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Multicentre, prospective, randomized, controlled, blinded-endpoint study to evaluate the efficacy and safety of sphenopalatine ganglion pulsed radiofrequency treatment for episodic cluster headache: study protocol

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-026608
Article Type:	Protocol
Date Submitted by the Author:	11-Sep-2018
Complete List of Authors:	Li, Jin; Beijing Tiantan Hospital, Capital Medical University, Department of Anesthesiology Ren, Hao; Beijing Tiantan Hospital, Capital Medical University, Department of Anesthesiology Wang, Baoguo; Beijing Sanbo Brian Hospital, Capital Medical University, Department of Anesthesiology Wu, Dasheng; Jilin Province People's Hospital, Department of Pain Management Luo, Fang; Beijing Tiantan Hospital, Capital Medical University, Department of Pain Management
Keywords:	Cluster headache, Pulsed radiofrequency, Randomized controlled trial, Protocol

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Manuscripts

Title:

Multicentre, prospective, randomized, controlled, blinded-endpoint study to evaluate the efficacy and safety of sphenopalatine ganglion pulsed radiofrequency treatment for episodic cluster headache: study protocol

Authors:

Jin Li, M.D., Department of Anesthesiology, Beijing Tiantan Hospital, Capital Medical University, Beijing, China.

Hao Ren, M.D., Department of Anesthesiology, Beijing Tiantan Hospital, Capital Medical University, Beijing, China.

Baoguo Wang, M.D., Department of Anesthesiology, Beijing Sanbo Brian Hospital, Capital Medical University, Beijing, China.

Dasheng Wu, M.D., Department of Pain Management, Jilin Province People's Hospital, Changchun, China.

Fang Luo, M.D., Department of Pain Management, Beijing Tiantan Hospital, Capital Medical University, Beijing, China.

Corresponding author contact details:

Fang Luo, M.D., Professor,

Department of Pain Management, Beijing Tiantan Hospital, Capital Medical University, Beijing 100050, China.

Phone: (86) 010 67096664.

Fax: (86) 010 67050177.

E-mail: luofangwt@yahoo.com.

Key words:

Cluster headache, Pulsed radiofrequency, Randomized controlled trial, Protocol

Word count :3311

ABSTRACT

Introduction Single-centre, small patient group case reports have shown that sphenopalatine ganglion pulsed radiofrequency treatment in patients with refractory cluster headache (CH) can quickly relieve pain without significant side effects. However, whether sphenopalatine ganglion pulsed radiofrequency treatment can be a treatment option for patients with CH that are not responding to drug treatment still requires evaluation in a properly designed randomized controlled trial.

Methods and analysis This is a multicentre, prospective, randomized, controlled, blinded-endpoint study. We enrol 80 patients with episodic cluster headache (ECH) that are not responding to mediations. The enrolled patients are randomly divided into two groups: the nerve block (NB) group or the pulsed radiofrequency (PRF) group. All patients undergo computed tomography (CT) -guided sphenopalatine ganglion puncture. A mixture containing steroids and local anaesthetics is slowly injected into the patients in the NB group. The patients in the PRF group are treated with PRF at 42 °C for 360 s. After treatment, the duration of cluster periods, degree of pain during headache attacks, headache attack frequency, duration of each headache attack, dose of auxiliary analgesic drugs, duration of remission period, patient satisfaction, effective rates at 1 day, 3 days, 1 week, 2 weeks, 1 month, 3 months, 6 months, and 1 year after surgery, and intraoperative and postoperative adverse events (AEs) are compared between the two groups.

Ethics and dissemination This study was approved by the institutional ethics committee (Approval Number: XXX). The results of the study will be published in peer-reviewed journals, and the findings will be presented at scientific meetings.

Trial registration number NCTXXX; Pre-results.

Strength and limitations of this study

This study explores whether PRF can replace nerve block as a minimally invasive and safe treatment option for patients with episodic cluster headache who are not responding to conservative drug treatment.

The participants in this study and the doctors who conducted the interventions are not

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kept blinded to the trial.

The follow-up period of this study is only 1 year, and long-term follow-up studies are still needed.

For peer review only

INTRODUCTION

Cluster headache (CH) is a primary headache characterized by severe pain and has a considerable impact on quality of life. CH attacks are very painful, and the patients can even become suicidal. Therefore, CH is also known as "suicidal headache"^{1 2}. Severe unilateral pains occur in the orbital, frontal, and temporal areas during CH attacks and can last 15 minutes to 3 hours, with ipsilateral oculofacial autonomic symptoms. CH includes two categories: episodic cluster headache (ECH) and chronic cluster headache (CCH). ECH can involve several attacks in a day, and an attack period of 2 weeks to 3 months is called a "cluster period", which is followed by a pain-free "remission period" of ≥ 3 months³. During the cluster period, headaches often recur every day at a fixed period of time. Generally, CCH attacks occur less frequently than ECH on a daily basis and have no remission period.

