BMJ Open

Intraoperative infusion of dexmedetomidine for prevention of postoperative delirium in elderly patients undergoing craniotomy: a protocol of randomised clinical trial

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ABSTRACT

Introduction Postoperative delirium (POD) is a common surgical complication. The incidence is 19% in neurological procedures, and advanced age is a risk factor for neurological procedures. Many studies have shown that dexmedetomidine (DEX) reduced the incidence of delirium after non-cardiac surgery in elderly patients. However, there are few studies focus on the effect of DEX on POD in elderly patients undergoing neurosurgery.

Methods and analysis This is a randomised, double-blinded, paralleled-group and controlled trial. Patients older than 65 years and scheduled for elective craniotomy will be randomly assigned to the DEX group and the control group. After endotracheal intubation, patients in the DEX group will be administered with continuous DEX infusion at rate of 0.4 μg/kg/hour until the surgical haemostasis. In the control group, patients will receive the identical volume of normal saline in the same setting. The primary outcome is the incidence of POD during the first 5 days. Delirium will be evaluated through a combination of three methods, including the Richmond Agitation Sedation Scale (RASS), the confusion assessment method for ICU (CAM-ICU) and the 3 min diagnostic interview for CAM (3D-CAM). The RASS, CAM-ICU and 3D-CAM will be evaluated two times per day (08:00–10:00 and 18:00–20:00 hours) during the first postoperative 5 days. Secondary outcomes include pain severity score, quality of recovery, quality of sleep, cognitive function, psychological health state, intraoperative data, physiological status, length of stay in ICU and hospital, hospitalisation costs, non-delirium complications, and 30-day all-cause mortality.

Ethics and dissemination The protocol (V.4.0) has been approved by the medical ethics committee of Beijing Tiantan Hospital, Capital Medical University (KY2021-194-03). The findings of the study will be disseminated in a peer-reviewed journal and at a scientific conference.

Trial registration number NCT05168280.

BACKGROUND

Delirium is one of the most common postoperative complications in aged surgical patients and manifests as an acute confusion state. The incidence of postoperative delirium (POD) varies significantly among different surgical types. Recently, a systematic review conducted for 18 studies showed the incidence of POD was 19% in neurosurgery patients,[1] and over 40% occurred after deep brain stimulation implantation surgery.[2] POD significantly prolongs the length of hospital stay,[3 4] decreases survival rate[5] and is associated with long-term postoperative cognitive dysfunction.[6]

Common risk factors for POD include advanced age, cognitive impairment, neurological disease, pain and longer surgery duration.[7–9] Several studies have demonstrated advanced age significantly increased the incidence of POD in neurosurgical patients.[1 3 5 10 11] Additionally, advanced age could deteriorate the complication (eg, sleep apnoea, heart failure and diabetes).[12] Frailty[13] and malnutrition[14] further indirectly increased the risk of delirium. Cognitive impairment is common among surgical

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The prospective, randomised, placebo-controlled and double-blinded trial is designed to investigate the effect of intraoperative infusion of dexmedetomidine on the incidence of postoperative delirium in elderly patients undergoing craniotomy.

⇒ This trial will add to the evidence on the safety of dexmedetomidine in geriatric neurosurgery.

⇒ We will apply standardised methods to assess the motoric as well as the severity to further characterise postoperative delirium in neurosurgical patients.

⇒ The impact of dexmedetomidine on haemodynamic fluctuation might weaken the efficiency of blinding to the anaesthesiologists.

⇒ This is a single-centre study that limits the generalisation of the conclusion.

patients who develop delirium, lasting up to 1 year postoperatively.[15] In addition, several studies demonstrated intracranial tumour and pain were risk factors of POD.[5 9 16] For patients undergoing neurosurgery with longer surgery duration, elderly patients with intracranial tumour might have low production of acetylcholine, abnormal inflammatory response and poor cognitive function, which may contribute to POD.[17]

Recent studies have demonstrated the benefits of dexmedetomidine (DEX) in reducing the incidence of POD. DEX is a highly selective α-2 adrenoreceptor agonist and provides anxiolysis, sedation and modest analgesia with minimal respiratory depression.[18] Intraoperative application of DEX reduced inflammatory response, stress response and the demand for opioids and benzodiazepines.[19] A large randomised controlled trial (RCT) study[20] showed that DEX significantly reduced the incidence of delirium in elderly patients in non-neurosurgical intensive care unit (ICU).[21] A meta-analysis included 16 RCTs and found DEX reduced the incidence of POD in geriatric non-cardiac surgical patients.[22] Another meta-analysis involving 13 RCTs confirmed that DEX significantly reduced the incidence of POD in adults after non-cardiac surgery.[23] However, the latter meta-analysis failed to suggest the delirium-sparing effect of DEX in patients over 65 years. Moreover, none of these analyses included neurosurgical patients.

