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Effect of Dexmedetomidine on Postoperative Delirium in Patients Undergoing Brain Tumor Resections: study protocol of a randomized controlled trial

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ABSTRACT

Introduction Postoperative delirium (POD) is a common complication. The incidence of POD is about 25% in noncardiac surgery and ranges from 10% to 30% after neurological surgery. Dexmedetomidine might help to alleviate delirium in patients undergoing cardiac surgery, however, the impact of dexmedetomidine on POD after neurosurgery is still unclear.

Methods and analysis The study is a prospective, single-center, randomized, paralleled-group controlled trial. Patients undergoing elective frontotemporal tumors 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 0.6μg/kg in 10 minutes followed by infusion at rate of 0.4μg/kg/h 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 3 days. The delirium assessment will be performed by using the Confusion Assessment Method in the first-5-consecutive day after surgery. Secondary outcomes include the pain score, quality of postoperative sleep and recovery from anesthesia.

Keywords Delirium, dexmedetomidine, frontotemporal, brain tumor.

Ethics and dissemination The protocol (version number: 1.0, November 10, 2020) has been approved by the Ethics Review Committee of Chinese Clinical Trial Registry (No. ChiECRCT-20200436). The findings of the study will be disseminated in peer-reviewed journal and at scientific conference.

Trial registration number NCT04674241

ARTICLE SUMMARY

Strengths and limitations of this study

- This prospective, randomized, placebo-controlled and double-blinded trial is designed to investigate the effect of intraoperative infusion of dexmedetomidine on the incidence of delirium after brain tumors resections.
- The results will optimize strategies for prevention of delirium in patients undergoing frontotemporal tumors resections, so as to improve satisfaction and early recovery.
- The sample size is estimated according to the previous studies conducted in the same medical center, which might guarantee the size adequacy.
- The data will be from a single center that might limit the generalization of the conclusion.

BACKGROUD

Delirium is an acute brain dysfunction characterized by disturbance in attention, cognition, consciousness level, sleep cycle and mood.[1] Postoperative delirium (POD) is a common but serious complication that usually occurs at 2 to 5 days after surgery. 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 is about 10% to 60%, but in high-risk populations, such as the aged, patients in intensive care units(ICU) and those with previous cognitive impairment, the incidence of POD is up to 40% to 60%.[6,7] Neurosurgical patients are also at high risk of POD.[8] Previous studies have reported that the total incidence of POD after neurosurgery is between 10% and 30%.[9,10] Wang et al. found that the incidence of POD in glioma patients was up to 30%.[10] The incidence is even as high as 40% in neurosurgical ICU.[11]

Several risk factors predispose the incidence of POD in neurosurgical patients. Previous studies suggested that frontal approach and tumor located at the temporal lobe (NCT03033693) were independent risk factors for POD after superatentorial tumor resections.[10] A recent retrospective cohort study showed that tumor invading bilateral cerebral hemisphere and the diameter more than 5cm were also risk factors for POD. In addition, intraoperative hemodynamic instability, long operation duration, and pain are all risk factors for POD.[12] Effective postoperative analgesia helped to prevent POD in neurosurgery.[13]

The mechanisms of POD in neurosurgical patients have not been cleared yet. Patients with brain tumors are frequently associated with increased intracranial pressure, decreased acetylcholine neurotransmitters and neuronal inflammatory response, these pathological changes may result in POD.[14] The process of tumor resection especially the extensive resection for large tumor damages blood-brain barrier resulting in inflammatory markers entering the blood circulation, therefore may lead to new cognitive dysfunction and POD.[15] Perioperative pharmacological intervention such as dexmedetomidine has some advantages in neuroanesthesia with respect to systemic and intracranial characteristics, which are potentially related to the prevention of POD.

Dexmedetomidine is a highly selective central presynaptic α2-adrenergic agonist, it does not only provide sedation, but also has little influence on respiratory function whereas providing adjunctive analgesic.[16] The latter benefit decreases demand for opioids and reduces perioperative pain, which are related to postoperative agitation and delirium.[17,18] A recent meta-analysis based on 8 randomized controlled trials (RCT) in 1425 ICU patients suggested that application of dexmedetomidine significantly reduced the incidence of delirium in ICU.[19,20] In a RCT involving 619 elderly patients undergoing noncardiac surgery, compared with normal saline, intraoperative administration of dexmedetomidine (0.5μg/kg/h) significantly decreased the incidence of POD. However, the effect of dexmedetomidine on delirium after neurosurgery is unclear.[21]

Dexmedetomidine provides stable hemodynamics and does not increase intracranial pressure and maintain unchanged cerebral metabolic rate equivalent.[22] A recent RCT showed that the target-controlled intraoperative infusion of dexmedetomidine during the surgery significantly reduced the tachycardia response during intubation and hypertension response during extubation.[23] Yun et al. investigated 150 patients undergoing supratentorial tumor surgery and found dexmedetomidine decreased the pain score within 4 hours after surgery.[24] Dexmedetomidine helps to stable hemodynamics and provides analgesia which might help to decrease delirium. However, the effect of intraoperative dexmedetomidine infusion on POD 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 tumors resections and will conduct a RCT to test the hypothesis.

METHODS AND ANALYSIS

Study design

This is a prospective, single-center, randomized, 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 December 19, 2020

(NCT04674241) and approved by the Ethics Review Committee of Chinese Clinical Trial Registry (No. 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 conduct of the study. There is no plan to disseminate the results to study participants. 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 tumors who are older than 18 years and scheduled for elective craniotomies will be screened for eligibility one 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 beats per minute), sick sinus syndrome or second-to-third degree atrioventricular block.
8. Severe hepatic or renal dysfunction.

Randomization and blinding

Stratified randomization with age (<65 years vs ≥ 65 years) 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 then distribute

to the researchers. The researcher will open the envelopes and prepare the research drug based on the grouping. The study agents (dexmedetomidine 200μg/2mL) will be diluted into 50ml with normal saline and marked as "trial drug". The preparation will be completed by an independent researcher who does not know the grouping. Patients will be randomly assigned to two groups with a 1: 1 ratio. Allocation will be concealed until the database lock. The researchers, patients, anesthesiologists-in-chief and outcome assessors will all be blinded to the allocation until the completion of the study analysis.

Intervention and grouping

After endotracheal intubation, patients in dexmedetomidine group will be administered with a loading dose of dexmedetomidine 0.6μg/kg in 10 minutes followed by infusion at rate of 0.4μg/kg/h 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 anesthesia induction. Propofol (1.5-2.5mg/kg), sufentanil (0.3-0.4μg/kg), and rocuronium (0.6mg/kg) or cisatracurium (0.15mg/kg) will be administered for anesthesia induction. After endotracheal intubation, mechanical ventilation will be performed, $ETCO_2$ will be maintained between 35 and 45 mmHg, with a tidal volume of 6 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 flow rate of 2 L/min.

Cranial nerve block will be performed with 0.5% ropivacaine before the head frame placement. As sevoflurane be maintained at 0.4 Minimal Alveolar Concentration, infusion of remifentanil (0.1-0.4μg/kg/min) and propofol (3-8mg/kg/h) will be administered to keep BIS between 35 and 45. Sufentanil (0.1-0.2μg/kg) will be supplemented as needed. 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 anesthetics, opioids and vasoactive drugs, blood loss and fluid input and output will also be closely monitored and recorded.

