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Ultrasound guided superficial cervical plexus block for analgesia in patients undergoing craniotomy via suboccipital retrosigmoid approach: study protocol of a randomized controlled trial

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Ultrasound guided superficial cervical plexus block for analgesia in patients undergoing craniotomy via suboccipital retrosigmoid approach: study protocol of a randomized controlled trial

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Abstract

Introduction Scalp nerve block has been proven to be an alternative choice to opioids in multimodal analgesia. However, for the infratentorial space-occupying craniotomy, especially the suboccipital retrosigmoid craniotomy, scalp nerve block is insufficient.

Methods and analysis The study is a prospective, single-center, randomized, paralleled-group controlled trial. Patients scheduled to receive elective suboccipital retrosigmoid craniotomy will be randomly assigned to the superficial cervical plexus block group or the control group. After anesthesia induction, superficial cervical plexus nerve block will be performed under the guidance of ultrasound. The primary outcome is the cumulative consumption of sufentanil by the PCA within 24 hours after surgery. Secondary outcomes include the cumulative consumption of sufentanil at other 5 time points, pain site and NRS pain severity score.

Keywords craniotomy, analgesia, superficial cervical plexus block, ultrasound

Ethics approval and dissemination The protocol (version number: 2.0, April 10, 2019) has been approved by the Ethics Review Committee of China Registered Clinical Trials (Ethics Review No. ChiECRCT-20190047). The findings of this study will be disseminated in peer-reviewed journals and at scientific conferences.

Trial registration number NCT03033693.

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Article Summary

Strengths and limitations of this study

- This is the first randomized controlled trial to observe the efficacy and safety of preoperative ultrasound-guided superficial cervical plexus block on postoperative analgesia in patients undergoing craniotomy via suboccipital retrosigmoid approach.
- The results will optimize postoperative analgesia in patients undergoing infratentorial craniotomy, thereby improving the short- and long-term prognosis of the patients.
- This is a single-center clinical trial design which might limit the generalization of the conclusion.

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Background

The procedure of craniotomy was previously assumed to be less painful than other sites of surgeries [1]. It had been believed nerve fiber density was lower in dura, less nerve fiber would be damaged by craniotomy and no nociceptive sensory nerve distributed in brain parenchyma [2]. However, in a prospective study of patients undergoing craniotomy, Gottchalk et al. found that the incidence of postoperative pain was as high as 87%, among of 55% patients experienced moderate to severe pain [3]. Inadequate analgesia after craniotomy leads to enormous catastrophe for patients [4]. Post-craniotomy pain is mainly caused by scalp incision, with enormous free nerve endings. After incision, nociceptors are activated by chemical mediators. These stimulus signals from the anterior scalp or posterior scalp are received by the trigeminal branches or cervical plexus branches, and then transmitted to the trigeminal nucleus and the dorsal horn of the spinal cord. Secondary neurons upload these signals to the thalamus and then project them to the cerebral cortex and form pain perception. The whole process is regulated by a variety of inflammatory mediators, peripheral nerve pathways and central nervous system[5].

The pain severity after craniotomy is closely associated with surgical approach. Gottschalk et al. evaluated postoperative pain in 187 craniotomy patients and found that the infratentorial approach was associated with severe postoperative pain and more perioperative analgesic requirements than the supratentorial approach[3]. The suboccipital retrosigmoid approach is a common approach for infratentorial mass craniotomy and mass located in cerebellopontine angle region. Rimaaja et al. reported

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that 32% of patients had no or only mild headache prior to removal of the cerebellopontine angle area mass via a suboccipital approach, while 64% of patients developed severe headache after craniotomy[6]. The high incidence of postoperative pain after craniotomy through infratentorial approach, especially suboccipital retrosigmoid approach may be related to the injury of neck muscles and posterior occipital muscles by the surgical approach, as well as the special position of the head and neck during craniotomy, leading to postoperative muscle spasm [7, 8].

Apart from that, it has been suggested that inadequately treated acute pain also increases the risk of postcraniotomy chronic pain, which affects the long-term quality of life of patients[9]. Schankin's study found that 32% of patients with suboccipital retrosigmoid craniotomy developed persistent headache syndrome with a severity greater than 6/10 via Visual Analogue Scale (VAS) at 6 months after surgery[10]. It is obvious that patients undergoing craniotomy via suboccipital retrosigmoid approach suffer sever acute and chronic pain, with high prevalence and severe adverse effect. Therefore, it is necessary to explore a compound analgesia model to prevent both acute and chronic pain.

The ideal postoperative analgesia after craniotomy should be a comprehensive analgesic regimen including multiple time points and multiple modes, to ensure achievement of an ideal analgesic state after craniotomy with exact analgesic effect and slight or no interference on respiration recovery or circulation stability. Meanwhile, the interference on consciousness and postoperative neurological function should be minimized during the recovery and evaluation period. At present, postoperative patient

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controlled intravenous analgesia (PCIA) with opioid is the most common analgesia model for patients received craniotomy. However, various adverse reactions of opioids, including respiratory depression, nausea, vomiting, pruritus, urinary retention, etc., not only bring discomfort to patients, but also affect neurological function evaluation by neurosurgeons[11]. Besides opioids, nonsteroidal anti-inflammatory drugs (NSAIDS) is another common used analgesia agent in clinical practice, however, NSAIDS is not suitable for postoperative analgesia after neurosurgery due to its effect on coagulation[12]. Gabapentin is an adjuvant antiepileptic agent with some analgesic effects. Our previous research demonstrated that preoperative oral gabapentin relieved early postoperative pain, with increased depth of sedation in early stage of post-craniotomy, which indicated gabapentin was not the appropriate candidate for postoperative neurosurgical analgesia[13].

The skin incision is the main source of pain during craniotomy. Scalp nerve block (SNB) has been proven to be an excellent alternative choice to opioids in this multimodal analgesia, and widely used in neurosurgical analgesia[14-16]. However, for the infratentorial space-occupying craniotomy, especially the suboccipital retrosigmoid craniotomy, the scalp innervation area is insufficient to cover the incision, resulting defective nerve blockage. Therefore, it is necessary to explore a comprehensive analgesic model to provide a more ideal analgesic regimen for patients undergoing suboccipital retrosigmoid craniotomy. The cervical plexus is from the anterior branch of C1-C4 cervical nerve, divided into by superficial plexus and deep plexus. The superficial plexus runs from medial to lateral under the sternocleidomastoid muscle and

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passes through the superficial cervical fascia at the midpoint behind it. The cutaneous branches of the superficial cervical plexus include the lesser occipital nerve, the greater auricular nerve, transverse cervical nerve and supraclavicular nerve, innervating the incision area of the suboccipital sigmoid sinus approach craniotomy [17]. Therefore, the superficial cervical plexus block (SCPB) is a potential candidate to satisfy the analgesic requirement of retrosigmoid craniotomy. Francois et al. observed the effect of transitional analgesia from SCPB before anesthesia recovery after elective infratentorial or occipital craniotomy in 30 patients [18]. In the control group, 0.1mg/kg morphine was administrated after close of the dura. It was found that the effect of SCPB on postoperative analgesia was not inferior to administration of morphine after dura closure. However, the sample size estimation is not sufficient. Second, the superficial cervical plexus was located not by ultrasound. This kind of method in location was not only easy to injury the adjacent muscles and vessels, but also unable to determine the correct anatomical level of the drug. The analgesic effect of SCPB may not be fully guaranteed. In addition, no related adverse effects were reported in that study. However, the study provided us a feasible method of SCPB analgesia for suboccipital retrosigmoid craniotomy. With the continual development of visualization techniques, ultrasound-guided nerve blocks have become increasingly popular [19-21]. For SCPB, the blind puncture has the potential to penetrate the prevertebral fascia to become a deep cervical plexus block. Ultrasound-guided SCPB, the operator can directly see nerve and adjacent anatomical structure, accurately locate the nerve, avoid accidental injury during the puncture, and inject the local anesthetic into the correct anatomical

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level, to avoid the unexpected deep cervical plexus block. It has the advantages of faster onset of action, less dosage, high success rate, and fewer complications.

Therefore, we propose the hypothesis that preoperative ultrasound-guided SCPB safely and effectively decreases the requirements for postoperative opioids drugs. The results are expected to optimize postoperative analgesia in patients undergoing infratentorial craniotomy, thereby improving the short- and long-term prognosis of the patients.

Methods

Study design

This is a prospective, single-center, randomized, paralleled-group controlled trial （Figure 1） being conducted at Beijing Tiantan Hospital, Capital Medical University, China. The study was approved by the Ethics Review Committee of China Registered Clinical Trials on April 8, 2019 (No. ChiECRCT-20190047). The study strategy was registered on the registration website http://clinicaltrals.gov/ on June 29, 2019 with the registration number NCT04036812. Preoperative interviews will be conducted by specially trained research assistants to inform patients of the study purposes, risks and benefits, and to obtain written informed consent from patients or legal representatives. The schedule of enrollment and assessments is shown in the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)（Figure 2).

Study population

Inclusion criteria

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Patients scheduled to undergo elective suboccipital retrosigmoid craniotomy will be recruited. Inclusion criteria include age between18 and 65 years, and American Society of Anesthesiologists (ASA) physical status I-III.