Postsynaptic stimulation of α-2 adrenoceptors inhibit sympathetic activity and subsequently cause decreases in blood pressure and heart rate (HR). The meta-analysis showed the prevalence of bradycardia was increased among patients in DEX group undergoing surgery.[24] However, DEX significantly relieved postoperative pain[25 26] and provided stable haemodynamics during intubation[27] and extubation[28] in patients undergoing intracranial tumour surgery. In addition, a pilot RCT supported feasibility of low-dose DEX (0.1 μg/kg/hour) for prevention of POD after intracranial operations.[29] Another RCT reported that 0.5 μg/kg/hour DEX infusion without loading dose maintained mean arterial blood pressure (MAP) and HR, and also shortened recovery time.[30]

According to the previous studies, we propose the hypothesis that intraoperative administration of DEX reduces the incidence of POD in elderly patients undergoing craniotomy compared with placebo, and we will conduct an RCT to test the hypothesis. The study aimed primarily to investigate the effect of intraoperative infusion of DEX on the incidence of POD in elderly patients undergoing craniotomy, second to observe the safety in elderly patients and its effect of relieving pain and improving sleep quality.

METHODS AND ANALYSIS
Study design
This is a randomised, double-blinded, paralleled-group and controlled trial (figure 1) and was conducted at Beijing Tiantan Hospital, Capital Medical University.

The study has been registered on ClinicalTrials.gov (NCT05168280). Ethical approval has been granted by the medical ethics committee of Beijing Tiantan Hospital, Capital Medicine University (KY2021-194-03). Preoperative interviews will be conducted by trained research assistants. Patients and their legal representatives will be informed of study objectives, risks and benefits. Written informed consent will be obtained from legal representatives.

Patient and public involvement
Patients will not be involved in the design or conducting of the study. At the completion of the trial, a manuscript will be prepared to present the trial results. Results of the study will be disseminated to all study participants through their preferred method of communication indicated at the time of enrolment.

Study population
Patients older than 65 years and scheduled for elective craniotomy will be screened for eligibility 1 day before surgery.
Exclusion criteria include:
1. Operation time less than 2 hours.
2. Refusal to provide written informed consent.
3. Cognitive impairment before surgery (Mini-Mental State Examination, MMSE ≤26 or Montreal Cognitive Assessment, MoCA ≤22).
4. Allergic to study drug.
5. Body mass index (BMI) ≤18 or ≥30 kg/m².
6. History of psychotropic drug, anticholinergic drug, antihistamine drug and dopaminergic drugs.
7. History of traumatic brain injury or neurosurgery.
8. Severe bradycardia (HR below 40 beats/min), sick sinus syndrome or second-to-third degree atrioventricular block.
9. Severe liver dysfunction (Child-Pugh grade C) or renal failure (requiring kidney replacement therapy).
10. The functional neurosurgery.

Randomisation and blinding
Block randomisation will be conducted based on a computer-generated table by an independent research assistant, and patients will be randomly assigned to two groups with 1:1 ratio. The block size is 6. The randomisation results are sealed in an opaque envelope and the allocation will not be revealed until all end point events have been evaluated for the last subject. The study agents (DEX 200 μg/2 mL, Jiangsu Hengrui Pharmaceuticals Co, China) will be diluted into 50 mL with normal saline and marked as 'trial drug'. The patients, responsible anaesthesiologists and outcome assessors will all be blinded to the allocation until the completion of the study analysis. The anaesthesiologist will not be involved in postoperative assessments and the postoperative assessors will not be involved in the intraoperative management. The enrolled patients and his/her legal representatives will also be blinded to the research treatment.
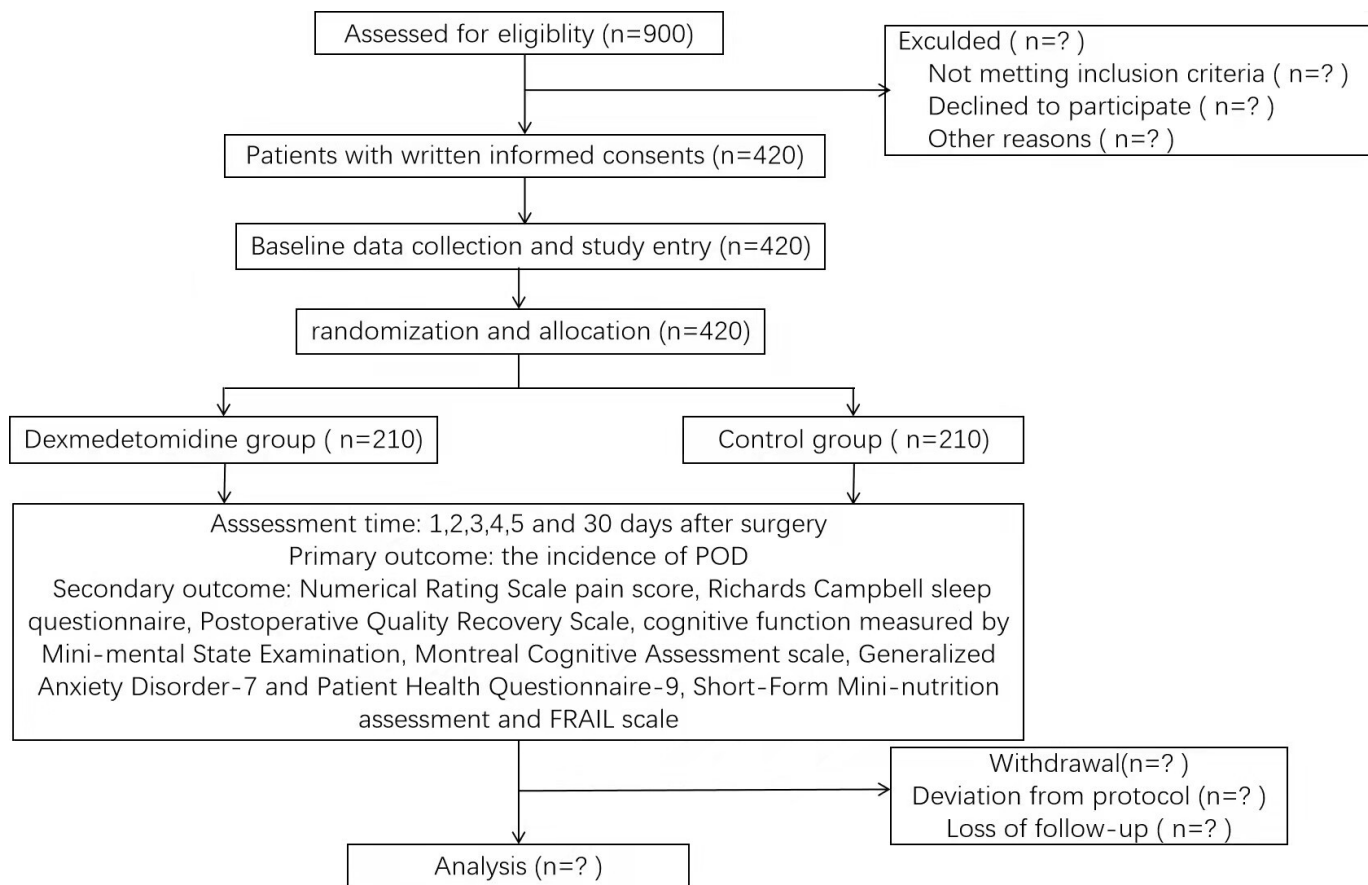
Figure 1 Study flow chart. POD, postoperative delirium. FRAIL, the FRAIL scale is a simple five-point screen that measures fatigue, resistance, ambulation, illness, and weight loss.

