The effects of subanaesthetic S-ketamine on postoperative delirium and cognitive function in elderly patients undergoing non-cardiac thoracic surgery: a protocol for a randomised, double-blinded, positive-controlled, non-inferiority trial

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Introduction

Postoperative delirium (POD) is a neuropsychiatric disorder in elderly patients, manifested as an acute onset of altered and fluctuating consciousness, inattention, and disorganised thinking. POD occurs in hospital up to 1 week postoperatively or until discharge (whichever occurs first), and typically the highest incidence is observed during the first 72 hours. [1] The incidence of POD varies between 4% to 60%, depending on the age and surgical type, although its incidence is underestimated since the hypoactive subtype is not well appreciated. [2-7] Postoperative delirium is associated with prolonged hospital stay, long-term cognitive and social dysfunction, and even death. [8-10] The 1-year survival probability is reduced by approximately 10% for each additional day of postoperative delirium. [11] The pathophysiological mechanisms of delirium have not been well-elucidated, and neuroinflammation remains a topic of mainstream research interest. Furthermore, its development results from the complicated interaction of multifactorial risks, such as pain, opioids, sleep deprivation, and inflammation, which poses a challenge for the prevention and treatment of postoperative delirium. [12] Although various techniques, including multi-component non-pharmacological interventions, are suggested to reduce the risks, there is limited pharmacological methods to reduce the incidence of delirium. [13]

Dexmedetomidine is a highly selective α-2 adrenergic receptor agonist that is associated with sedative, sympatholytic, and anti-inflammatory effects, and has the highest-ranking possibility of preventing postoperative delirium in a recent network meta-analysis. [10] Furthermore, the plausibility of dexmedetomidine's positive effects on postoperative delirium is enhanced by evidence of less anticholinergic activity and opioid-sparing properties. [14] Postoperative prophylactic low-dose dexmedetomidine could remarkably reduce the incidence of delirium during seven days after non-cardiac surgery; [15] moreover, perioperative infusion of dexmedetomidine halved the incidence of delirium in the elderly after major cardiac and non-cardiac surgery without the increase in adverse effects. [16,17] A randomised controlled trial found that intraoperative dexmedetomidine did not decrease postoperative delirium or affect cognitive function in the elderly undergoing major non-cardiac surgery. [18] A meta-analysis including 11 RCTs revealed that perioperative dexmedetomidine reduced the incidence of POD in elderly patients after

non-cardiac surgery, but this came at the cost of an increased incidence of hypotension and bradycardia. [19] A meta-analysis of 1301 patients undergoing cardiac surgery revealed that dexmedetomidine decreased postoperative delirium. [20] Nevertheless, this meta-analysis should be interpreted with caution, because several of the included studies did not consider delirium as the primary outcome, the methodology of delirium assessment varied, and dexmedetomidine administration was also inconsistent, with differing doses and durations. Furthermore, the finding that dexmedetomidine prevents postoperative delirium is also controversial. In the DECADE trial, continuous infusions of dexmedetomidine, started at induction and maintained for 24 hours, failed to reduce delirium in patients recovering from cardiac surgery. Notably, dexmedetomidine non-significantly aggravated delirium, probably mediated by hypotension. [21] However, the plausibility that dexmedetomidine prevents POD should be discussed separately, because physiopathology and incidence of delirium is quite different between non-cardiac surgery and cardiac surgery (frequent cerebral embolism). The heterogenous ways that dexmedetomidine is administrated (pre- or post-operative or both, bolus, continuous et al) also complicated the analysis even more. As with all pharmacological treatment options, the side effects of dexmedetomidine are bradycardia and hypotension in a dose-dependent manner, and more strikingly in the elderly; hence, close haemodynamic monitoring is warranted.

