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, placebo- and positive-controlled, non-inferiority trial

(SKED Trial)

Identifier: NCT05242692

Date of the document: June 1, 2022

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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 fifth 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	60-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			♦—	—	—♦						
Normal Saline			♦—	—	—♦						
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							
Plasma biomarkers (ACh，BDNF, TNF-α)			X	X					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

A randomisation code will be generated in a block size of six on the website of http://www.Randomization.com and kept in a sealed opaque envelope by an anaesthetist nurse. The patients will be randomly allocated by a ratio of 1:1:1 to the S-ketamine group (S group), dexmedetomidine group (D group), or control group (C group) by an anaesthetist nurse. Dispensing and labelling of the study drugs will be performed by a pharmacist. Both the anaesthetist nurse and the pharmacist will not be involved in the following research or follow-up. The randomisation protocol will be kept secure by the anaesthetist nurse. The primary investigator, and the clinicians collecting the data, are allowed to unmask the randomization protocol only when both recruitment and the database are closed.

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 0.5 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 > 5 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; the control group only receives 50 ml normal saline in light

of blindness. 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 ***μ***g/kg dexmedetomidine lead to obvious bradycardia and transient hypertension events. Therefore, we modified the loading dose of dexmedetomidine to 0.2 ***μ***g/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 ***μ***g/ml	0.2 ***μ***g/kg	0.2 ***μ***g/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			
Control	Normal saline	——	——
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 < 94%, 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).
10. Plasma biomarker concentrations at the end of operation (T2).

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 60 days after surgery.

7. Plasma biomarker concentrations at the 4th day after surgery (T3).

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 between 4 h after surgery and the 4th postoperative day.

Secondary outcomes

The main secondary outcome will be the subtype, severity and duration of postoperative delirium.

Other prespecified secondary outcomes will be the incidence of emergence delirium; pain severity at 4 h, 1 and 2 days after surgery; quality of sleep within 4 days after surgery; cognitive function at 30 and 60 days after surgery; plasma biomarker (ACh, BDNF, TNF-α) concentrations at T1-3; and incidence of adverse events.

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]

Biomarkers concentration measurement

Venous blood (approximately 6 ml) will be sampled and stored on ice in vacutainer tubes containing EDTA. Within 30 min, the samples will be centrifuged at 4°C for 20 min at 2000× g to obtain plasma and then stored at -80°C. We will measure ACh, BDNF, and TNF-α levels by enzyme-linked immunosorbent assay method (in accordance to manufacturer's instructions). The biomarker assay will be performed by a specialist who is blinded to the randomization. (Supplementary text for the rationales of biomarkers selected)

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 Moderate Severe Life-threatening	SBP 80-89 mm Hg SBP 70-79 mm Hg>2 min SBP 60-69 mm Hg>1 min SBP 60-69 mm Hg and unresponsive to noradrenaline or SBP<60 mm Hg	Close monitoring Noradrenaline 4 μg $^{\$}$ Noradrenaline 8 μg $^{\#}$ Intensive intervention and suspend the study
Hypertension (SBP>140 mm Hg or DBP>90 mm Hg or MAP>120% baseline)	Mild Moderate Severe Life-threatening	SBP 141-160 mm Hg or DBP 91-100 mm Hg SBP 160-170 mm Hg or DBP 101-110 mm Hg >3 min SBP 171-180 mm Hg or DBP 111-120 mm Hg >2 min SBP>180 mm Hg or DBP>120 mm Hg and	Close monitoring Urapidil 12.5 mg Urapidil 25 mg or NG 50 μg Intensive intervention and suspend the study

		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<60 bpm)	Mild	HR 90-100 bpm	Close monitoring
	Moderate	HR 101-110 bpm>3 min	Esmolol 20 mg
	Severe		Esmolol 40 mg
	Life-threatening	HR 111-130 bpm>2 min	Intensive intervention
		HR>130 bpm and unresponsive to Esmolol	and suspend the study
Hypoxemia (SpO_2<94%)	Mild	SpO_2 90%-94%	Close monitoring
	Moderate	SpO_2 80%-90%>3 min	CPAP
	Severe		Two-lung ventilation
	Life-threatening	SpO_2 70%-79%>2 min	Intensive intervention
		SpO_2<70% and unresponsive to two-lung ventilation	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 11.0. 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 rate ratio (RR) of S-ketamine versus dexmedetomidine will be set at 1.5. [15,27,47,48] To achieve a two-sided type I error of 5% and 80% power, 729 participants (243 patients per arm) will be recruited. To accommodate a 5% dropout rate, the final sample size will be 780 (260 patients per arm).