Intervention and grouping

After endotracheal intubation, patients in DEX group will be administered with continuous DEX infusion at rate of 0.4 μg/kg/hour until the start of surgical haemostasis. In the control group, patients will receive the identical volume of normal saline in the same setting.

Concomitant treatment

Routine monitoring will include ECG, non-invasive blood pressure, pulse oxygen saturation, body temperature and bispectral index (BIS). Peripheral venous access and peripheral arterial catheterisation will be established before anaesthesia induction. Continuous arterial pressure, urine output and end-tidal carbon dioxide will be monitored after anaesthesia induction. BIS will be electronically recorded. Physiological variables will be recorded at the critical time points of operation.

Midazolam and penehyclidine will not be used before surgery. Propofol (1.5–2.5 mg/kg) or etomidate (0.3–0.4 mg/kg), sufentanil (0.3–0.4 μg/kg) and rocuronium (0.6 mg/kg) or cis-atracurium (0.2 mg/kg) will be administered for anaesthesia induction. After endotracheal intubation, mechanical ventilation will be performed to maintain $PaCO_2$ at the range between 35 and 45 cmH_2O. Tidal volume will be set of 6–8 mL/kg, respiratory rate of 12–14/min, inspiration-exhalation ratio of 1:2 and a fraction of inspired oxygen of 60% at a flow rate of 2 L/min.

Before the head frame placement, 0.5% ropivacaine will be used for cranial nerve block. Anaesthesia will be maintained by intravenous-inhalation combined anaesthesia. The minimal alveolar concentration of sevoflurane is maintained at 0.4–0.6, and the BIS will be maintained between 40 and 60 by infusion of propofol (3–5 mg/kg/hour) and remifentanil (0.05–0.2 μg/kg/min). Sufentanil will be supplemented as needed (0.1–0.2 μg/kg) at the noxious stimulation. Blood pressure and HR will be maintained within±20% of baseline, and vasoactive drugs will be used. Sevoflurane will be discontinued at the bone flap replacement. Propofol and remifentanil infusion will be ceased at the end of the operation. Postoperative controlled intravenous analgesia will be filled with sufentanil (2 ug/kg) and ondansetron (16 mg) diluted with 100 mL normal saline. The background dose is set of 2 mL/hour and each single bolus dose of 0.5 mL, and the locking time of 15 min.

Data collection

An independent research assistant will initiate baseline information collection. Demographics, medical history, medication history, supplementary examination and preoperative assessment will be collected. The preoperative assessment includes Short-Form Mini-Nutrition Assessment (MNA-SF)[31] and FRAIL scale.[32] The primary and secondary outcome assessment will be performed

by the trained research assessors who are blinded to the group allocation. The training meeting of research assessors will be organised by the principal investigator. Every assessor will be trained and evaluated the assessment accuracy. All personal information will be kept confidential for research purposes only.