Ketamine, a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, is pharmacologically rationalised as an effective medication for reducing postoperative delirium, probably due to its neuroprotective properties. Under surgical conditions, the enhanced AMPA/NMDA signalling caused by the activation of cytokine receptors, and high mobility group box 1 facilitate an increased influx of glutamate in hippocampal neurones, which ultimately promotes glutamate toxicity. [22] Ketamine can mitigate neuronal apoptosis by inhibiting the activation of NMDA receptors and the transduction of excitatory signals. [23] The assumption of ketamine's beneficial effects on delirium is also strengthened by evidence of its opioid-sparing and antidepressant effects. Depression and delirium, induced by similar pathophysiological mechanisms, are thought to overlap. [24,25] A small sample size of a randomised controlled trial indicated that a low-dose single bolus

of ketamine at induction significantly attenuated delirium after cardiac surgery. However, the PODCAST study showed that low-dose ketamine failed to decrease postoperative delirium, pain, and opioid consumption, and generated a dose-dependent increase in the occurrence of negative experiences. [26] The PRIDe study offered no possibility for ketamine to prevent postoperative cognitive decline, including delirium. [27] Ketamine remains an off-label treatment for treatment-POD with factors that limit widespread use including its dissociative effects and abuse potential.

S-ketamine is the S (+) enantiomer of ketamine, which has a higher affinity with aspartate receptor and μ opioid receptor. The anaesthetic potency of S-ketamine is two-fold higher than that of racemic ketamine, and it has higher in vivo clearance rate characterized by lower incidence of adverse reactions. [28] Animal experiments showed that S-ketamine, rather than racemic ketamine, could alleviate the injury of hippocampal neurones exposed to glutamate in rodents; a subanaesthetic dose of S-ketamine could remarkably mitigate neuroinflammation by inhibiting microglia proliferation and TLR4/NF-κB signalling pathway activation, which consequently improved neurocognitive function. [29,30] Additionally, S-ketamine could promote the plasticity of hippocampal neurones and improve the function of neurones in the prefrontal and hippocampal neural circuits. [31] A study on healthy volunteers showed that S-ketamine exhibited pro-neuroplastic effects on hippocampal structure, which may improve cognitive function after surgery. [32] Moreover, a recent study on human metabolome revealed that S-ketamine decreases the levels of circulating branched chain amino acids which inhibit the synthesis and release of serotonin and noradrenaline in the brain. Thus, S-ketamine could, in theory, increase the effects of serotonin and noradrenaline in the brain, and contribute to the improvement of depression and cognitive impairment. [33] Furthermore, we hypothesize that the sympathomimetic and analgesic properties of S-ketamine might partially explain its non-inferior property for delirium prevention compared to dexmedetomidine. Though S-ketamine has stronger potency and lower incidence of adverse reactions, the evidence that it reduces the incidence of postoperative delirium is fairly insufficient.

Since the effects of S-ketamine on postoperative delirium are lack of good quality

evidences, we designed the current prospective, randomised, double-blinded, placebo- and positive-controlled, non-inferiority trial to investigate the effect of intraoperative prophylactic S-ketamine on postoperative delirium in elderly patients undergoing thoracic surgery compared to dexmedetomidine.

Methods

Study setting and design

This study will be conducted at the Cancer Hospital and Institute of Guangzhou Medical University (Guangzhou, Guangdong, China, with principal investigator [PI] Dr Yonghua Yao). The study activities are expected to commence in March 2022 and be completed in December 2023. The study design is in accordance with the standard protocol items for randomised trials guidelines. The overall schedule is illustrated in Table 1, and the Consolidated Standards of Reporting Trials flow diagram is shown in Figure 1. The current study protocol is the sixth version.

Table 1. Schedule of enrolment, interventions, and assessments for the trial

	Enrolment	Allocation	Post-allocation								Closeout
	Preoperative assessment	Allocation	Before induction	recovery	4-hour after surgery	24-hour after surgery	48-hour after surgery	72-hour after surgery	96-hour after surgery	30-day after surgery	90-day after surgery
TIME POINT	$-T_1$	T_0	T_1	T_2	F_1	F_2	F_3	F_4	F_5	F_6	F_7
ENROLMENT:											
Eligibility screen	X										
Informed consent	X										
Allocation		X									
INTERVENTIONS:											
S-ketamine			◆—	——	—◆						
Dexmedetomidine			◆—	——	—◆						
ASSESSMENTS:											
Postoperative delirium (3D-CAM)					X	X	X	X	X		
Pain severity (NRS)					X	X	X				
Sleep quality (NRS)						X	X	X	X		
Cognitive function (TICS-40)										X	X
Haemodynamic variables			◆—	——	——	—◆					
Emergence delirium (RASS)				X							

