilepsy, increased intraocular pressure, increased intracranial pressure, history of cerebrovascular accident, allergy and a family history of malignant hyperthermia; (6) patients with a high risk of malignant hyperthermia, such as those with strabismus and scoliosis; (7) patients who cannot cooperate or provide informed consent.

Drop-out criteria

Participants may withdraw from the trial, including but not limited to (1) the investigator deems it necessary to halt the trial due to ethical considerations; (2) the occurrence of severe adverse events renders the participant unsuitable to proceed with the trial; (3) the investigator determines that withdrawing from the study would be in the best interest of the participant; (4) poor adherence to the study protocol and (5) the participant retains the option to discontinue participation in the trial at any point, either by withdrawing their informed consent or by opting not to receive the study intervention.

Recruitment

Between July 2024 and July 2025, this trial plans to enrol participants at The Affiliated Hospital of Qingdao University. Anaesthesiologists will disseminate information about

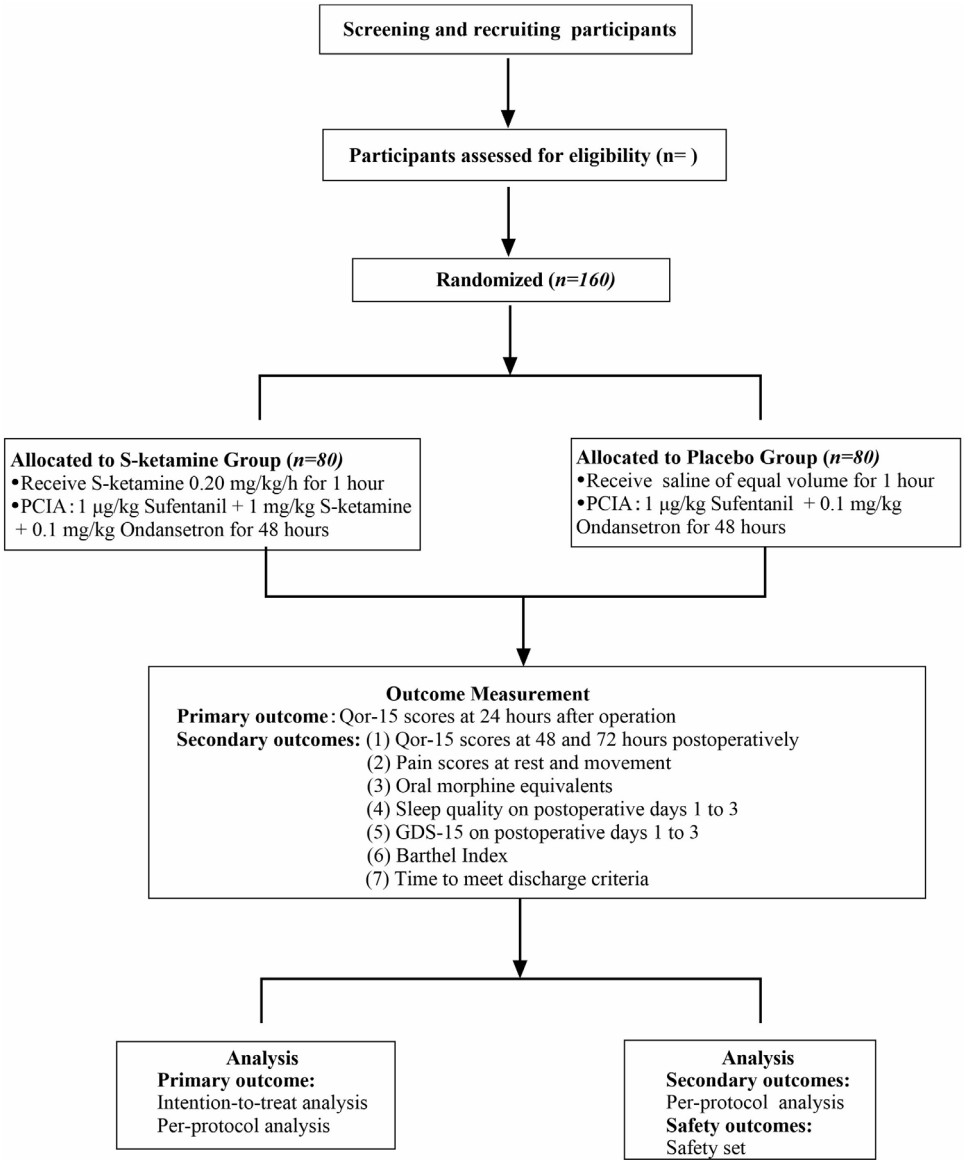

Figure 2 Consolidated standards of reporting trials (CONSORT) flow diagram. GDS, Geriatric Depression Scale; PCIA, patient-controlled intravenous analgesia.

the clinical trial to patients through various mediums, such as posters and brochures, in outpatient departments specialising in orthopaedics or anaesthesiology. Additionally, surgeons may extend invitations to eligible patients during clinical consultations.