Electric analgesia pumps (Rhythmic Plus, Micrel Medical Devices SA, Greece European Union) preprogrammed by the research assistants will be initiated for routine postoperative analgesia. The pump will be filled with sufentanil (100μg) and ondansetron (16mg) diluted in 100 mL by 0.9% saline. Insufficient postoperative analgesia will be defined as the numerical rating scale (NRS) score higher than 4 lasting over 15 min or higher than 6, and be treated with receive rescue analgesic.

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 assessment of primary and the other secondary outcomes will be performed by the trained research assessors who are blinded to the group allocation.

Outcomes measures

The aim of the study is to assess the effect of dexmedetomidine on postoperative delirium in patients undergoing brain tumors resections.

The primary outcome is the incidence of postoperative delirium during the first-5 day. Delirium will be evaluated twice per day (08:00 to 10:00 and 18:00 to 20:00) during the postoperative-5 day through a combination of three methods including the Richmond Agitation Sedation Scale (RASS), the Confusion assessment method for intensive care unit (CAM-ICU) and the 3-minute diagnostic interview for CAM (3D-CAM) as needed.[25-27] In ICU, the delirium assessment will be performed in two steps. The arousal level will be firstly assessed through RASS. If the patient is not responsive to verbal stimuli (i.e. RASS score ≤ -4), the remaining assessment will be aborted, and the patient is recorded as comatose. When the RASS score is higher than or equal to -3, delirium will be evaluated by CAM-ICU. In general ward, patients will be evaluated with RASS and 3D-CAM. 3D-CAM refines the four characteristics of

delirium assessment into 20 questions, which are more convenient for evaluation.[28] The assessors will be trained by psychiatrists before the study initiation.

The secondary outcomes include the other efficacy and safety outcomes.

1. Pain severity score will be assessed from 2 hours after the surgery to the first 5 postoperative days. The degree of surgical incision pain will be assessed at rest and on movement by NRS pain score. NRS ranges from 0-10 and the higher 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 previous night.[29] The scale is composed of five items: sleep depth, sleep latency, wake-up times, relapse to sleep, and overall sleep quality. The 0-100 mm visual analog scale (1 mm = 1 point) is used. The total score of the scale is divided into 5 items, and the higher the score, the better the sleep quality.

3. Cognitive function will be assessed one day before surgery and 5 days after surgery. MMSE includes seven items: time orientation, place orientation, immediate memory, attention and calculation, delayed memory, language, and visual space.[30] A total of 30 questions, 1 point for each correct answer, 0 point for wrong answer or unknown answer, and the total score range 0 to 30.

4. Postoperative quality of recovery will be assessed through The Post-operative Quality Recovery Scale (PQRS) at 30 minutes after endotrancheal extubation. It consists of six domains (physiologic, nociceptive, emotive, activities of daily living, cognitive, and overall patient perspective).[31] The higher score indicates the better quality of postoperative recovery. Anesthesia Steward Emergence Scale will be applied at 1 day after surgery to evaluate the recovery quality of anesthesia.[32]

5. Incidence of non-delirium complications within one month after surgery, include incision infection, intracranial hematoma (reoperations), intracranial edema, myocardial infarction, pulmonary infection, pulmonary embolism and infection. Cardiovascular adverse effect of dexmedetomidine infusion will be recorded and classified as following: hypotension (systolic blood pressure < 95 mmHg, or lower than

30% of baseline), hypertension (systolic blood pressure ≥180 mmHg, or higher than 30% of baseline), bradycardia (heart rate < 40 beats/min), tachycardia (heart rate ≥ 100 beats/min) or hypoxemia (pulse oxygen saturation < 90%). Detailed definition and standard treatment for adverse effect is presented in Supplemental Table 1).

Supplementary Table 1. Definitions and treatments for adverse events.

Hemodynamic Fluctuation	Definition*	Standard Treatment Algorithm
Hypertension	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
Hypotension	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.

6. Length of stay in ICU and hospital.

7. All-cause 30-day mortality.

Data management and monitoring

Figure 2. shows data collection at each time point. All the data will be recorded on a case report form. Raw, non-numerical data are coded for data storage, review, tabulation and analysis. Data will be entered at the medical center, stored and monitored securely in an electronic database. Double data entry will be used. All data-entering individuals will request to use standardized 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 in the data will be summarized along with detailed descriptions and queried by checking the original forms. Data safety and monitoring inspectors will evaluate the trial safety, efficacy, and any ethical issues. Data monitoring committee (DMC) composed of five external specialists in anesthesiology, 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 a period of 5 years after completion of the study.

Reporting of adverse events

Adverse effect of dexmedetomidine will be closely monitored from the start of infusion to one day after the surgery. Investigators will record all the adverse effect including the type, the diagnosis time, the duration and the consequences. Anesthesiologist-in-chief has 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, treatment measures, prognosis.

Sample size estimation and statistical analysis

According to previous studies, the incidence of delirium after surgery is about 20%.[33] A large prospective cohort study recently found the incidence of POD was 31.2% among 154 patients with temporal tumors.[10] A meta-analysis reported that dexmedetomidine reduced the incidence of delirium by approximately 54%.[19] We hypothesized that the incidence in the study was 30%, and the incidence 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 a significant difference is 242 patients. Taking into account about 5% of the loss in follow-up, 260 (130 in each group) patients need to be enrolled.

Analysis will be done by using SPSS software (Version 23.0). The continuous variables will be described with mean and standard deviation (SD) or median and inter-quartile range (IQR). Categorical date will be presented with counts (percentage). The difference in cumulative incidence of POD between the dexmedetomidine and control groups will be analyzed by the chi-square test. The primary outcome will also be analyzed in the subgroups including age, gender, American Society of Anesthesiologists, physical status and World Health Organization classification of tumors in the central nervous system. [34] The changes in NRS scores and the cumulative consumption of opioids will be compared by using repeated measurement. For other secondary outcomes such as MMSE score, quality of sleep and postoperative quality of recovery, the difference between the two groups will be analyzed 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 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 (e.g. changes to eligibility criteria, outcomes, analyses), the principle investigator will communicate and gain approval from the China Ethics Committee of Registering Clinical Trials prior to implementation.

Ethics and dissemination

The protocol (version number: 1.0, November 10, 2020) has been approved by the Ethics Review Committee of Chinese Clinical Trial Registry (No. ChiECRCT-20200436). The findings of this study will be disseminated in peer-reviewed journals and at scientific conferences.

Discussion

The prospective, randomized, 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 tumors resections.