Since the pathogenesis of CH remains unclear, there is a lack of targeted aetiological treatment⁴. It is currently believed that the pathogenesis of CH may involve the trigeminovascular system and the activation of parasympathetic system and ipsilateral hypothalamic grey matter^{4 5}. The sphenopalatine ganglion (SPG) plays a very important role in the pathophysiology of CH⁶.

The clinical treatment of CH is still extremely difficult. For patients who do not respond to drug therapy, an SPG block via the application of local anaesthetics and steroid hormones has a certain effect⁷. Generally, a single SPG block is not sufficient to achieve satisfactory results; therefore, multiple SPG blocks are required, which increases the risk of puncture and steroid hormone-related side effects. In addition, multiple punctures also bring the risk of radiation exposure and increase medical costs. For intractable CH that does not respond to conservative treatment, deep brain stimulation⁸, SPG ablation⁹, and SPG electrical stimulation¹⁰⁻¹² can relieve CH in some patients. Research has shown that high frequency stimulation of the SPG has preventive effects⁶. However, the above methods all have problems, such as trauma caused by surgery, serious side effects, and high medical costs. Therefore, it is urgent to explore new minimally invasive, safe, and effective technologies for the treatment of CH in clinical practice.

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3 The percutaneous pulsed radiofrequency (PRF) technique is a non-destructive pain
4 treatment technology¹³. Different from the radiofrequency thermocoagulation, PRF
5 uses the following parameters: pulse frequency of 2 Hz, output voltage of 45 V, output
6 frequency of 500 kHz, continuous current action of 20 ms, intermittent time of 480
7 ms, and treatment temperature not exceeding 42 °C. This intervention technology
8 does not cause local tissue damage, and there are few side effects.

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11 In 2011, Chua et al. first reported the use of SPG PRF treatment in 3 patients with CH,
12 of which 2 patients had complete remission of pain, 1 patient had partial remission of
13 pain, and all had no neurological side effects or complications after treatment¹⁴. In
14 2016, we reported the computed tomography (CT) -guided SPG PRF treatment in 13
15 patients with ECH who had not responded to drugs and nerve block, and found that
16 SPG PRF could quickly, safely and effectively relieve the patients from their cluster
17 periods¹⁵. However, to verify whether early intervention via PRF can be a treatment
18 option for patients with ECH who are not responding to drug therapy, we still need to
19 obtain strong evidence via properly designed randomized controlled trial with nerve
20 block as the control condition. Therefore, this study proposes a multicentre,
21 prospective, randomized, controlled, blinded-endpoint study to compare the pain
22 relief effects of CT-guided PRF and traditional nerve blockade of SPG for the
23 treatment of ECH patients who are not responding to drug treatment.

24 **METHODS**

25 **Trial design**

26 This is a multicentre, prospective, randomized, controlled, blinded-endpoint study.
27 ECH patients who are not responding to drug therapy receive either CT-guided
28 percutaneous puncture SPG nerve block or PRF, and efficacy and safety are compared
29 between the two groups of patients (Figure 1).

30 **Setting**

31 Patients are selected from three research centres: XXX Hospital, XXX Hospital, XXX
32 Hospital. All researchers were trained based on the same training protocol. All
33 researchers are required to have more than 1 year of clinical experience with both
34 treatment methods prior to participating in the study.

Ethics, trial registration and dissemination

This clinical study follows the relevant regulations of the Declaration of Helsinki (version 19 October 2013) of the World Medical Association. The research protocol (protocol version 1.0) is approved by the Ethics Committee of the XXX Hospital (Approval Number: XXX). All patients sign the informed consent at a screening visit. Before patient enrolment, the study design was registered at clinicaltrials.gov (NCTXXX). This study, which has been begun in July 5, 2018, will last for 3 years. The results of the study will be published in peer-reviewed journals, and the findings will be presented at scientific meetings.

Participants

Suitable participants are screened in the pain management centre of each hospital to participate in the study.

Inclusion criteria comprise the following: (1) diagnosis of ECH is confirmed according to the diagnostic criteria of the International Classification of Headache Disorders 3rd edition (ICHD-3)³; (2) patient's age is between 18 and 60 years; (3) patients seek treatment in the pain clinics of hospitals participating in the study within 5 days of the onset of the cluster period; pain conditions of patients remain the same after conservative treatment of conventional oral medication (rizatriptan, verapamil, lithium or steroid), or the reduction rates are less than 50% in pain degree during headache attacks, headache attack frequency, duration of each headache attack, and auxiliary analgesic drug dosage.