Outcome measures

The primary outcome is the incidence of POD during the first 5 days. Delirium will be evaluated two times per day (08:00–0:00 and 18:00–20:00 hours) during the first postoperative 5 days through three methods, including the Richmond Agitation Sedation Scale (RASS),[33] the confusion assessment method for ICU (CAM-ICU)[34] and the 3 min diagnostic interview for CAM (3D-CAM).[35] The arousal level will be first assessed through RASS. If the patient is not responsive to verbal stimuli (ie, RASS score ≤−4), the remaining assessment will be aborted and the patient is recorded as comatose. When the RASS score ≥−3, delirium will be evaluated.

The CAM-ICU consists of four key features: (1) acute onset of a change in mental status or a fluctuating level of consciousness; (2) inattention; (3) disorganised thinking and (4) an altered level of consciousness.[34] 3D-CAM refines the four characteristics of delirium assessment into 20 questions, which is convenient for evaluation.[36] Delirium is diagnosed when the patient displays the first and second features, plus either the third or fourth feature. Delirium patients will be divided into three motoric subtypes: hyperactive delirium (continuous RASS score 1–4), hypoactive delirium (persistent RASS score −3–0) and mixed delirium (both subtypes at different points in time, changes in RASS scores).[37]

In addition, the Delirium Rating Scale-Revised-98 (DRS-R-98) will be applied to evaluate the severity of delirium.[38] The DRS-R-98 is a 16-item clinician-rated scale with 2 sections composed of 13 severity items and 3 diagnostic items. Severity items are each rated from 0 to 3 points, and diagnostic items from 0 to 2 or 3 points. The assessors will be trained by psychiatrists before the study initiation.

The secondary outcomes include other efficacy and safety outcomes.

1. Pain severity score will be assessed first 5 days after surgery. The degree of surgical incision pain will be assessed at rest and on movement by Numerical Rating Scale (NRS).[39] NRS ranges from 0 to 10, with the highest score indicating the worst pain.
2. The quality of recovery will be assessed by 15-item Quality of Recovery Questionnaire (QoR-15) postoperative 1 day. The QoR-15 measures cognitive function, physical activity, language and mood on a 150-point scale, with higher scores indicating better quality of recovery.[40]
3. Quality of sleep will be assessed by the Richards Campbell Sleep Questionnaire (RCSQ) from the first to the third day after surgery. RCSQ is mainly used to evaluate the sleep quality of the previous night. The scale comprises five items: sleep depth, sleep latency, wake up times, relapse to sleep and overall sleep quality.[41] The 0–100 mm Visual Analogue Scale (1 mm=1 point) is used. The total score of the scale is the average of five items, and the lower the score, the better the sleep quality.
4. Cognitive function will be assessed 1 day before surgery and 5 days after surgery using MMSE scale and MoCA scale. MMSE includes seven items: time orientation, place orientation, immediate memory, attention and calculation, delayed memory, language and visual space.[42] MoCA would appear to be a useful brief tool to assess cognition in those with mild cognitive impairment.[43]
5. Psychological health state will be assessed by Generalised Anxiety Disorder-7[44] and Patient Health Questionnaire-9[45] 1 day before surgery and postoperative 5 days. There areseven and nine items to screen anxiety and depression, respectively. The point of each item is 3. The total points >4 will be regarded as anxiety and depression.
6. Intraoperative data include total dose of anaesthetics, BIS value and cardiovascular adverse events will be recorded and classified as hypotension (systolic blood pressure <95 mm Hg or lower than 30% baseline), hypertension (systolic blood pressure ≥180 mm Hg or higher than 30% baseline), bradycardia (HR <40 beats/min), tachycardia (HR ≥100 beats/min) or hypoxaemia (pulse oxygen saturation <90%).
7. Length of stay in ICU and hospital, hospitalisation costs, non-delirium complications, and 30-day all-cause mortality. Non-delirium complications include cardiac arrest, infection of the incision, sepsis, intracranial haematoma, severe intracranial oedema (base on brain images), stroke, myocardial infarction, pulmonary infection and embolism.
8. The physiological status of the patients will be assessed by MNA-SF and FRAIL scale 1 day before surgery. MNA-SF includes six questions about loss of appetite, weight loss, mobility, psychological stress or acute disease, neuropsychological problems, BMI or calf circumference in the past 3 months, with 4 scoring grades (0, 1, 2, 3) and a total score of 14 points. A total score of 12–14 is normal nutritional status, 8–11 is at risk of malnutrition and 0–7 is malnutrition.[31] The FRAIL scale is a simple five-point screen that measures fatigue, resistance (ability to climb one flight of stairs), ambulation (ability to walk one block), illness (more than five past or current diagnoses) and weight loss (more than 5%).[32] Each positive response within a domain scores 1 point, yielding a maximum score of 5. Higher scores indicate increased frailty; and a score of 3 or more and a score of 1–2 are defined as frail and prefrail, respectively.