Delirium consists of four main characteristics including acute onset of a change in mental status or a fluctuating level of consciousness, inattention, disorganized thinking and an altered level of consciousness. The patient will be diagnosed as delirium if both the first and second features are present, and either the third or fourth is present. Delirium is divided into three sub-types: hyperactive delirium, defined as persistent positive RASS score (1-4); hypoactive delirium, defined as persistent neutral or negative RASS score (-3-0); and mixed delirium, defined as two subtypes will appear at different time points, RASS score has changed.[35]

In accordance with the recommendation, we will screen POD twice a day within the postoperative 5 days.[2] The first assessment will be performed at postoperative 1 day in order to avoid the interference of recovery agitation.[36] To avoid possible drug-related hemodynamic adverse events such as severe bradycardia and hypotension, we design to apply low-loaded dose followed by infusion of dexmedetomidine in the present study. The impact of dexmedetomidine on intraoperative hemodynamic fluctuation might weaken the efficiency of blinding to the anesthesiologists. In addition, the efficacy and safety of the dexmedetomidine using in neurosurgical anesthesia been already proved in some studies.[23,24] We will use 3D-CAM to assess patients in the general wards which has high sensitivity to mild delirium.[28]

The main strength of the study is the design of randomized, 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 anesthesia depth monitored by BIS which is indicated that heavy sedation levels led to POD. [37]

Our study will improve the prevention and treatment of postoperative delirium for patients undergoing frontotemporal tumors craniotomy, so as to improve early recovery and shorten 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 January 18, 2021, and we expect to complete the study by December 2022.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Author Contributions DXW, RWL, SL, JW, MZ, JD, XYL, NL, YMP: conceived the study, contributed to the study design and analytical plans. RWL: drafted the protocol. All authors read and approved the final protocol.

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Competing interests The experimental agents (dexmedetomidine hydrochloride and normal saline) are manufactured, packed and provided by the Jiangsu Nhwa Pharmaceutical Co., (Jiangsu, China). 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.

Ethics approval This study has been approved by the Ethics Review Committee of Chinese Clinical Trial Registry (No. ChiECRCT-20200436).

Availability of data and materials The data-sets used and analyzed during the current study are available from the corresponding author (Yuming Peng, florapym766@163.com) on reasonable.

Request Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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Figure and Table legends

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

Figure 2. Data collection at each time point

Supplementary Table 1. Definitions and treatments for adverse events

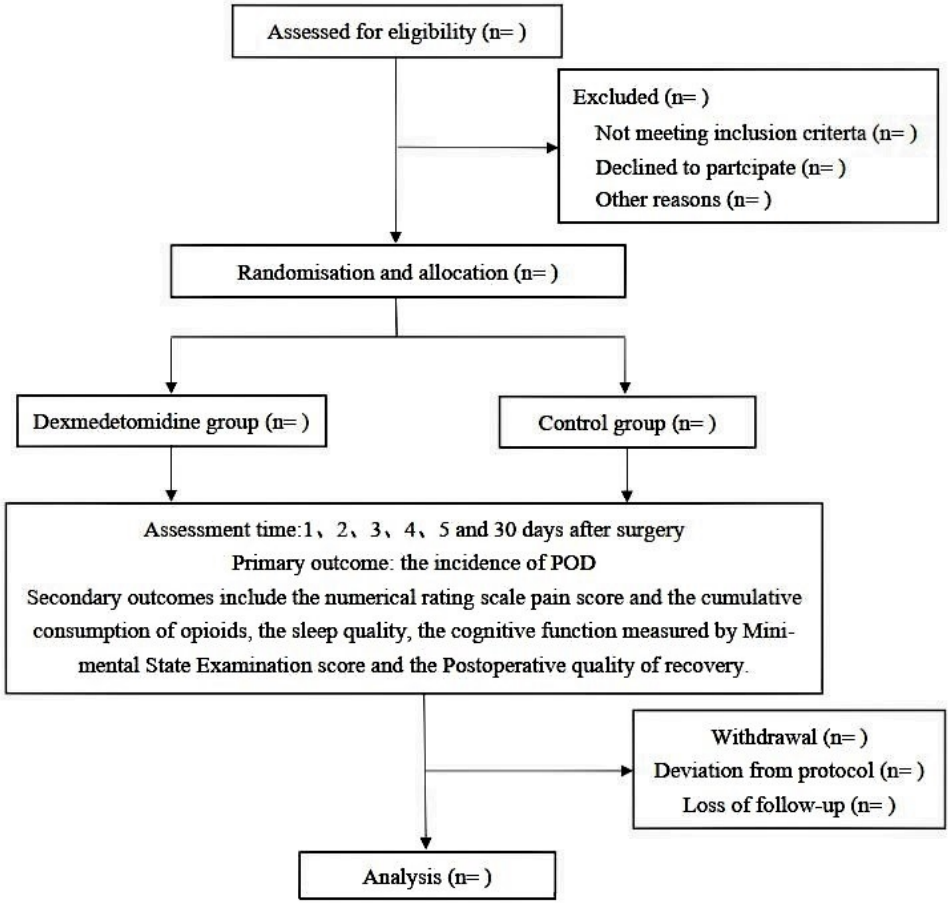

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram

198x183mm (96 x 96 DPI)

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	
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

511x476mm (96 x 96 DPI)

To: Dr. Li Ruo-wen / Dr. Peng Yu-ming, A/Professor of Medicine
From: Taixiang WU, Secretary General, Chinese Ethics Committee of Registering Clinical Trials
Email: chictr001@chictr.org.cn
Date: December 28, 2020

Application for ethical review for clinical study involving human subjects

I write to inform you that approval has been given to your application for human subjects ethics review of the following project for a period from December 29, 2020 to December 28, 2022.

Project title: Effect of Dexmedetomidine on Postoperative Delirium in Patients Undergoing Brain Tumor Resections: a randomized controlled trial

Institute: Beijing Tiantan Hospital, Capital Medical University

Principal investigator: Dr. Li Ruo-wen / Dr. Peng Yu-ming, A/Professor of Medicine

Expected start date of project: December 28, 2020

Reference number: ChiECRCT20200436

You will be held responsible for the ethical approval granted for the project and the ethical conduct of the personnel involved in the project.

You are responsible for informing the Chinese Ethics Committee of Registering Clinical Trials in advance of any changes in the proposal or procedures which may affect the validity of this ethical approval.

Taixiang WU, Professor
Secretary General,
Chinese Ethics Committee of Registering Clinical Trials

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Checklist for **Effect of Dexmedetomidine on Postoperative Delirium in Patients Undergoing Brain Tumor Resections: study protocol of a randomized controlled trial**

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1 & 14
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	14
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	10-11

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
	6b	Explanation for choice of comparators	4-5
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5-6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5-6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	7
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	7
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7-8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8-10
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	see Figure 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11-12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6-7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6-7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6-7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6-7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6- 7
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8 -10
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10-11
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11-12
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11-12
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11-12
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Not Applicable
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	11
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	2 & 12 &14
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	12

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	14
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	8
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	14
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	in consent form
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	2&12
	31b	Authorship eligibility guidelines and any intended use of professional writers	2 & 12
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	14
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	has been proved by IRB
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not Applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Effect of Dexmedetomidine on Postoperative Delirium in Patients Undergoing Brain Tumor Resections: study protocol of a randomized controlled trial

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Secondary Subject Heading:	Anaesthesia, Neurology
Keywords:	Delirium & cognitive disorders < PSYCHIATRY, Head & neck tumours < ONCOLOGY, Neurosurgery < SURGERY

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Effect of Dexmedetomidine on Postoperative Delirium in Patients Undergoing Brain Tumor Resections: study protocol of a randomized controlled trial

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ABSTRACT

Introduction Postoperative delirium (POD) is a common complication. The incidence of POD is about 25% in noncardiac surgery and ranges from 10% to 30% in neurological procedures. Dexmedetomidine might help to reduce the incidence of delirium in patients undergoing cardiac surgery. However, the impact of dexmedetomidine on POD after neurosurgery remains unclear.

