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Effect of dexmedetomidine on postoperative delirium in patients undergoing brain tumour resections: study protocol of a randomised controlled trial

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ABSTRACT

Introduction Postoperative delirium (POD) is a common complication. The incidence of POD is about 25% in non-cardiac surgery and ranges from 10% to 30% in neurological procedures. A lot of trials show that dexmedetomidine might help to reduce the incidence of delirium in patients undergoing non-cardiac surgery. However, the impact of dexmedetomidine on POD for patients undergoing craniotomy and tumour resections remains unclear.

Methods and analysis The study is a prospective, single-centre, randomised, double-blinded, paralleled-group controlled trial. Patients undergoing elective frontotemporal tumour resections will be randomly assigned to the dexmedetomidine group and the control group. After endotracheal intubation, patients in the dexmedetomidine group will be administered with a loading dose of dexmedetomidine 0.6 µg/kg in 10 min followed by continuous infusion at a rate of 0.4 µg/kg/hour until the start of dural closure. In the control group, patients will receive the identical volume of normal saline in the same setting. The primary outcome will be the cumulative incidence of POD within 5 days. The delirium assessment will be performed by using the confusion assessment method in the first 5 consecutive days after surgery. Secondary outcomes include the pain severity assessed by Numerical Rating Scale pain score, quality of postoperative sleep assessed by the Richards Campbell sleep questionnaire and postoperative quality of recovery from anaesthesia by the Postoperative Quality Recovery Scale.

Ethics and dissemination The protocol (V.1.0, 10 November 2020) has been approved by the Ethics Review Committee of the Chinese Clinical Trial Registry (number ChiECRCT-20200436). The findings of the study will be disseminated in a peer-reviewed journal and at a scientific conference.

Trial registration number NCT04674241.

Strengths and limitations of this study

- This prospective, randomised, placebo-controlled and double-blinded trial is designed to investigate the intraoperative infusion of dexmedetomidine on the incidence of delirium after brain tumour resections.
- The results will optimise strategies to prevent delirium in patients undergoing frontotemporal tumour resections to improve early recovery.
- The sample size is estimated according to the previous studies conducted in the same medical centre, which might guarantee the size adequacy.
- The data will be from a single centre that might limit the generalisation of the conclusion.

BACKGROUND

Delirium is an acute brain dysfunction characterised by disturbance in attention, cognition, consciousness level, sleep cycle and mood.[1]

Postoperative delirium (POD) is a common but serious complication that usually occurs 2–5 days after surgery.[2] POD prolongs the length of hospital stay, increases mortality and is closely related to long-term postoperative cognitive dysfunction.[3–5] In general, the incidence of POD ranges from 10% to 60%, but in high-risk populations, such as the aged, patients in intensive care units (ICU) and with previous cognitive impairment, the incidence of POD is as high as 40% to 60%.[6 7] Neurosurgical patients are also potential candidates for POD.[8] Previous studies have reported that the total incidence of POD in neurosurgical patients is between 10% and 30%.[9 10] In our institution, the POD was reported in 30% of glioma patients,[10] while Krewulak *et al* found that POD incidence is even as high as 40% in neurosurgical ICU.[11]

Several risk factors predispose the neurosurgical population to the development of POD. Previous studies suggested that frontal approach[10] and tumour located at the temporal lobe (NCT03033693, result not

published) were independent risk factors for POD after supratentorial tumour resections. Tumours located in the frontal and temporal lobe could lead to different degrees of cognitive impairment resulting in POD.[12] A recent retrospective cohort study showed that tumours invading the bilateral cerebral hemisphere and a diameter more than 5 cm were also risk factors for POD. In addition, intraoperative haemodynamic instability, long operation duration and postoperative pain are associated with POD,[13] while adequate postoperative analgesia helped to prevent POD in neurosurgery.[14]

The mechanisms of POD in neurosurgical patients are not clear. Patients with brain tumours are always with increased intracranial pressure, decreased acetylcholine neurotransmitters and neuronal inflammatory response, all of which may contribute to the POD development.[15] The process of tumour resection, especially the extensive resection for large tumours, damages the blood–brain barrier and, hence, results in inflammatory markers entrance into the blood circulation, leading to new cognitive dysfunction and POD.[16] Perioperative pharmacological intervention such as dexmedetomidine has some advantages in neuroanaesthesia with respect to systemic and intracranial characteristics, which may be a candidate treatment to prevent POD.