Data management and monitoring

Figure 2 shows data collection at each time point. All the data will be recorded in a case report form. Raw and non-numerical data will be coded for data storage,

			STUDY PERIOD					
	Enrolment	Allocation	Post-allocation					
			Post-craniotomy (day)					
Timepoint	-1 day	Surgery	1	2	3	4	5	30(one time)
			ENROLLMENT					
Eligibility screen	X							
Informed consent	X							
Allocation		X						
			INTERVATIONS					
Dexmedetomidine group		X						
Control group		X						
			ASSESSMENTS					
Baseline variables		X	X	X	X	X	X	
Intraoperative data		X						
15-item quality of recovery questionnaire			X					
Richmond Agitation Sedation Scale			X	X	X	X	X	
Confusion Assessment Method for Intensive Care Unit			X	X	X	X	X	
3-Minute Diagnostic Interview for CAM			X	X	X	X	X	
Mini-mental State Examination score	X						X	
Montreal Cognitive Assessment scale	X						X	
Generalized Anxiety Disorder-7 and Patient Health Questionnaire-9	X						X	
Short-Form Mini-nutrition assessment	X							
FRAIL scale	X							
Numerical Rating pain Score			X	X	X	X	X	
Richards Campbell sleep questionnaire			X	X	X			
Non-delirium complications			X	X	X	X	X	X
All-cause death								X

Figure 2 Data collection at each time point. CAM, confusion assessment method; NRS, Numerical Rating Scale.

review, tabulation and analysis. Data will be entered, stored and monitored securely in an electronic database at the medical centre. Double data entry will be applied. All data-entering individuals will request to use standardised terminologies and abbreviations. Training will be performed regarding entering data on forms, data discrepancy queries and general concerns about overall quality. Any missing data or errors will be summarised along with the detailed descriptions and queried by checking the original forms.

The electronic data will be saved in a database with password protection, and the passwords will be changed on a regular basis. Database backup will be performed once a month. All the original files will be maintained in storage for 5 years after completion of the study.

Reporting of adverse events

The adverse effect will be closely monitored from the start of infusion to the 5 days after the surgery. Investigators will record all the adverse effects, including the type, the diagnosis time, the duration and the consequences. Responsible anaesthesiologists have the obligation to stop the infusion of study agent and record the reasons. All adverse events will be closely monitored until a stable situation has been reached. The principal investigator will be informed of any serious adverse events and determine the severity and causality of these events. All adverse events associated with the study will be recorded and reported to the ethics committee as part of the annual report. The principal investigator will be responsible for the adverse events.

Sample size estimation and statistical analysis

The incidence of POD is about 15%–20% in patients undergoing neurosurgery,[1] and a number of studies have shown that age is the independent risk factors of POD in neurosurgery patients.[19] Therefore, the incidence of POD might be higher in elderly neurosurgery patients. According to a previously meta-analysis, intraoperative application of DEX could reduce the incidence of POD by approximately 54%.[21] We assumed a 20% incidence of POD in this study and a 50% reduction (from 20% to 10%) in DEX group. With a significance and power set at 0.05 (two sided) and 80%, respectively, the sample size required to detect the difference is 394 patients. Considering about 5% of the lost to follow-up, 420 (210 in each group) patients need to be enrolled.

The analysis will be done by SPSS software (V.22.0). The continuous variables will be described with mean and SD or median and IQR. Categorical data will be presented with counts (percentage). The independent sample t-test will be used to compare the normally distributed continuous data, and the independent sample Mann-Whitney U test will be used to compare the non-normally distributed continuous data. The difference in cumulative incidence of POD between the DEX and control groups will be analysed by the $\chi 2$ test. Kaplan-Meier survival analysis will be used to analyse time-to-event data, and logarithmic rank test will be used to evaluate differences between groups. The primary outcome will be analysed in the subgroups, including delirium severity, delirium motoric subtype, gender, American Society of Anesthesiologists physical status, tumour type, study drug dose and anaesthesia duration.

Other secondary outcomes such as cognitive score, quality of sleep, postoperative quality of recovery and intraoperative haemodynamic parameters will be analysed by t-test or Mann-Whitney U test, or repeated measurements. We will apply the intention-to-treat analysis on the primary outcome according to group allocation. In addition, missing data will be imputed by using the worst-case imputation scenarios, and will be analysed in sensitivity analysis.

DISCUSSION

The prospective, randomised, placebo-controlled and double-blinded trial is designed to investigate the effect of intraoperative infusion of DEX on the incidence of POD in elderly patients undergoing brain tumour resections.

The perioperative haemodynamic stability is quite important for elderly neurosurgical patients. Intraoperative hypertension increases the risk of massive bleeding, brain oedema and postoperative haematoma.[46] In addition, lower intraoperative diastolic pressure was independently associated with perioperative ischaemic stroke in patients underwent brain tumour resections.[47] An intravenous bolus of DEX leads to a biphasic blood pressure response. DEX infusion induces an initial transient increase in MAP, followed by a decrease in MAP and HR.