Participant recruitment

Inclusion criteria

1. Aged 60 to 90 years old.
2. Both sexes.
3. American Society of Anaesthesiologists (ASA) physical status classification I-III.
4. Diagnosed with pulmonary, oesophageal or mediastinal disorders.
5. Undergoing open or video-assisted thoracic surgery, including lobectomy, segmentectomy, pneumonectomy, oesophagectomy, or resection of the mediastinal tumour.
6. General anaesthesia with one lung ventilation (OLV) or bronchial blocker.
7. An expected operation duration of 2 hours or more.
8. Voluntary participation in the trial and signed informed consent.

Exclusion criteria

1. History of severe psychiatric disease.
2. History of glaucoma or hyperthyroidism.
3. History of severe hepatic (Child-Pugh grade C) or renal (requirement for renal replacement therapy) disorders.
4. Body mass index (BMI) > 35 kg/m^2.
5. Dementia history or baseline Mini-Mental State Examination (MMSE) score of < 23.
6. Severe audio-visual impairments, or inability to speak Mandarin or Cantonese precluding communication.
7. Sinus bradycardia (heart rate < 50 beats per minute, bpm), sick sinus or Wolff-Parkinson-White syndrome, or 2nd degree atrioventricular block and over.
8. Uncontrolled hypertension (baseline value > 200/110 mm Hg).
9. Allergic to dexmedetomidine or S-ketamine.
10. Taking sedatives, antidepressants or glucocorticoids.
11. Alcohol or Illicit drug misuse disorder.
12. Life expectancy of less than two months due to extensive tumour metastasis.

Participants consent

All patients scheduled for thoracic surgery will be screened one day before the operation for eligibility at the preoperative evaluation clinic (or on Friday for those who will undergo surgery the following Monday). Eligible patients will be informed by the study team coordinator. For the sake of voluntary participation, all patients will be informed about the aims, procedures, benefits, possible risks of study, and how to react if risks occur. If interested in enrolment, the patients or their next of kin will sign the written consent form in triplicate.

Randomisation and blindness

Eligible patients were randomly assigned in a 1:1 ratio to receive either S-ketamine or dexmedetomidine. Randomization was computer-generated with a permuted block size of 4, and assignments were concealed in sequentially numbered, opaque envelopes by an independent anaesthetist nurse. Study drugs were prepared by an independent research associate not involved in the study. All study drugs were identical in appearance and packaged in identical 50-ml syringes labeled ‘study medication’. To avoid unblinding due to clinical speculation regarding allocation, study medications were formulated to be administered at identical infusion rates (ml/h). Patients, clinicians, and outcome assessors remained fully blinded to treatment assignment until the completion of final statistical analyses. In the event of an emergency (e.g., significant clinical deterioration), the anaesthesia team could request unblinding or adjust the study medication as necessary.

The labelled “Study medication” syringes (50 ml), identical in appearance, and the infusion regimen formulated by the pharmacist based on the randomisation, will be distributed to the attending anaesthesiologists responsible for anaesthetic management as soon as the research team informs the central pharmacy about the patient heading for surgery. In order to avoid anaesthesiologists’ speculation about the randomised assignment, the study drugs will be infused at the same rate (see Table 2). The anaesthesiologists, patients, investigators responsible for follow-up, and statisticians will be all blinded to the randomised allocations until the final statistical analyses are completed.

The blindness will be unmasked by the primary investigator in a medical emergency, including deterioration of the patient's condition intraoperatively or adverse events postoperatively.

Standard anaesthetic management

On the day of the operation, the patients will be admitted to the operating room after random assignment. Vital signs will be routinely monitored, including heart rate (HR), blood pressure (BP), oxyhaemoglobin saturation by pulse oximetry (SpO_2), end-tidal carbon dioxide partial pressure ($EtCO_2$), nasopharyngeal temperature, and urine output throughout surgery. Pre-oxygenation with 100% oxygen for 15 min before the induction of anaesthesia will be delivered to the patient using a face mask. Atropine will be administered intravenously in avoidance of excessive secretions.