Dexmedetomidine is a highly selective central presynaptic α2-adrenergic agonist. It not only provides sedation and analgesia but also has little influence on respiratory function.[17] The analgesic benefit reduces demand for opioids and lowers postoperative pain scores related to postoperative agitation and delirium.[18 19] Yun *et al* investigated 150 patients undergoing supratentorial tumour surgery and found dexmedetomidine decreased the pain score within 4 hours after surgery.[20] A recent meta-analysis based on eight randomised controlled trials (RCT) in 1425 ICU patients suggested that the application of dexmedetomidine significantly reduced the incidence of delirium in ICU.[21 22] In an RCT involving 619 aged patients undergoing non-cardiac surgery, compared with normal saline, intraoperative administration of dexmedetomidine (0.5 µg/kg/hour) remarkably decreased the incidence of POD.[23] On the other hand, dexmedetomidine provides stable haemodynamics and maintains an unchanged cerebral metabolic rate equivalent.[24] A recent RCT indicated that target-controlled intraoperative infusion of dexmedetomidine significantly reduced the tachycardia response during intubation and hypertension response during extubation.[25] Tang *et al* randomised 112 patients undergoing intracranial aneurysm embolisation and found dexmedetomidine decreased the incidence of POD.[26] However, the effect of intraoperative dexmedetomidine infusion on POD in patients undergoing craniotomy and tumour resections is still unclear.

According to the previous studies, we propose the hypothesis that intraoperative administration of dexmedetomidine reduces the incidence of POD in patients undergoing frontotemporal tumour resections, and we will conduct a RCT to test the hypothesis.

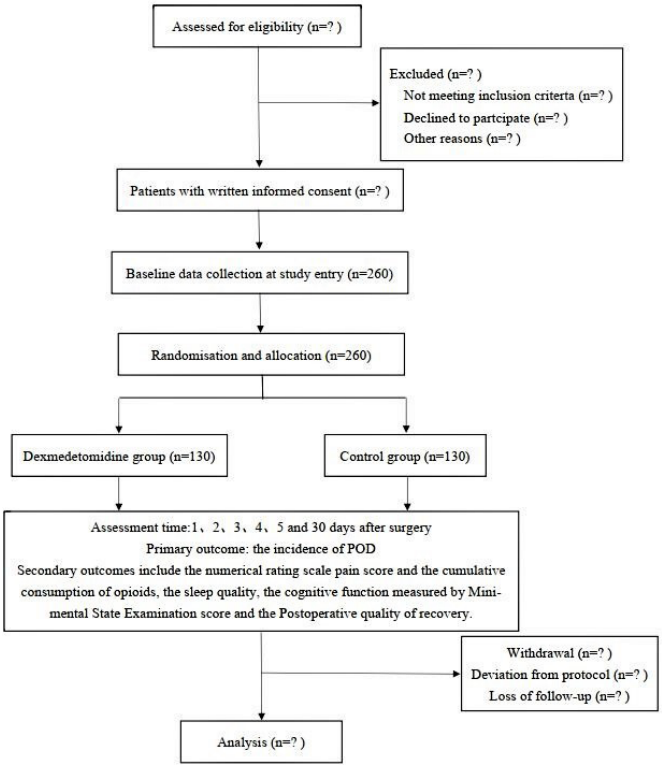

Figure 1 Consolidated Standards of Reporting Trials flow diagram. POD, postoperative delirium.

METHODS AND ANALYSIS

Study design

This is a single-centre, randomised, double-blinded, paralleled-group and controlled trial (figure 1) and will be conducted at Beijing Tiantan Hospital, Capital Medical University. The study has been registered on ClinicalTrials.gov on 19 December 2020 and approved by the Ethics Review Committee of Chinese Clinical Trial Registry (number ChiECRCT-20200436). Preoperative interviews will be conducted by trained research assistants. Patients will be informed of study objectives, risks and benefits. Written informed consent will be obtained from legal representatives.

Patient and public involvement

Patients are not 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 final study will be disseminated to all study participants through their preferred method of communication indicated at the time of enrolment. The burden of intervention will not be taken by participants themselves.

Study population

Patients with frontotemporal brain tumours older than 18 years and scheduled for elective craniotomy will be screened for eligibility 1 day before surgery.

Exclusion criteria include:

1. Refusal to provide written informed consent.
2. Preoperative severe cognitive impairment (mini-mental state examination, MMSE ≤20).