The omission of the DEX loading bolus can prevent initial hypertension.[48] Although DEX has been confirmed to reduce the incidence of POD, its adverse effects of bradycardia and hypotension cannot be ignored.[24] Some case reports indicated DEX-related cardiac arrest following severe bradycardia. However, most of the adverse events associated with DEX occurred during or shortly after load infusion.[49] Therefore, considering the frail condition of elderly patients and the long duration of neurosurgery, we will not apply loading dose in order to reduce drug-related haemodynamic fluctuation. In addition, the bradycardia induced by DEX infusion may interfere with the anaesthetists blindness to the intervention. However, both high intracranial pressure and intraoperative use of remifentanil could cause bradycardia, so the bradycardia is not necessarily due to DEX. In addition, both DEX and placebo will be kept in syringes (50 mL) with the same appearance and labelled with 'trial drug'. The anaesthesiologists, outcome assessors and patients will be blinded to the type of drug administered during surgery. The anaesthesiologists will not be involved in postoperative assessments and the postoperative outcome assessors will not be involved in the intraoperative management. In the final analysis, we will analyse all intraoperative medication types and dosage.

The haemodynamic change caused by DEX is dose-dependent.[50] An RCT has shown that the protective effects of DEX in delirium are also dose-dependent.[20] Previous studies have demonstrated that continuous intraoperative infusion DEX of 0.2–0.7 µg/kg/hour (with or without loading dose) can reduce the incidence of POD in elderly patients.[51 52]

In another RCT, intraoperative infusion DEX by loading dose of 0.6 µg/kg and maintenance dose of 0.5 µg/kg/hour showed that intraoperative infusion of DEX reduced the incidence of POD in elderly non-cardiac patients, but the rate of bradycardia with treatment (p=0.013) was higher.[53] However, another study showed the negative results for prevention of POD (p=0.94) by applied DEX maintenance dose of 0.5 µg/kg/hour until 2 hours postoperatively, while intraoperative bradycardia was not statistically significant.[54] Xie and Xi and He *et al* found that intraoperative infusion DEX by loading dose of 0.5 µg/kg and maintenance dose of 0.4 µg/kg/hour reduced POD in elderly orthopaedic patients.[55 56] In a large RCT study,[57] intraoperative continuous infusion DEX of 0.2–0.4 µg/kg/hour also effectively reduced the incidence of POD in elderly patients. Based on these conclusions, the intraoperative infusion DEX of 0.4 µg/kg/hour might be effective and safe for elderly neurosurgery patients to prevent POD.

There are other delirium prevention medications, such as haloperidol, ziprasidone and ketamine in clinical setting. However, an RCT study indicated the use of haloperidol or ziprasidone in patients with delirium in the ICU did not significantly alter the duration of delirium compared with placebo.[58] In addition, the ketamine also failed to prevent the POD, according to a randomised, placebo-controlled,

double-blind clinical trial.[59] In our study, the neurosurgeon may administer haloperidol or other medications to patients with POD after surgery, and all postoperative medications will be fully recorded in our case report forms.

In summary, our study is a prospective, randomised, placebo-controlled and double-blinded trial that aims to investigate the effect of intraoperative infusion of DEX on the incidence of POD in elderly patients undergoing craniotomy. If the result of this study is positive, we will provide evidence of prevention and treatment of POD for elderly neurosurgery patients.

Timeline
The study will take approximately 2 years to complete enrolment and outcome assessment. The recruitment started on 18 July 2022. We expect to complete the study by May 2024.

Protocol amendment
The chief investigator will be responsible for amending the protocol and making final decision. If there is any modification (eg, changes to eligibility criteria, outcomes, analyses), the principal investigator will communicate and gain approval from the medical ethics committee prior to implementation.

Dissemination
The results of this study will be disseminated through presentations at scientific conferences and publication in scientific journals.

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REFERENCES
1 Kappen PR, Kakar E, Dirven CMF, et al. Delirium in neurosurgery: a systematic review and meta-analysis. *Neurosurg Rev* 2022;45:329–41.

2 Tanaka M, Tani N, Maruo T, et al. Risk factors for postoperative delirium after deep brain stimulation surgery for parkinson disease. *World Neurosurg* 2018;114:e518–23.

3 Chen H, Jiang H, Chen B, et al. The incidence and predictors of postoperative delirium after brain tumor resection in adults: a cross-sectional survey. *World Neurosurg* 2020;140:e129–39.

4 French J, Weber T, Ge B, et al. Postoperative delirium in patients after brain tumor surgery. *World Neurosurg* 2021;155:e472–9.

5 Flanigan PM, Jahangiri A, Weinstein D, et al. Postoperative delirium in glioblastoma patients: risk factors and prognostic implications. *Neurosurgery* 2018;83:1161–72.

6 Goldberg TE, Chen C, Wang Y, et al. Association of delirium with long-term cognitive decline: a meta-analysis. *JAMA Neurol* 2020;77:1373–81.

7 Inouye SK, Westendorp RGJ, Saczynski JS. Delirium in elderly people. *Lancet* 2014;383:911–22.

8 Jin Z, Hu J, Ma D. Postoperative delirium: perioperative assessment, risk reduction, and management. *Br J Anaesth* 2020;125:492–504.

9 Wang C-M, Huang H-W, Wang Y-M, et al. Incidence and risk factors of postoperative delirium in patients admitted to the ICU after elective intracranial surgery: a prospective cohort study. *Eur J Anaesthesiol* 2020;37:14–24.