Sample size

The primary outcome of this study is the Quality of Recovery-15 (QoR-15) scores at 24 hours following TKA. According to the findings of our pilot study, elderly patients with diminished IC in the placebo group exhibited an average QoR-15 score of 99, with a SD of 17. Based on prior studies, the minimal clinically important difference for postoperative QoR-15 scores was established at 8.[46] In the S-ketamine group, we hypothesise that the QoR-15 score at 24 hours following TKA for elderly patients with decreased IC will be 107, with a standard deviation (SD) of 17. Using Power Analysis and Sample Size V.15.0 (Stata Corp., LP, College Station, TX, USA), we determined that each group should consist of 72 participants, based on a significance level (α) of 0.05 and a power (1–β) of 80%. Considering a 10% dropout rate, each group should have at least 80 participants, totalling 160 participants for the study.

Randomisation and allocation concealment

A clinical trial centre staff member, independent of all other aspects of the trial, generated a random allocation sequence in a 1:1 ratio using R (V.4.3.1). The block randomisation process based on the order of enrolment will follow a predefined block design with varying block sizes of 2, 4, 6 and 8, ensuring unpredictability while maintaining group balance. The randomisation scheme will be securely stored within sealed, opaque envelopes. Quality controller will open the envelopes following the order of enrolment before the commencement of the trial,

assigning participants to their respective groups based on the scheme contained within. These quality control personnel will not be involved in any other aspects of the trial.

Blinding

This study follows a double-blind design for both participants and investigators. To maintain investigator blinding, the drug administrator will prepare two identical syringes containing either S-ketamine at a concentration of 2.0 mg·mL^{-1} or 0.9% saline, each totalling 20 mL. The Drug Administrator will also configure the patient-controlled intravenous analgesia (PCIA) devices according to the participant's allocation scheme. The PCIA devices will not display detailed information about the drugs to maintain participants' blinding. The outcome assessors and statistical analysts will remain blind to the participant's assignment and intervention received during the trial. An independent data and safety monitoring committee will supervise the process and refrain from revealing participant allocation until after the statistical analysis is finalised. During emergency scenarios, such as the rapid deterioration of the patient's clinical condition, the anaesthesiologist may seek to unblind the participant's intervention or modify or cease the infusion of the study drug. These occurrences will be documented. Unblinded participants will be included in the intention-to-treat (ITT) analysis set but excluded from the per-protocol (PP) analysis set.

Assessment of intrinsic capacity

We will comprehensively assess the five dimensions of IC proposed by WHO 1 day before surgery, including locomotion, vitality, cognition, psychological and sensory. This study has selected the following methods for evaluating the five dimensions of IC: cognitive (time orientation, memory and processing),[47] locomotion (walking speed, sit-to-stand test and balance),[48] vitality (nutrition),[49] sensory (hearing and vision)[50] and psychological (depression).[51]

Cognition

Cognitive function is assessed using the Mini-Mental State Examination (MMSE), which consists of 30 questions. It evaluates various aspects of cognitive function including immediate memory, orientation to time and place, delayed recall, language, visuospatial abilities, attention and calculation skills. The maximum score on the MMSE is 30, with higher scores indicating better cognitive abilities.[47] Scores are classified into three categories: severe cognitive impairment (≤9), mild to moderate cognitive impairment (10–26) and normal cognitive function (27–30).

Locomotion

Locomotion is assessed using the Short Physical Performance Battery,[48] which includes three components: standing balance, chair stands and walking speed tests. Each component is scored on a scale from 0 to 4, with a maximum total score of 12. For the balance assessment, we assess whether patients can maintain three different standing positions for 10 s each: feet together, semi-tandem and tandem. A score of '1' will be given if the participant can maintain feet together but not the semi-tandem standing position for 10 s. A score of '2' will be given if the participant can maintain the semi-tandem standing position for 10 s but not the tandem standing position for more than 3 s. A score of '3' will be given if the participant can maintain the semi-tandem standing position for more than 10 s and the tandem standing position for 3–9 s. A score of '4' will be given if the participant can maintain the tandem standing position for 10 s. For the walking test, we assessed the patient's walking speed for 4 m on flat ground, repeating the test twice and selecting the shortest time as the test result. Scores are categorised based on the time taken: 1 point for over 8.70 s, 2 points for 6.21–8.70 s, 3 points for 4.82–6.20 s and 4 points for under 4.82 s. For the chair standing test, there are two tests consisting of a single standing and five standing. For the single standing, patients cross their arms and stand up once from a seated position. Scores are assigned as follows: 0 points if the single standing is not completed or if the time for five standing exceeds 60 s, 1 point for a time between 16.70 and 60 s for five standing, 2 points for a time between 13.70 and 16.69 s, 3 points for a time between 11.20 and 13.69 s and 4 points for a time under 11.19 s. After completing these assessments, the scores from all three components are summed. A total score of ≤2 indicates moderate to severe impairment in locomotion, 3–9 points indicate mild to moderate impairment and 10–12 points indicate normal locomotion. In this study, a score of ≤9 points indicates a decline in the locomotion domain.