Methods and analysis The study is a prospective, single-center, randomized, double-blinded, paralleled-group controlled trial. Patients undergoing elective frontotemporal tumors 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 0.6μg/kg in 10 minutes followed by continuous infusion at a rate of 0.4μg/kg/h 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 day 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 anesthesia by the Postoperative Quality Recovery Scale.

Keywords Delirium, dexmedetomidine, frontotemporal, brain tumor.

Ethics and dissemination The protocol (version number: 1.0, November 10, 2020) has been approved by the Ethics Review Committee of the Chinese Clinical Trial Registry (No. ChiECRCT-20200436). The findings of the study will be disseminated in a peer-reviewed journal and at a scientific conference.

Trial registration number NCT04674241

ARTICLE SUMMARY

Strengths and limitations of this study

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

BACKGROUND

Delirium is an acute brain dysfunction characterized 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 to 5 days after surgery. 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 KD 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 tumor located at the temporal lobe (NCT03033693, result not published) were independent risk factors for POD after supratentorial tumor resections. Tumors 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 tumors invading the bilateral cerebral hemisphere and a diameter more than 5cm were also risk factors for POD. In addition, intraoperative hemodynamic 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 tumors 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 tumor resection, especially the extensive resection for large tumors, 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 neuroanesthesia 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 tumor surgery and found dexmedetomidine decreased the pain score within 4 hours after surgery.[20] A recent meta-analysis based on 8 randomized controlled trials (RCT) in 1425 ICU patients suggested that the application of dexmedetomidine significantly reduced the incidence of delirium in ICU.[21,22] In a RCT involving 619 aged patients undergoing noncardiac surgery, compared with normal saline, intraoperative administration of dexmedetomidine (0.5μg/kg/h) remarkably decreased the incidence of POD. [23] On the other hand, Dexmedetomidine provides stable hemodynamics 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] However, the effect of intraoperative dexmedetomidine infusion on POD 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 tumors resections, and we will conduct a RCT to test the hypothesis.

METHODS AND ANALYSIS

Study design

This is a single-center, randomized, 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 December 19, 2020

(NCT04674241) and approved by the Ethics Review Committee of Chinese Clinical Trial Registry (No. ChiECRCT-20200436). Preoperative interviews will be conducted by a 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 tumors older than 18 years and scheduled for elective craniotomy will be screened for eligibility one 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 beats per minute), sick sinus syndrome or second-to-third degree atrioventricular block.
8. Severe hepatic or renal dysfunction.

Randomization and blinding

Randomization 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 200μg/2mL) will be diluted into 50ml 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 anesthesiologists 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 0.6μg/kg for 10 minutes followed by continuous infusion at a rate of 0.4μg/kg/h 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 anesthesia induction. BIS will be electronically recorded. Physiological variables will be recorded every 10 minutes manually at the critical time points of operation and every 10 seconds electronically.

Propofol (1.5-2.5mg/kg), sufentanil (0.3-0.4μg/kg), and rocuronium (0.6mg/kg) or cisatracurium (0.15mg/kg) will be administered for anesthesia induction. After endotracheal intubation, mechanical ventilation will be performed, and $ETCO_2$ will be maintained between 35 and 45 mmHg, with a tidal volume of 6 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 (0.1-0.2μg/kg/min) and propofol (3-5mg/kg/h) will be administered to keep BIS between 35 and 45. Sufentanil (0.1-0.2μg/kg) will be supplemented as needed.

Heart rate and mean arterial pressure (MAP) 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 anesthetics, 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/h with a bolus dose of 0.5ml (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 outcomes assessment will be performed by the trained research assessors who are blinded to the group allocation.

Outcomes measures

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

The primary outcome is the incidence of POD during the first-5 day. Delirium will be evaluated twice per day (08:00 to 10:00 and 18:00 to 20:00) during the first-postoperative-5 day through a combination of three methods, including the Richmond Agitation Sedation Scale (RASS), the Confusion assessment method for intensive care unit (CAM-ICU) and the 3-minute diagnostic interview for CAM (3D-CAM) as needed.[26-28] In ICU, the delirium assessment will be performed in two steps. The arousal level will be firstly assessed through RASS. If the patient is not responsive to verbal stimuli (i.e. 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.[29] 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 day after surgery. The degree of surgical incision pain will be assessed at rest and on movement by Numerical Rating Scale (NRS).[30] 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.[31] The scale comprises five items: sleep depth, sleep latency, wake-up times, relapse to sleep, and overall sleep quality. The 0-100 mm visual analog scale (1 mm = 1 point) is used. The total score of the scale is divided into 5 items, and the higher the score, the better the sleep quality.

3. Cognitive function will be assessed one 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.[32] 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 (PQRS) 30 minutes after endotracheal extubation. It consists of six domains (physiologic, nociceptive, emotive, activities of daily living, cognitive, and overall patient perspective).[33] 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 anesthesia.[34]

5. Incidence of non-delirium complications within one month after surgery, including incision infection, intracranial hematoma (reoperations), severe intracranial edema (base on Computed Tomography and Magnetic Resonance Imaging images),

myocardial infarction, pulmonary infection, pulmonary embolism and infection.

6. Intra-operative data include the total dosage of anesthetics, BIS values and cardiovascular parameters will be recorded and classified as following: hypotension (systolic blood pressure < 95 mmHg, or lower than 30% of baseline), hypertension (systolic blood pressure ≥180 mmHg, or higher than 30% of baseline), bradycardia (heart rate < 40 beats/min), tachycardia (heart rate ≥ 100 beats/min) or hypoxemia (pulse oxygen saturation < 90%). A detailed definition and standard treatment for adverse effect are presented in 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 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 center. Double data entry will be applied. All data-entering individuals will request to use standardized 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 summarized 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 (DMC), composed of five external specialists in anesthesiology, 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 fifth day after the surgery. Investigators will record all the adverse effects, including the type, the diagnosis time, the duration and the consequences. Responsible anesthesiologists 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%.[35] In our institution, POD incidence was 31.2% among 154 patients with temporal tumors in a prospective cohort study.[10] A meta-analysis reported that dexmedetomidine relatively reduced the incidence of delirium by approximately 54%.[21] We hypothesize 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 (Version 23.0). The continuous variables will be described with mean and standard deviation (SD) or median and inter-quartile range (IQR). Categorical data will be presented with counts (percentage). The difference in cumulative incidence of POD between the dexmedetomidine and control groups will be analyzed by the chi-square test. The primary outcome will also be analyzed in the subgroups including, age (more than 65 years or not), gender, American Society of Anesthesiologists physical status, and World Health Organization classification of tumors in the central nervous system. [36] 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 hemodynamic parameters) will be analyzed 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 (e.g., changes to eligibility criteria, outcomes, analyses), the principle investigator will communicate and gain approval from the China Ethics Committee of Registering Clinical Trials prior to implementation.

Ethics and dissemination

The protocol (version number: 1.0, November 10, 2020) has been approved by the Ethics Review Committee of the Chinese Clinical Trial Registry (No. ChiECRCT-20200436). The findings of this study will be disseminated in peer-reviewed journals and at scientific conferences.

Discussion

The prospective, randomized, 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 tumors resections.