Exclusion criteria

Exclusion criteria include refuse to provide written informed consent, local infection, preoperative impairment of consciousness and cognitive function, severe hepatic or renal dysfunction, uncontrolled hypertension, diabetes, severe arrhythmia and unstable angina pectoris, inability to communicate; allergic to experimental drugs; refuse to receive post-operative analgesia; history of drug abuse; history of chronic headache; aphasia and hearing impairment; second craniotomy; body mass index < 18.5 kg/m^2 or > 30.0 kg/m^2 .

Randomization and blinding

Randomization will be conducted via a computer-generated table by independent research assistant to ensure the allocation sequence of random codes. Patients will be randomly assigned to two groups with a 1: 1 ratio. The allocation sequence will be packed with identical shape and size opaque envelopes and distributed to the anesthesiologists who will not involve in intraoperative management or postoperative follow-up. The random allocation form will be sealed in triplicate with opaque envelopes, and one copy will be kept by the study director, pharmacy nurse and statistician, respectively. Patients, anesthesiologists responsible for intraoperative management and outcome assessors will be blinded to the participants' group

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assignment till end of the study unless specific circumstances, such as the occurrence of a serious adverse event (SAE).

Intervention

Patients will be randomly assigned to the superficial cervical plexus block group or the control group. After anesthesia induction, SCPB will be performed under the guidance of ultrasound (HITACHI company, Noblus). Patients will be at supine position with ipsilateral shoulder relaxed and slightly elevated while head tilting to the opposite side. After marking the midpoint of the posterior border of clavicular head of the sternocleidomastoid muscle (about cricoid cartilage level, about 3-4 cm above the clavicle), an ultrasound probe (50 mm high frequency linear array) warped with sterilize plastic dress will be placed in the transverse position at the previous measuring mark. The scanning depth will be 3-4 cm and the focusing position will be 2-3 cm. After confirming the sternocleidomastoid muscle, we move the probe backwards until the posterior border of the sternocleidomastoid muscle in the center of the screen, and identify the investing fascia and prevertebral fascia from the shallow to the deep layer. Using long-axis in-plane technique, a 50 mm long, 20G short bevel needle will be inserted from the lateral border of sternocleidomastoid muscle. Under guidance of ultrasound, we will confirm the needle tip locating between the deep layer of investing fascia and the superficial layer of prevertebral fascia, close to the border of sternocleidomastoid muscle. After negative aspiration of blood and cerebrospinal fluid, 1 ml of 0.5% ropivacaine will be administered to confirm the location of the needle tip. Then, 10-15 mL of 0.5% ropivacaine will be infused on the superficial layer of

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prevertebral fascia. The puncture site will be covered with opaque infusion dressing after completing of superficial cervical plexus block.

In the control group, ultrasound guidance will be used to determine the location of superficial cervical plexus nerve, but no puncture will be performed with opaque infusion dressing used to cover the proposed puncture site.

Concomitant treatment

Peripheral venous access will be established upon arrival in operating room. Routine monitoring will include electrocardiograph (ECG), pulse oxygen saturation, noninvasive blood pressure (NIBP), body temperature and bispectral index (BIS). Continuous arterial pressure, urine output and end-tidal carbon dioxide partial pressure ($ETCO_2$) will be monitored after anesthesia induction. All patients will be premedicated with midazolam (0.05 mg/kg) intravenously 5 minutes before anesthesia induction. Anesthesia will be induced with propofol (1.5 to 2.5 mg/kg), sufentanil (0.3 to 0.4 μg/kg), and rocuronium (0.9 mg/kg) or cisatracurium (0.2 mg/kg). After tracheal intubation, mechanical ventilation will be performed, at a tidal volume 6-8 ml/kg, a respiratory rate of 12-15/min, an I:E of 1:2, a 50% fraction of inspired oxygen in the air and fresh gas at a flow rate of 2 L/min to maintain the $ETCO_2$ between 35 and 40 mmHg. Local infiltration anesthesia with 2% lidocaine will be performed at the site of head pins before placing head holder.

Anesthesia will be maintained with total intravenous anesthesia (TIVA). Remifentanil will be titrated (0.1-0.4 μg/kg/min) immediately after induction to maintain intraoperative analgesia. During tumor resection (from dura incision to dura suture),

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the infusion rate of remifentanil will be adjusted between 0.2 and 0.4 μg/kg/min. Along with the remifentanil infusion, anesthesia will be maintained with propofol infusion (3-8 mg/kg/h) to keep BIS values between 40 and 50. No muscle relaxant will be used during the procedure to meet intraoperative electronical physiological neuro-monitoring requirements. No additional local anesthetics or analgesics will be administered intraoperatively. Propofol and remifentanil infusion will be discontinued at the end of surgery.

The patients will be extubated after full recovery from anesthesia and transferred to the post-anesthesia care unit (PACU). The patients will remain in the PACU for 120 minutes and receive nasal oxygen inhalation with ECG, NIBP, pulse oximetry monitoring. Sufentanyl-loaded electric analgesia pumps (Rhythmic Plus, Micrel Medical Devices S.A., Greece-European Union) which pre-programmed by the research assistant will be connected to the patients for routine postoperative analgesia. The PCA electric pumps will be filled with sufentanyl (100 μg) and ondansetron (16 mg) diluted in 100 mL of 0.9% saline. This regimen will provide a bolus of 1 μg sufentanyl on demand with a 15-minute lockout time, without continuous background infusion dose or loading dose. Insufficient postoperative analgesia will be defined as an NRS score >40 over 15 minutes or > 60. Once inadequate postoperative analgesia was confirmed, patients will receive intravenous tramadol (50 mg). If the patient vomited or reported nausea for more than 15 minutes, ondansetron 8 mg will be administered intravenously.

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Physiologic parameters, the total doses of anesthetic drugs and vasoactive drugs will be recorded. Fluid input and output will also be closely monitored and recorded. Anesthesia and surgery duration will be summarized.

Outcomes and safety measures

The aim of this study is to observe the effect of SCPB on postoperative analgesia in patients with suboccipital retrosigmoid craniotomy.

Primary outcome

The primary outcome is the cumulative consumption of sufentanil by the PCA within 24 hours after surgery. The primary outcomes will be assessed by trained research assistants at 24 hours after surgery through reading the PCA data. During preoperative visits, patients will be informed of NRS pain score, analgesic satisfaction score, sleep quality score and other criteria. They also will be familiarized with the PCA pump, follow-up visit and criteria for chronic pain.

Secondary outcomes

The secondary outcomes include the other efficacy parameters and safety outcomes.

1) The first-time point that the patients use PCA, the total and effective requests of PCA at 6 different time-point after surgery and the cumulative consumption of sufentanil at other 5 time-points after surgery, except 24 hours after surgery.

2) Pain site and NRS pain severity score. Pain will be assessed at 6 time-points after surgery. The surgical incision pain as well as head and neck pain will be assessed at rest and on movement. If patients report pain in one or more of the above three sites, NRS (0-10, 0 = no pain and 10 = worst pain imaginable) will be used to further evaluate

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the degree of pain. Insufficient postoperative analgesia is defined as an NRS score that exceeds 4 and exceeds 6 lasted for 15 minutes. Information of analgesic drugs administrated in case of insufficient postoperative analgesia was also recorded.

3) Anesthesia recovery quality score. Anesthesia Steward Emergence Scale[22] will be used at 1 and 2 hours after surgery to evaluate the recovery quality of anesthesia.

4) Analgesic satisfaction and sleep quality. Patient satisfaction with overall pain management and sleep quality will be evaluated separately at 24 and 48 hours after surgery using NRS.

5) Adverse events. Ramsay score[23] and Nausea and vomiting scores as well other adverse events (dizziness, fatigue, hematoma, local anesthetic poisoning and hoarseness) will be evaluated at the 6 time points after surgery.

6) Chronic pain assessment. Follow-up visit will be conducted by telephone at 3 and 6 months after surgery. If patients report chronic headache, the NRS score will be assessed. The nature of pain will also be assessed by the Chinese version of the McGill Pain Questionnaire-2[24]. The pain index will be calculated by daily pain duration (pain hours/day), monthly pain duration (pain days/month) and pain NRS score.

Data collection

An independent research assistant will initiate baseline information collection at the day before surgery. Basic demographic information, including gender, age, vital signs, height, weight, past medical history, family history, medication history, pre-treatment supplementary examination and assessment (ASA classification, headache and severity, treatment, dizziness, tinnitus, facial paralysis, nausea, vomiting and other symptoms)

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will be collected. All personal information will be kept strictly confidential for research purposes only. The assessment of primary and other secondary outcomes will be performed by trained research assistants blinded to the group allocation. Only designated researchers can obtain the interim results and final data.

Sample size calculation

We estimate the sample size according to the primary outcome of postoperative-24-hour PCA sufentanil consumption by using PASS 2011 software (NCSS LLC). Based on the previous literature [25, 26], SNB reduces PCA sufentanil consumption by 40-50% within postoperative 24 hours. Our preliminary study found that the postoperative 24 hours PCA sufentanil consumption in the control group is about 50 ± 30 μg. We estimate the effect size was 20 μg, the standard deviation was 30 μg. The initial sample size of 106 patients will be sufficient to detect the difference at a two-tailed significant level of 0.05 and a power of 90% using Student t test, with a drop-out rate of 10%.