3. Allergic to the study drug.
4. History of psychotropic drugs.
5. Pregnant or lactating women.
6. History of traumatic brain injury or neurosurgery.
7. Severe bradycardia (heart rate less than 40 bpm), sick sinus syndrome or second-to-third degree atrioventricular block.
8. Severe haepatic or renal dysfunction.

Randomisation and blinding

Randomisation will be conducted based on a computer-generated table by an independent research assistant who will pack the allocation sequence in opaque envelopes with identical shape and size and then distribute the envelope to the researcher. The researcher will open the envelopes and prepare the research drug based on the grouping. The study agents (dexmedetomidine 200 µg/2 mL) will be diluted into 50 mL with normal saline and marked as 'trial drug'. Patients will be randomly assigned to two groups with a 1: 1 ratio. Allocation will be concealed until the database lock. The patients, responsible anaesthesiologists and outcome assessors, will all be blinded to the allocation until the completion of the study analysis. The enrolled patients and his/her legal representatives will also be blinded to the research treatment.

Intervention and grouping

After endotracheal intubation, patients in dexmedetomidine group will be administered with a loading dose of dexmedetomidine 0.6 µg/kg for 10 min followed by continuous infusion at a rate of 0.4 µg/kg/hour until the start of dural closure. In the control group, patients will receive the identical volume of normal saline in the same setting.

Concomitant treatment

Routine monitoring will be established, including pulse oxygen saturation, non-invasive blood pressure, electrocardiograph, body temperature, minimal alveolar concentration of inhalation agent and bispectral index (BIS). Continuous arterial pressure, urine output and end-tidal carbon dioxide ($ETCO_2$) will be monitored after anaesthesia induction. BIS will be electronically recorded. Physiological variables will be recorded every 10 min manually at the critical time points of operation and every 10 s electronically.

Propofol (1.5–2.5 mg/kg), sufentanil (0.3–0.4 µg/kg) and rocuronium (0.6 mg/kg) or cisatracurium (0.15 mg/kg) will be administered for anaesthesia induction. After endotracheal intubation, mechanical ventilation will be performed, and $ETCO_2$ will be maintained between 35 and 45 mm Hg, with a tidal volume of 6 mL/kg to 8 mL/kg, a respiratory rate of 12 to 15 /min, an inspiratory/expiratory ratio of 1:2 and a fraction of inspired oxygen of 50% at a flow rate of 2 L/min.

The cranial nerve block will be performed with 0.5% ropivacaine before the head frame placement. As sevoflurane is maintained at 0.4 minimal alveolar concentration, remifentanil (0.1–0.2 µg/kg/min) and propofol (3–5 mg/kg/hour) will be administered to keep BIS between 35 and 45. Sufentanil (0.1–0.2 µg/kg) will be supplemented as needed. Heart rate and mean arterial pressure will be maintained within ±20% of baseline. Sevoflurane will be discontinued until the bone flap replacement. Propofol and remifentanil infusion will be ceased at the end of surgery. Physiological signs, the total dosage of anaesthetics, opioids and vasoactive drugs, blood loss and fluid input and output will also be closely monitored and recorded. The postoperative patient-controlled intravenous analgesia (PCIA) regimen will be comprised of a mixture of sufentanil (2 µg/kg) and ondansetron (16 mg) and normal saline in a total volume of 100 mL. The PCIA maintenance dose will be 2 mL/hour with a bolus dose of 0.5 mL (15 min lock-out time).

Data collection

An independent research assistant will initiate baseline information collection. Demographics, medical history, medication history, supplementary examination and preoperative assessment will be collected. All personal information will be kept confidential for research purposes only. The primary and secondary outcome assessment will be performed by the trained research assessors who are blinded to the group allocation.

Outcome measures

The study aims to assess the effect of dexmedetomidine on POD in patients undergoing brain tumour resections.

The primary outcome is the incidence of POD during the first 5 days. Delirium will be evaluated two times per day (08:00 to 10:00 and 18:00 to 20:00) during the first postoperative 5 days 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) as needed.[27–29] In ICU, the delirium assessment will be performed in two steps. 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 is equal to or higher than −3, delirium will be evaluated by CAM-ICU. In the general ward, patients will be evaluated with RASS and 3D-CAM. 3D-CAM refines the four characteristics of delirium assessment into 20 questions, which is convenient for evaluation.[30] 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 from 2 hours to the first 5 days after surgery. The degree of surgical incision pain will be assessed at rest and on movement by Numerical Rating Scale (NRS).[31] NRS ranges from 0 to 10, with the highest score indicating the worst pain. Postoperative analgesia will be recorded.

