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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-040939
Article Type:	Protocol
Date Submitted by the Author:	26-May-2020
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Keywords:	Adult intensive & critical care < ANAESTHETICS, NEUROSURGERY, Delirium & cognitive disorders < PSYCHIATRY

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Dexmedetomidine for the prevention of postoperative delirium in patients after intracranial operation for brain tumours (DEPOD study): a study protocol and statistical plan for a multicentre randomised controlled trial

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Keywords: delirium, postoperative, intracranial operation, prevention, dexmedetomidine

Word count: 3292

ABSTRACT

Introduction Postoperative delirium (POD) is prevalent in patients after major surgery and is associated with adverse outcomes. Several studies have reported that dexmedetomidine, a highly selective α2-adrenergic receptor agonist, can decrease the incidence of POD. However, neurosurgical patients are usually excluded from previous studies. The present study was designed to investigate the impact of prophylactic use of low-dose dexmedetomidine on the incidence of POD in patients after intracranial operation.

Methods and analysis This is a multicentre, randomised, double-blinded and placebo-controlled trial. Seven hundred intensive care unit admitted patients after elective intracranial operation for brain tumours under general anaesthesia are randomly assigned to the dexmedetomidine group or the placebo group with a 1:1 ratio. For patients in the dexmedetomidine group, a continuous infusion of dexmedetomidine will be started at a rate of 0.1 μg/kg/hour immediately after enrolment on the day of operation and continued until 08:00 AM on the postoperative day one. For patients in the placebo group, normal saline will be administered at the same rate as in the dexmedetomidine group. The patients will be followed up for 28 days after enrolment. The primary endpoint is the incidence of POD, which is assessed twice daily using the Confusion Assessment Method for the Intensive Care Unit, during the first five postoperative days. The secondary endpoints include the incidence of dexmedetomidine related adverse events and non-delirium complications, the length of stay in the ICU and hospital and all-cause 28-day

mortality after the operation.

Ethics and dissemination The study protocol was approved by the Institutional Review Board of Beijing Tiantan Hospital Affiliated to Capital Medical University (No KY2019-091-02) and registered at ClinicalTrials.gov. The results of the trial will be presented at national and international conferences relevant to subject fields and submitted to international peer-reviewed journals.

Trial registration number NCT04399343; Pre-results.

Main strengths and limitations of the study

- The study design will be multicentre, randomised, double-blinded and placebo-controlled, with a relatively large sample size.
- To the best of our knowledge, this is the first study to evaluate the effect of prophylactic use of dexmedetomidine on postoperative delirium in neurosurgical patients.
- Only intensive care unit admitted patients are included, which will limit the generalizability of the results.
- Only early outcomes are assessed including the incidence of postoperative delirium and other endpoints up to 28 days after the operation.
- The hemodynamic effects of dexmedetomidine may weaken the efficiency of masking to the physicians responsible for care of the patients.

BACKGROUND

Postoperative delirium (POD) is one of the main postoperative complications after major surgery, especially in patients admitted to the intensive care unit (ICU) [1, 2]. Studies have shown that POD is associated with adverse outcomes, including prolonged length of stay in the ICU and hospital, higher morbidity and mortality risks, increased healthcare costs, and reduced long-term quality of life [3-5]. However, patients with neurological illness are usually excluded from previous researches, and delirium is underestimated due to potential consciousness and cognition impairment [6, 7]. Recently, more attention has been devoted to POD in patients after neurosurgery [8-11]. In our cohort with 800 adult patients admitted to the ICU after elective intracranial operation under general anaesthesia, delirium was screened within three days after the surgery [8]. The incidence of POD is about 20%, which is comparable to the results in the control group of randomised controlled trials with non-neurosurgical patients (18% to 21%) [12-14]. Potential associations between POD and adverse outcomes have also been reported in neurosurgical patients [8-11]. These results indicate that early prevention of POD should be employed in this population.

Perioperative preventive medications have been an active area of clinical POD researches [15]. As a highly selective α_2-adrenergic receptor agonist, dexmedetomidine has been investigated as a preventive agent for POD [12-14]. Systematic reviews and meta-analyses of randomised controlled trials have shown that perioperative administration of dexmedetomidine may decrease the incidence of

POD [12], in patients after either cardiac [13] or non-cardiac surgery [14]. However, neurosurgical patients are often excluded in randomised controlled trials of POD [12, 14].

In a randomised controlled trial in patients with delayed extubation after craniotomy [16], we found that early prophylactic use of dexmedetomidine during the first 24 hours after the operation significantly reduced the incidence of agitation, which might include some hyperactive delirium. In this study, an infusion rate of dexmedetomidine was set at 0.6 μg/kg/hour, which did not produce respiratory depression but increased the incidence of bradycardia. In a recent randomised controlled trial in elderly patients after non-cardiac surgery and admitted to the ICU, prophylactic use of low-dose (0.1 μg/kg/hour) dexmedetomidine significantly decreased the incidence of POD without the increased occurrence of hypotension and bradycardia [17]. A randomised controlled trial in critically ill adults also demonstrated that nocturnal administration of low-dose dexmedetomidine reduced the incidence of delirium during the ICU stay [18].

The above findings encouraged us to design a multicentre randomised controlled trial, DExmedetomidine for the prevention of PostOperative Delirium (DEPOD study), aiming to evaluate the efficacy and safety of low-dose dexmedetomidine for prevention of POD in patients after intracranial operation for brain tumours. The primary hypothesis is that, compared to the placebo group, the prophylactic use of low-dose dexmedetomidine can decrease the incidence of POD without significant adverse events in this population.

METHODS AND ANALYSIS

Study design

This prospective, multicentre, randomised, double-blinded and placebo-controlled trial with two parallel arms was designed to test whether the prophylactic use of low-dose dexmedetomidine would decrease the incidence of POD in adult patients admitted to the ICU after elective intracranial operation for brain tumours. The design of the present study has adhered to the Standard Protocol Items for Randomized Trials [19].

The flow chart of the trial is shown in figure 1.

Patient and public involvement

Patients and the public are not involved in the design or conduct of the study. There is no plan to disseminate our results to study participants.

Study locations

The study will be conducted in five ICUs in four teaching hospitals including Beijing Tiantan hospital (one general ICU and one neurosurgical ICU with a total of 50 beds) and Xuanwu hospital (one neurosurgical ICU with 30 beds) affiliated to Capital Medical University, Peking University Third Hospital (one general ICU with 30 beds), and Beijing Tsinghua Changgung Hospital affiliated to Tsinghua University (one general ICU with 20 beds), in Beijing, China.

Participants

Potential eligible participants are screened on admission to the ICU.

The inclusion criteria are adult patients after elective intracranial operation for brain tumours under general anaesthesia and who are admitted to the ICU directly from the operating room or postoperative care unit.