Vitality

In the vitality domain, we will measure by using the Mini Nutritional Assessment Short Form, a 6-item screening questionnaire validated as a sensitive tool for rapid nutritional screening. The highest score is 14 points, with scores less than 8 indicating malnutrition and scores between 8 and 11 indicating a risk of malnutrition.[49]

Sensation

The sensory domain primarily includes auditory and visual functions, assessed through self-report methods. Visual function is primarily assessed by asking elderly patients, 'How do you feel about seeing things at a distance? For example, can you recognize a friend across the street (with or without glasses)?' Hearing function is assessed by asking elderly patients, 'How is your hearing?' In this study, impairment in either hearing or vision scores 1 point, while impairment in both scores 0 points.

Psychological

In the psychological domain, assessment is conducted using the 15-item Geriatric Depression Scale (GDS-15),[51] which consists of 15 questions with a total score of 15

points. Mild depression is defined as a GDS-15 score ≥5, while severe depression is defined as a score ≥10.

A composite score for intrinsic capacity

López-Ortiz *et al*[52] proposed a composite score for IC, integrating cognitive, locomotion, vitality, sensory and psychological dimensions into a single measure. Each dimension is assessed on a scale ranging from 0 to 2, with 0 indicating severe impairment, 1 indicating partial impairment and 2 indicating minimal impairment or normal function. The total IC score ranges from 0 (worst) to 10 (best). The present study employs a consistent calculation method where the total IC score is derived by summing the individual scores for locomotion, vitality, cognitive, psychological and sensory domains. The scores from all dimensions are summed to form a complete IC score, where 0–4 indicates severe disability or dependency on care, 5–8 indicates functional decline and 9–10 indicates high and stable IC. Lower scores indicate a more pronounced decline in IC and ≤8 points denote IC decline in this study.

Anaesthesia procedure and pain management

Patients will receive 200 mg of oral celecoxib capsules (Celebrex Pfizer Pharmaceuticals Co, Shanghai, China) 1 day before the scheduled surgical procedure. On admission to the anaesthesia induction room, routine monitoring will be conducted, which includes an ECG, systolic blood pressure, diastolic blood pressure and pulse oximetry saturation. All participants will undergo an ultrasound-guided adductor canal block. The effectiveness will be assessed by the absence of cold sensation in the distribution area of the saphenous nerve 30 min after the nerve block. Following the completion of the nerve block, participants will be transported to the operating room for intraspinal anaesthesia. Anaesthesiologists can choose various types of intraspinal anaesthesia according to actual conditions, including spinal anaesthesia, continuous epidural anaesthesia and combined spinal–epidural anaesthesia. Intraspinal anaesthesia will be administered at the $L_{3/4}$ or $L_{2/3}$ intervertebral space, utilising either a straight or lateral approach. The efficacy of intraspinal anaesthesia will be evaluated based on the absence of cold sensation at the T_{10}–T_{12} level. During the surgical procedure, the anaesthesiologist may opt for a suitable medication regimen through clinical assessment. However, the anaesthesia team should follow the guidance of the drug administrator regarding the use of study drugs, avoiding the use of open-label S-ketamine and other NMDARs antagonists. Before prosthesis implantation, the surgical team will administer a drug mixture consisting of 100 mg of ropivacaine hydrochloride injection (AstraZeneca Pharmaceutical Co, Jiangsu, China), 2 mg of compound betamethasone injection (Hangzhou MSD Pharmaceutical Co, Hangzhou, China) and 0.9% normal saline (total volume: 20 mL) into the posterior capsule, collateral ligament, retinaculum, quadriceps tendon, fat pad and subcutaneous tissue.

In the postanaesthesia care unit, the PCIA device will be initiated. At our centre, we employ a limited use of opioids for the management of postoperative analgesia via PCIA devices, which constitutes our normal practice. On discharge to the general ward, patients will be scheduled to receive the first dose of acetaminophen oxycodone tablet 5 mg (Fujian Minglong Pharmaceutical Co, Fujian, China) orally 2 hours postoperatively, followed by subsequent doses administered every 8 hours, totalling up to three doses within a 24-hour timeframe. Participants will be permitted to self-administer bolus doses via the PCIA device at 10 min intervals when their Numeric Rating Scale (NRS) pain score is ≥4. If pain relief is not achieved with the maximum dose allowed by the PCIA device, participants will be given an intramuscular injection of 50 mg meperidine (Qinghai Pharmaceutical Factory Co, Qinghai, China), which may be repeated every 6 hours, up to a maximum cumulative dose of 300 mg.