Statistical analysis

Analysis will be done using SPSS software (version 23.0). If necessary, consider the number of missing outcomes as poor prognosis and conduct sensitivity analysis. The continuous variables will be summarized with mean (standard deviation) or median (interquartile range, IQR), depending on normality determined with Shapiro-Wilk test. Normally distributed and continuous variables will be compared with Student's t-test, while skewed variables will be compared using the Mann-Whitney U test. The categorical variables will be described as counts (percentages) and compared with chi-square analysis or Fisher's exact test. The repeated measurement data will be

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analyzed by repeated measurements of variance analysis. Bonferroni correction will be used for multiple comparisons. A significance level of $P<0.05$ was used to indicate statistical significance.

Reporting of adverse events

All adverse events will be closely monitored until a stable situation has been reached. It will be immediately recorded and reported to the research site in case of any adverse events. The chief investigator will be informed of any serious adverse events and determine the severity and causality of these events. All adverse events associated with this study will be recorded and reported to the ethics committee as part of the annual report. The chief investigator will be responsible for all reported adverse events.

Protocol Amendment

The chief investigator will be responsible for any decision to amend the protocol. If there is any modification (eg, 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, and communicate with relevant other parties (eg, investigators, trial participants, trial registries, journals, regulators)

Data Monitoring Committee（DMC）

The data monitoring committee (DMC) will be composed of anesthesiologists, ethicists, statisticians and methodologists, serving as an independent unit to monitor the safety, efficacy, ethical issues and progress of trial. The DMC reserves the right to review patient recruitment at any time. The audit process will be independent of investigators.

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Discussion

This is a prospective, single-center, randomized, parallel-group controlled trial to explore the efficacy and safety of preoperative ultrasound-guided superficial cervical plexus block for analgesia in patients undergoing suboccipital retrosigmoid craniotomy. With the continuous development of ultrasound guidance technology, utilization of visualized nerve block became more popular in clinical practice [20, 21, 27]. We design the current study to use ultrasound-guided cervical plexus block to explore the efficacy and safety of postoperative analgesia in patients undergoing suboccipital sigmoid approach for craniotomy. Although ultrasound guidance greatly improves the efficacy and safety of the block, we still can't ignore the risk associated with the cervical plexus block for the anatomic complexity of superficial cervical plexus. Therefore, in this study we will observe these complications such as hematoma, high epidural block or total spinal anesthesia, overdose and hoarseness. At the same time, in order to ensure the accuracy and consistency of ultrasound-guided puncture, the anesthesiologists who perform nerve block are the fixed group of people and will receive specific training before the first patients are enrolled, the corresponding ultrasound image data of puncture will be preserved, so as to ensure the uniformity of block effect in each patient. Although SCPB may reduce postcraniotomy pain, it is not routinely used in our current clinical practice. To maintain the analgesic effect on the patients in the control group, the patients will be given the same analgesic dosage regimen following the clinical routine of our medical center, which fully ensure that the patients are safe and painless

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during surgery. Postoperative PCA analgesia will be routinely given to all patients, and rescue analgesics will be promptly administered when analgesia is insufficient.

Our study will improve the ideal analgesic regimen for patients undergoing suboccipital retrosigmoid craniotomy, so as to reduce perioperative stress response and complications, improve patient satisfaction, promote early recovery, reduce the occurrence of chronic pain and ultimately provide a better long-term quality of life.

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

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Competing interests: None declared.

Ethics approval: This study is approved by the Ethics Review Committee of China Registered Clinical Trials (Ethics Review No. ChiECRCT-20190047).

Data sharing statement The manuscript is a protocol for a randomized controlled trial, which does not include data.

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Figure legends

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

Figure 2. Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)

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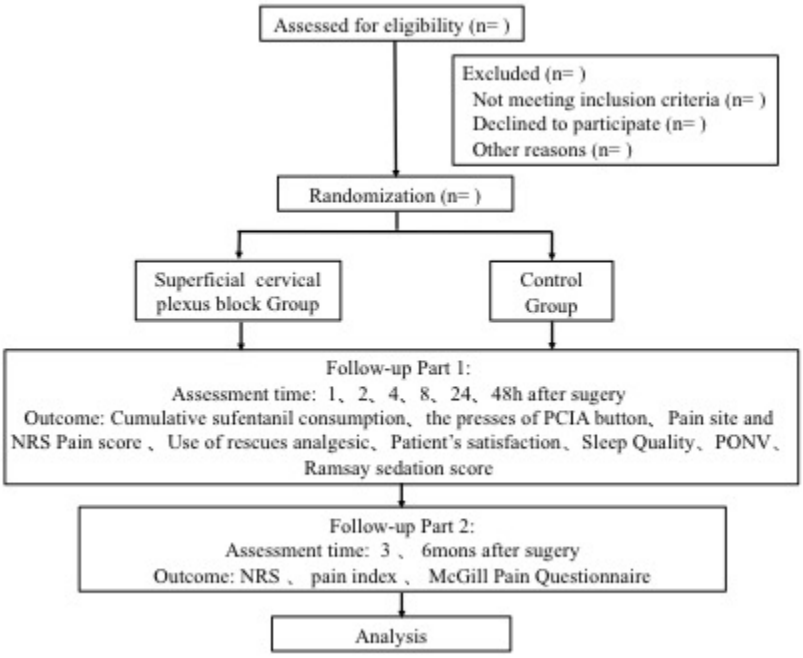

Consolidated Standards of Reporting Trials (CONSORT) flow diagram

146x117mm (72 x 72 DPI)

STUDY PERIOD											
	Enrolment	Allocation	Post-allocation								
TIMEPOINT	-1day	Sugery day	Post-craniotomy(hour)					Post-craniotomy(day)			
			1	2	4	8	12	1	2	90	180
ENROLMENT											
Eligibility screen	X										
Informed consent	X										
Allocation		X									
INTERVENTIONS											
SCPB group		X									
Control group		X									
ASSESSMENTS											
Baseline variables		X	X	X	X	X	X	X	X		
Intraoperative data		X									
Anesthesia recovery quality score			X	X							
Ramsay Score			X	X	X	X	X	X	X		
Cumulative sufentanil consumption of PCA			X	X	X	X	X	X	X		
Requests of PCA			X	X	X	X	X	X	X		
Dose and frequency of rescue analgesic			X	X	X	X	X	X	X		
Pain location			X	X	X	X	X	X	X		
Pain intensity（NRS)			X	X	X	X	X	X	X		
Analgesia Satisfaction								X	X		
Sleep quality								X	X		
Adverse Event			X	X	X	X	X	X	X		
Chronic pain										X	X

Standard Protocol Items- Recommendations for Interventional Trials

331x219mm (72 x 72 DPI)

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Checklist for **Ultrasound guided superficial cervical plexus block for analgesia in patients undergoing craniotomy via suboccipital retrosigmoid approach: 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	3
	2b	All items from the World Health Organization Trial Registration Data Set	3
Protocol version	3	Date and version identifier	3
Funding	4	Sources and types of financial, material, and other support	18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1 & 17
	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	18&17
	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)	Not Applicable

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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	4-8
	6b	Explanation for choice of comparators	4-8
Objectives	7	Specific objectives or hypotheses	8
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)	8-9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-11
	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)	10-11
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	10-11
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11-13
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	13-14
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 2

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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	15
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8

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	9
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	9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	9

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	9 - 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	10

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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	13-14
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	10 - 11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15-16
	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)	15-16
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	16
	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	15-16
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	16
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Not Applicable
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	8 & 18
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)	16

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Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not 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	15
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	18
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	18
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	3
	31b	Authorship eligibility guidelines and any intended use of professional writers	3
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	3
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.

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Ultrasound guided superficial cervical plexus block for analgesia in patients undergoing craniotomy via suboccipital retrosigmoid approach: study protocol of a randomized controlled trial

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Ultrasound guided superficial cervical plexus block for analgesia in patients undergoing craniotomy via suboccipital retrosigmoid approach: study protocol of a randomized controlled trial

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Abstract

Introduction Scalp nerve block has been proven to be an alternative choice to opioids in multimodal analgesia. However, for the infratentorial space-occupying craniotomy, especially the suboccipital retrosigmoid craniotomy, scalp nerve block is insufficient.

Methods and analysis The study is a prospective, single-center, randomized, paralleled-group controlled trial. Patients scheduled to receive elective suboccipital retrosigmoid craniotomy will be randomly assigned to the superficial cervical plexus block group or the control group. After anesthesia induction, superficial cervical plexus nerve block will be performed under the guidance of ultrasound. The primary outcome is the cumulative consumption of sufentanil by the patient controlled intravenous analgesia pump within 24 hours after surgery. Secondary outcomes include the cumulative consumption of sufentanil at other 4 time points and numerical rating scale pain severity score.

Keywords craniotomy, analgesia, superficial cervical plexus block, ultrasound

Ethics approval and dissemination The protocol (version number: 2.0, April 10, 2019) has been approved by the Ethics Review Committee of China Registered Clinical Trials (Ethics Review No. ChiECRCT-20190047). The findings of this study will be disseminated in peer-reviewed journals and at scientific conferences.

Trial registration number NCT03033693.