The exclusion criteria include:

1. Age younger than 18 years;
2. Admitted to the ICU after 22:00 PM;
3. Medical records documented preoperative history of mental or cognitive disorders including schizophrenia, epilepsy, Parkinsonism, or dementia;
4. Medical records documented inability to communicate in the preoperative period due to coma or language barrier;
5. History of drug abuse of psychoactive and anaesthetic drugs;
6. Known preoperative severe bradycardia (lower than 50 beats/min), sick sinus syndrome, second- or third-degree atrioventricular block, or left ventricular ejection fraction lower than 30%;
7. Serious hepatic dysfunction (Child-Pugh class C);
8. Severe renal dysfunction requiring renal replacement therapy before the surgery;
9. Allergies to ingredients or components of 5-[(1S)-1-(2,3-dimethylphenyl)ethyl]-1H-imidazole (dexmedetomidine hydrochloride);
10. American Society of Anesthesiologists (ASA) classification of IV to VI;
11. Moribund condition with a low likelihood of survival for more than 24 hours;

12. Pregnancy or lactation women;

13. Current enrolment in another clinical trial;

14. Refusal to participate.

Once the patient's eligibility is confirmed, a 24-hour on-call study coordinator will be contacted. Each relevant aspect of the project will be described and written informed consent will be obtained from the patient. If the patient cannot provide consent, written informed consent will be obtained from their authorized representatives. The study coordinator will be particularly careful to assure the patients or their authorized representatives that they are free to decline consent without consequences, and that they can withdraw consent at any time without an impact on treatment.

Randomisation, allocation concealment and blinding

After obtaining informed consent, the enrolled patients are randomly allocated to receive a continuous intravenous infusion of dexmedetomidine or placebo (normal saline).

To ensure allocation concealment of the randomisation, a password-protected central randomisation system is established and applied. A biostatistician who will not participate in data management and statistical analysis generates random numbers in a 1:1 ratio using the SAS 9.2 software (SAS Institute, Cary, NC). The stratification is performed among the five participating ICUs with prespecified block sizes depending on the anticipated number of recruitments. The random allocation sequence remains concealed from investigators in charge of enrolment. When the patient's enrolment is

confirmed, the investigator will log in to the central randomisation system, complete the checklist of inclusion and exclusion criteria, and acquire the random number. A pharmacist in each centre who has no knowledge of patients before the randomisation and will not participate in the rest of the study provides the study agents according to the randomisation results.

The experimental agents (dexmedetomidine hydrochloride 200 μg/2 ml or normal saline 2 ml) are manufactured and provided by the Jiangsu Nhwa Pharmaceutical Co., Ltd (Jiangsu, China). The agents are packed as clear aqueous solutions with the same character in the same 3-ml ampoules.

Information on randomisation and group allocation will be blinded from the patients, the investigators who perform data collection and follow-up, the ICU physicians and other healthcare providers who are responsible for patients care. Blinding will be maintained throughout the entire research period.

During the study, group allocation can be unmasked in order to protect the patient's safety. Investigators can request an urgent unmasking to the central randomisation system if considered necessary in case of the occurrence of severe adverse events or any unexpected deterioration of the patient's condition. Because each ampoule containing an experimental drug or placebo has a unique randomisation number, this emergency unmasking will not reveal the group allocations in other enrolled patients. The unmasked patients will be included in the intention-to-treat analysis.

Data collected at study entry

At baseline, demographic data, history of past illnesses and diagnosis of the patients are obtained. The surgical site and approach, body position, malignant tumour, intraoperative medications, fluid balance during operation, the amount of bleeding and blood transfusion during operation, episode of hypoxemia and hypotension during operation and duration of operation are recorded. The presence of an endotracheal tube and the need for mechanical ventilation on ICU admission are documented. The Acute Physiology and Chronic Health Evaluation II score (APACHE II) and Glasgow Coma Scale (GCS) are calculated. The time interval between the end of operation and study drug infusion is recorded.

Before the start of study agent infusion, delirium is evaluated using the Confusion Assessment Method for the ICU (CAM-ICU) [20-22] and documented as emergence delirium.

Trial interventions and management of pain, agitation and delirium

All enrolled patients will be randomly allocated to receive a continuous intravenous infusion of dexmedetomidine hydrochloride (dexmedetomidine group) or normal saline (placebo group).

The study agent (dexmedetomidine hydrochloride 200 μg/2 ml or normal saline 2 ml) is diluted with normal saline to 50 ml and continuously infused at a rate of 0.025 ml/kg/hour. This represents an infusion rate of 0.1 μg/kg/hour dexmedetomidine hydrochloride in the dexmedetomidine group.

The intravenous infusion will be started immediately after enrolment and continued

until 08:00 AM on the postoperative day one. During the study, scopolamine and penehyclidine will not be given. Open-labelled dexmedetomidine will be prohibited. Atropine can only be applied to treat bradycardia.

Routine clinical managements of pain, agitation and delirium have been established according to the recommendations in guidelines proposed by the American Society of Critical Care Medicine [23] and the European Society of Anaesthesiology [1] in all participating ICUs [8, 16, 24-26]. During the study protocol group discussion and training, several key elements in comprehensive approaches to reduce POD have been highlighted and emphasized as following:

1. Regular pain assessment is performed using patient's self-reported scales such as the Numeric Rating Scale (NRS) and the Visual Analogue Scale (VAS), and if impossible, using behavioural pain scales such as the Behavioral Pain Scale (BPS) and the Critical-Care Pain Observation Tool (CPOT);
2. Opioids or nonsteroidal anti-inflammatory drugs should be used in patients who require analgesia;
3. Regular agitation-sedation assessment is performed using the Richmond Agitation-Sedation Scale (RASS) or the Sedation-Agitation Scale (SAS);
4. If the patients exhibit agitation, sedation should be initiated using common sedatives including propofol and midazolam. Although midazolam is available, it is not recommended as the priority of sedative drugs;
5. A light sedation depth is recommended to maintain a RASS score of -2 to +1 or a SAS score of 3 to 5.

6. In conjunction with the recent clinical guidelines for ICU delirium [27], we recommend that repeated reorientation, cognitive stimulation, early mobilization, sleep-promotion strategies, and hearing or vision aids should be performed as long as possible;
7. Patients who develop POD are first given non-pharmacological treatments listed above. Pharmacological treatment is only reserved for patients with hyperactive delirium with disorientated agitation. Haloperidol (0.5 to 2 mg) can be intravenously injected followed by the administration of half of the loading dose for every 4 to 6 hours until the control of the severe hyperactive delirium.

The routine patient management and ICU discharge will be decided by the responsible ICU physicians. The hospital discharge will be decided by the responsible neurosurgeons.

Adverse events management

Adverse events will be monitored from the start of study agent infusion until 24 hours or until ICU discharge. Investigators should record all the adverse events including the type, diagnosis time, duration and consequences. Predicted adverse events in the present study include bradycardia (defined as heart rate lower than 50 beats/min), hypotension (defined as systolic blood pressure lower than 90 mmHg), and hypoxemia (defined as pulse oxygen saturation lower than 90%) [16, 17].