10 Harasawa N, Mizuno T. A novel scale predicting postoperative delirium (pod) in patients undergoing cerebrovascular surgery. *Arch Gerontol Geriatr* 2014;59:264–71.

11 Wu X, Sun W, Tan M. Incidence and risk factors for postoperative delirium in patients undergoing spine surgery: a systematic review and meta-analysis. *Biomed Res Int* 2019;2019:2139834.

12 Ansaloni L, Catena F, Chattat R, et al. Risk factors and incidence of postoperative delirium in elderly patients after elective and emergency surgery. *Br J Surg* 2010;97:273–80.

13 Susano MJ, Grasfield RH, Friese M, et al. Brief preoperative screening for frailty and cognitive impairment predicts delirium after spine surgery. *Anesthesiology* 2020;133:1184–91.

14 Zhao Y, Ge N, Xie D, et al. The geriatric nutrition risk index versus the mini-nutritional assessment short form in predicting postoperative delirium and hospital length of stay among older non-cardiac surgical patients: a prospective cohort study. *BMC Geriatr* 2020;20:107.

15 Saczynski JS, Marcantonio ER, Quach L, et al. Cognitive trajectories after postoperative delirium. *N Engl J Med* 2012;367:30–9.

16 Ma J-H, Liu Y-F, Hong H, et al. Effect of acute pain on the association between preoperative cognitive impairment and postoperative delirium: a secondary analysis of three trials. *Br J Anaesth* 2022;

17 Hadjivassiliou M, Tooth CL, Romanowski CA, et al. Aneurysmal SAH: cognitive outcome and structural damage after clipping or coiling. *Neurology* 2001;56:1672–7.

18 Bhana N, Goa KL, McClellan KJ. Dexmedetomidine. *Drugs* 2000;59:263–8.

19 Duan X, Coburn M, Rossaint R, et al. Efficacy of perioperative dexmedetomidine on postoperative delirium: systematic review and meta-analysis with trial sequential analysis of randomised controlled trials. *Br J Anaesth* 2018;121:384–97.

20 Su X, Meng Z-T, Wu X-H, et al. Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: a randomised, double-blind, placebo-controlled trial. *Lancet* 2016;388:1893–902.

21 Ng KT, Shubash CJ, Chong JS. The effect of dexmedetomidine on delirium and agitation in patients in intensive care: systematic review and meta-analysis with trial sequential analysis. *Anaesthesia* 2019;74:380–92.

22 Lin C, Tu H, Jie Z, et al. Effect of dexmedetomidine on delirium in elderly surgical patients: a meta-analysis of randomized controlled trials. *Ann Pharmacother* 2021;55:624–36.

23 Qin C, Jiang Y, Lin C, et al. Perioperative dexmedetomidine administration to prevent delirium in adults after non-cardiac surgery: a systematic review and meta-analysis. *J Clin Anesth* 2021;73:110308.

24 Peng K, Ji F-H, Liu H-Y, et al. Effects of perioperative dexmedetomidine on postoperative mortality and morbidity: a systematic review and meta-analysis. *Clin Ther* 2019;41:138–54.

25 Peng K, Jin X, Liu S, et al. Effect of intraoperative dexmedetomidine on post-craniotomy pain. *Clin Ther* 2015;37:1114–21.

26 Kang R, Jeong JS, Ko JS, et al. Intraoperative dexmedetomidine attenuates norepinephrine levels in patients undergoing transsphenoidal surgery: a randomized, placebo-controlled trial. *BMC Anesthesiol* 2020;20:100.

27 Yun Y, Wang J, Tang RR, et al. Effects of an intraoperative dexmedetomidine bolus on the postoperative blood pressure and pain subsequent to craniotomy for supratentorial tumors. *J Neurosurg Anesthesiol* 2017;29:211–8.

28 Tanskanen PE, Kyttä JV, Randell TT, et al. Dexmedetomidine as an anaesthetic adjuvant in patients undergoing intracranial tumour

surgery: a double-blind, randomized and placebo-controlled study. *Br J Anaesth* 2006;97:658–65.

29 He X, Cheng K-M, Duan Y-Q, *et al*. Feasibility of low-dose dexmedetomidine for prevention of postoperative delirium after intracranial operations: a pilot randomized controlled trial. *BMC Neurol* 2021;21:472.

30 Ibrahim IM, Hassan R, Mostafa RH, *et al*. Efficacy of dexmedetomidine infusion without loading dose on hemodynamic variables and recovery time during craniotomy: a randomized double-blinded controlled study. *Anesth Pain Med* 2021;11:e113410.

31 Rubenstein LZ, Harker JO, Salvà A, *et al*. Screening for undernutrition in geriatric practice: developing the short-form mini-nutritional assessment (MNA-SF). *J Gerontol A Biol Sci Med Sci* 2001;56:M366–72.

32 Abellan van Kan G, Rolland YM, Morley JE, *et al*. Frailty: toward a clinical definition. *J Am Med Dir Assoc* 2008;9:71–2.

33 Ely EW, Truman B, Shintani A, *et al*. Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond agitation-sedation scale (RASS). *JAMA* 2003;289:2983–91.