2. 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.[32] The scale comprises five items: sleep depth, sleep latency, wake-up times, relapse to sleep and overall sleep quality. The 0–100 mm visual analogue scale (1 mm=1 point) is used. The total score of the scale is divided into five items, and the higher the score, the better the sleep quality.
3. Cognitive function will be assessed 1 day before surgery and 30 days after surgery using MMSE scale. MMSE includes seven items: time orientation, place orientation, immediate memory, attention and calculation, delayed memory, language and visual space.[33] A total of 30 questions will be asked, 1 point for each correct answer, 0 point for a wrong answer or unknown answer and the total scores range from 0 to 30.
4. Postoperative quality of recovery will be assessed through the Postoperative Quality Recovery Scale 30 min after endotracheal extubation. It consists of six domains (physiologic, nociceptive, emotive, activities of daily living, cognitive and overall patient perspective).[34] The higher score indicates a better quality of postoperative recovery. Anesthesia Steward Emergence Scale will be applied at 1 day after surgery to evaluate the recovery quality of anaesthesia.[35]
5. Incidence of non-delirium complications within 1 month after surgery, including incision infection, intracranial haematoma (reoperations), severe intracranial oedema (base on CT and MRI images), myocardial infarction, pulmonary infection, pulmonary embolism and infection.
6. Intraoperative data include the total dosage of anaesthetics. BIS values and cardiovascular parameters will be recorded and classified as following: hypotension (systolic blood pressure <95 mm Hg or lower than 30% of baseline), hypertension (systolic blood pressure ≥ 180 mm Hg or higher than 30% of baseline), bradycardia (heart rate <40 bpm), tachycardia (heart rate ≥100 bpm) or hypoxemia (pulse oxygen saturation <90%). A detailed definition and standard treatment for adverse effect are presented in online supplemental table 1.
7. Length of stay in ICU and hospital.
8. All-cause 30-day mortality.

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

STUDY PERIOD								
	Enrollment	Allocation	Post-allocation					
TIMEPOINT	-1 day	Surgery day	Post-craniotomy (day), two times per day					
			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						
Post-operative Quality Recovery Scale		X						
Anesthesia recovery quality score			X					
Ramsay score			X	X	X	X	X	
Confusion Assessment Method for Intensive Care Unit, CAM-ICU			X	X	X	X	X	
3-Minute Diagnostic Interview for CAM,3D-CAM			X	X	X	X	X	
Mini-mental State Examination score	X							X
NRS pain score		X	X	X	X	X	X	
Requests of PCA			X	X				
Cumulative sufentanil consumption of PCA			X	X				
Sleep quality			X	X	X			
Adverse events			X	X	X	X	X	X
All-cause death			X	X	X	X	X	X

Figure 2 Data collection at each time point. CAM-ICU, confusion assessment method for intensive care unit; 3D-CAM, 3 min diagnostic interview for CAM; NRS, Numerical Rating Scale; PCA, Patient Controlled Analgesia.

non-numerical data are coded for data storage, 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. Data safety and monitoring inspectors will evaluate the trial safety and any ethical issues. Data monitoring committee, composed of five external specialists in anaesthesiology, ethics, statistics and methodology, will audit through regular interviews. These experts will be responsible for terminating the trial in case of severe adverse events.

The electronic data will be saved in a database with password protection, and the passwords will be changed on a regular basis. Date base 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 of dexmedetomidine will be closely monitored from the start of infusion to the 5th day 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

According to previous studies, the incidence of delirium after surgery is about 20%.[36] In our institution, POD incidence was 31.2% among 154 patients with temporal tumours in a prospective cohort study.[10] A meta-analysis reported that dexmedetomidine relatively reduced the incidence of delirium by approximately 54%.[21] We hypothesise that the incidence of POD is 30% and would be reduced by 50% after administration of dexmedetomidine comparing with the placebo. With a significance and power set at 0.05 (two sided) and 80%, respectively, the sample size required to detect the difference is 242 patients. Considering about 5% of the loss in follow-up, 260 (130 in each group) patients need to be enrolled.