Attending ICU physicians can stop the study agent infusion in the following cases:

1. Heart rate lower than 40 beats/min after atropine in 0.25 mg intravenous bolus;

2. Systolic blood pressure lower than 90 mmHg after fluid resuscitation with 250 ml crystalloid solution infusion within 15 min;
3. Peripheral pulse oxygen saturation lower than 90% after administration of oxygen and adjustment of mechanical ventilation for patients without and with endotracheal intubation, respectively;
4. Other conditions deemed necessary by the ICU physician.

In these cases, the reasons that lead to any protocol interruption are documented and reported to the Institutional Review Board of Beijing Tiantan Hospital Affiliated to Capital Medical University within 24 hours. Patients with study protocol interruption will be included in the intention-to-treat analysis.

Outcome measurements

The patients will be followed up twice daily during the first five postoperative days, and then weekly until hospital discharge or until 28 days after the operation. Investigators who are responsible for follow-up will not involve in the study agent infusion and patient care, and they are not allowed to exchange patient's information with ICU physicians taking care of the patients.

The primary endpoint is the incidence of POD during the first five postoperative days [1]. Delirium is evaluated twice daily (08:00 AM to 10:00 AM and 18:00 PM to 20:00 PM) until the fifth postoperative day by the CAM-ICU [20-22]. Before the initiation of the trial, investigators in each participating ICU are trained to follow the study protocol and to perform the CAM-ICU evaluation. Thereafter, the training will be

performed at an interval of 3 months during the study. An expert from the Department of Psychiatry is invited to provide the training. The training courses consist of three phases: (1) group training with information about delirium, RASS and CAM-ICU, as well as a video demonstrating the detailed conduction of CAM-ICU assessment; (2) one-to-one instruction at the bedside; (3) examination on five patients who have been pre-assessed by the expert. Different results of delirium assessment between the trainee and the expert will be discussed until 100% agreement is reached.

Secondary endpoints include:

1. Incidence of adverse events from the start of study agent infusion until 24 hours or until ICU discharge;
2. Incidence of non-delirium complications after the operation until 28 days, including airway obstruction and apnoea, respiratory failure, cardiac events, coma, epilepsy, cerebral haemorrhage or infarction, renal injury and infection;
3. Length of stay in the ICU and hospital after the operation;
4. All-cause 28-day mortality after the operation.

Additional pre-specified endpoints include the use of sedatives and analgesics during the study agent infusion, pain intensity (assessed by CPOT) [23, 27] and subjective sleep quality (assessed by NRS) [28] in the morning of postoperative day one.

Data management and monitoring

Before the initiation of the study, an electronic case report form (eCRF) is established and available online at a dedicated website with password-protected access for each

participating centre. Each enrolled patient will be assigned an identification number. Patient data will be coded and kept confidential. Related paper records will be stored in a locked cabinet in an access-controlled room.

Each participating centre will indicate a local coordinator in charge of the study. The local coordinators guarantee the integrity of data collection and timely completion of the eCRF.

Data quality and safety will be monitored by an independent Data and Safety Monitoring Board, which will be composed of five multidisciplinary experts who are not have subordinate relationships with any members of the research team. Data management and statistical analysis will be performed by the China National Clinical Research Center for Neurological Diseases in Beijing Tiantan Hospital. Because dexmedetomidine has been widely used in the ICU and its safety has been confirmed in the previous studies [16, 17], an interim analysis will not be scheduled. Severe adverse events will be reported to the Institutional Review Board of Beijing Tiantan Hospital Affiliated to Capital Medical University within 24 hours.

Current sample size justification

In four observational studies, including 2769 patients after intracranial operation, POD occurred in 349 patients with an overall pooled crude incidence of 13% [8-11]. A recent meta-analysis of non-cardiac patients showed that the incidence of POD reduced by approximately half when dexmedetomidine was used perioperatively [14]. We assume that the incidence of POD would be reduced by half in the

dexmedetomidine group compared with the placebo group in the present study. With a significance and power set at 0.05 (two-sided) and 80%, respectively, the sample size required to detect difference is 648 patients. Taking into account about 6% of the loss to follow-up rate, 700 (350 in each group) patients need to be enrolled.

Statistical analysis

All analyses will be conducted according to the intention-to-treat principle, that is, all randomised patients will be analysed in the groups to which they have been originally allocated and will be blinded to treatment assignment.

Categorical variables will be presented as numbers and percentages, and analysed by the χ^2-test. Continuous variables will be checked for normal distribution and presented as mean and standard deviation or median and interquartile range as appropriate. Comparison of continuous variables will be performed by Student's t-test for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables. Time-to-event variables will be analysed by survival analysis, with the difference between groups assessed with Log-Rank test.

Statistical analysis will be performed using SPSS 20.0 (SPSS Inc., Chicago, IL, USA) and SAS 9.2 software (SAS Institute, Cary, NC). A *p*-value of less than 0.05 is considered statistically significant.

SUMMARY

This multicentre, randomised, placebo-controlled, double-blinded trial is designed to investigate the effect of prophylactic use of low-dose dexmedetomidine on the incidence of POD in adult patients admitted to the ICU after intracranial operation for brain tumours.

In the present study, the CAM-ICU is used for the POD diagnosis. The CAM-ICU has been validated in mechanically ventilated patients [20] and non-intubated ICU patients [21]. The Chinese version of the CAM-ICU has been validated in the ICU setting in mainland China [22], and the feasibility has been established in studies reported by our group and others [8, 17]. We will conduct the screening of delirium twice daily from postoperative day one to day five, which is in accordance with the recommendation provided by the European Society of Anaesthesiology evidence-based and consensus-based guideline on POD [1]. The first POD assessment is performed in the morning on postoperative day one, which will be around 24 hours after the operation. This timing of the first assessment is selected to avoid the bias resulting from the diagnosis of emergence delirium, which may be only related to the influence of hypnotics [5, 29]. Furthermore, investigators in each participating ICU who are in charge of postoperative follow-up are trained by a psychiatrist before the initiation of the study to guarantee the quality of the CAM-ICU evaluation.

We design a low-dose dexmedetomidine infusion (0.1 μg/kg/hour) in the present study to avoid drug-related hemodynamic adverse events such as severe bradycardia demonstrated in our previous study [16]. The efficacy and safety of this

dexmedetomidine dosing regimen have been validated in previous studies in elderly patients after non-cardiac surgery [30].

The main strength of the present study is the design of a multicentre, randomised, placebo-controlled and double-blinded trial with a relatively large sample size. To the best of our knowledge, this is the first study to evaluate the impact of pharmacological interventions on POD in neurosurgical patients admitted to ICU. The results of the study will provide high-quality evidence. There are also several limitations to our study. First, we will only enrol patients admitted to the ICU, which may represent a population at high risk of POD [3-5]. Thus, our results may be limited for generalizing to the entire population of patients undergoing intracranial surgery. Second, we only evaluate early outcomes up to 28 days after the operation. Third, the hemodynamic effects of dexmedetomidine such as bradycardia might weaken the efficiency of masking to the treating physicians in the ICU. However, investigators who are responsible for follow-up will not involve in the study agent infusion and patient care. Additionally, the exchange of patient's information is not allowed between investigators in charge of follow-up and ICU physicians taking care of the patients. This will decrease the risk of unmasking to the greatest extent.