Statistical methods

Kolmogorov-Smirnov test will be used to evaluate the normal distribution of continuous variables. Normally distributed data will be presented as means ± standard deviation (SD), and non-normally distributed data will be presented as medians with interquartile ranges. Categorical data will be summarised as counts (proportions).

The absolute standardised difference (ASD) will be used for the comparison of baseline data among the three groups, that is, the absolute difference in means, mean ranks, or proportions divided by the combined SD. Baseline variables with ASD>0.013 (i.e.,$1.96 \times \sqrt{(260+260+260)/(260\times 260\times 260)}$) are considered to be imbalanced and will be adjusted for in all analyses when necessary.

For the primary outcome, the incidence of postoperative delirium, the intention-to-treat approach and per-protocol (PP) approach will be performed. Pearson's chi-square test will be applied to compare proportions with the primary outcome among groups. The difference among groups will be expressed as RR and 95% confidence interval (CI), while non-inferiority will be identified if the upper limit of 95% CI of RR is < 1.5. For the secondary outcomes, only the PP approach will be used. Normally distributed data will be analysed with one-way analysis of variance (ANOVA); Non-normally distributed data will be analysed with Kruskal-Wallis test. The median

difference will be calculated using the Hodges-Lehmann estimation on the basis of the Kruskal-Wallis test. Adverse events that are presented as incidences will be compared by calculating the 95% CI of the incidence difference: incidence (S group) – incidence (D group), and noninferiority will be achieved if the upper limit of 95% CI is < 5%. The superiority for outcomes will be assessed when noninferiority is verified.

To account for correlation among repeated measurements, such as numeric rating scores for pain and sleep quality, plasma biomarker concentrations, and cognitive function, will be compared using generalised estimating equation analysis among groups. The time to delirium will be calculated with the Kaplan-Meier estimator, and the differences among groups will be assessed by the log-rank test. The number needed to treat will be estimated for the primary outcome.

Missing values will be adjusted using random forest imputation in the missForest package. However, missing values, due to fatigue in the assessment or the patient's inability to cooperate, will be imputed with positive results or means in the corresponding treatment group and time point. If the patient did not have a delirium assessment at all (e.g. dropout or death), no values will be imputed. The last assessment is used to replace the missing value to estimate the incidence of postoperative delirium in patients who are discharged or die within 4 days, while the missing value of assessment per day does not need to be replaced.

The *P* values and CIs reported from one-way ANOVA and Kruskal-Wallis test will be considered to illustrate statistical significance if they are less than 0.017 and 98.3%, respectively, accounting for three pairwise comparisons. The family-wise significance and CI levels among the three groups will be set at 0.05% and 95%, respectively. For the pain intensity score, a 1.1 decrease will be considered the minimal clinically important difference. [49]

Analyses will be conducted using IBM SPSS version 25.0 (SPSS Software, Chicago, IL, USA), R statistics version 4.1.2 (R Project for Statistical

Computing), and GraphPad Prism version 8.0 (GraphPad Software, San Diego, CA, USA).

Ethics and confidentiality

Ethical approval was obtained from the Institutional Review Board of the Cancer Hospital and the Institute of Guangzhou Medical University (ZN202119). The study has also been registered at Chictr.org.cn with the identifier ChiCTR2100052750. The personal information of the participants will not be disclosed unless authorisation is approved. In addition, each participant will be provided with a unique identity code, the information of which will be properly secured. The CRF and Epidata database will be retained for a minimum of 10 years.

Patient and Public Involvement

No patients or public representatives were involved in the design of this trial.

Dissemination

At the end of the trial, we commit to making public disclosure available despite the outcome. Public disclosure will include publication in an appropriate journal or oral presentation at an academic meeting. The PI will be considered the first or corresponding author. The investigators who contribute a minimum of four months to the trial will be co-authors; otherwise, they will be acknowledged in the publication.

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 1.5 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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Figure legends

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram.

Figure 2. Overview of 3-minute Diagnostic Confusion Assessment Method (3D-CAM) assessment.