Intervention

Five minutes after the completion of intraspinal anaesthesia, the S-ketamine group will be administered an intravenous infusion of S-ketamine hydrochloride injection (Jiangsu Heng Rui Medicine Co, Jiangsu, China) following a standard dilution protocol (40 mg S-ketamine diluted in 0.9% saline to a total volume of 20 mL, concentration of 2.0 $mg \cdot mL^{-1}$). The infusion rate is set at 0.1 $mL \cdot kg^{-1} \cdot h^{-1}$ (equivalent to 0.2 $mg \cdot kg^{-1} \cdot h^{-1}$), with a total infusion duration of 1 hour. Participants in the placebo group will be administered an intravenous infusion of 0.9% saline at the same rate and duration as that of the S-ketamine group. After the surgical procedure, PCIA devices in the S-ketamine group are filled with sufentanil citrate injection (Yichang Renfu Pharmaceutical Co, Hubei, China) at a dosage of 1.0 $\mu g \cdot kg^{-1}$, S-ketamine at a dosage of 1.0 $mg \cdot kg^{-1}$ and ondansetron hydrochloride injection (Qilu Pharmaceutical Co, Shandong, China) at a dosage of 0.1 $mg \cdot kg^{-1}$, which were subsequently diluted to a total volume of 100 mL with saline solution. In the placebo group, the PCIA devices are configured to administer sufentanil citrate injection at a dosage of 1.0 $\mu g \cdot kg^{-1}$ and ondansetron hydrochloride injection at a dosage of 0.1 $mg \cdot kg^{-1}$. The PCIA device was set to deliver a continuous background infusion of 1 $mL \cdot h^{-1}$, a bolus dose of 2 mL, a lockout period of 10 min and a maximum infusion rate of 13 $mL \cdot h^{-1}$. PCIA devices have an operational duration of 48 hours.

Strategies to improve intervention adherence

During the recruitment and screening phase, the investigator will provide a comprehensive overview of the study's objectives, the drug intervention, the research protocol, the trial process and the drug delivery plan. Additionally, the investigator will outline the clinical assessments, the potential risks and benefits associated with participation and the compensation offered. This thorough dissemination of information aims to ensure that each participant is fully informed before consenting to participate, thereby

enhancing adherence to the study protocol. Before the commencement of the trial, the Quality Controller and Drug Administrator will meticulously verify the participant's identification number, randomisation group, dosage and pump speed. Following the intervention, these investigators will conduct a thorough inventory of the remaining research drugs, empty packaging and drug delivery devices.

Outcomes

Primary outcome

The primary outcome is the quality of recovery score at 24 hours following TKA, as evaluated through the QoR-15 questionnaire.

Secondary outcomes

1. The QoR-15 scores at 48 and 72 hours postoperatively.
2. The pain scores will be documented using the NRS during periods of rest and movement on days 1–3 after surgery, from 8:00 to 10:00 and 16:00 to 18:00. Resting pain is defined as the participant lying quietly in the supine position, while movement pain is defined as the participant lifting the affected limb at least five times to a height of at least 30 cm.
3. Total consumption of rescue analgesic medication will be evaluated. Rescue analgesic medication (sufentanil and meperidine) will be converted to oral morphine equivalents (OME).
4. Sleep quality on postoperative days 1–3 will be assessed using the NRS.
5. Depression scores on postoperative days 1–3 will be assessed using the GDS-15.
6. The Barthel Index will be assessed at discharge.
7. The time to meet discharge criteria will be recorded. Discharge criteria are defined as the participant's ability to independently walk from the bed to the bathroom and walk along the corridor without assistance.

Safety outcomes

Adverse events will be observed from the intervention period to 48 hours after surgery or until the resolution of any adverse event. Nausea and vomiting will be continuously monitored for 48 hours following the surgical procedure. Hypertension is characterised by a systolic blood pressure exceeding 180 mm Hg or a rise of over 20% from the baseline, while hypotension is defined by a systolic blood pressure below 90 mm Hg or a decrease of more than 20% from the baseline. Bradycardia is characterised by a heart rate of less than 45 beats per minute, whereas tachycardia is characterised by a heart rate exceeding 100 beats per minute. Hypoxaemia is defined as a blood oxygen saturation level below 90% without supplemental oxygen. Psychotic symptoms, potentially induced by S-ketamine, including dizziness, hallucinations (visual, auditory and somatic), nightmares, delirium, agitation and dissociative symptoms, will be observed and recorded. Additionally, complications related to nerve blocks, such as local anaesthetic toxicity and nerve injury, as well as surgical complications, including infections, thrombotic events and hospital readmissions, will be systematically documented.

Trial safety

Elderly patients (aged ≥60 years) with an IC score of ≤8 frequently present with comorbidities, including cardiovascular and cerebrovascular diseases, thereby increasing their susceptibility to adverse events associated with S-ketamine. This study will employ strategies to balance the potential therapeutic benefits against the inherent risks.

Before the study enrolment, all participants, or their legal representatives, will be provided with detailed information about the study's objectives, procedures, investigational drug, potential benefits and possible adverse effects. The research team will ensure a thorough explanation before obtaining written informed consent, explicitly informing participants that they may withdraw from the study at any time without affecting their subsequent medical care.