After arterial line and central venous line are cannulated under ultrasound guidance, anaesthesia induction will be performed by administration of midazolam (0.05 mg/kg), propofol (1-2 mg/kg) or etomidate (0.2 mg/kg), and sufentanil (0.2-0.4 μg/kg). After the patient becomes unconscious, rocuronium (0.6 mg/kg) will be injected intravenously. Bronchial intubation will be performed smoothly with a video laryngoscope after 3-minute positive pressure ventilation. The tip of double lumen tubes (DLTs) will be inserted into the glottis under direct vision and advanced until a mild resistance is perceived. After the fibreoptic bronchoscope is fully lubricated, it will be advanced into the tracheal lumen of the DLTs until the carina is identified. Afterwards, the ideal position of the bronchial lumen (the blue bronchial cuff should be invisible for left DLTs, the opening in the upper lobe of the right lung should be visible for right DLTs) will be verified. Dual-controlled ventilator modes (i.e. pressure-controlled ventilation with volume guaranteed or pressure-regulated volume control) will be applied. One-lung protective ventilation regimen will be conducted by a combination of tidal volumes (Vt) of 6 ml/kg or lower, by predicted body weight, with a positive end-expiratory pressure of 6 cmH_2O or beyond based upon guidelines and expert opinion for optimal practice during OLV. [34] High inspiratory fractions of oxygen (FiO_2 > 70%) will be administered to maintain SpO_2 higher than 94%. In addition, continuous positive airway pressure (CPAP) regimen will be considered when necessary.

The respiratory rate will be adjusted to maintain $EtCO_2$ at 35-45 mmHg. Sedative maintenance will be performed with a TCI (target-controlled infusion) of propofol according to the Schnider model at a plasma concentration (Cp) of 2-3 μg/ml to maintain the bispectral index value between 40 and 60. Analgesic maintenance will be achieved with a TCI of remifentanil according to the Minto model at a Cp of 1-6 ng/ml to fluctuate the HR and BP within the baseline value ± 20%. An intermittent bolus of rocuronium will be administered to maintain TOF < 1 intraoperatively. Forced air-warm blankets will be used to ensure an intraoperative body temperature of 36-37°C. The surgeon will implement an intercostal nerve block (T3-7) with 20 ml of 0.5% ropivacaine under direct thoracoscopic view before placing a chest tube. The sign of a successful block is the presence of pleural displacement. All participants will be given hydromorphone (0.015 mg/kg) when a chest tube is placed for the sake of prophylaxis of hyperalgesia.

A patient-controlled analgesia (PCA) device, with hydromorphone (0.15 mg/kg) and ondansetron (12 mg) in a total volume of 100 ml, will be connected to the intravenous cannula at the end of surgery. The device is programmed to administer a background dose of 2 ml/h, as well as a bolus dose of 2 ml with a lockout interval of 15 min for 48 hours. Hydromorphone (0.008 mg/kg) will be administered if the numeric rating scale (NRS) score is > 3 despite the PCA regimen. Residual neuromuscular blockade will be routinely reversed with neostigmine (40 μg/kg) and atropine (20 μg/kg), and the endotracheal tube will be removed when the patients are able to follow verbal commands.

Study drugs administration

S-ketamine (50 mg, 2 ml) is diluted to 50 ml (1 mg/ml) with 48 ml normal saline; dexmedetomidine (200 μg, 2 ml) is diluted to 100 ml (2 μg/ml) with 98 ml normal saline. All drugs are identical in appearance, packaged in identical 50 ml syringes labelled with “Study medications”. The loading dose of study drugs will be infused within 10 minutes before induction, and the maintenance dose will be infused at a constant rate continuously until skin closure. In the preliminary trial, we found that a loading dose of 0.4 μg/kg dexmedetomidine lead to obvious bradycardia and transient hypertension events.

Therefore, we modified the loading dose of dexmedetomidine to 0.2 μg/kg; In addition, in order to ensure blindness, the infusion speed of dexmedetomidine is consistent with that of S-ketamine, which also reduces the side effects of dexmedetomidine. The detailed administrative protocol of study drugs is shown in Table 2.