Trial status

At the time of manuscript submission, the study is in the preparation phase for recruitment.

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Contributors

J-XZ planned the study. H-QG performed the statistical design of the study. All authors contributed to the design and development of the trial (XH, K-MC, LZ, H-QG, XQ, YX, P-LM and J-XZ). XH and J-XZ drafted the manuscript. LZ critically revised the manuscript. All authors read and approved the final manuscript.

Funding

The study was supported by a grant from the Chinese Stroke Association (CSA2019KY005). The sponsors have no role in the study design and conduct; the data collection, management, analysis and interpretation; or the preparation and approval of the manuscript.

Competing interests

The experimental agents (dexmedetomidine hydrochloride and normal saline) are manufactured, packed and provided by the Jiangsu Nhwa Pharmaceutical Co., Ltd (Jiangsu, China). Agents provider has no role in the study design and conduct; the data collection, management, analysis and interpretation; or the preparation and approval of the manuscript.

The authors declare that they have no other competing interests.

Patient consent

Obtained.

Ethics approval

The study protocol (V2.0/2019-10-10 issue date October 2019) was approved by the Institutional Review Board of Beijing Tiantan Hospital Affiliated to Capital Medical

University (No KY2019-091-02). The trial was registered at ClinicalTrials.gov with identifier NCT04399343 on May 21, 2020.

Figure legend

Figure 1 Flow chart of the trial

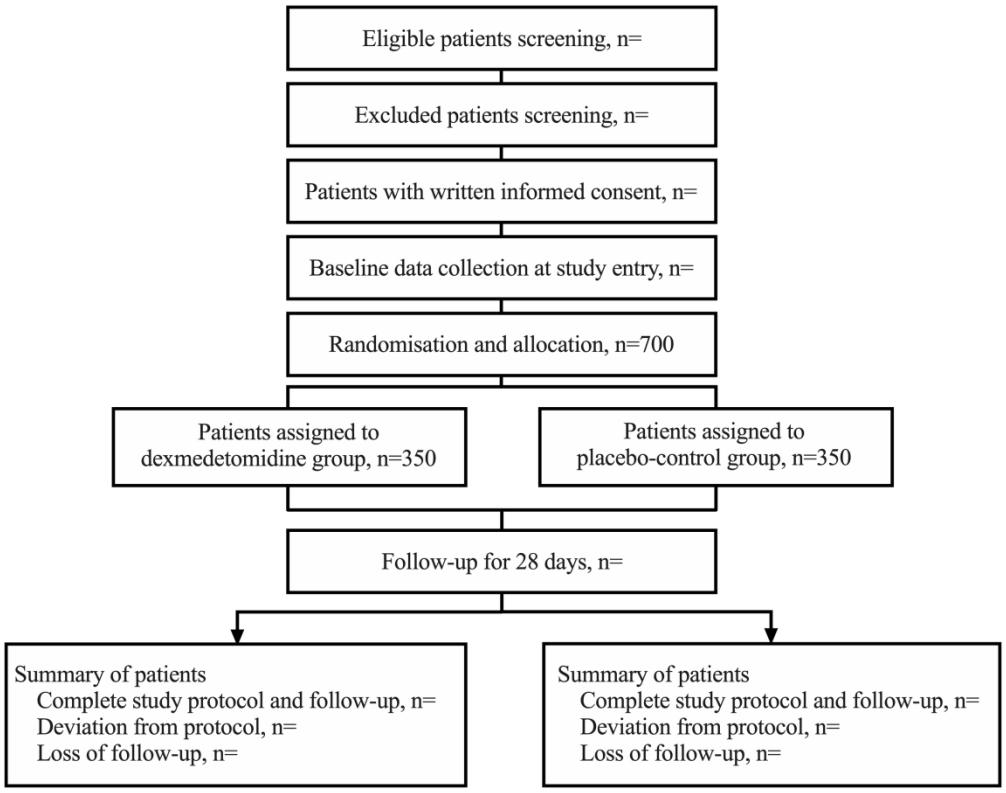

Figure 1 Flow chart of the trial

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SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description
Administrative information		
Title	1√	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2a√	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3√	Date and version identifier
Funding	4√	Sources and types of financial, material, and other support
Roles and responsibilities	5a√	Names, affiliations, and roles of protocol contributors
	5b√	Name and contact information for the trial sponsor
	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
	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)
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
	6b√	Explanation for choice of comparators
Objectives	7√	Specific objectives or hypotheses
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)

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
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)
Interventions	11a√	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	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)
	11c√	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d√	Relevant concomitant care and interventions that are permitted or prohibited during the trial
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
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)
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
Recruitment	15√	Strategies for achieving adequate participant enrolment to reach target sample size

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

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
Implementation	16c√	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	17a√	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b√	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial
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
	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
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
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
	20b√	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	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)
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

	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
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
Auditing	23√	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval	24√	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
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)
Consent or assent	26a√	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b√	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
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
Declaration of interests	28√	Financial and other competing interests for principal investigators for the overall trial and each study site
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
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
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
	31b√	Authorship eligibility guidelines and any intended use of professional writers
	31c√	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

Appendices

Informed consent materials	32√	Model consent form and other related documentation given to participants and authorised surrogates
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

*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

Dexmedetomidine for the prevention of postoperative delirium in patients after intracranial operation for brain tumours (DEPOD study): a study protocol and statistical plan for a multicentre randomised controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-040939.R1
Article Type:	Protocol
Date Submitted by the Author:	13-Oct-2020
Complete List of Authors:	He, Xuan; Beijing Tiantan Hospital, Department of Critical Care Medicine; Capital Medical University Cheng, Kun-Ming; Beijing Tiantan Hospital, Department of Critical Care Medicine; Capital Medical University Zhang, Linlin; Beijing Tiantan Hospital, Department of Critical Care Medicine; Capital Medical University Gu, Hongqiu; Beijing Tiantan Hospital, Qu, Xin; Xuanwu Hospital, Department of Neurosurgery; Capital Medical University Xu, Yuan; Tsinghua University; Beijing Tsinghua Changgung Hospital, ICU Ma, Penglin; Peking University Third Hospital, Zhou, Jian-Xin; Beijing Tiantan Hospital, Department of Critical Care Medicine; Capital Medical University
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Anaesthesia
Keywords:	Adult intensive & critical care < ANAESTHETICS, NEUROSURGERY, Delirium & cognitive disorders < PSYCHIATRY

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Dexmedetomidine for the prevention of postoperative delirium in patients after intracranial operation for brain tumours (DEPOD study): a study protocol and statistical plan for a multicentre randomised controlled trial

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Keywords: delirium, postoperative, intracranial operation, prevention, dexmedetomidine

Word count: 3481

ABSTRACT

Introduction Postoperative delirium (POD) is prevalent in patients after major surgery and is associated with adverse outcomes. Several studies have reported that dexmedetomidine, a highly selective α2-adrenergic receptor agonist, can decrease the incidence of POD. However, neurosurgical patients are usually excluded from previous studies. The present study was designed to investigate the impact of prophylactic use of low-dose dexmedetomidine on the incidence of POD in patients after intracranial operation.