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Article Summary

Strengths and limitations of this study

- This is the randomized controlled trial to observe the efficacy and safety of preoperative ultrasound-guided superficial cervical plexus block on postoperative analgesia in patients undergoing craniotomy via suboccipital retrosigmoid approach.
- The results will optimize postoperative analgesia in patients undergoing infratentorial craniotomy, thereby improving prognosis of the patients.
- This is a single-center clinical trial design which might limit the generalization of the conclusion.

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Background

The procedure of craniotomy was previously assumed to be less painful than other sites of surgeries [1-3]. However, in the prospective study of patients undergoing craniotomy, Gottchalk et al. found that the incidence of postoperative pain was as high as 87%, among of 55% patients experienced moderate to severe pain [4].

Post-craniotomy pain is mainly caused by scalp incision, with abundant free nerve endings. After incision, noxious stimulus signals from the scalp is received by the trigeminal branches or cervical plexus branches, and then transmitted through the trigeminal nucleus and the dorsal horn of the spinal cord to the hypothalamus and cerebral cortex. The whole process is regulated by a variety of inflammatory mediators, peripheral nerve pathways and central nervous system [5].

The pain severity after craniotomy is closely associated with surgical approach. Gottschalk et al. evaluated pain after craniotomy and found that the infratentorial approach was associated with severe postoperative pain and more perioperative analgesic requirements [4]. Rimaaja et al. reported that 32% of patients had no or only mild headache prior to removal of the cerebellopontine angle area mass, while 64% of patients developed severe headache after craniotomy [6]. The high incidence of postoperative pain after craniotomy through infratentorial approach, especially suboccipital retrosigmoid approach may be related to the injury of neck muscles and posterior occipital muscles by the surgical approach, as well as the special position of the head and neck during craniotomy, leading to postoperative muscle spasm [7, 8].

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Therefore, it is necessary to explore an ideal analgesic modality that can effectively provide surgical analgesia with minimal or no systemic changes for this population.

The skin incision is the main source of pain during craniotomy. Scalp nerve block (SNB) has been proven to be an excellent alternative analgesic choice in supratentorial surgeries [9-11]. However, for the suboccipital retrosigmoid craniotomy, the scalp innervation area is insufficient to cover the incision, resulting defective nerve blockage. Therefore, it is necessary to explore an analgesic modality to provide a more ideal analgesic regimen for patients undergoing suboccipital retrosigmoid craniotomy.

The cervical plexus is from the anterior branch of C1-C4 cervical nerve, divided into superficial plexus and deep plexus. The cutaneous branches of the superficial cervical plexus include the lesser occipital nerve, the greater auricular nerve, transverse cervical nerve and supraclavicular nerve, innervating the incision area of the suboccipital sigmoid sinus approach craniotomy [12]. Therefore, the superficial cervical plexus block (SCPB) is a potential candidate to satisfy the analgesic requirement of retrosigmoid craniotomy. Francois et al. observed the effect of transitional analgesia from SCPB after elective infratentorial or occipital craniotomy in 30 patients [13]. In the control group, 0.1mg/kg morphine was administrated after close of the dura. It was found that the effect of SCPB on postoperative analgesia was not inferior to administration of morphine after dura closure. However, the sample size estimation they made is too small. Second, SCPB wasn't guided by ultrasound. The analgesic effect of SCPB may not be fully guaranteed. In addition, no related adverse effects were

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reported in that study. However, the study provided us a feasible method of SCPB analgesia for suboccipital retrosigmoid craniotomy.

With the continual development of visualization techniques, ultrasound-guided nerve blocks have become increasingly popular [14-16]. Ultrasound-guided SCPB, the operator can directly see adjacent anatomical structure, inject the local anesthetic into the correct anatomical level, avoid accidental injury during the puncture, and avoid the unexpected deep cervical plexus block. Ultrasound-guided SCPB has the advantages of faster onset of action, less dosage, high success rate, and fewer complications [17, 18]. Therefore, we propose the hypothesis that preoperative ultrasound-guided SCPB could safely and effectively provide analgesia for patients undergoing craniotomy via suboccipital retrosigmoid approach. The objective is to compare the cumulative consumption of postoperative opioids between groups.

Methods

Study design

This is a prospective, single-center, randomized, paralleled-group controlled trial (Figure 1.) being conducted at Beijing Tiantan Hospital, Capital Medical University, China. The study was approved by the Ethics Review Committee of China Registered Clinical Trials on April 8, 2019 (No. ChiECRCT-20190047). The study was registered within clinicaltrials.gov on June 29 with the registration number NCT04036812. Preoperative interviews will be conducted by specially trained research assistants to inform patients of the study objectives, risks and benefits, and to obtain written informed consent from patients or legal representatives. The schedule of

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enrollment and assessments is shown in the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) (Figure 2.).

Study population

Inclusion criteria

Patients scheduled to undergo elective suboccipital retrosigmoid craniotomy will be recruited for screening eligibility one day before surgery. Inclusion criteria include age between 18 and 65 years, and American Society of Anesthesiologists (ASA) physical status I-III.

Exclusion criteria

Exclusion criteria include refuse to provide written informed consent, local infection, preoperative impairment of consciousness and cognitive function, uncontrolled hypertension, inability to communicate; allergic to experimental drugs; history of drug abuse; history of chronic headache; aphasia and hearing impairment; second craniotomy; body mass index < 18.5 kg/m^2 or > 35.0 kg/m^2 .

Randomization and blinding

Randomization will be conducted via a computer-generated table by an independent research assistant who will be pack the allocation sequence with identical shape and size opaque envelopes and distribute to the researcher. The researcher will open the envelopes and perform a SCPB or only puncture based on the grouping. Patients will be randomly assigned to two groups with a 1: 1 ratio. The researcher assistant, patients, the anesthesiologist responsible for intraoperative management and outcome assessors

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will all be blinded to the allocation until the completion of the study analysis unless specific circumstances, such as the occurrence of a serious adverse event (SAE).

Data collection

After obtaining informed consent, an independent research assistant will initiate baseline information collection one day before surgery. Basic demographic information, including gender, age, vital signs, height, weight, past medical history/family history, medication history, supplementary examination, assessment (ASA classification, headache and severity, treatment, dizziness, tinnitus, facial paralysis, nausea, vomiting and other symptoms) will be collected. All personal information will be kept strictly confidential for research purposes only. The assessment of primary and other secondary outcomes will be performed by trained research assessors who are blinded to the group allocation.

Intervention

Patients will be randomly assigned to the SCBP group or the control group. Peripheral venous access will be established upon arrival in operating room. After anesthesia induction, SCPB will be performed under the guidance of ultrasound (HITACHI Company, Noblus) by the independent researcher who will not involve in intraoperative management or postoperative follow-up. Patients will be at supine position with ipsilateral shoulder relaxed and slightly elevated while head tilting to the opposite side. After marking the midpoint of the posterior border of clavicular head of the sternocleidomastoid muscle (about cricoid cartilage level, about 3-4 cm above the clavicle), an ultrasound probe (50 mm high frequency linear array) warped with sterilize

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plastic dress will be placed in the transverse position at the previous measuring mark. The scanning depth will be 3-4 cm and the focusing position will be 2-3 cm. After confirming the sternocleidomastoid muscle, we move the probe backwards until the posterior border of the sternocleidomastoid muscle in the center of the screen, and identify the investing fascia and prevertebral fascia from the shallow to the deep layer. Using long-axis in-plane technique, a 50 mm long, 20 G short bevel needle will be inserted from the lateral border of sternocleidomastoid muscle. Under guidance of ultrasound, we will confirm the needle tip locating between the deep layer of investing fascia and the superficial layer of prevertebral fascia, close to the border of sternocleidomastoid muscle. After negative aspiration of blood and cerebrospinal fluid, 1 ml of 0.5% ropivacaine will be administered to confirm the location of the needle tip. Then, 10mL of 0.5% ropivacaine will be infused on the superficial layer of prevertebral fascia. The puncture site will be covered with opaque infusion dressing after completing of SCBP.

In the control group, the puncture will also be performed by ultrasound guidance, covered with opaque infusion dressing but performed without infusion.

Concomitant treatment

Routine monitoring will include electrocardiograph (ECG), pulse oxygen saturation, noninvasive blood pressure (NIBP), body temperature, minimal alveolar concentration (MAC) of inhalation agent and bispectral index (BIS). Continuous arterial pressure, urine output and end-tidal carbon dioxide partial pressure ($ETCO_2$) will be monitored after anesthesia induction. All patients will be premedicated with midazolam (0.05

mg/kg) intravenously 5 minutes before anesthesia induction. Anesthesia will be induced with propofol (1.5 to 2.5 mg/kg), sufentanil (0.3 to 0.4 μg/ kg), and rocuronium (0.9 mg/kg) or cisatracurium (0.2 mg/kg). After tracheal intubation, mechanical ventilation will be performed, at a tidal volume 6-8 ml/kg, a respiratory rate of 12-15/min, an I:E of 1:2, a 50% fraction of inspired oxygen in the air and fresh gas at a flow rate of 2 L/min to maintain the $ETCO_2$ between 35 and 40 mmHg.

Anesthesia will be maintained with combined intravenous anesthesia and inhalational anesthesia. Along with the inhalational anesthesia maintained with 0.5 MAC, infusion of remifentanil (0.1-0.4 μg/kg/min) and propofol (3-8 mg/kg/h) will be maintained to keep BIS values between 40 and 50. No muscle relaxant will be used during the procedure to meet intraoperative electronical physiological neuro-monitoring requirements. No additional local anesthetics or analgesics will be administered intraoperatively. Propofol and remifentanil infusion will be discontinued at the end of surgery.