Delirium consists of four main characteristics: acute onset of a change in mental status or a fluctuating level of consciousness, inattention, disorganized 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.[37] In accordance with the recommendation, we will screen POD twice 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. [29]

To avoid possible drug-related hemodynamic 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

hemodynamic fluctuation might weaken the efficiency of blinding to the anesthesiologists. In addition, the efficacy and safety of dexmedetomidine administered in neurosurgical anesthesia have already been proved in some studies.[20, 25]

The main strength of the study is the design of a randomized, 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 anesthesia depth monitored by BIS. [38]

Our study will improve the prevention and treatment of postoperative delirium for patients undergoing frontotemporal tumors 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 January 18, 2021, and we expect to complete the study by December 2022.

Acknowledgments The authors would like to express their sincere gratitude to the colleagues of the Department of Anesthesiology and the Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, for their supports and cooperation.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

Author Contributions DXW, RWL, SL, JW, MZ, JD, XYL, NL, YMP: conceived the study, contributed to the study design and analytical plans. RWL: drafted the protocol. All authors read and approved the final protocol.

Funding This work was supported by the National Key Research and Development Program of China (2018YFC2001901), Capital Development Research Fund Project (grant number: 2018-2-2044), Research and application of Capital clinical diagnosis and treatment technology (grant number: Z191100006619068) and Beijing Municipal Administration of Hospitals Incubating Program (PX2018023).

Competing interests The experimental agents (dexmedetomidine hydrochloride and normal saline) are manufactured, packed and provided by the Jiangsu Nhwa Pharmaceutical Co., (Jiangsu, China). 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.

Ethics approval The study has been approved by the Ethics Review Committee of the Chinese Clinical Trial Registry (No. ChiECRCT-20200436).

Availability of data and materials The datasets used and analyzed during the current study are available from the corresponding author (Yuming Peng, florapym766@163.com) on reasonable.

Request Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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Figure and Table legends

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

Figure 2. Data collection at each time point

Supplementary Table 1. Definitions and treatments for adverse events

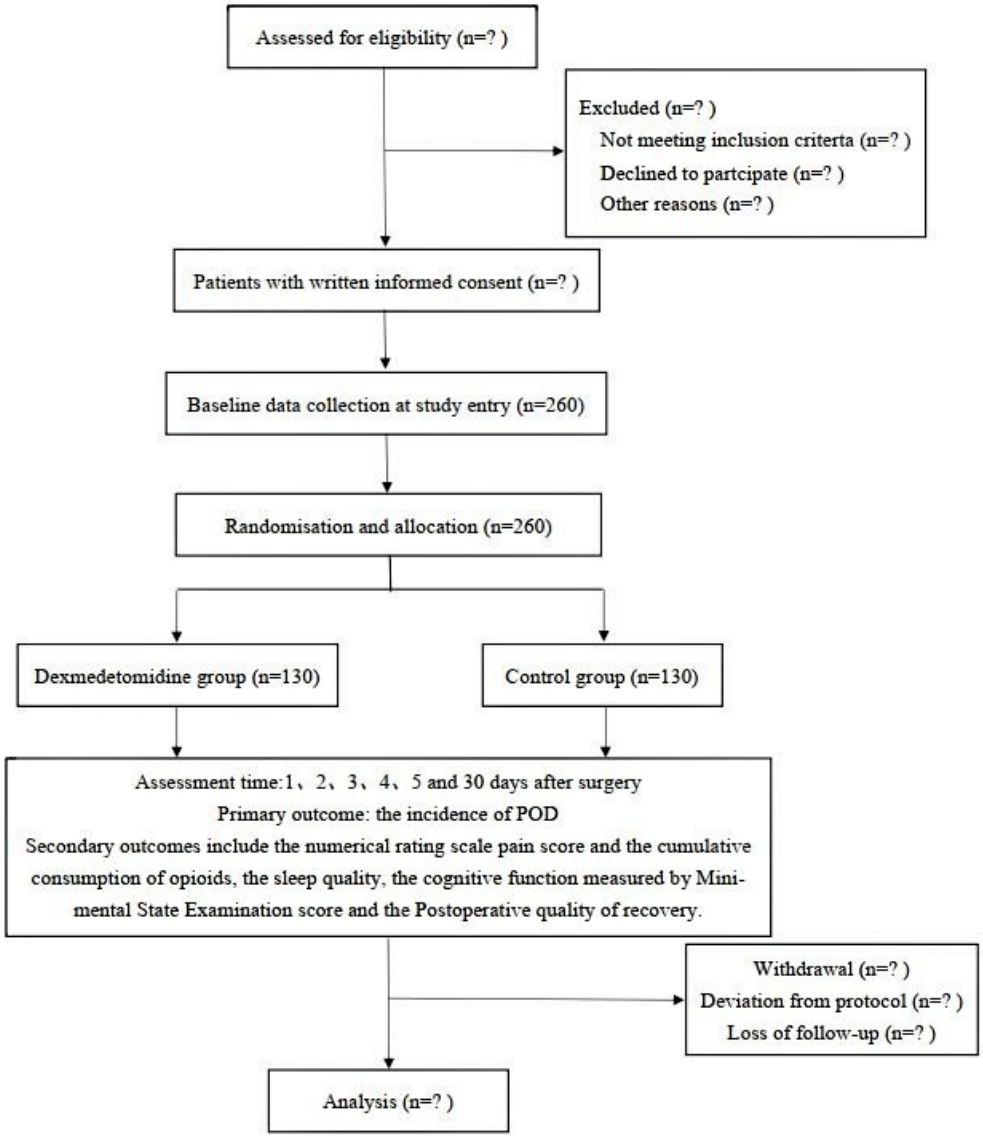

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram

110x126mm (144 x 144 DPI)

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

135x124mm (144 x 144 DPI)

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.

INFORMED CONSENT
INFORMATION SHEET

Dear Patient：

You have been diagnosed with ***frontotemporal brain tumors***. We would like to invite you to participate our study, which is "***Effect of Dexmedetomidine on Postoperative Delirium in Patients Undergoing Brain Tumor Resections***". This clinical trial has been approved by China Ethics Committee of Registering Clinical Trials

Before you decide whether to participate this clinical trial, please take time to review this information carefully. This form describes the purpose, risks and possible benefits of participating the study. You may also wish to talk to others (for example, your friends, family, or other doctors) about your participation in this study.

I. BACKGROUND and OBJECTIVE

1.1 BURDEN of DISEASE and CURRENT STATE of TREATMENT

Delirium is an acute brain dysfunction characterized by disturbance in attention, cognition, consciousness level, sleep cycle and mood.Postoperative delirium (POD) is a common but serious complication that usually occurs at 2 to 5 days after surgery. POD prolongs the length of hospital stay, increases mortality, and is closely related to long-term postoperative cognitive dysfunction.

Several risk factors predispose the incidence of POD in neurosurgical patients. Previous studies suggested that frontal approach and tumor located at the temporal lobe (NCT03033693) were independent risk factors for POD after superatentorial tumor resections. A recent retrospective cohort study showed that tumor invading bilateral cerebral hemisphere and the diameter more than 5cm were also risk factors for POD. In addition, intraoperative hemodynamic instability, long operation duration, and pain are all risk factors for POD. Effective postoperative analgesia helped to prevent POD in neurosurgery.