The dosage and administration regimen of S-ketamine will be determined based on prior literature,[44 45] previous research findings[40 53] and prescribing information, with consideration of the physiological characteristics of elderly patients to optimise efficacy and minimise adverse effects. A quality control officer will verify the medications and emergency equipment prior to the trial to ensure their completeness and efficacy. During the study, participants will be continuously monitored for blood pressure, heart rate and oxygen saturation. The research team, consisting of clinicians with extensive experience and specialised training in critical care, will ensure a prompt and effective response to emergencies while prioritising participant safety.

Management of adverse events

The management of adverse reactions of S-ketamine should primarily address its cardiovascular and neuropsychiatric impacts. In the event of cardiovascular complications, such as hypertension (eg, blood pressure >180/110 mm Hg), immediate electrocardiographic monitoring is necessary and other potential causes should be excluded. Beta-blockers (eg, esmolol) are the first-line agents for blood pressure control, with calcium channel blockers considered if further intervention is required. For sympathomimetic-induced tachycardia, beta-blockers (eg, esmolol) should be administered to regulate heart rate, while lidocaine or amiodarone may be used to treat concomitant ventricular arrhythmias. Sympathomimetic-induced sweating or tremors may be managed by adjusting the ambient temperature, administering fluids and using low-dose atropine. For neuropsychiatric effects, if S-ketamine–induced symptoms such as dizziness, hallucinations, agitation or dissociation occur, vital signs should be closely monitored. The severity of the symptoms should be promptly assessed to identify any serious disturbances of consciousness, including severe delirium or seizures. Mild symptoms should be

managed by minimising external stimuli, reassuring the patient and providing explanations to stabilise emotional state. Moderate to severe symptoms may require intravenous benzodiazepines (eg, midazolam), with haloperidol added if necessary for enhanced symptom control. If nausea and vomiting occur, the underlying cause should be determined, and the risk of dehydration or aspiration assessed. In severe cases, rescue antiemetic agents such as droperidol should be administered.

Postoperatively, patients should undergo continuous monitoring in the PACU, with particular attention to hypertension, tachycardia, respiratory depression, psychiatric symptoms and nausea or vomiting to ensure a stable transition to the general ward. Continuous monitoring should be maintained for at least 48 hours in the ward, including electrocardiographic assessment, oxygen saturation measurement and blood pressure monitoring. In the event of cardiovascular instability (eg, persistent hypertension, tachycardia or arrhythmias), beta-blockers or antiarrhythmic agents should be administered as appropriate. Persistent or worsening psychiatric symptoms may necessitate further intervention with benzodiazepines or antipsychotic agents. A structured management approach enables the timely identification and treatment of S-ketamine–related adverse effects, optimising patient safety and recovery.

Adverse event reporting

Adverse events are defined as any unfavourable medical occurrences experienced by participants following the administration of the investigational drug, regardless of their potential association with the drug. These events may manifest as symptoms, signs, diseases or laboratory test abnormalities. In this study, adverse event recording will commence immediately on participant signing of the informed consent form and will continue throughout the trial until its conclusion. All adverse events, whether observed by the investigators or self-reported by participants, must be documented and reported clearly and concisely. During the study, the research team will inquire if participants have experienced any adverse events. All adverse events will be managed in strict accordance with the standard operating procedures established by the clinical trial centre. Adverse event data will be systematically recorded in the designated section of the Case Report Form, including the time of occurrence, severity, duration, interventions implemented and final outcome.

Serious adverse events are defined as those meeting any of the following criteria: resulting in death, life-threatening, leading to permanent or severe disability or loss of function, requiring hospitalisation or prolonged hospitalisation, causing congenital abnormalities or birth defects or other events deemed medically significant by the investigator. In the event of a serious adverse event, the participant will be immediately withdrawn from the study to ensure safety, with emergency medical intervention provided as necessary. The investigator must complete a detailed serious adverse event report, documenting all relevant clinical information, and sign and date the form. Serious adverse events must be reported to the principal investigator and the Ethics Committee of The Affiliated Hospital of Qingdao University within 24 hours of being informed of the events.

Data collection

Investigators involved in data collection will receive rigorous systematic training and will be unaware of patient grouping and interventions. Data will be gathered through in-person interviews with participants and their family members and retrieved from the Health Information System (table 1).