Table 2 Study drugs and administrative protocol (take a 60 kg patient as an example)

Group	Concentration	Loading dose	Maintenance dose
S-ketamine	1 mg/ml	0.25 mg/kg	0.1 mg/kg/h
i.e. The administrative protocol of a 60 kg patient will be a loading dose of 15 ml and a maintenance dose of 6ml/h			
Dexmedetomidine	2 μg/ml	0.2 μg/kg	0.2 μg/kg/h
i.e. The administrative protocol of a 60 kg patient will be a loading dose of 15 ml and a maintenance dose of 6 ml/h			

Data collection

The following data will be collected through patient interviews and abstractions from the electronic medical record system:

Preoperative data collection

1. Patient demographic data including age (years), sex, height (cm), weight (kg), BMI (kg/m^2), and education level (years).
2. ASA classification, Charlson comorbidity index, baseline MMSE, and type of surgery.
3. Plasma biomarker concentrations including acetylcholine (ACh), brain-derived neurotrophic factor (BDNF) and tumour necrosis factor-α (TNF-α) before the administration of study drugs (T1).

Intraoperative data collection

1. Haemodynamic parameters including HR (bpm), mean arterial pressure (MAP, mmHg), SpO_2 and BIS value at 15-minute intervals.
2. Hypotension and bradycardia episodes (see Table 3).
3. Hypertension and tachycardia episodes (see Table 3).

4. Duration of desaturation (SpO_2 < 90%, minutes).
5. The cumulative dosage of noradrenaline (μg) and atropine (mg).
6. The consumption of propofol (mg) and opioids (converted to morphine milligram equivalent by Global RPH, MME).
7. Surgery, anaesthesia and OLV duration (minutes).
8. Time to extubation (minutes, duration from discontinuation of propofol to removal of the tracheal tube).
9. Emergence agitation (Richmond Agitation-Sedation Scale, RASS score ≥ 1).

Postoperative data collection

1. Incident postoperative delirium between 4 h after surgery and the 4th postoperative day, and twice daily from postoperative day 1 to postoperative day 4 (8:00-10:00 am) with an interval of at least 6 hours.
2. Severity and duration of delirium.
3. Postoperative pain at 4 h, 1 and 2 days after surgery.
4. Consumption of hydromorphone (mg).
5. Quality of sleep within 4 days after surgery.
6. Cognitive function at 30 and 90 days after surgery.

Data Safety and Monitoring Committee (DSMB) is consist of three senior anaesthesiologists and one surgeon who are blinded to the study. The DSMB will provide independent oversight of the SKED trial and will review the study data for the participant safety as well as CRF storage. The data will be entered into the Epidata V4.6 database protected by password only accessible to DSMB. Then, the data will be exported from Epidata database to a statistical package for analysis by biostatisticians independent of the study.

Outcomes

Primary outcomes

The primary outcome will be the incidence of postoperative delirium as defined by any positive assessment within the first postoperative 4 days.

Secondary outcomes

Secondary outcomes included postoperative delirium severity, motroic subtypes, episodes, and duration. Additional prespecified outcomes were emergence delirium; time to delirium onset; time to extubation; postoperative pain intensity at rest and during cough at 4, 24, and 48 h postoperatively; postoperative opioid consumption and rescue analgesia requirements; subjective sleep quality within the initial 4 days after surgery; postoperative length of hospital stay; and cognitive function and mortality at 30- and 90-day follow-up.

Measurement of outcomes

Measurement of delirium

Delirium will be assessed using a validated 3-minute diagnostic confusion assessment method (3D-CAM Chinese version, with a sensitivity of 84%–99% and specificity of 90%–97%) [35,36] or Confusion Assessment Method for the Intensive Care Unit (CAM-ICU), for patients who have a tracheal tube or underwent tracheostomy. [37] 3D-CAM resolves the four diagnostic features of delirium: (1) acute onset and fluctuating course, (2) inattention, (3) disorganised thinking, and (4) altered level of consciousness. A patient who displays both features 1 and 2, with either feature 3 or 4, will be diagnosed with delirium (see Figure 2). [35] Delirium assessments will be performed only when patients can be aroused sufficiently with an RASS score of -3 to 4 (Supplementary Table 1). Patients with postoperative delirium will be classified into three subtypes. Hyperactive delirium will be defined when the RASS score ranges from 1 to 4; hypoactive delirium will be defined when the RASS score ranges from -1 to -3, and mixed delirium will be defined when the RASS score ranges from 1 to 4 and -1 to -3 alternatively. The severity of postoperative delirium will be rated using the CAM-Severity short-form scale (Supplementary Table 2). Mild-to-moderate delirium will be defined as a CAM-S score of 3 to 5, while severe delirium will be defined as a CAM-S score of 6 to 7. [38]