Dexmedetomidine is a highly selective central presynaptic α2-adrenergic agonist, it does not only provide sedation, but also has little influence on respiratory function whereas providing adjunctive analgesic.The latter benefit decreases demand for opioids and reduces perioperative pain, which are related to postoperative agitation and delirium.A recent meta-analysis based on 8 randomized controlled trials (RCT) in 1425 ICU patients suggested that application of dexmedetomidine significantly reduced the incidence of delirium in ICU. In a RCT involving 619 elderly patients undergoing noncardiac surgery, compared with normal saline, intraoperative administration of dexmedetomidine (0.5μg/kg/h) significantly decreased the incidence of POD. However, the effect of dexmedetomidine on delirium after neurosurgery is unclear.

1.2 OBJECTIVE of THIS STUDY

We aim to observe the effect of intraoperative infusion of dexmedetomidine on the incidence of delirium after brain tumors resections, so as to achieve the prospective prevention and treatment of POD.

1.3 RASEARCH AFFILIATION AND EXPECTED NUMBER of PARTICIPANTS

The study will be conducted at Beijing Tiantan Hospital, Capital Medical University. And 260 participants will be included in the study.

II. WHO SHOULD NOT PARTICIPATE in the STUDY

Exclusion criteria include patients with preoperative severe cognitive impairment (mini-mental state examination, MMSE $\leqslant$ 20); past history of traumatic brain injury or neurosurgery; severe bradycardia (heart rate less than 40 beats per minute), sick sinus syndrome or second-to-third degree atrioventricular block; severe hepatic or renal dysfunction; medical history of psychotropic drugs; allergic to the study drug; pregnant or lactating women; or refusal to provide written informed consent.

III. WHAT WILL YOU NEED TO DO IF YOU PARTICIPATE in the STUDY?

1. Before you participate in the study, your doctor will record your medical history and conduct a physical examination.

If you meet the standard, you can volunteer to participate in the study and sign the informed consent form.

If you are not willing to participate in the study, we will treat you based on the routine practice.

2. If you are willing to participate in the study, the following steps will be followed.

Participants will be randomly divided into the dexmedetomidine group and the control group. You cannot select your treatment group and will not be informed which treatment regimen to receive. Your response to different treatment regimen and your health status will be collected through close monitoring during the procedure, follow-up visits at 1,2,3,4,5 and 30 days after the procedure, and related scale assessments

Your follow-up visit is very important, because your doctor will judge whether the treatment you receive works and timely guide you.

IV. POSSIBLE BENEFITS of PARTICIPATING in the STUDY

Your prognosis may or may not improve as the result of participating in this study, however, the information from this study will help determine which treatments are safer and more effective in treating other participants with similar conditions of yours. Besides, you will gain more care about your postoperative outcome assessment and treatment.

V. POSSIBLE ADVERSE REACTIONS, RISKS and DISCOMFOT, INCONVENIENCES of PARTICIPATING in the STUDY

The monitoring methods, anesthesia methods, anesthetic drugs and anesthesia maintenance are all routine clinical procedures, without additional adverse reactions

and discomfort. If you suffer adverse reactions or discomfort due to surgical procedures, anesthesia, or unexpected changes in your condition during the course of the study, the researchers will make prompt assessment and treatment as needed.

If you experience any discomfort, changes of your condition, or any unexpected conditions during the study, whether or not related to the study, you should promptly notify your doctor, who will make judgment and give appropriate medical treatment.

During the study, you need to answer inquiry or fill out questionnaire, which may cause inconvenience to you.

VI. RELATED EXPENSES

Anesthetic drugs and surgical procedures are not free of charge. Doctors will do their best to prevent and treat any possible harm caused by this study. If adverse events occur in a clinical trial, a committee of medical experts will determine whether it is related to dexmedetomidine. The sponsor will provide treatment cost and corresponding economic compensation for the trial-related damages in accordance with "the provisions of China standard of quality management for drug in clinical trials".

VII. CONFIDENTIALITY of PERSONAL INFORMATION

Your medical records (study records /CRF, lab sheets, etc.) will be kept intact at the hospital. Your doctor will record the results of tests in your medical record. Researchers, ethics committees, and drug regulators will be allowed access to your medical records. Any public reports on the results of this study will not disclose your personal identity. We will make every effort to protect the privacy of your personal medical data within the law.

According to medical research ethics, apart from personal privacy information, the trial data will be available for public inquiry and sharing, which will be limited to web-based electronic databases to ensure that no personal privacy information will be disclosed.

VIII. HOW TO GET MORE INFORMATION?

You can ask any questions about this study at any time and get answers.

Your doctor will inform you most important information that may affect your willingness to continue the study.

IX. YOU MAY VOLUNTARILY CHOOSE TO PARTICIPATE in the STUDY and WITHDRAW from the STUDY

Whether to participate in the study is entirely up to you. You may refuse to participate in or withdraw from the study at any time during the study, which will not affect your relationship with your doctor or gaining your medical and other benefits.

In some conditions, the physician or investigator may discontinue your participation at any time during the study.

If you withdraw from the study for any reason, you may also be required to undergo physical examinations if it necessary.

X. WHAT SHOULD BE DONE NOW?

Whether to participate in this study is up to you (and your family).

Ask your doctor questions as many as possible before you make the decision to participate in the study.

Thank you for reading the above information. If you decide to participate in this study, please tell your doctor, he/she will arrange everything related to the study for you. Please keep this information.

INFORMED CONSENT

SIGNATURE PAGE of AGREEMENT

NAME of STUDY PROGRAM: _____

PROJECT INSTITUTION: _____

COOPERATIVE INSTITUTION: _____

PROJECT ASSIGNMENT NUMBER:_____

DECLARATION of CONSENT

I have read the above introduction about the study, have the opportunity to discuss with doctors and ask the questions about the study. All my questions have been answered satisfactorily.

I am aware of the possible risk and benefits of participating in this study. I know that participating in the study is voluntary. I have taken it into full consideration, and known that:

- I can ask my doctor for more information at any time.
- I can withdraw from this study at any time without discrimination or retaliation, and my medical treatment and rights will not be affected.

If I need to take any other medication due to the change in my condition, I will consult my doctor beforehand or tell him afterwards truthfully.

I will be provided with a signed and dated copy of the informed consent.

In the end, I agree to participate in the study and promise to follow the advice and the requirements as much as possible.

SIGNATURE by PATIENT: _____ DATE: _____

PHONE:_____

I confirm that I have explained the details of the trial to the participants, including the rights, possible benefits and the risks, and have given them a signed copy of the informed consent.

SIGNATURE by DOCTOR: _____ DATE: _____

WORK PHONE: _____

To: Dr. Li Ruo-wen / Dr. Peng Yu-ming, A/Professor of Medicine
From: Taixiang WU, Secretary General, Chinese Ethics Committee of Registering Clinical Trials
Email: chictr001@chictr.org.cn
Date: December 28, 2020

Application for ethical review for clinical study involving human subjects

I write to inform you that approval has been given to your application for human subjects ethics review of the following project for a period from December 29, 2020 to December 28, 2022.