Preoperative data

1. Age (years), gender, height, weight, ASA classification (I–III), education level (<elementary school, elementary school and ≥middle school), comorbidities, disease course, long-term use of analgesics (use of pain medication for at least seven consecutive days within the past 6 months, use of long-acting analgesics within the past 3 days or use of any opioids within the past 24 hours), smoking (defined as smoking more than one cigarette per day for more than 6 months) and alcohol consumption (defined as drinking alcohol more than once a month for more than 6 months).[54]
2. Baseline NRS scores at resting and movement, baseline Barthel Index and baseline QoR-15 score. The NRS categorises pain levels on a scale of 0–10, with 0 representing the absence of pain, 1–3 denoting mild pain, 4–6 indicating moderate pain, 7–9 signifying severe pain and 10 representing excruciating pain. The Barthel Index is a reliable scale for measuring a patient's functional ability.[55] It includes 10 aspects and has a total score of 100 points. A total Barthel Index score of 0–20 indicates complete dependence, 21–60 indicates severe dependence, 61–90 indicates moderate dependence, 91–99 indicates slight dependence and a score of 100 indicates that the patient is independent of assistance from others. The QoR-15 questionnaire is the most widely used tool for evaluating the quality of recovery.[56] It was developed from the QoR-40 and has undergone extensive systematic review.[57] The QoR-15 measures the quality of recovery, and most patients can complete it within 3 minutes,[58] making it easy to assess in clinical practice.[57 59] The QoR-15 is a more concise form but maintains the same reliability as the QoR-40, with greater sensitivity to change[58 60] and excellent feasibility.[58] The QoR-15 questionnaire consists of 15 items that evaluate overall postoperative recovery across five domains: physical comfort (five items), emotional state (four items), physical independence (two items), psychological support (two items) and pain (two items). Each item is scored from 0 to 10, where 0 indicates absence and 10 indicates continuous or intense presence. For negative indicators, the scoring is reversed. The scores of the 15 items are summed to obtain a total score ranging from 0 to 150 points.

Table 1 Enrolment schedules, interventions and assessments

Outcome measure		Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Time		**1 day presurgery**	**During operation**	**24 hours postoperative**	**48 hours postoperative**	**72 hours postoperative**	**Hospital discharge**
Enrolment	Eligibility screening	X					
	Informed consent	X					
	Demographic characteristics	X					
	Baseline measures	X	X				
	Randomisation	X					
Interventions	S-ketamine group		X	X	X		
	Placebo group		X	X	X		
Assessments	Primary outcome						
	QoR-15 score at 24 hours			X			
	Secondary outcomes						
	QoR-15 score at 48 and 72 hours				X	X	
	NRS at resting and movement	X		X	X	X	
	Opioid consumption			X	X	X	
	Sleep quality scores	X		X	X	X	
	GDS-15 scores	X		X	X	X	
	Barthel Index	X					X
	Time to meet discharge criteria			X	X	X	
	Safety outcomes	Events will be observed from the intervention period to 48 hours after surgery or until the resolution.					

GDS-15, 15-item Geriatric Depression Scale; NRS, Numeric Rating Scale; QoR-15, Quality of Recovery-15.

A higher QoR-15 score indicates better postoperative recovery quality for the patient.
3. Composite score of IC and subscores in five domains (cognitive, locomotion, vitality, sensory and psychological).

Intraoperative data

Surgery duration (minutes), anaesthesia duration (defined as the time from spinal anaesthesia completion to the end of the surgery, minutes), tourniquet usage time (minutes), infusion volume (defined as the total volume of crystalloids and colloids, mL) and the dose of steroids.

Postoperative data

1. QoR-15 scores at 24 hours, 48 hours and 72 hours postoperatively.
2. Rest and movement pain scores from 8:00 to 10:00 and 16:00 to 18:00 on postoperative days 1–3.
3. OME. Use the formula: strength per unit × (number of units/day (or total)) × OME conversion factor=OME units per day (or total).[61]
4. Sleep quality on postoperative days 1–3 will be assessed using the NRS. The NRS for sleep quality ranges from 0 to 10, where 0 indicates excellent or good sleep and 10 indicates the inability to sleep throughout the night. Postoperative sleep disturbance is defined as a total score of 6 or higher.
5. GDS-15 scores on postoperative days 1–3. This scale consists of 15 questions, with a total score of 15 points. Higher scores indicate more severe depressive symptoms.
6. Barthel Index at discharge.
7. The time to meet discharge criteria.