The patients will be extubated after full recovery from anesthesia and transferred to the post-anesthesia care unit (PACU). The patients will remain in the PACU for 120 minutes and receive nasal oxygen inhalation with ECG, NIBP, pulse oximetry monitoring. Sufentanyl-loaded electric analgesia pumps (Rhythmic Plus, Micrel Medical Devices S.A., Greece-European Union) which pre-programmed by the research assistant will be connected to the patients for routine postoperative analgesia. The patient controlled intravenous analgesia (PCIA) pumps will be filled with sufentanyl (100 μg) and ondansetron (16 mg) diluted in 100 mL of 0.9% saline. This

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regimen will provide a bolus of 1 μg sufentanyl on demand with a 10-minute lockout time, without continuous background infusion dose or loading dose. Insufficient postoperative analgesia will be defined as an NRS score >4 lasting over 15 minutes or > 6. Once inadequate postoperative analgesia was confirmed, patients will receive rescue analgesic. If the patient vomit or report nausea for more than 15 minutes, rescue antiemetic will be administered. The type, the frequency and the dose of rescue analgesic and antiemetic will be recorded. The reason for administration will also be recorded giving drugs with analgesic or/and antiemetic.

Physiologic parameters, the total doses of anesthetic drugs and vasoactive drugs will be recorded. Fluid input and output will also be closely monitored and recorded. Anesthesia and surgery duration will be summarized.

Outcomes and safety measures

The aim of this study is to observe the effect of SCPB on postoperative analgesia in patients with suboccipital retrosigmoid craniotomy. During preoperative visits, patients will be informed of the score how to assess the pain, analgesic satisfaction, sleep quality and anesthesia recovery quality.

Primary outcome

The primary outcome is the cumulative consumption of sufentanil by the PCIA within 24 hours after surgery. The primary outcomes will be assessed by trained research assistants at 24 hours after surgery through reading the PCIA data.

Secondary outcomes

The secondary outcomes include the other efficacy parameters and safety outcomes.

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1) The first-time point that the patients use PCIA, the total and effective requests of PCIA at 5 different time points after surgery (1, 2, 4, 24, 48 hours) and the cumulative consumption of sufentanil at 4 different time points (1, 2, 4, 48 hours) after surgery.

2) Pain severity score. Pain will be assessed at 6 time-points after surgery. The degree of surgical incision pain will be assessed at rest and on movement NRS pain score. Insufficient postoperative analgesia is defined as an NRS score that exceeds 4 lasted for 15 minutes or exceeds 6. Information of analgesic drugs administrated in case of insufficient postoperative analgesia was also recorded. Pain severity score in NRS is 0 to 10, 0 representing no pain and 10 representing worst pain imaginable.

3) Anesthesia recovery quality score. Anesthesia Steward Emergence Scale [19]will be used at 1 and 2 hours after surgery to evaluate the recovery quality of anesthesia. Anesthesia recovery quality score will be assessed by the Anesthesia Steward Emergence Scale which is divided into three parts: the degree of wakefulness (2 points for complete recovery, 1 point for response to stimulation, 0 point for no response to stimulation), the degree of airway patency (2 points for cough according to the doctor's order, 1 point for maintenance of airway patency without support, 0 point for support required for respiratory tract) and the degree of limb mobility (2 points for conscious activities of limbs, 1 point for unconscious activities of limbs, 0 point for no activities of limbs).

4) Analgesic satisfaction and sleep quality. Patient satisfaction with overall pain management and sleep quality will be evaluated separately at 24 and 48 hours after surgery using NRS. Analgesic satisfaction score in NRS is 0 to 10, 0 representing

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extremely dissatisfied and 10 representing extremely satisfied. Sleep quality score in NRS is scored as 0 to 10, 0 representing unable to sleep and 10 representing deep sleep. 5) Adverse events. Ramsay score [20] and Nausea and vomiting scores as well other adverse events (dizziness, fatigue, hematoma, local anesthetic poisoning and hoarseness) will be evaluated at the 5 time points after surgery.

Sample size calculation

We estimate the sample size according to the primary outcome of postoperative-24-hour PCIA sufentanil consumption by using PASS 2011 software (NCSS LLC). Based on the previous literature [21], Akcil et al. demonstrated the mean [95% confidence interval (CI)] postoperative cumulative morphine consumption was 30 mg (25 to 35) in the scalp block group and 50 mg (40 to 60) in the control group. Considering that 1 mg morphine is equivalent to 1 μg sufentanil, we estimated the scalp block in their study reduced PCIA sufentanil consumption by 20 μg within postoperative 24 hours. In the routine practice without SCBP, we also apply PCIA for the patients undergoing craniotomy via suboccipital retrosigmoid approach with the dosage of sufentanil as 50 ug during the first 24 hours after surgery. So, we estimated the effect size of mean as 20 μg with the standard deviation of 30 μg for the SCBP group comparing with the control group. The sample size of 106 patients will be sufficient to detect the difference at a two-tailed significant level of 0.05 and a power of 90% using Student t test, with a drop-out rate of 10%.

Statistical analysis

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Analysis will be done using SPSS software (version 23.0). We will apply the intention-to-treat and per-protocol analysis on the primary outcome. If necessary, consider the number of missing outcomes as poor prognosis and conduct sensitivity analysis. The continuous variables will be summarized with mean (standard deviation) or median (interquartile range, IQR), depending on normality determined with Shapiro-Wilk test. Normally distributed and continuous variables will be compared with Student's t-test, while skewed variables will be compared using the Mann-Whitney U test. The categorical variables will be described as counts (percentages) and compared with chi-square analysis or Fisher's exact test. The repeated measurement data will be analyzed by repeated measurements of variance analysis. Bonferroni correction will be used for multiple comparisons. A significance level of $P<0.05$ was used to indicate statistical significance.

Reporting of adverse events

All adverse events will be closely monitored until a stable situation has been reached. The chief investigator will be informed of any serious adverse events and determine the severity and causality of these events. All adverse events associated with this study will be recorded and reported to the ethics committee as part of the annual report. The chief investigator will be responsible for a getting the details about causes of AEs, treatment measures, prognosis, and reporting serious adverse events to the Ethics Committee immediately.

Protocol Amendment

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The chief investigator will be responsible for any decision to amend the protocol. If there is any modification (eg, 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, and communicate with relevant other parties (eg, investigators, trial participants, trial registries, journals, regulators)

Discussion

An ideal analgesic should be able to provide analgesia for entire surgical period and with minimal or no systemic changes. Meanwhile, the interference on consciousness and postoperative neurological function should be minimized during the recovery and evaluation period. At present, PCIA with opioid is the most common analgesia modality for patients received craniotomy [21, 22]. However, undesirable effects of opioids, including respiratory depression, nausea, vomiting, urinary retention, etc., not only bring discomfort to patients, but also affect neurological function evaluation by neurosurgeons[23]. Besides opioids, nonsteroidal anti-inflammatory drugs (NSAIDS), another common analgesia agent is not suitable for postoperative analgesia after neurosurgery due to its effect on coagulation [24]. Gabapentin is an adjuvant antiepileptic agent with some analgesic effects. Our previous research demonstrated that oral gabapentin relieved early postoperative pain, with increased depth of sedation in post-craniotomy, which indicated gabapentin was not the appropriate candidate for postoperative neurosurgical analgesia[25]. Therefore, it is necessary to explore an ideal

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analgesic modality that can effectively provide surgical analgesia with minimal or no systemic changes for this population.

This is a prospective, single-center, randomized, parallel-group controlled trial to assess the efficacy and safety of preoperative ultrasound-guided SCBP for analgesia in patients undergoing suboccipital retrosigmoid craniotomy. With the continuous development of ultrasound guidance technology, utilization of visualized nerve block became more popular in clinical practice [15, 16, 18]. We design the current study to use ultrasound-guided SCBP to explore the efficacy and safety of postoperative analgesia in patients undergoing suboccipital sigmoid approach for craniotomy. Although ultrasound guidance greatly improves the efficacy and safety of the block, we still can't ignore the risk associated with the cervical plexus block. Therefore, in this study we will observe these complications such as hematoma, dizziness, fatigue, hematoma, local anesthetic poisoning and hoarseness. At the same time, in order to ensure the accuracy and consistency of ultrasound-guided puncture, the anesthesiologists who will receive specific training before the first patients are enrolled, the corresponding ultrasound image data of puncture will be preserved, so as to ensure the uniformity of block effect in each patient.

Although SCPB may reduce postcraniotomy pain, it is not routinely used in our current clinical practice. To maintain the analgesic effect on the patients in the control group, the patients will be given the same analgesic dosage regimen following the clinical routine of our medical center, which fully ensure that the patients are safe and painless

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during surgery. Postoperative PCIA analgesia will be routinely given to all patients, and rescue analgesics will be promptly administered when analgesia is insufficient.

Our study will improve the ideal analgesic regimen for patients undergoing suboccipital retrosigmoid craniotomy, so as to reduce perioperative stress response and complications, improve patient satisfaction and early recovery.