Exclusion criteria include the following: (1) abnormalities in blood measurements, liver and kidney function, blood glucose, coagulation, electrocardiogram, and chest radiograph; (2) infection at the puncture site; (3) previous mental illness; (4) previous history of narcotic drug abuse; (5) preceding anticoagulant or antiplatelet therapy; (6) implantable pulse generator; (7) previous history of invasive treatments such as SPG radiofrequency thermocoagulation and chemical destruction; and (8) pregnant or breastfeeding patients.

Recruitment and informed consent

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3 All enrolled patients have the right to be informed of the purpose of the study, the
4 experimental procedures, the participants' benefits, and possible risks, and then sign
5 the informed consent. All patients should be given enough time to consider whether
6 they would like to participate in this study. Patients participating in the study also
7 have the right to freely obtain more information at any time and can freely withdraw
8 their consent form or can withdraw from the study without restrictions at any stage.

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Once the patient signs the informed consent, the researchers complete the eligibility
checklists based on the items listed on the case report form and record the enrolment
failure.

Interventions

Randomization and allocation concealment

All participants are randomly divided into two groups in a 1:1 ratio. The researchers
perform randomization in three centres. After confirming that the enrolled patient
satisfies the baseline inclusion/exclusion criteria, the patient is randomly assigned to
one of the two study groups. The random sequence is generated using SAS 9.1.3
(SAS Institute Inc., Cary, NC U.S.A.) software.

Each research centre has a research nurse who is responsible for implementing the
allocation. According to a pre-generated random sequence, each enrolled patient is
given a sealed opaque random envelope based on the order of enrolment. After
puncturing the SPG during the surgery, the research nurse opens the sealed envelope
and assigns the patient to the corresponding group according to the random number in
the envelope, and the corresponding treatment is then performed on the patient.

Blinding

This study is an open-label study. In this study, participants and doctors could not all
be blinded to the study. The telephone follow-up at different time points after surgery
is conducted by trained research assistants, who are blinded to the allocation status of
the patients. The data input is completed by the data entry personnel, who are not
from the research team, and the data analysis is completed by the statisticians who are
blinded to allocation information.

Study interventions

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3 The patient is in a supine position on a CT scan couch with their head turned to the
4 contralateral side by approximately 50 degrees. Blood pressure, heart rate,
5 electrocardiogram, and pulse oximetry are continuously monitored. The negative plate
6 of the PMG-230 pain treatment generator (Baylis Medical Inc., Montreal, Canada) is
7 applied to the upper abdominal skin of the patient. Aseptic drapes are routinely
8 applied to the patient's face. The puncture point is located under the zygomatic arch
9 of the affected side, 3-4 cm in front of the tragus. After the administration of 1%
10 lidocaine for local anaesthesia, a trocar needle with a length of 10 cm, 21-gauge is
11 inserted vertically into the puncture point. With an approximate depth of 4 cm, the
12 trocar needle can reach the bone surface of the lateral pterygoid plate of the sphenoid.
13 The trocar needle is then withdrawn by 2 cm and reinserted towards the upper middle
14 third of the pterygopalatine fossa until the tip of the needle glides over the leading
15 edge of the lateral pterygoid plate of the sphenoid. The needle is then inserted another
16 0.5 cm to enter the pterygopalatine fossa. We use a CT scanner (medical X-ray CT
17 scanner, model SOMATOM, SIEMENS, Munich, Germany) during the procedure to
18 verify the position of the puncture needle in the pterygopalatine fossa. The orientation
19 and depth of the puncture needle are adjusted according to the CT image until the
20 needle is close to the SPG. The stylet is removed, and the electrode needle for PRF
21 treatment (PMF-21-100-5, Baylis Medical Inc., Montreal, Canada) is placed. The pain
22 treatment generator is connected with the RF needle, and the sensory threshold is
23 measured with 50 Hz electrical stimulation. Induction of sensory abnormality of the
24 nasal roots via 0.1-0.3 V indicates accurate puncture, and the depth and direction of
25 the puncture needle can be appropriately adjusted according to the patient's response.
26 Treatment will be performed after positioning as follow.

27
28 PRF group: The pulse treatment generator is set to the pulsed radiofrequency
29 automatic mode, with a temperature of 42 °C, pulse frequency of 2 Hz, pulse width of
30 20 ms, and treatment duration of 360 s¹⁵.

31
32 NB group: A mixture of 40 mg triamcinolone + 2 ml of 1% bupivacaine + 2 ml of 2%
33 mepivacaine + 1:100000 epinephrine is injected for nerve block treatment using a
34 puncture needle^{16 17}.