Four investigators who are not involved in perioperative care will be responsible for postoperative delirium assessments and will be trained by a psychiatrist with regard to symptoms, diagnosis, and treatment of delirium. Furthermore, the psychiatrist will explain the protocols of 3D-CAM and CAM-ICU in detail, and will perform the simulation training of

delirium assessment until a kappa value over 0.8 is achieved between investigators and psychiatrists. The training process will be repeated every 4-6 months throughout the study. In addition, the chart-based delirium identification instrument with the information primarily derived from electronic medical records system and recalling descriptions of caregivers will be employed to detect any cases of delirium in patients that may occur outside of in-person delirium assessments (Supplementary Table 3). [39]

Pain and sleep quality measurement

Postoperative pain at rest and during a cough will be evaluated using an 11-point NRS (0 = [no pain], 0 < NRS < 4 [mild pain], 4 ≤ NRS < 7 [moderate pain], 7 ≤ NRS <10 [severe pain], NRS = 10 [worst pain imaginable]). Postoperative sleep quality will also be evaluated using the NRS (0 = best-quality sleep, 10 = worst-quality sleep).

Cognitive function measurement

Postoperative cognitive function will be assessed using the Chinese version of the Telephone Interview for Cognitive Status-40 (TICS-40). The TICS-40 scale used in this study consists of nine items with a maximum score of 40 points, including the following variables and corresponding points: address (3 points), current date (5 points), counting backwards (2 points), word-list recalling (10 points), subtractions (5 points), object naming (2 points), repetition (1 point), the president and prime minister's names (2 points), and delayed recall of the word list (10 points). A score below 21 will be defined as mild cognitive impairment (Supplementary Table 4). [40]

Adverse events

An adverse event (AE) can be any unfavourable and unintended symptom or side effect temporally associated with the use of study medications. The potential AEs that may be considered in this trial are bradycardia, hypotension, tachycardia, hypertension, arrhythmia, nystagmus, hypersalivation, euphoria, emergence agitation, hallucinations, and nightmares. It is possible, but very unlikely, that low-dose S-ketamine (50 mg in total) administered intraoperatively will cause these psychiatric effects. Potential adverse events and medical rescue are shown in Table 3. [41]

Serious AEs are rare, life-threatening events that may be associated with the study drugs or perioperative incidents, such as death or serious cardio-cerebral vascular events.

Table 3 The definitions of adverse events and corresponding medication rescue

Adverse events	Severity	Definition	Treatment
Hypotension (SBP<90 mm Hg or DBP<50 mm Hg or MAP<80% baseline)	Mild	SBP 80-89 mm Hg	Close monitoring
	Moderate	SBP 70-79 mm Hg>2 min	Noradrenaline 4 μg $
	Severe	SBP 60-69 mm Hg>1 min	Noradrenaline 8 μg #
	Life-threatening	SBP 60-69 mm Hg and unresponsive to noradrenaline or SBP<60 mm Hg	Intensive intervention and suspend the study
Hypertension (SBP>140 mm Hg or DBP>90 mm Hg or MAP>120% baseline)	Mild	SBP 141-160 mm Hg or DBP 91-100 mm Hg	Close monitoring
	Moderate	SBP 160-170 mm Hg or DBP 101-110 mm Hg >3 min	Urapidil 12.5 mg Urapidil 25 mg or NG 50 μg
	Severe	SBP 171-180 mm Hg or DBP 111-120 mm Hg >2 min	Intensive intervention and suspend the study
	Life-threatening	SBP>180 mm Hg or DBP>120 mm Hg and unresponsive to NG	
Bradycardia (HR<60 bpm)	Mild	HR 55-60 bpm	Close monitoring
	Moderate	HR 50-54 bpm>3 min	Atropine 0.5 mg
	Severe	HR 40-50 bpm>2 min	Atropine 1.0mg
	Life-threatening	HR<40 bpm and unresponsive to atropine	Intensive intervention and suspend the study
Tachycardia (HR>100 bpm)	Mild	HR 90-100 bpm	Close monitoring
	Moderate	HR 101-110 bpm>3 min	Esmolol 20 mg
	Severe	HR 111-130 bpm>2 min	Esmolol 40 mg
	Life-threatening	HR>130 bpm and unresponsive to Esmolol	Intensive intervention and suspend the study
Hypoxemia (SpO_2<90%)	Mild	SpO_2 90%-94%	Close monitoring
	Moderate	SpO_2 80%-90%>3 min	CPAP
	Severe	SpO_2 70%-79%>2 min	Two-lung ventilation
	Life-threatening	SpO_2<70% and unresponsive to two-lung ventilation	Intensive intervention and suspend the study
Emergence delirium	Mild	RASS 1-2	Limb restraint
	Severe	RASS 3-4	Propofol 30 mg
Hallucination/Nystagmus	NA	3D-CAM	Haloperidol 10 mg