The analysis will be done by using SPSS software (V.23.0). The continuous variables will be described with mean and SD or median and IQR. Categorical data will be presented with counts (percentage). The difference in cumulative incidence of POD between the dexmedetomidine and control groups will be analysed by the χ^2 test. The primary outcome will also be analysed in the subgroups, including age (more than 65 years or not), gender, American Society of Anesthesiologists physical status and WHO classification of tumours in the central nervous system.[37] The changes in NRS scores and the cumulative consumption of opioids will be compared by using repeated measurement. Other secondary outcomes such as MMSE score, quality of sleep, postoperative quality of recovery and intraoperative data (BIS and haemodynamic parameters) will be analysed by t test or Mann-Whitney U test. 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.

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 China Ethics Committee of Registering Clinical Trials prior to implementation.

Ethics and dissemination

The protocol (V.1.0, 10 November 2020) has been approved by the Ethics Review Committee of the Chinese Clinical Trial Registry (number ChiECRCT-20200436). The findings of this study will be disseminated in peer-reviewed journals and at scientific conferences.

DISCUSSION

The prospective, randomised, placebo-controlled and double-blinded trial is designed to investigate the effect of intraoperative infusion of dexmedetomidine on the incidence of POD in adult patients after frontotemporal tumours resections.

Delirium consists of four main characteristics: acute onset of a change in mental status or a fluctuating level of consciousness, inattention, disorganised thinking and an altered level of consciousness. The patient will be diagnosed with delirium if both the first and second features are present and either the third or fourth is present. The first assessment will be performed at postoperative 1 day in order to avoid the interference of recovery agitation.[38] In accordance with the recommendation, we will screen POD two times a day within the postoperative 5 days.[2] We will use 3D-CAM to assess patients in the general wards, which is highly sensitive to mild delirium.[30]

To avoid possible drug-related haemodynamic adverse events such as severe bradycardia and hypotension, we design to apply a lower loading dose followed by continuous infusion of dexmedetomidine in the present study. The impact of dexmedetomidine on haemodynamic fluctuation might weaken the efficiency of blinding to the anaesthesiologists. In addition, the efficacy and safety of dexmedetomidine administered in neurosurgical anaesthesia have already been proved in some studies.[20 25]

The main strength of the study is the design of a randomised, placebo-controlled and double-blinded trial. To the best of our knowledge, this is one of the early studies to evaluate the impact of intraoperative interventions on preventing POD in neurosurgical patients. The strengths of the present study also include anaesthesia depth monitored by BIS.[39]

Our study will improve the prevention and treatment of POD for patients undergoing frontotemporal tumours craniotomy to improve early recovery and shorten the length of hospital stay.

Trial status

At the time of manuscript submission, the study is in the phase of recruiting. We enrolled the first patient on 18 January 2021, and we expect to complete the study by December 2022.

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Contributors DW, RL, SL, JW, MZ, JD, XL, NL, YP: conceived the study, contributed to the study design and analytical plans. RL: drafted the protocol. All authors read and approved the final protocol.

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Disclaimer Agents provider has no role in the study design and conducts; the data collection, management, analysis and interpretations; or the preparation and approval of the manuscript.

Competing interests None declared.

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Supplementary Table 1. Definitions and treatments for adverse events.

Hemodynamic Fluctuation	Definition*	Standard Treatment Algorithm
Hypotension	SBP less than 95 mmHg, or lower than 30% of baseline	Increase propofol or remifentanil infusion rate according to BIS, increase, or administer sufentanil (0.1-0.2μg/kg); if correction still not achieved, nicardipine will be given as bolus and/or infusion
Hypertension	SBP higher than 180 mmHg, or higher than 30% of baseline	Decrease propofol or remifentanil infusion rate according to BIS; if correction still not achieved, vasoactive agent administration (dopamine, norepinephrine, or phenylephrine) will be given and adjusted according to the blood pressure response
Tachycardia Episode	HR higher than 100 bpm	Esmolol bolus and/or infusion according to heart rate response
Bradycardia Episode	HR lower than 40 bpm	Atropine administration
Hypoxemia	Pulse oxygen saturation lower than 90%	Administration of oxygen and adjustment of mechanical ventilation for patients without and with endotracheal intubation.

* if any of the below changes are sustained for equal and/or longer than 5 min; Abbreviations: SBP, systolic blood pressure; HR, heart rate; bpm, beat per minute.