Methods and analysis This is a multicentre, randomised, double-blinded and placebo-controlled trial. Seven hundred intensive care unit admitted patients after elective intracranial operation for brain tumours under general anaesthesia are randomly assigned to the dexmedetomidine group or the placebo group with a 1:1 ratio. For patients in the dexmedetomidine group, a continuous infusion of dexmedetomidine will be started at a rate of 0.1 μg/kg/hour immediately after enrolment on the day of operation and continued until 08:00 AM on the postoperative day one. For patients in the placebo group, normal saline will be administered at the same rate as in the dexmedetomidine group. The patients will be followed up for 28 days after enrolment. The primary endpoint is the incidence of POD, which is assessed twice daily using the Confusion Assessment Method for the Intensive Care Unit, during the first five postoperative days. The secondary endpoints include the incidence of dexmedetomidine related adverse events and non-delirium complications, the length of stay in the ICU and hospital and all-cause 28-day

mortality after the operation.

Ethics and dissemination The study protocol was approved by the Institutional Review Board of Beijing Tiantan Hospital Affiliated to Capital Medical University (No KY2019-091-02) and registered at ClinicalTrials.gov. The results of the trial will be presented at national and international conferences relevant to subject fields and submitted to international peer-reviewed journals.

Trial registration number NCT04399343; Pre-results.

Main strengths and limitations of the study

- The study design will be multicentre, randomised, double-blinded and placebo-controlled, with a relatively large sample size.
- To the best of our knowledge, this is the first study to evaluate the effect of prophylactic use of dexmedetomidine on postoperative delirium in neurosurgical patients.
- Only intensive care unit admitted patients are included, which will limit the generalizability of the results.
- Only early outcomes are assessed including the incidence of postoperative delirium and other endpoints up to 28 days after the operation.
- Although patients with medical records documented preoperative history of mental or cognitive disorders are excluded, no systematic cognitive assessment will be performed before the intracranial operation.

BACKGROUND

Postoperative delirium (POD) is one of the main postoperative complications after major surgery, especially in patients admitted to the intensive care unit (ICU) [1, 2]. Studies have shown that POD is associated with adverse outcomes, including prolonged length of stay in the ICU and hospital, higher morbidity and mortality risks, increased healthcare costs, and reduced long-term quality of life [3-5]. However, patients with neurological illness are usually excluded from previous researches, and delirium is underestimated due to potential consciousness and cognition impairment [6, 7]. Recently, more attention has been devoted to POD in patients after neurosurgery [8-11]. In our cohort with 800 adult patients admitted to the ICU after elective intracranial operation under general anaesthesia, delirium was screened within three days after the surgery [8]. The incidence of POD is about 20%, which is comparable to the results in the control group of randomised controlled trials with non-neurosurgical patients (18% to 21%) [12-14]. Potential associations between POD and adverse outcomes have also been reported in neurosurgical patients [8-11]. These results indicate that early prevention of POD should be employed in this population.

Perioperative preventive medications have been an active area of clinical POD researches [15]. As a highly selective α_2-adrenergic receptor agonist, dexmedetomidine has been investigated as a preventive agent for POD [12-14]. Systematic reviews and meta-analyses of randomised controlled trials have shown that perioperative administration of dexmedetomidine may decrease the incidence of

POD [12], in patients after either cardiac [13] or non-cardiac surgery [14]. However, neurosurgical patients are often excluded in randomised controlled trials of POD [12, 14].

In a randomised controlled trial in patients with delayed extubation after craniotomy [16], we found that early prophylactic use of dexmedetomidine during the first 24 hours after the operation significantly reduced the incidence of agitation, which might include some hyperactive delirium. In this study, an infusion rate of dexmedetomidine was set at 0.6 μg/kg/hour, which did not produce respiratory depression but increased the incidence of bradycardia. In a recent randomised controlled trial in elderly patients after non-cardiac surgery and admitted to the ICU, prophylactic use of low-dose (0.1 μg/kg/hour) dexmedetomidine significantly decreased the incidence of POD without the increased occurrence of hypotension and bradycardia [17]. A randomised controlled trial in critically ill adults also demonstrated that nocturnal administration of low-dose dexmedetomidine reduced the incidence of delirium during the ICU stay [18].

The above findings encouraged us to design a multicentre randomised controlled trial, DExmedetomidine for the prevention of PostOperative Delirium (DEPOD study), aiming to evaluate the efficacy and safety of low-dose dexmedetomidine for prevention of POD in patients after intracranial operation for brain tumours. The primary hypothesis is that, compared to the placebo group, the prophylactic use of low-dose dexmedetomidine can decrease the incidence of POD without significant adverse events in this population.

METHODS AND ANALYSIS

Study design

This prospective, multicentre, randomised, double-blinded and placebo-controlled trial with two parallel arms was designed to test whether the prophylactic use of low-dose dexmedetomidine would decrease the incidence of POD in adult patients admitted to the ICU after elective intracranial operation for brain tumours. The design of the present study has adhered to the Standard Protocol Items for Randomized Trials [19].

The flow chart of the trial is shown in figure 1.

Patient and public involvement

Patients and the public are not involved in the design or conduct of the study. There is no plan to disseminate our results to study participants.

Study locations

The study will be conducted in five ICUs in four teaching hospitals including Beijing Tiantan hospital (one general ICU and one neurosurgical ICU with a total of 50 beds) and Xuanwu hospital (one neurosurgical ICU with 30 beds) affiliated to Capital Medical University, Peking University Third Hospital (one general ICU with 30 beds), and Beijing Tsinghua Changgung Hospital affiliated to Tsinghua University (one general ICU with 20 beds), in Beijing, China.

Participants

Potential eligible participants are screened on admission to the ICU.

The inclusion criteria are adult patients after elective intracranial operation for brain tumours under general anaesthesia and who are admitted to the ICU directly from the operating room or postoperative care unit.