3D-CAM, 3 minutes diagnostic confusion assessment method; CPAP, constant positive

airway pressure; HR, heart rate; NA, not applicable; NG, nitro-glycerine; RASS, Richmond Agitation-Sedation Scale.

$ followed by continuous infusion with 0.01-0.1 μg/kg/min when necessary

followed by continuous infusion with 0.1-0.2 μg/kg/min when necessary

Sample size calculation

The sample size was calculated for the main outcome, the incidence of postoperative delirium, using PASS software version 15.0. Based on previous studies and our recently completed data, we estimated that the incidence of POD in elderly patients undergoing non-cardiac thoracic surgery was 40%. [12,42-46] Assuming that dexmedetomidine is associated with a 40% relative reduction in the incidence of postoperative delirium, the non-inferiority margin risk difference (RD) of S-ketamine versus dexmedetomidine will be set at 12%. [15,27,47,48] To achieve 80% statistical power at a one-sided significance level of $\alpha = 0.025$, a total of 520 participants were required, allowing for an anticipated 5% dropout rate (260 per group).

Statistical methods

Categorical data were presented as frequency and percentage, and analyzed using $\chi 2$ test with continuity correction or the Fisher's exact test. Continuous variables were presented as mean (SD) or median with interquartile range, and compared using the unpaired t test or Mann-Whitney U test, as appropriate. The differences (95% CI) in medians were calculated using the Hodges-Lehmann estimator. Baseline characteristics with absolute standardized difference > 0.172 ($1.96 \times \sqrt{\frac{1}{260}+\frac{1}{260}}$) were regarded as imbalanced and adjusted for in the primary outcome analysis.

The primary outcome was assessed on both the modified intention-to-treat (mITT) and per-protocol (PP) datasets. The mITT set included all randomized patients who received the study medication, while the PP set excluded those with major protocol deviations. To estimate the RR and corresponding 95% CI, we used a log-link Poisson regression model with robust standard errors to account for potential misspecification of the variance

structure. Non-inferiority of S-ketamine to dexmedetomidine was claimed if the upper bound of the 95% CI for RD did not exceed the predefined NIM of 12%.

Secondary outcomes analyses were conducted using the PP dataset, whereas safety ananlyses were performed with the mITT dataset. Longitudinal data, specifically pain intensity scores, sleep quality scores, and TICS-40 scores, were analyzed using generalized estimating equations (GEE) with an exchangeable working correlation structure to account for within-subject correlations over time. Given the multiple comparisons across repeated time points, a Bonferroni correction was applied. Time-to-events results (delirium onset and extubation) were analyzed with Kaplane-Meier survival analyses with differences between groups tested using log-rank tests, and univariable Cox proportional hazards models were used to calculate hazard ratios and 95% CI.

For sensitivity analyses, multivariable logistic regression was performed to evaluate the association between the treatment allocation and postoperative delirium. The model was adjusted for established risk factors not prespecified in the original protocol, including age, baseline MMSE score, education attainment, age-adjusted Charlson Comorbidity Index, Clinical Frailty Scale (CSF) score, Pittsburgh Sleep Quality Index (PSQI), surgical duration, and emergence delirium. To account for the distribution of delirium frequency, including both the probability of occurrence and the number of subsequent episodes, a Poisson hurdle model was applied, with adjustment for the same set of risk factors.