Patient and public involvement: Patients and the public were not directly consulted in the development of the research question or outcome measures. Patients were not involved in the design, the recruitment and conduct of the study. At the completion of this 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 enrollment. The burden of intervention will not be taken by participants themselves.

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

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Competing interests: None declared.

Ethics approval: This study is approved by the Ethics Review Committee of China Registered Clinical Trials (Ethics Review No. ChiECRCT-20190047).

Data sharing statement The manuscript is a protocol for a randomized controlled trial, which does not include data.

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Figure legends

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

Figure 2. Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)

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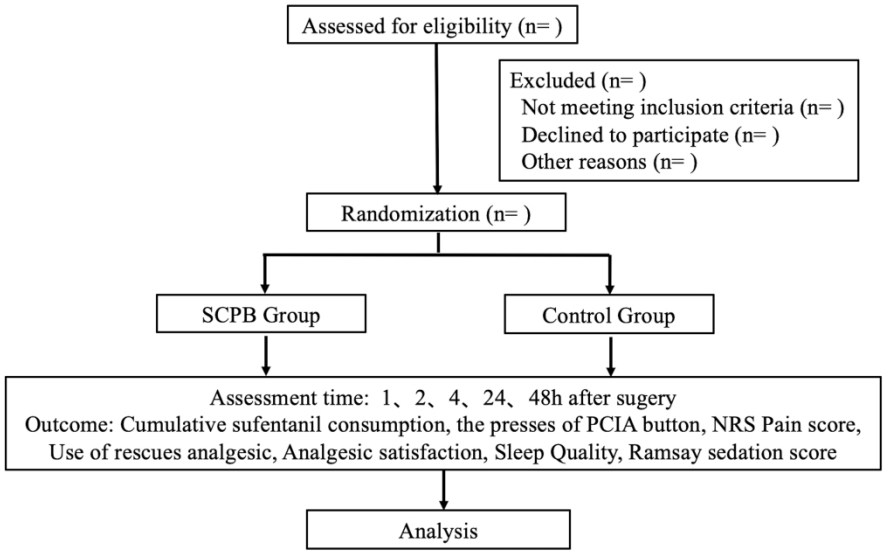

Consolidated Standards of Reporting Trials (CONSORT) flow diagram

STUDY PERIOD							
	Enrolment	Allocation	Post-allocation				
TIMEPOINT	-1day	Sugery day	Post-craniotomy(hour)				
			1	2	4	24	48
ENROLMENT							
Eligibility screen	X						
Informed consent	X						
Allocation		X					
INTERVENTIONS							
SCPB group		X					
Control group		X					
ASSESSMENTS							
Baseline variables		X	X	X	X	X	X
Intraoperative data		X					
Anesthesia recovery quality score			X	X			
Ramsay Score			X	X	X	X	X
Cumulative sufentanil consumption of PCA			X	X	X	X	X
Requests of PCA			X	X	X	X	X
Dose and frequency of rescue analgesic			X	X	X	X	X
Pain intensity（NRS)			X	X	X	X	X
Analgesia Satisfaction						X	X
Sleep quality						X	X
Adverse Event			X	X	X	X	X

Standard Protocol Items- Recommendations for Interventional Trials

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Checklist for **Ultrasound guided superficial cervical plexus block for analgesia in patients undergoing craniotomy via suboccipital retrosigmoid approach: 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	17&18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1 & 17
	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	17&18
	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)	Not Applicable

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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	4-6
	6b	Explanation for choice of comparators	4-6
Objectives	7	Specific objectives or hypotheses	6
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)	6-7
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	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)	7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-9
	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)	8-9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8-9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9-11
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	11-12
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 2

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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	13
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	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	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	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 &12
	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&12

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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	Not Applicable
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	14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
	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)	14
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	Not Applicable
	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	14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Not Applicable
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	2 & 6 &18
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)	15

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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	Not 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	8
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	18
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	18
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
	31b	Authorship eligibility guidelines and any intended use of professional writers	Not Applicable
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Not Applicable
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.

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Ultrasound guided superficial cervical plexus block for analgesia in patients undergoing craniotomy via suboccipital retrosigmoid approach: study protocol of a randomized controlled trial

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Ultrasound guided superficial cervical plexus block for analgesia in patients undergoing craniotomy via suboccipital retrosigmoid approach: study protocol of a randomized controlled trial

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Abstract

Introduction Scalp nerve block has been proven to be an alternative choice to opioids in multimodal analgesia. However, for the infratentorial space-occupying craniotomy, especially the suboccipital retrosigmoid craniotomy, scalp nerve block is insufficient.

Methods and analysis The study is a prospective, single-center, randomized, paralleled-group controlled trial. Patients scheduled to receive elective suboccipital retrosigmoid craniotomy will be randomly assigned to the superficial cervical plexus block group or the control group. After anesthesia induction, superficial cervical plexus nerve block will be performed under the guidance of ultrasound. The primary outcome is the cumulative consumption of sufentanil by the patient controlled intravenous analgesia pump within 24 hours after surgery. Secondary outcomes include the cumulative consumption of sufentanil at other 4 time points and numerical rating scale pain severity score.

Ethics and dissemination The protocol (version number: 2.0, April 10, 2019) has been approved by the Ethics Review Committee of China Registered Clinical Trials (Ethics Review No. ChiECRCT-20190047). The findings of this study will be disseminated in peer-reviewed journals and at scientific conferences.

Trial registration number NCT04036812.

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Article Summary

Strengths and limitations of this study

- This is the randomized controlled trial to observe the efficacy and safety of preoperative ultrasound-guided superficial cervical plexus block on postoperative analgesia in patients undergoing craniotomy via suboccipital retrosigmoid approach.
- The results will optimize postoperative analgesia in patients undergoing infratentorial craniotomy, thereby improving prognosis of the patients.
- This is a single-center clinical trial design which might limit the generalization of the conclusion.

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Background

The procedure of craniotomy was previously assumed to be less painful than other sites of surgeries [1-3]. However, in the prospective study of patients undergoing craniotomy, Gottchalk et al. found that the incidence of postoperative pain was as high as 87%, among of 55% patients experienced moderate to severe pain [4].

Post-craniotomy pain is mainly caused by scalp incision, with abundant free nerve endings. After incision, noxious stimulus signals from the scalp is received by the trigeminal branches or cervical plexus branches, and then transmitted through the trigeminal nucleus and the dorsal horn of the spinal cord to the hypothalamus and cerebral cortex. The whole process is regulated by a variety of inflammatory mediators, peripheral nerve pathways and central nervous system [5].

The pain severity after craniotomy is closely associated with surgical approach. Gottschalk et al. evaluated pain after craniotomy and found that the infratentorial approach was associated with severe postoperative pain and more perioperative analgesic requirements [4]. Rimaaja et al. reported that 32% of patients had no or only mild headache prior to removal of the cerebellopontine angle area mass, while 64% of patients developed severe headache after craniotomy [6]. The high incidence of postoperative pain after craniotomy through infratentorial approach, especially suboccipital retrosigmoid approach may be related to the injury of neck muscles and posterior occipital muscles by the surgical approach, as well as the special position of the head and neck during craniotomy, leading to postoperative muscle spasm [7, 8].

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Therefore, it is necessary to explore an ideal analgesic modality that can effectively provide surgical analgesia with minimal or no systemic changes for this population.

The skin incision is the main source of pain during craniotomy. Scalp nerve block (SNB) has been proven to be an excellent alternative analgesic choice in supratentorial surgeries [9-11]. However, for the suboccipital retrosigmoid craniotomy, the scalp innervation area is insufficient to cover the incision, resulting defective nerve blockage. Therefore, it is necessary to explore an analgesic modality to provide a more ideal analgesic regimen for patients undergoing suboccipital retrosigmoid craniotomy.

The cervical plexus is from the anterior branch of C1-C4 cervical nerve, divided into superficial plexus and deep plexus. The cutaneous branches of the superficial cervical plexus include the lesser occipital nerve, the greater auricular nerve, transverse cervical nerve and supraclavicular nerve, innervating the incision area of the suboccipital sigmoid sinus approach craniotomy [12]. Therefore, the superficial cervical plexus block (SCPB) is a potential candidate to satisfy the analgesic requirement of retrosigmoid craniotomy. Francois et al. observed the effect of transitional analgesia from SCPB after elective infratentorial or occipital craniotomy in 30 patients [13]. In the control group, 0.1mg/kg morphine was administrated after close of the dura. It was found that the effect of SCPB on postoperative analgesia was not inferior to administration of morphine after dura closure. However, the sample size estimation they made is too small. Second, SCPB wasn't guided by ultrasound. The analgesic effect of SCPB may not be fully guaranteed. In addition, no related adverse effects were

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reported in that study. However, the study provided us a feasible method of SCPB analgesia for suboccipital retrosigmoid craniotomy.

With the continual development of visualization techniques, ultrasound-guided nerve blocks have become increasingly popular [14-16]. Ultrasound-guided SCPB, the operator can directly see adjacent anatomical structure, inject the local anesthetic into the correct anatomical level, avoid accidental injury during the puncture, and avoid the unexpected deep cervical plexus block. Ultrasound-guided SCPB has the advantages of faster onset of action, less dosage, high success rate, and fewer complications [17, 18]. Therefore, we propose the hypothesis that preoperative ultrasound-guided SCPB could safely and effectively provide analgesia for patients undergoing craniotomy via suboccipital retrosigmoid approach. The objective is to compare the cumulative consumption of postoperative opioids between groups.