The exclusion criteria include:

1. Age younger than 18 years;
2. Admitted to the ICU after 22:00 PM;
3. Medical records documented preoperative history of mental or cognitive disorders including schizophrenia, epilepsy, Parkinsonism, or dementia;
4. Medical records documented inability to communicate in the preoperative period due to coma or language barrier;
5. History of drug abuse of psychoactive and anaesthetic drugs;
6. Known preoperative severe bradycardia (lower than 50 beats/min), sick sinus syndrome, second- or third-degree atrioventricular block, or left ventricular ejection fraction lower than 30%;
7. Serious hepatic dysfunction (Child-Pugh class C);
8. Severe renal dysfunction requiring renal replacement therapy before the surgery;
9. Allergies to ingredients or components of 5-[(1S)-1-(2,3-dimethylphenyl)ethyl]-1H-imidazole (dexmedetomidine hydrochloride);
10. American Society of Anesthesiologists (ASA) classification of IV to VI;
11. Moribund condition with a low likelihood of survival for more than 24 hours;

12. Pregnancy or lactation women;

13. Current enrolment in another clinical trial;

14. Refusal to participate.

Once the patient's eligibility is confirmed, a 24-hour on-call study coordinator will be contacted. Each relevant aspect of the project will be described and written informed consent will be obtained from the patient. If the patient cannot provide consent, written informed consent will be obtained from their authorized representatives. The study coordinator will be particularly careful to assure the patients or their authorized representatives that they are free to decline consent without consequences, and that they can withdraw consent at any time without an impact on treatment.

Randomisation, allocation concealment and blinding

After obtaining informed consent, the enrolled patients are randomly allocated to receive a continuous intravenous infusion of dexmedetomidine or placebo (normal saline).

To ensure allocation concealment of the randomisation, a password-protected central randomisation system is established and applied. A biostatistician who will not participate in data management and statistical analysis generates random numbers in a 1:1 ratio using the SAS 9.2 software (SAS Institute, Cary, NC). The stratification is performed among the five participating ICUs with prespecified block sizes depending on the anticipated number of recruitments. The random allocation sequence remains concealed from investigators in charge of enrolment. When the patient's enrolment is

confirmed, the investigator will log in to the central randomisation system, complete the checklist of inclusion and exclusion criteria, and acquire the random number. A pharmacist in each centre who has no knowledge of patients before the randomisation and will not participate in the rest of the study provides the study agents according to the randomisation results.

The experimental agents (dexmedetomidine hydrochloride 200 μg/2 ml or normal saline 2 ml) are manufactured and provided by the Jiangsu Nhwa Pharmaceutical Co., Ltd (Jiangsu, China). The agents are packed as clear aqueous solutions with the same character in the same 3-ml ampoules.

Information on randomisation and group allocation will be blinded from the patients, the investigators who perform data collection and follow-up, the ICU physicians and other healthcare providers who are responsible for patients care. Blinding will be maintained throughout the entire research period.

During the study, group allocation can be unmasked in order to protect the patient's safety. Investigators can request an urgent unmasking to the central randomisation system if considered necessary in case of the occurrence of severe adverse events or any unexpected deterioration of the patient's condition. Because each ampoule containing an experimental drug or placebo has a unique randomisation number, this emergency unmasking will not reveal the group allocations in other enrolled patients. The unmasked patients will be included in the intention-to-treat analysis.

Data collected at study entry

At baseline, demographic data, history of past illnesses and diagnosis of the patients are obtained. The surgical site and approach, body position, malignant tumour, intraoperative medications, fluid balance during operation, the amount of bleeding and blood transfusion during operation, episode of hypoxemia and hypotension during operation and duration of operation are recorded. The presence of an endotracheal tube and the need for mechanical ventilation on ICU admission are documented. The Acute Physiology and Chronic Health Evaluation II score (APACHE II) and Glasgow Coma Scale (GCS) are calculated. The time interval between the end of operation and study drug infusion is recorded.

Before the start of study agent infusion, delirium is evaluated using the Confusion Assessment Method for the ICU (CAM-ICU) [20-22] and documented as emergence delirium.

Trial interventions and management of pain, agitation and delirium

All enrolled patients will be randomly allocated to receive a continuous intravenous infusion of dexmedetomidine hydrochloride (dexmedetomidine group) or normal saline (placebo group).

The study agent (dexmedetomidine hydrochloride 200 μg/2 ml or normal saline 2 ml) is diluted with normal saline to 50 ml and continuously infused at a rate of 0.025 ml/kg/hour. This represents an infusion rate of 0.1 μg/kg/hour dexmedetomidine hydrochloride in the dexmedetomidine group.

The intravenous infusion will be started immediately after enrolment and continued

until 08:00 AM on the postoperative day one. During the study, scopolamine and penehyclidine will not be given. Open-labelled dexmedetomidine will be prohibited. Atropine can only be applied to treat bradycardia.

Routine clinical managements of pain, agitation and delirium have been established according to the recommendations in guidelines proposed by the American Society of Critical Care Medicine [23] and the European Society of Anaesthesiology [1] in all participating ICUs [8, 16, 24-26]. During the study protocol group discussion and training, several key elements in comprehensive approaches to reduce POD have been highlighted and emphasized as following:

1. Regular pain assessment is performed using patient's self-reported scales such as the Numeric Rating Scale (NRS) and the Visual Analogue Scale (VAS), and if impossible, using behavioural pain scales such as the Behavioral Pain Scale (BPS) and the Critical-Care Pain Observation Tool (CPOT);
2. Opioids or nonsteroidal anti-inflammatory drugs should be used in patients who require analgesia;
3. Regular agitation-sedation assessment is performed using the Richmond Agitation-Sedation Scale (RASS) or the Sedation-Agitation Scale (SAS);
4. If the patients exhibit agitation, sedation should be initiated using common sedatives including propofol and midazolam. Although midazolam is available, it is not recommended as the priority of sedative drugs;
5. A light sedation depth is recommended to maintain a RASS score of -2 to +1 or a SAS score of 3 to 5.

6. In conjunction with the recent clinical guidelines for ICU delirium [27], we recommend that repeated reorientation, cognitive stimulation, early mobilization, sleep-promotion strategies, and hearing or vision aids should be performed as long as possible;
7. Patients who develop POD are first given non-pharmacological treatments listed above. Pharmacological treatment is only reserved for patients with hyperactive delirium with disorientated agitation. Haloperidol (0.5 to 2 mg) can be intravenously injected followed by the administration of half of the loading dose for every 4 to 6 hours until the control of the severe hyperactive delirium.

The routine patient management and ICU discharge will be decided by the responsible ICU physicians. The hospital discharge will be decided by the responsible neurosurgeons.

Adverse events management

Adverse events will be monitored from the start of study agent infusion until 24 hours or until ICU discharge. Investigators should record all the adverse events including the type, diagnosis time, duration and consequences. Predicted adverse events in the present study include bradycardia (defined as heart rate lower than 50 beats/min), hypotension (defined as systolic blood pressure lower than 90 mmHg), and hypoxemia (defined as pulse oxygen saturation lower than 90%) [16, 17].

Attending ICU physicians can stop the study agent infusion in the following cases:

1. Heart rate lower than 40 beats/min after atropine in 0.25 mg intravenous bolus;

2. Systolic blood pressure lower than 90 mmHg after fluid resuscitation with 250 ml crystalloid solution infusion within 15 min;
3. Peripheral pulse oxygen saturation lower than 90% after administration of oxygen and adjustment of mechanical ventilation for patients without and with endotracheal intubation, respectively;
4. Other conditions deemed necessary by the ICU physician.