Post-hoc subgroup analyses for the primary outcome were performed based on age, CFS score, baseline MMSE score, PSQI and ASA physical status. To assess the association between postoperative delirium and long-term cognitive function, a GEE model was applied to estimate differences in TICS-40 scores at 30 and 90 days postoperatively between delirious and non-delirious patients, adjusting for potential confounders identified in prior multivariable logistic regression, with TICS-40 score as the dependent variable and delirium as the primary exposure. Given negligible incidence of missing data (< 1%), a complete-case analysis was adopted without multiple imputation.

All tests were two-sided ($P < 0.05$) except for the one-sided non-inferiority assessment ($\alpha = 0.025$). Statistical analyses were conducted using SPSS 26.0 (IBM Corp., Armonk, NY, USA) and R version 4.3.5 (R Foundation for Statistical Computing, Vienna, Austria).

Discussion

Lung cancer ranks first among all malignancies in China, and anatomic pulmonary resection is a major component of multimodal therapy according to the lung cancer guidelines. [12] However, more than 40% of patients undergoing lung cancer surgery are inflicted by severe depression-related psychological suffering postoperatively. [50] Depression is an independent predictor of postoperative delirium in patients who undergo orthopaedic and cancer surgeries. [24] Based on its pharmacological mechanisms and antidepressant effects, we speculate that S-ketamine would be non-inferior to dexmedetomidine in reducing postoperative delirium to some extent in the elderly, with fewer episodes of hypotension or less opioid consumption. Hypotension is pertinent to delirium, and minimisation of intraoperative hypotension episodes is recommended to reduce postoperative delirium. [51] Additionally, the administration of opioids (long-acting opioids in particular) is closely related to postoperative delirium in a dose-dependent manner. Hence, it is critical to abate opioid consumption in order to curtail delirium. [8]

Although previous studies have demonstrated that ketamine failed to reduce the incidence of postoperative delirium in patients undergoing major cardiac or non-cardiac surgery, we will deploy a different administrative protocol to evaluate the effect of an isomer of ketamine on postoperative delirium accompanied by dexmedetomidine as a positive comparator and by an optimal sample size. Dexmedetomidine is a highly recommended agent in the prevention and treatment of postoperative delirium; however, it is commonly accompanied by hypotension and bradycardia in the elderly. As the prevention of postoperative delirium is more practical and effective than the treatment itself, creating a means of prevention for delirium is extraordinarily indispensable. We believe that the possible result will be one of the following: (1) S-ketamine will be non-inferior to dexmedetomidine in the prevention of postoperative delirium; meanwhile, more stable haemodynamics, lower postoperative pain severity, or other beneficial secondary outcomes will be observed with S-ketamine intervention. Side effects will be compared between groups, all of which will be our desirables. This suggests that S-ketamine will be an optimal choice for limiting delirium emergence in the elderly, and further studies should be performed to evaluate its effect on long-term cognitive function. (2) S-ketamine will be

non-inferior to dexmedetomidine in postoperative delirium prevention with comparable secondary outcomes; however, it will be accompanied by frequent side effects. This indicates that S-ketamine will be clinically valueless for delirium prevention, which is also possible in view of the results from previous studies on ketamine (PODCAST and PRIDe study). (3) S-ketamine will be inferior to dexmedetomidine in the prevention of postoperative delirium, which is probably because dexmedetomidine is recognised as the most effective medication for delirium, and fewer studies have compared the two drugs.

The SKED protocol has many limitations. First, the current trial is launched at special time when inclusion may be constrained by local SARS-CoV-2 pandemic. As such, the research period may take longer than anticipated. Second, this is a single-centre study that exclusively involves thoracic surgery; therefore, the generalisability may not be extrapolated. Third, an anticipated non-inferiority margin ratio of 12% in our trial may be too large, and consequently, the sample size may be underestimated. Fourth, a dropout rate of 5% seems a bit low as advert events due to dexmedetomidine may be higher than that, if so, we would enlarge the sample size upon approval from the IRB.

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