34 Ely EW, Inouye SK, Bernard GR, *et al*. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA* 2001;286:2703–10.

35 Marcantonio ER, Ngo LH, O'Connor M, *et al*. 3D-CAM: derivation and validation of a 3-minute diagnostic interview for CAM-defined delirium: a cross-sectional diagnostic test study. *Ann Intern Med* 2014;161:554–61.

36 Kuczmarska A, Ngo LH, Guess J, *et al*. Detection of delirium in hospitalized older general medicine patients: a comparison of the 3D-CAM and CAM-ICU. *J Gen Intern Med* 2016;31:297–303.

37 Cascella M, Fiore M, Leone S, *et al*. Current controversies and future perspectives on treatment of intensive care unit delirium in adults. *World J Crit Care Med* 2019;8:18–27.

38 Trzepacz PT, Mittal D, Torres R, *et al*. Validation of the delirium rating scale-revised-98: comparison with the delirium rating scale and the cognitive test for delirium. *J Neuropsychiatry Clin Neurosci* 2001;13:229–42.

39 Karcioglu O, Topacoglu H, Dikme O, *et al*. A systematic review of the pain scales in adults: which to use? *Am J Emerg Med* 2018;36:707–14.

40 Stark PA, Myles PS, Burke JA. Development and psychometric evaluation of a postoperative quality of recovery score: the QoR-15. *Anesthesiology* 2013;118:1332–40.

41 Richards KC, O'Sullivan PS, Phillips RL. Measurement of sleep in critically ill patients. *J Nurs Meas* 2000;8:131–44.

42 Galea M, Woodward M. Mini-mental state examination (MMSE). *Aust J Physiother* 2005;51:198.

43 Jia X, Wang Z, Huang F, *et al*. A comparison of the mini-mental state examination (MMSE) with the Montreal cognitive assessment (MoCA) for mild cognitive impairment screening in Chinese middle-aged and older population: a cross-sectional study. *BMC Psychiatry* 2021;21:485.

44 Spitzer RL, Kroenke K, Williams JBW, *et al*. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med* 2006;166:1092–7.

45 Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med* 2001;16:606–13.

46 Jian M, Li X, Wang A, *et al*. Flurbiprofen and hypertension but not hydroxyethyl starch are associated with post-craniotomy intracranial haematoma requiring surgery. *Br J Anaesth* 2014;113:832–9.

47 Bette S, Wiestler B, Wiedenmann F, *et al*. Safe brain tumor resection does not depend on surgery alone - role of hemodynamics. *Sci Rep* 2017;7:5585.

48 Castillo RL, Ibacache M, Cortínez I, *et al*. Dexmedetomidine improves cardiovascular and ventilatory outcomes in critically ill patients: basic and clinical approaches. *Front Pharmacol* 2019;10:1641.

49 Lee S. Dexmedetomidine: present and future directions. *Korean J Anesthesiol* 2019;72:323–30.

50 Bloor BC, Ward DS, Belleville JP, *et al*. Effects of intravenous dexmedetomidine in humans. *Anesthesiology* 1992;77:1134–42.

51 Lee C, Lee CH, Lee G, *et al*. The effect of the timing and dose of dexmedetomidine on postoperative delirium in elderly patients after laparoscopic major non-cardiac surgery: a double blind randomized controlled study. *J Clin Anesth* 2018;47:27–32.

52 van Norden J, Spies CD, Borchers F, *et al*. The effect of peri-operative dexmedetomidine on the incidence of postoperative delirium in cardiac and non-cardiac surgical patients: a randomised, double-blind placebo-controlled trial. *Anaesthesia* 2021;76:1342–51.

53 Li C-J, Wang B-J, Mu D-L, *et al*. Randomized clinical trial of intraoperative dexmedetomidine to prevent delirium in the elderly undergoing major non-cardiac surgery. *Br J Surg* 2020;107:e123–32.

54 Deiner S, Luo X, Lin H-M, *et al*. Intraoperative infusion of dexmedetomidine for prevention of postoperative delirium and cognitive dysfunction in elderly patients undergoing major elective noncardiac surgery: a randomized clinical trial. *JAMA Surg* 2017;152:e171505.

55 Xie S, Xie M. Effect of dexmedetomidine on postoperative delirium in elderly patients undergoing hip fracture surgery. *Pak J Pharm Sci* 2018;31(5(Special)):2277–81.

56 He F, Shen L, Zhong J. A study of dexmedetomidine in the prevention of postoperative delirium in elderly patients after vertebral osteotomy. *Int J Clin Exp Med* 2018;11:4984–90.

57 Liu Y, Ma L, Gao M, *et al*. Dexmedetomidine reduces postoperative delirium after joint replacement in elderly patients with mild cognitive impairment. *Aging Clin Exp Res* 2016;28:729–36.

58 Girard TD, Exline MC, Carson SS, *et al*. Haloperidol and ziprasidone for treatment of delirium in critical illness. *N Engl J Med* 2018;379:2506–16.

59 Hollinger A, Rüst CA, Riegger H, *et al*. Ketamine vs. haloperidol for prevention of cognitive dysfunction and postoperative delirium: a phase IV multicentre randomised placebo-controlled double-blind clinical trial. *J Clin Anesth* 2021;68:110099.