In these cases, the reasons that lead to any protocol interruption are documented and reported to the Institutional Review Board of Beijing Tiantan Hospital Affiliated to Capital Medical University within 24 hours. Patients with study protocol interruption will be included in the intention-to-treat analysis.

Outcome measurements

The patients will be followed up twice daily during the first five postoperative days, and then weekly until hospital discharge or until 28 days after the operation. Investigators who are responsible for follow-up will not involve in the study agent infusion and patient care, and they are not allowed to exchange patient's information with ICU physicians taking care of the patients.

The primary endpoint is the incidence of POD during the first five postoperative days [1]. Delirium is evaluated twice daily (08:00 AM to 10:00 AM and 18:00 PM to 20:00 PM) until the fifth postoperative day by the CAM-ICU [20-22]. Before the initiation of the trial, investigators in each participating ICU are trained to follow the study protocol and to perform the CAM-ICU evaluation. Thereafter, the training will be

performed at an interval of 3 months during the study. An expert from the Department of Psychiatry is invited to provide the training. The training courses consist of three phases: (1) group training with information about delirium, RASS and CAM-ICU, as well as a video demonstrating the detailed conduction of CAM-ICU assessment; (2) one-to-one instruction at the bedside; (3) examination on five patients who have been pre-assessed by the expert. Different results of delirium assessment between the trainee and the expert will be discussed until 100% agreement is reached.

Secondary endpoints include:

1. Incidence of adverse events from the start of study agent infusion until 24 hours or until ICU discharge;
2. Incidence of non-delirium complications after the operation until 28 days, including airway obstruction and apnoea, respiratory failure, cardiac events, coma, epilepsy, cerebral haemorrhage or infarction, renal injury and infection;
3. Length of stay in the ICU and hospital after the operation;
4. All-cause 28-day mortality after the operation.

Additional pre-specified endpoints include the use of sedatives and analgesics during the study agent infusion, pain intensity (assessed by CPOT) [23, 27] and subjective sleep quality (assessed by NRS) [28] in the morning of postoperative day one.

Data management and monitoring

Table 1 shows data collection at each time point.

Before the initiation of the study, an electronic case report form (eCRF) is established

and available online at a dedicated website with password-protected access for each participating centre. Each enrolled patient will be assigned an identification number. Patient data will be coded and kept confidential. Related paper records will be stored in a locked cabinet in an access-controlled room.

Each participating centre will indicate a local coordinator in charge of the study. The local coordinators guarantee the integrity of data collection and timely completion of the eCRF.

Data quality and safety will be monitored by an independent Data and Safety Monitoring Board, which will be composed of five multidisciplinary experts who are not have subordinate relationships with any members of the research team. Data management and statistical analysis will be performed by the China National Clinical Research Center for Neurological Diseases in Beijing Tiantan Hospital. Because dexmedetomidine has been widely used in the ICU and its safety has been confirmed in the previous studies [16, 17], an interim analysis will not be scheduled. Severe adverse events will be reported to the Institutional Review Board of Beijing Tiantan Hospital Affiliated to Capital Medical University within 24 hours.

Current sample size justification

In four observational studies, including 2769 patients after intracranial operation, POD occurred in 349 patients with an overall pooled crude incidence of 13% [8-11]. A recent meta-analysis of non-cardiac patients showed that the incidence of POD reduced by approximately half when dexmedetomidine was used perioperatively [14].

We assume that the incidence of POD would be reduced by one-third in the dexmedetomidine group compared with the placebo group in the present study. With a significance and power set at 0.05 (two-sided) and 80%, respectively, the sample size required to detect difference is 1088 patients. Taking into account about 5% of the loss to follow-up rate, 1140 (570 in each group) patients need to be enrolled.

Statistical analysis

All analyses will be conducted according to the intention-to-treat principle, that is, all randomised patients will be analysed in the groups to which they have been originally allocated and will be blinded to treatment assignment.

Categorical variables will be presented as numbers and percentages, and analysed by the χ^2-test. Continuous variables will be checked for normal distribution and presented as mean and standard deviation or median and interquartile range as appropriate. Comparison of continuous variables will be performed by Student's t-test for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables. Time-to-event variables will be analysed by survival analysis, with the difference between groups assessed with Log-Rank test.

Post-hoc analyses were be performed by stratifying the patients with intra-axial vs. extra-axial tumour, tumour located in supratentorial vs. infratentorial region, and craniotomy via frontal vs. non-frontal approach.

Statistical analysis will be performed using SPSS 20.0 (SPSS Inc., Chicago, IL, USA) and SAS 9.2 software (SAS Institute, Cary, NC). A *p*-value of less than 0.05 is considered statistically significant.

Ethics and dissemination

The study protocol was approved by the Institutional Review Board of Beijing Tiantan Hospital Affiliated to Capital Medical University (No KY2019-091-02) and registered at ClinicalTrials.gov (NCT04399343, Pre-results). The results of the trial will be presented at national and international conferences relevant to subject fields and submitted to international peer-reviewed journals.

SUMMARY

This multicentre, randomised, placebo-controlled, double-blinded trial is designed to investigate the effect of prophylactic use of low-dose dexmedetomidine on the incidence of POD in adult patients admitted to the ICU after intracranial operation for brain tumours.

In the present study, the CAM-ICU is used for the POD diagnosis because all enrolled patients will be admitted to the ICU for postoperative care. In our previous cohort study with 800 neurosurgical patients admitted to the ICU after intracranial operations, 28% of the patients remained endotracheal intubation [8]. The CAM-ICU has been validated in mechanically ventilated patients [20] and non-intubated ICU patients [21]. The Chinese version of the CAM-ICU has been validated in the ICU setting in mainland China [22], and the feasibility has been established in studies reported by our group and others [8, 17]. The CAM-ICU is recommended as a delirium screening tool by the American Society of Critical Care Medicine in adult ICU patients [23, 27] and by the European Society of Anaesthesiology in postoperative patients [1]. We will conduct the screening of delirium twice daily from postoperative day one to day five, which is in accordance with the recommendation provided by the European Society of Anaesthesiology evidence-based and consensus-based guideline on POD [1]. The first POD assessment is performed in the morning on postoperative day one, which will be around 24 hours after the operation. This timing of the first assessment is selected to avoid the bias resulting from the diagnosis of emergence delirium, which may be only related to the influence of hypnotics [5,

29]. Furthermore, investigators in each participating ICU who are in charge of postoperative follow-up are trained by a psychiatrist before the initiation of the study to guarantee the quality of the CAM-ICU evaluation.

We design a low-dose dexmedetomidine infusion (0.1 μg/kg/hour) in the present study to avoid drug-related hemodynamic adverse events such as severe bradycardia demonstrated in our previous study [16]. The efficacy and safety of this dexmedetomidine dosing regimen have been validated in previous studies in elderly patients after non-cardiac surgery [30].