Safety data

1. Tachycardia, bradycardia, hypertension, hypotension, respiratory depression, hypoxemia, and nausea/vomiting.
2. S-ketamine-related psychiatric complications, such as dizziness, hallucinations, nightmares, agitation and dissociative symptoms. Dizziness is frequently characterised by sensations of instability or rotational movement and may be accompanied by additional symptoms. To evaluate the presence of hallucinations, the assessors will utilise direct questioning methodologies. Specifically, for visual hallucinations, the assessors will inquire whether patients perceived images, people or lights that others could not see. For auditory hallucinations, the assessors will ask if patients heard sounds, conversations or noises that were not perceptible to others. For somatic hallucinations, the assessors will inquire whether patients experienced sensations such as touch, crawling or other bodily perceptions in the absence of external stimuli. In evaluating the occurrence of nightmares, the assessors will inquire of patients whether they experienced nightmares during their S-ketamine treatment and 48 hours after surgery. Additionally, patients will be requested to provide detailed descriptions of their nightmares, encompassing the specific episodes, characters and emotions involved. The assessor will assess delirium within 48 hours after surgery using the Chinese version of 3D-CAM.[40] The 3D-CAM identifies delirium through a diagnostic algorithm based on the four essential features of delirium: (A) acute changes or fluctuations in mental status; (B) inattention; (C) disorganised thinking and (D) altered level of consciousness. Diagnosis of delirium requires criteria A and B and either or both of criteria C and D. Agitation will be assessed by the Riker Sedation-Agitation Scale (RSAS).[62] The RSAS scale consists of seven levels ranging from 'unable to be aroused' to 'dangerously agitated'. A score of 5 or more is considered to indicate agitation.[63] The clinician-administered dissociative symptom scale (CADSS) is a commonly used measure in studies evaluating the dissociative symptoms of S-ketamine. The simplified 6-item clinician-administered dissociative symptom scale (CADSS-6) is derived from the CADSS and provides a quicker method to assess dissociative symptoms.[64] CADSS-6 includes three aspects: depersonalisation, derealisation and amnesia. The CADSS-6 total score ranges from 0 to 24, where a score of 0 signifies the absence of dissociative symptoms, and a score of 24 denotes severe dissociation. A CADSS-6 score of ≥3 indicates the presence of dissociative symptoms.
3. Complications related to nerve block, such as local anaesthetic toxicity, pneumothorax, haematoma, nerve injury, and puncture site infection.
4. Postoperative surgical site infections, thrombosis, and readmission rates.

Data management and monitoring

This trial will utilise an Electronic Data Capture system (https://www.clinicaledc.com) for data management. The data manager will be responsible for creating the electronic case report form (eCRF) and developing the data management and verification plans to establish a standardised data management process. Trial data will be entered into the eCRF by study personnel trained in Good Clinical Practice as designated by the principal investigator. Data entry must be complete, accurate, truthful and timely. The database will be regularly backed up during the study. The database is hosted on an Alibaba Cloud Virtual Machine and automatically backed up daily at a predetermined time. Following the prescribed verification protocol, the clinical research associate is responsible for conducting timely data verification. Any queries arising during the verification process are to be addressed and resolved by the study director. On confirming the integrity, coherence and comprehensiveness of the data, the database will be securely locked and transferred to the statistical analysis system. The original data source and backup copies of the database will be securely stored in a confidential location, ensuring accessibility for inspection by the Data Monitoring Committee (DMC) at all times. The DMC is composed of investigators, statisticians and

ethicists who are tasked with overseeing experiments, safeguarding data integrity, conducting risk assessments and providing decision-making support. The DMC communicates trial progress, safety data and efficacy data through written reports. Independence from sponsoring agencies and conflicting interests is essential for the DMC to make unbiased decisions free from external influences.

Statistical methods

Data analysis will be conducted utilising Statistical Package for Social Science V.25.0 software and R V.4.3.1. The Shapiro-Wilk test will be employed to assess the normality of continuous variables. Normally distributed data will be presented as means±SD, while non-normally distributed data will be presented as medians and IQR. Categorical data will be presented as numbers (n) and percentages (%). Continuous variables for demographic data, baseline characteristics and intraoperative data will be compared using an independent sample t-test or Mann-Whitney U test. Categorical variables will be subjected to analysis through χ^2 tests, continuity correction χ^2 tests or Fisher's exact test. The primary outcome will be assessed through the utilisation of generalised linear regression models to compare the effect sizes and their corresponding 95% CI between the S-ketamine group and the placebo group. Three different generalised linear regression models will be constructed. Model 1 will include only the grouping factor and will not control for confounding factors, providing the crude effect size and 95% CI; model 2 will adjust for sex, age, ASA classification, comorbidities, educational level, smoking and drinking history, baseline resting and movement NRS, baseline Barthel index and baseline QoR-15 score; model 3 will further adjust for surgery duration, tourniquet time and the dose of steroids, in addition to the factors included in model 2. Adjusted effect sizes and 95% CI will be calculated using models 2 and 3. Sensitivity analyses will be performed on the primary outcome to evaluate the consistency of the findings among various analysis sets, including ITT and PP analysis sets. The ITT analysis set will include all participants who were randomly assigned, regardless of the intervention received. The PP analysis set will include participants who have complete baseline data, meet eligibility criteria, complete all outcome assessments and demonstrate good adherence to the study protocol. In the ITT analysis set, missing data will be handled using multiple imputation methods. The number of imputations will be set to 5, with a maximum of 50 iterations. Continuous variables will be imputed using the predictive mean matching model, while categorical variables will be imputed using the logistic regression model.