Methods

Study design

This is a prospective, single-center, randomized, paralleled-group controlled trial (Figure 1.) being conducted at Beijing Tiantan Hospital, Capital Medical University, China. The study was approved by the Ethics Review Committee of China Registered Clinical Trials on April 8, 2019 (No. ChiECRCT-20190047). The study was registered within clinicaltrials.gov on June 29 with the registration number NCT04036812. Preoperative interviews will be conducted by specially trained research assistants to inform patients of the study objectives, risks and benefits, and to obtain written informed consent from patients or legal representatives. The schedule of

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enrollment and assessments is shown in the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) (Figure 2.).

Study population

Inclusion criteria

Patients scheduled to undergo elective suboccipital retrosigmoid craniotomy will be recruited for screening eligibility one day before surgery. Inclusion criteria include age between 18 and 65 years, and American Society of Anesthesiologists (ASA) physical status I-III.

Exclusion criteria

Exclusion criteria include refuse to provide written informed consent, local infection, preoperative impairment of consciousness and cognitive function, uncontrolled hypertension, inability to communicate; allergic to experimental drugs; history of drug abuse; history of chronic headache; aphasia and hearing impairment; second craniotomy; body mass index < 18.5 kg/m^2 or > 35.0 kg/m^2 .

Randomization and blinding

Randomization will be conducted via a computer-generated table by an independent research assistant who will be pack the allocation sequence with identical shape and size opaque envelopes and distribute to the researcher. The researcher will open the envelopes and perform a SCPB or only puncture based on the grouping. Patients will be randomly assigned to two groups with a 1: 1 ratio. The researcher assistant, patients, the anesthesiologist responsible for intraoperative management and outcome assessors

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will all be blinded to the allocation until the completion of the study analysis unless specific circumstances, such as the occurrence of a serious adverse event (SAE).

Data collection

After obtaining informed consent, an independent research assistant will initiate baseline information collection one day before surgery. Basic demographic information, including gender, age, vital signs, height, weight, past medical history/family history, medication history, supplementary examination, assessment (ASA classification, headache and severity, treatment, dizziness, tinnitus, facial paralysis, nausea, vomiting and other symptoms) will be collected. All personal information will be kept strictly confidential for research purposes only. The assessment of primary and other secondary outcomes will be performed by trained research assessors who are blinded to the group allocation.

Intervention

Patients will be randomly assigned to the SCBP group or the control group. Peripheral venous access will be established upon arrival in operating room. After anesthesia induction, SCPB will be performed under the guidance of ultrasound (HITACHI Company, Noblus) by the independent researcher who will not involve in intraoperative management or postoperative follow-up. Patients will be at supine position with ipsilateral shoulder relaxed and slightly elevated while head tilting to the opposite side. After marking the midpoint of the posterior border of clavicular head of the sternocleidomastoid muscle (about cricoid cartilage level, about 3-4 cm above the clavicle), an ultrasound probe (50 mm high frequency linear array) warped with sterilize

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plastic dress will be placed in the transverse position at the previous measuring mark. The scanning depth will be 3-4 cm and the focusing position will be 2-3 cm. After confirming the sternocleidomastoid muscle, we move the probe backwards until the posterior border of the sternocleidomastoid muscle in the center of the screen, and identify the investing fascia and prevertebral fascia from the shallow to the deep layer. Using long-axis in-plane technique, a 50 mm long, 20 G short bevel needle will be inserted from the lateral border of sternocleidomastoid muscle. Under guidance of ultrasound, we will confirm the needle tip locating between the deep layer of investing fascia and the superficial layer of prevertebral fascia, close to the border of sternocleidomastoid muscle. After negative aspiration of blood and cerebrospinal fluid, 1 ml of 0.5% ropivacaine will be administered to confirm the location of the needle tip. Then, 10mL of 0.5% ropivacaine will be infused on the superficial layer of prevertebral fascia. The puncture site will be covered with opaque infusion dressing after completing of SCBP.

In the control group, the puncture will also be performed by ultrasound guidance, covered with opaque infusion dressing but performed without infusion.

Concomitant treatment

Routine monitoring will include electrocardiograph (ECG), pulse oxygen saturation, noninvasive blood pressure (NIBP), body temperature, minimal alveolar concentration (MAC) of inhalation agent and bispectral index (BIS). Continuous arterial pressure, urine output and end-tidal carbon dioxide partial pressure ($ETCO_2$) will be monitored after anesthesia induction. All patients will be premedicated with midazolam (0.05

mg/kg) intravenously 5 minutes before anesthesia induction. Anesthesia will be induced with propofol (1.5 to 2.5 mg/kg), sufentanil (0.3 to 0.4 μg/ kg), and rocuronium (0.9 mg/kg) or cisatracurium (0.2 mg/kg). After tracheal intubation, mechanical ventilation will be performed, at a tidal volume 6-8 ml/kg, a respiratory rate of 12-15/min, an I:E of 1:2, a 50% fraction of inspired oxygen in the air and fresh gas at a flow rate of 2 L/min to maintain the $ETCO_2$ between 35 and 40 mmHg.

Anesthesia will be maintained with combined intravenous anesthesia and inhalational anesthesia. Along with the inhalational anesthesia maintained with 0.5 MAC, infusion of remifentanil (0.1-0.4 μg/kg/min) and propofol (3-8 mg/kg/h) will be maintained to keep BIS values between 40 and 50. No muscle relaxant will be used during the procedure to meet intraoperative electronical physiological neuro-monitoring requirements. No additional local anesthetics or analgesics will be administered intraoperatively. Propofol and remifentanil infusion will be discontinued at the end of surgery.

The patients will be extubated after full recovery from anesthesia and transferred to the post-anesthesia care unit (PACU). The patients will remain in the PACU for 120 minutes and receive nasal oxygen inhalation with ECG, NIBP, pulse oximetry monitoring. Sufentanyl-loaded electric analgesia pumps (Rhythmic Plus, Micrel Medical Devices S.A., Greece-European Union) which pre-programmed by the research assistant will be connected to the patients for routine postoperative analgesia. The patient controlled intravenous analgesia (PCIA) pumps will be filled with sufentanyl (100 μg) and ondansetron (16 mg) diluted in 100 mL of 0.9% saline. This

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regimen will provide a bolus of 1 μg sufentanyl on demand with a 10-minute lockout time, without continuous background infusion dose or loading dose. Insufficient postoperative analgesia will be defined as an NRS score >4 lasting over 15 minutes or >6. Once inadequate postoperative analgesia was confirmed, patients will receive rescue analgesic. If the patient vomit or report nausea for more than 15 minutes, rescue antiemetic will be administered. The type, the frequency and the dose of rescue analgesic and antiemetic will be recorded. The reason for administration will also be recorded giving drugs with analgesic or/and antiemetic.

Physiologic parameters, the total doses of anesthetic drugs and vasoactive drugs will be recorded. Fluid input and output will also be closely monitored and recorded. Anesthesia and surgery duration will be summarized.

Outcomes and safety measures

The aim of this study is to observe the effect of SCPB on postoperative analgesia in patients with suboccipital retrosigmoid craniotomy. During preoperative visits, patients will be informed of the score how to assess the pain, analgesic satisfaction, sleep quality and anesthesia recovery quality.

Primary outcome

The primary outcome is the cumulative consumption of sufentanil by the PCIA within 24 hours after surgery. The primary outcomes will be assessed by trained research assistants at 24 hours after surgery through reading the PCIA data.

Secondary outcomes

The secondary outcomes include the other efficacy parameters and safety outcomes.

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1) The first-time point that the patients use PCIA, the total and effective requests of PCIA at 5 different time points after surgery (1, 2, 4, 24, 48 hours) and the cumulative consumption of sufentanil at 4 different time points (1, 2, 4, 48 hours) after surgery.

2) Pain severity score. Pain will be assessed at 5 time-points after surgery. The degree of surgical incision pain will be assessed at rest and on movement NRS pain score. Insufficient postoperative analgesia is defined as an NRS score that exceeds 4 lasted for 15 minutes or exceeds 6. Information of analgesic drugs administrated in case of insufficient postoperative analgesia was also recorded. Pain severity score in NRS is 0 to 10, 0 representing no pain and 10 representing worst pain imaginable.

3) Anesthesia recovery quality score. Anesthesia Steward Emergence Scale [19]will be used at 1 and 2 hours after surgery to evaluate the recovery quality of anesthesia. Anesthesia recovery quality score will be assessed by the Anesthesia Steward Emergence Scale which is divided into three parts: the degree of wakefulness (2 points for complete recovery, 1 point for response to stimulation, 0 point for no response to stimulation), the degree of airway patency (2 points for cough according to the doctor's order, 1 point for maintenance of airway patency without support, 0 point for support required for respiratory tract) and the degree of limb mobility (2 points for conscious activities of limbs, 1 point for unconscious activities of limbs, 0 point for no activities of limbs).

4) Analgesic satisfaction and sleep quality. Patient satisfaction with overall pain management and sleep quality will be evaluated separately at 24 and 48 hours after surgery using NRS. Analgesic satisfaction score in NRS is 0 to 10, 0 representing

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extremely dissatisfied and 10 representing extremely satisfied. Sleep quality score in NRS is scored as 0 to 10, 0 representing unable to sleep and 10 representing deep sleep. 5) Adverse events. Ramsay score [20] and Nausea and vomiting scores as well other adverse events (dizziness, fatigue, hematoma, local anesthetic poisoning and hoarseness) will be evaluated at the 5 time points after surgery.