The main strength of the present study is the design of a multicentre, randomised, placebo-controlled and double-blinded trial with a relatively large sample size. To the best of our knowledge, this is the first study to evaluate the impact of pharmacological interventions on POD in neurosurgical patients admitted to ICU. The results of the study will provide high-quality evidence. There are also several limitations to our study. First, we will only enrol patients admitted to the ICU, which may represent a population at high risk of POD [3-5]. Thus, our results may be limited for generalizing to the entire population of patients undergoing intracranial surgery. Second, we only evaluate early outcomes up to 28 days after the operation. Third, although we exclude patients with medical records documented preoperative history of mental or cognitive disorders, no systematic cognitive assessment will be performed before the intracranial operation. Forth, the hemodynamic effects of dexmedetomidine such as bradycardia might weaken the efficiency of masking to the treating physicians in the ICU. However, investigators who are responsible for

follow-up will not involve in the study agent infusion and patient care. Additionally, the exchange of patient's information is not allowed between investigators in charge of follow-up and ICU physicians taking care of the patients. This will decrease the risk of unmasking to the greatest extent.

Trial status

At the time of manuscript submission, the study is in the preparation phase for recruitment.

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Contributors

J-XZ planned the study. H-QG performed the statistical design of the study. All authors contributed to the design and development of the trial (XH, K-MC, LZ, H-QG, XQ, YX, P-LM and J-XZ). XH and J-XZ drafted the manuscript. LZ critically revised the manuscript. All authors read and approved the final manuscript.

Funding

The study was supported by a grant from the Chinese Stroke Association (CSA2019KY005). The sponsors have no role in the study design and conduct; the data collection, management, analysis and interpretation; or the preparation and approval of the manuscript.

Competing interests

The experimental agents (dexmedetomidine hydrochloride and normal saline) are manufactured, packed and provided by the Jiangsu Nhwa Pharmaceutical Co., Ltd (Jiangsu, China). Agents provider has no role in the study design and conduct; the data collection, management, analysis and interpretation; or the preparation and approval of the manuscript.

The authors declare that they have no other competing interests.

Patient consent

Obtained.

Ethics approval

The study protocol (V2.0/2019-10-10 issue date October 2019) was approved by the Institutional Review Board of Beijing Tiantan Hospital Affiliated to Capital Medical

University (No KY2019-091-02). The trial was registered at ClinicalTrials.gov with identifier NCT04399343 on May 21, 2020.

Figure legend

Figure 1 Flow chart of the trial

Table 1. Data collection at each time point

	At study entry	Postoperative day 1 to 5, twice daily	Postoperative day 7, 14, 21 and 28, once daily
Demographic data	√		
Data of history and diagnosis	√		
Intraoperative data	√		
Data on ICU admission	√		
Data during ICU stay		√, if not discharged from ICU	
Delirium assessment	√	√	

Study drug interruption		√	
Adverse events		√, if not discharged from ICU	
Non-delirium complications		√	√, if not discharged from hospital
Length of stay in ICU		√, if not discharged from ICU	√, if not discharged from ICU
Length of stay in hospital		√, if not discharged from hospital	√, if not discharged from hospital
All-cause death		√	√, if not discharged from hospital

ICU: intensive care unit

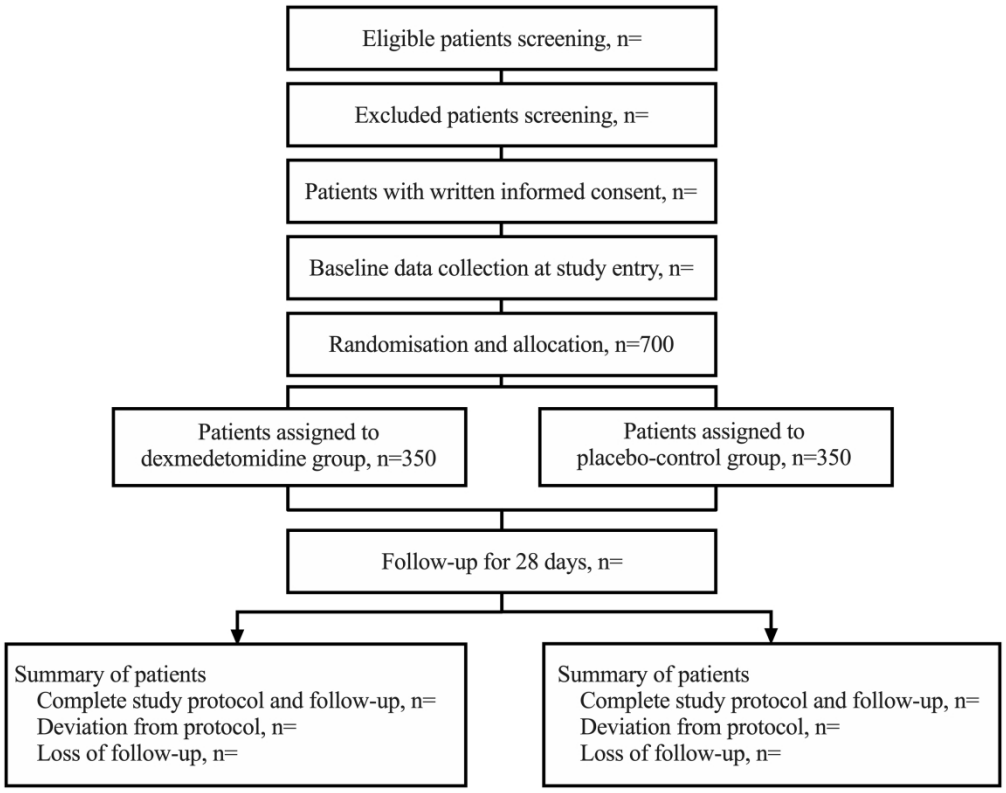

Figure 1 Flow chart of the trial

238x186mm (300 x 300 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Mark	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	4
		2b	All items from the World Health Organization Trial Registration Data Set	/
√	Protocol version	3	Date and version identifier	28
√	Funding	4	Sources and types of financial, material, and other support	28
√	Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
		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	28
		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)	17&19

	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	6-7
		6b	Explanation for choice of comparators	7
√	Objectives	7	Specific objectives or hypotheses	7
√	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)	8
	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	8
√	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)	9-10
√	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12-13
		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)	11
		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	11-12
		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	13-14
√	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	15-16
√	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)	Figure1&Table 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	17-18
√	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	17-18
	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	10
	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	10-11
	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10-11
√	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11
		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	11
	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	15-16
		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	15

√	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	16-17
√	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	18
		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	18
		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)	15
	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	17
		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	19
√	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	14-15&19
√	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	19
	Ethics and dissemination			
√	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	18-19
√	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)	28-29

√	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
√	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	16-17
√	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	28
√	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	16-17
√	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	14-15&17
√	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	18-19
		31b	Authorship eligibility guidelines and any intended use of professional writers	18-19
		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
	Appendices			
√	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary file
/	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	NA

*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.