The PP analysis set will be exclusively utilised for secondary outcomes. Given the exploratory nature of secondary outcomes, no corrections for type I errors will be applied for multiple comparisons. Repeated measures data will be analysed using generalised estimating equations to calculate effect sizes and 95% CI. Time to meet discharge criteria and OME will be analysed using the Mann-Whitney U test or independent samples t-test, calculating effect sizes and 95% CI. Analysis of covariance will be used to compare preoperative and discharge Barthel index scores between two groups, adjusting for baseline measurements and estimating least squares mean differences and 95% CI. Safety outcomes will be evaluated utilising the safety set, which comprises all randomised participants who were administered at least one dose of the investigational drug. The safety outcomes will be assessed as categorical variables, reported as case numbers (percentages), and analysed through χ^2 tests, continuity correction χ^2 tests or Fisher's exact tests. Subgroup analyses will be conducted to evaluate the potential influence of age (<75 and ≥75 years), gender (male and female), ASA classification (≤II and ≥III), disease duration (<10 and ≥10 years), long-term analgesic use (yes and no) and tourniquet time (<70 min and ≥70 min) on the primary outcome, including any interactions. All statistical tests will be conducted as two-tailed tests, with statistical significance defined as a $p<0.05$.

Ethics and dissemination

Prior to commencing the trial, written informed consent will be obtained from all patients by the research team to safeguard the legal rights of the participants. Approval for the trial was granted by the Medical Ethics Committee of The Affiliated Hospital of Qingdao University (no. QYFYEC2024-74). The ethics committee is required to grant reapproval for any amendments to the trial protocol that are implemented during the study. All eligible and consenting patients will provide signed, written informed consent before randomisation. Personal information about potential and enrolled participants will be collected confidentially to protect their privacy throughout the trial. Before enrolment, personal information will be obtained with the consent of the participants and stored securely according to institutional guidelines. Only essential personnel involved in the study will have access to this information.

During the trial, personal information will be identified through unique participant identifiers rather than direct personal identifiers to maintain confidentiality. Data will be stored in a password-protected Electronic Data Capture system. After the trial, personal information will be retained for a specified period as required by institutional policies and will then be securely disposed of to ensure confidentiality is maintained. Any publications or reports resulting from the study will not include identifiable personal information to protect the privacy of the participants. Access to the final trial data set will be restricted to authorised personnel directly involved in the study, including principal investigators, coinvestigators and designated research staff. These individuals will be granted access to the data set for data analysis, interpretation and reporting. The trial results will be disseminated to the subjects, healthcare professionals, the general public and other interested parties through publications

or presentations at academic conferences following the completion of the trial.

DISCUSSION

As the population continues to age, TKA has become increasingly prevalent.[65] However, postoperative recovery in the elderly presents significant challenges. Studies indicate that more than 85% of patients undergoing knee or hip arthroplasty are aged 60 years or older.[66] Elderly patients often experience IC impairments,[67] such as muscle atrophy and cognitive decline, which predispose them to postoperative complications, including inadequate pain management, functional impairment and psychological stress, all of which can hinder recovery. Furthermore, research suggests that S-ketamine's analgesic, anti-inflammatory, neuroprotective and antidepressant effects may support recovery in this population.[34–36] Thus, this study was designed as a randomised, controlled, double-blind trial to evaluate the impact of S-ketamine on postoperative recovery in elderly patients aged 60 years and older with impaired IC following TKA.

Extensive research has confirmed that S-ketamine facilitates postoperative recovery in elderly patients[45 67 68]; however, variations exist in dosage selection across studies. The dosage selection in this study was based on previous clinical trial experience and existing research on recovery quality. Our previous study found that participants receiving S-ketamine at 0.3 $mg \cdot kg^{-1} \cdot h^{-1}$ experienced hallucinations and dreaminess.[53] In another study, the dosage was adjusted to 0.2 $mg \cdot kg^{-1} \cdot h^{-1}$, which significantly reduced the incidence of adverse reactions.[40] Another study on the effects of S-ketamine on postoperative recovery quality in patients undergoing modified radical mastectomy found that compared with a dosage of 0.1 $mg \cdot kg^{-1} \cdot h^{-1}$, an intravenous infusion of 0.2 $mg \cdot kg^{-1} \cdot h^{-1}$ significantly improved recovery quality at 24 hours postoperatively without increasing the incidence of adverse reactions.[45] These findings provided a critical rationale for selecting an optimal dosage in this study, aiming to maximise postoperative recovery quality in elderly patients while minimising the risk of adverse reactions.

This study offers several notable strengths. First, its rigorous design, characterised by randomisation, double-blinding and placebo control, effectively mitigates potential biases, thereby enhancing the robustness and validity of the findings. Second, the focus on elderly patients with impaired IC, who are particularly vulnerable to postoperative complications, further underscores the clinical relevance of the study's outcomes. Nevertheless, certain limitations should be acknowledged. The relatively short follow-up period may not fully capture the long-term impact of S-ketamine on functional recovery. Future research should consider extending the follow-up duration to generate more comprehensive data on the sustained efficacy of S-ketamine.

In conclusion, this randomised controlled trial aimed to investigate the effect of S-ketamine on postoperative recovery quality in elderly patients with impaired IC. This study is expected to provide new pharmacological intervention options for postoperative recovery in elderly patients with impaired IC.

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