Project title: Effect of Dexmedetomidine on Postoperative Delirium in Patients Undergoing Brain Tumor Resections: a randomized controlled trial

Institute: Beijing Tiantan Hospital, Capital Medical University

Principal investigator: Dr. Li Ruo-wen / Dr. Peng Yu-ming, A/Professor of Medicine

Expected start date of project: December 28, 2020

Reference number: ChiECRCT20200436

You will be held responsible for the ethical approval granted for the project and the ethical conduct of the personnel involved in the project.

You are responsible for informing the Chinese Ethics Committee of Registering Clinical Trials in advance of any changes in the proposal or procedures which may affect the validity of this ethical approval.

Taixiang WU, Professor
Secretary General,
Chinese Ethics Committee of Registering Clinical Trials

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Checklist for **Effect of Dexmedetomidine on Postoperative Delirium in Patients Undergoing Brain Tumor Resections: study protocol of a randomized controlled trial**

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1 & 14
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	14
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	10-11

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
	6b	Explanation for choice of comparators	4-5
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5-6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5-6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	7
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	7
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7-8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8-10
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	see Figure 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11-12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6-7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6-7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6-7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6-7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6- 7
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8 -10
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10-11
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11-12
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11-12
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11-12
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Not Applicable
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	11
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	2 & 12 &14
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	12

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	14
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	8
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	14
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	in consent form
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	2&12
	31b	Authorship eligibility guidelines and any intended use of professional writers	2 & 12
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	14
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	has been proved by IRB
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not Applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Effect of Dexmedetomidine on Postoperative Delirium in Patients Undergoing Brain Tumor Resections: study protocol of a randomized controlled trial

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Effect of Dexmedetomidine on Postoperative Delirium in Patients Undergoing Brain Tumor Resections: study protocol of a randomized controlled trial

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ABSTRACT

Introduction Postoperative delirium (POD) is a common complication. The incidence of POD is about 25% in noncardiac 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 tumor resections remains unclear.

Methods and analysis The study is a prospective, single-center, randomized, double-blinded, paralleled-group controlled trial. Patients undergoing elective frontotemporal tumors 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 0.6μg/kg in 10 minutes followed by continuous infusion at a rate of 0.4μg/kg/h 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 day 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 anesthesia by the Postoperative Quality Recovery Scale.

Keywords Delirium, dexmedetomidine, frontotemporal, brain tumor.

Ethics and dissemination The protocol (version number: 1.0, November 10, 2020) has been approved by the Ethics Review Committee of the Chinese Clinical Trial Registry (No. ChiECRCT-20200436). The findings of the study will be disseminated in a peer-reviewed journal and at a scientific conference.

Trial registration number NCT04674241

ARTICLE SUMMARY

Strengths and limitations of this study

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

BACKGROUND

Delirium is an acute brain dysfunction characterized 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 to 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 KD 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 tumor located at the temporal lobe (NCT03033693, result not published) were independent risk factors for POD after supratentorial tumor resections. Tumors 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 tumors invading the bilateral cerebral hemisphere and a diameter more than 5cm were also risk factors for POD. In addition, intraoperative hemodynamic 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 tumors 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 tumor resection, especially the extensive

resection for large tumors, 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 neuroanesthesia 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 tumor surgery and found dexmedetomidine decreased the pain score within 4 hours after surgery.[20] A recent meta-analysis based on 8 randomized controlled trials (RCT) in 1425 ICU patients suggested that the application of dexmedetomidine significantly reduced the incidence of delirium in ICU.[21,22] In a RCT involving 619 aged patients undergoing noncardiac surgery, compared with normal saline, intraoperative administration of dexmedetomidine (0.5μg/kg/h) remarkably decreased the incidence of POD. [23] On the other hand, Dexmedetomidine provides stable hemodynamics 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. randomized 112 patients undergoing intracranial aneurysm embolization and found dexmedetomidine decreased the incidence of POD.[26] However, the effect of intraoperative dexmedetomidine infusion on POD in patients undergoing craniotomy and tumor 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 tumors resections, and we will conduct a RCT to test the hypothesis.

METHODS AND ANALYSIS

Study design

This is a single-center, randomized, 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 December 19, 2020 (NCT04674241) and approved by the Ethics Review Committee of Chinese Clinical Trial Registry (No. ChiECRCT-20200436). Preoperative interviews will be conducted by a 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 tumors older than 18 years and scheduled for elective craniotomy will be screened for eligibility one 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 beats per minute), sick sinus syndrome or second-to-third degree atrioventricular block.
8. Severe hepatic or renal dysfunction.

Randomization and blinding

Randomization 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 200μg/2mL) will be diluted into 50ml 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 anesthesiologists 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 0.6μg/kg for 10 minutes followed by continuous infusion at a rate of 0.4μg/kg/h 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 anesthesia induction. BIS will be electronically recorded. Physiological variables will be recorded every 10 minutes manually at the critical time points of operation and every 10 seconds electronically.

Propofol (1.5-2.5mg/kg), sufentanil (0.3-0.4μg/kg), and rocuronium (0.6mg/kg) or cisatracurium (0.15mg/kg) will be administered for anesthesia induction. After endotracheal intubation, mechanical ventilation will be performed, and $ETCO_2$ will be maintained between 35 and 45 mmHg, with a tidal volume of 6 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 (0.1-0.2μg/kg/min) and propofol (3-5mg/kg/h) will be administered to keep BIS between 35 and 45. Sufentanil (0.1-0.2μg/kg) will be supplemented as needed. Heart rate and mean arterial pressure (MAP) 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 anesthetics, 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/h with a bolus dose of 0.5ml (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 outcomes assessment will be performed by the trained research assessors who are blinded to the group allocation.

Outcomes measures

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

The primary outcome is the incidence of POD during the first-5 day. Delirium will be evaluated twice per day (08:00 to 10:00 and 18:00 to 20:00) during the first-postoperative-5 day through a combination of three methods, including the Richmond Agitation Sedation Scale (RASS), the Confusion assessment method for intensive care unit (CAM-ICU) and the 3-minute 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 firstly assessed through RASS. If the patient is not responsive to verbal stimuli (i.e. 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 day 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 analog scale (1 mm = 1 point) is used. The total score of the scale is divided into 5 items, and the higher the score, the better the sleep quality.

3. Cognitive function will be assessed one 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 (PQRS) 30 minutes 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 anesthesia.[35]

5. Incidence of non-delirium complications within one month after surgery, including incision infection, intracranial hematoma (reoperations), severe intracranial edema (base on Computed Tomography and Magnetic Resonance Imaging images), myocardial infarction, pulmonary infection, pulmonary embolism and infection.