Sample size calculation

We estimate the sample size according to the primary outcome of postoperative-24-hour PCIA sufentanil consumption by using PASS 2011 software (NCSS LLC). Based on the previous literature [21], Akcil et al. demonstrated the mean [95% confidence interval (CI)] postoperative cumulative morphine consumption was 30 mg (25 to 35) in the scalp block group and 50 mg (40 to 60) in the control group. Considering that 1 mg morphine is equivalent to 1 μg sufentanil, we estimated the scalp block in their study reduced PCIA sufentanil consumption by 20 μg within postoperative 24 hours. In the routine practice without SCBP, we also apply PCIA for the patients undergoing craniotomy via suboccipital retrosigmoid approach with the dosage of sufentanil as 50 μg during the first 24 hours after surgery. So, we estimated the effect size of mean as 20 μg with the standard deviation of 30 μg for the SCBP group comparing with the control group. The sample size of 106 patients will be sufficient to detect the difference at a two-tailed significant level of 0.05 and a power of 90% using Student t test, with a drop-out rate of 10%.

Statistical analysis

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Analysis will be done using SPSS software (version 23.0). We will apply the intention-to-treat and per-protocol analysis on the primary outcome. If necessary, consider the number of missing outcomes as poor prognosis and conduct sensitivity analysis. The continuous variables will be summarized with mean (standard deviation) or median (interquartile range, IQR), depending on normality determined with Shapiro-Wilk test. Normally distributed and continuous variables will be compared with Student's t-test, while skewed variables will be compared using the Mann-Whitney U test. The categorical variables will be described as counts (percentages) and compared with chi-square analysis or Fisher's exact test. The repeated measurement data will be analyzed by repeated measurements of variance analysis. Bonferroni correction will be used for multiple comparisons. A significance level of $P<0.05$ was used to indicate statistical significance.

Reporting of adverse events

All adverse events will be closely monitored until a stable situation has been reached. The chief investigator will be informed of any serious adverse events and determine the severity and causality of these events. All adverse events associated with this study will be recorded and reported to the ethics committee as part of the annual report. The chief investigator will be responsible for a getting the details about causes of AEs, treatment measures, prognosis, and reporting serious adverse events to the Ethics Committee immediately.

Protocol Amendment

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The chief investigator will be responsible for any decision to amend the protocol. If there is any modification (eg, 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, and communicate with relevant other parties (eg, investigators, trial participants, trial registries, journals, regulators)

Discussion

An ideal analgesic should be able to provide analgesia for entire surgical period and with minimal or no systemic changes. Meanwhile, the interference on consciousness and postoperative neurological function should be minimized during the recovery and evaluation period. At present, PCIA with opioid is the most common analgesia modality for patients received craniotomy [21, 22]. However, undesirable effects of opioids, including respiratory depression, nausea, vomiting, urinary retention, etc., not only bring discomfort to patients, but also affect neurological function evaluation by neurosurgeons [23]. Besides opioids, nonsteroidal anti-inflammatory drugs (NSAIDS), another common analgesia agent is not suitable for postoperative analgesia after neurosurgery due to its effect on coagulation [24]. Gabapentin is an adjuvant antiepileptic agent with some analgesic effects. Our previous research demonstrated that oral gabapentin relieved early postoperative pain, with increased depth of sedation in post-craniotomy, which indicated gabapentin was not the appropriate candidate for postoperative neurosurgical analgesia[25]. Therefore, it is necessary to explore an ideal

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analgesic modality that can effectively provide surgical analgesia with minimal or no systemic changes for this population.

This is a prospective, single-center, randomized, parallel-group controlled trial to assess the efficacy and safety of preoperative ultrasound-guided SCBP for analgesia in patients undergoing suboccipital retrosigmoid craniotomy. With the continuous development of ultrasound guidance technology, utilization of visualized nerve block became more popular in clinical practice [15, 16, 18]. We design the current study to use ultrasound-guided SCBP to explore the efficacy and safety of postoperative analgesia in patients undergoing suboccipital sigmoid approach for craniotomy. Although ultrasound guidance greatly improves the efficacy and safety of the block, we still can't ignore the risk associated with the cervical plexus block. Therefore, in this study we will observe these complications such as hematoma, dizziness, fatigue, hematoma, local anesthetic poisoning and hoarseness. At the same time, in order to ensure the accuracy and consistency of ultrasound-guided puncture, the anesthesiologists who will receive specific training before the first patients are enrolled, the corresponding ultrasound image data of puncture will be preserved, so as to ensure the uniformity of block effect in each patient.

Although SCPB may reduce postcraniotomy pain, it is not routinely used in our current clinical practice. To maintain the analgesic effect on the patients in the control group, the patients will be given the same analgesic dosage regimen following the clinical routine of our medical center, which fully ensure that the patients are safe and painless

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during surgery. Postoperative PCIA analgesia will be routinely given to all patients, and rescue analgesics will be promptly administered when analgesia is insufficient.

Our study will improve the ideal analgesic regimen for patients undergoing suboccipital retrosigmoid craniotomy, so as to reduce perioperative stress response and complications, improve patient satisfaction and early recovery.

Patient and public involvement: Patients and the public were not directly consulted in the development of the research question or outcome measures. Patients were not involved in the design, the recruitment and conduct of the study. At the completion of this 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 enrollment. The burden of intervention will not be taken by participants themselves.

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

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Competing interests: None declared.

Ethics approval: This study is approved by the Ethics Review Committee of China Registered Clinical Trials (Ethics Review No. ChiECRCT-20190047).

Data sharing statement The manuscript is a protocol for a randomized controlled trial, which does not include data.

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Figure legends

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

Figure 2. Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)

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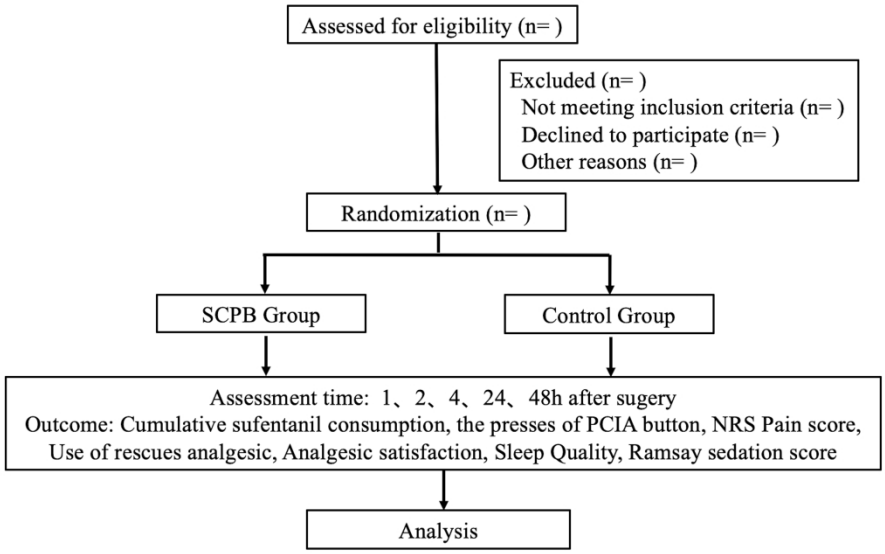

Consolidated Standards of Reporting Trials (CONSORT) flow diagram

STUDY PERIOD							
	Enrolment	Allocation	Post-allocation				
TIMEPOINT	-1day	Sugery day	Post-craniotomy(hour)				
			1	2	4	24	48
ENROLMENT							
Eligibility screen	X						
Informed consent	X						
Allocation		X					
INTERVENTIONS							
SCPB group		X					
Control group		X					
ASSESSMENTS							
Baseline variables		X	X	X	X	X	X
Intraoperative data		X					
Anesthesia recovery quality score			X	X			
Ramsay Score			X	X	X	X	X
Cumulative sufentanil consumption of PCA			X	X	X	X	X
Requests of PCA			X	X	X	X	X
Dose and frequency of rescue analgesic			X	X	X	X	X
Pain intensity（NRS)			X	X	X	X	X
Analgesia Satisfaction						X	X
Sleep quality						X	X
Adverse Event			X	X	X	X	X

Standard Protocol Items- Recommendations for Interventional Trials

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Checklist for **Ultrasound guided superficial cervical plexus block for analgesia in patients undergoing craniotomy via suboccipital retrosigmoid approach: 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	17&18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1 & 17
	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	17&18
	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)	Not Applicable

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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	4-6
	6b	Explanation for choice of comparators	4-6
Objectives	7	Specific objectives or hypotheses	6
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)	6-7
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	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)	7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-9
	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)	8-9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8-9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9-11
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	11-12
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 2

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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	13
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	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	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	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 &12
	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&12

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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	Not Applicable
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	14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
	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)	14
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	Not Applicable
	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	14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Not Applicable
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	2 & 6 &18
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)	15

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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	Not 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	8
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	18
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	18
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
	31b	Authorship eligibility guidelines and any intended use of professional writers	Not Applicable
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Not Applicable
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.

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