6. Intra-operative data include the total dosage of anesthetics, BIS values and cardiovascular parameters will be recorded and classified as following: hypotension (systolic blood pressure < 95 mmHg, or lower than 30% of baseline), hypertension (systolic blood pressure ≥180 mmHg, or higher than 30% of baseline), bradycardia (heart rate < 40 beats/min), tachycardia (heart rate ≥ 100 beats/min) or hypoxemia (pulse oxygen saturation < 90%). A detailed definition and standard treatment for adverse effect are presented in 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 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 center. Double data entry will be applied. All data-entering individuals will request to use standardized 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 summarized 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 (DMC), composed of five external specialists in anesthesiology, 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 fifth day after the surgery. Investigators will record all the adverse effects, including the type, the diagnosis time, the duration and the consequences. Responsible anesthesiologists 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 tumors in a prospective cohort study.[10] A meta-analysis reported that dexmedetomidine relatively reduced the incidence of delirium by approximately 54%.[21] We hypothesize 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 (Version 23.0). The continuous variables will be described with mean and standard deviation (SD) or median and inter-quartile range (IQR). Categorical data will be presented with counts (percentage). The difference in cumulative incidence of POD between the dexmedetomidine and control groups will be analyzed by the chi-square test. The primary outcome will also be analyzed in the subgroups including, age (more than 65 years or not), gender, American Society of Anesthesiologists physical status, and World Health Organization classification of tumors 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 hemodynamic parameters) will be analyzed 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 (e.g., changes to eligibility criteria, outcomes, analyses), the principle investigator will communicate and gain approval from the China Ethics Committee of Registering Clinical Trials prior to implementation.

Ethics and dissemination

The protocol (version number: 1.0, November 10, 2020) has been approved by the Ethics Review Committee of the Chinese Clinical Trial Registry (No. ChiECRCT-20200436). The findings of this study will be disseminated in peer-reviewed journals and at scientific conferences.

Discussion

The prospective, randomized, 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 tumors resections.

Delirium consists of four main characteristics: acute onset of a change in mental status or a fluctuating level of consciousness, inattention, disorganized 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 twice 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 hemodynamic 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

hemodynamic fluctuation might weaken the efficiency of blinding to the anesthesiologists. In addition, the efficacy and safety of dexmedetomidine administered in neurosurgical anesthesia have already been proved in some studies.[20, 25]

The main strength of the study is the design of a randomized, 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 anesthesia depth monitored by BIS. [39]

Our study will improve the prevention and treatment of postoperative delirium for patients undergoing frontotemporal tumors 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 January 18, 2021, and we expect to complete the study by December 2022.

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Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

Author Contributions DXW, RWL, SL, JW, MZ, JD, XYL, NL, YMP: conceived the study, contributed to the study design and analytical plans. RWL: drafted the protocol. All authors read and approved the final protocol.

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Competing interests The experimental agents (dexmedetomidine hydrochloride and normal saline) are manufactured, packed and provided by the Jiangsu Nhwa Pharmaceutical Co., (Jiangsu, China). 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.

Ethics approval The study has been approved by the Ethics Review Committee of the Chinese Clinical Trial Registry (No. ChiECRCT-20200436).

Availability of data and materials The datasets used and analyzed during the current study are available from the corresponding author (Yuming Peng, florapym766@163.com) on reasonable.

Request Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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Figure and Table legends

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

Figure 2. Data collection at each time point

Supplementary Table 1. Definitions and treatments for adverse events

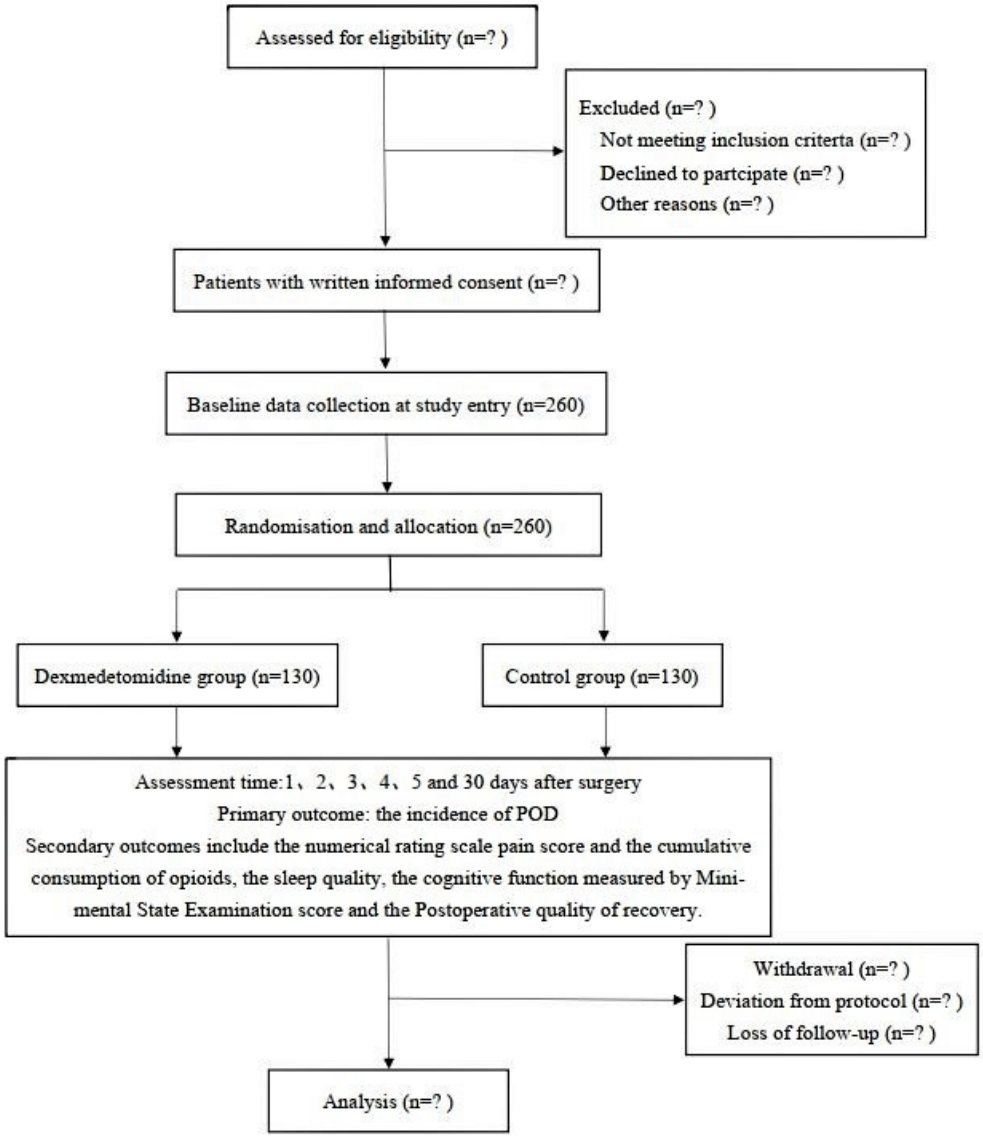

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram

110x126mm (144 x 144 DPI)

STUDY PERIOD								
TIMEPOINT	Enrollment	Allocation	Post-allocation					
	-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

135x124mm (144 x 144 DPI)

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.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Checklist for **Effect of Dexmedetomidine on Postoperative Delirium in Patients Undergoing Brain Tumor Resections: study protocol of a randomized controlled trial**

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1 & 14
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	14
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	10-11

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
	6b	Explanation for choice of comparators	4-5
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5-6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5-6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	7
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	7
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7-8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8-10
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	see Figure 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11-12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6-7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6-7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6-7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6-7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6- 7
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8 -10
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10-11
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11-12
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11-12
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11-12
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Not Applicable
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	11
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	2 & 12 &14
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	12

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	14
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	8
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	14
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	in consent form
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	2&12
	31b	Authorship eligibility guidelines and any intended use of professional writers	2 & 12
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	14
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	has been proved by IRB
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not Applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.