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3 After the operation, the patients will be delivered to the outpatient recovery room and
4 they will be discharged if no adverse signs are noted within 2 hours. The doctor will
5 decide whether to continue auxiliary drugs such as rizatriptan and its dosage
6 according to their condition. Participants can be treated with salvage therapy of other
7 more invasive therapies such as SPG ablation, electrical stimulation of the SPG, and
8 deep brain stimulation if the pain and the dosage of auxiliary drugs are no different
9 from the preoperative level.
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12 **Variables and measurements**

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14 Prior to the intervention, the age, gender, the side of the headache (left or right),
15 previous duration of cluster periods, current numeric rating scale (NRS, 0 points for
16 no pain and 10 points for the most severe pain) score during headache attacks,
17 headache attack frequency, duration of each headache attack, dose of auxiliary
18 analgesics, and previous duration of remission period of the enrolled patients are
19 recorded.
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23 The patients are followed up by telephone at 1 day, 3 days, 1 week, 2 weeks, 1 month,
24 3 months, 6 months, and 1 year after surgery by trained research assistants who are
25 blinded to the allocation status of the patients. The primary outcome is the duration of
26 the cluster periods. The duration of the cluster period is defined as the total duration
27 of the headache, including the pain attack time before and after treatment. The
28 secondary outcomes include the degree of pain during headache attacks (NRS scores),
29 headache attack frequency, duration of each headache attack, dose of auxiliary
30 analgesic drugs, duration of remission period, patient satisfaction scale (0 point for
31 unsatisfactory, and 10 points for very satisfied), effective rates, and intraoperative and
32 postoperative adverse events (AEs) are compared between the two groups of patients.
33
34 Efficiency at each time point will be calculated. Both complete relief and partial relief
35 of pain are considered to be effective, and the effectiveness rate is calculated as
36 follows: effectiveness rate = number of effective patients / total number of patients in
37 this group × 100%. Complete pain relief: NRS = 0, discontinued administration of
38 drugs. Partial relief of pain: postoperative pain levels during headache attacks,
39 headache attack frequency, duration of each headache attack, and auxiliary analgesic
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3 drug dosage are less than 50% of the preoperative levels. No remission of pain: the
4 pain is no different from the preoperative level, or the degree of pain during headache
5 attacks, the frequency of headache attacks, the duration of each headache attack, and
6 the reduction in the use of adjuvant analgesics are still over 50% of the preoperative
7 levels. The partial pain remission time, complete pain remission time, number of
8 interventional treatments and treatment interval, and the number of cases receiving
9 electrical stimulation of the SPG are recorded.

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11 The details of the AEs are recorded during the surgery and at various time points
12 during the postoperative follow-up (1 day, 3 days, 1 week, 2 weeks, 1 month, 3
13 months, 6 months, and 1 year after surgery). For intraoperative AEs, the occurrences
14 of puncture pain, headache, dizziness, nausea, vomiting, facial haematoma, and others
15 are recorded. For postoperative AEs, headache, dizziness, facial numbness, and others
16 are also recorded.

27 **Sample size**

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29 This study adopts a one-sided superiority test, $\alpha = 0.025$, $\beta = 0.10$. After examining
30 the literature, combined with the authors' published articles and clinical experience¹⁵,
31 the duration of the cluster period of the PRF group is approximately 15.5 days, and
32 the standard deviation is 9.3 days, while the cluster duration of the NB group is
33 approximately 45 days, and the standard deviation is approximately 15 days.
34 Shortening the duration of the cluster period by 20 days has clinical significance. The
35 number of cases needed in each group is 36, calculated by PASS 11. Considering the
36 10% loss rate, 40 cases are required in each group, and a total of 80 cases are required
37 for both groups.

46 **Statistical analysis**

47 The SAS9.4 statistical analysis system is used to analyse the data with the full
48 analysis set and the per-protocol set. The Shapiro-Wilk test is used to check data for
49 normal distribution. Normally distributed data are expressed as the means \pm standard
50 deviations. Parameters that do not meet the normal distribution are expressed as
51 medians \pm quartiles. The t-test is used for measurement data with normal distributions,
52 the rank sum test is used for measurement data with non-normal distributions, and the
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chi-square test is used for count data. Efficacy analysis is conducted via both intention-to-treat (ITT) analysis and the per-protocol analysis set in SAS. The t-test is used to compare the measurement data of efficacy outcome indicators between the RFP group and the NB group, such as duration of cluster periods, pain degree during headache attacks, frequency of headache attacks, the duration of each headache attack, the dose of auxiliary analgesics, duration of remission period, and patient satisfaction. The chi-square test is used to compare the count data of efficacy outcome indicators between the PRF and NB groups. The chi-square test or exact probability analysis is used to evaluate intraoperative and postoperative AEs.

DISCUSSION

The SPG is one of the four major parasympathetic ganglia of the head and neck. It is the largest group of neurons within the calvarium outside of the brain and is the only ganglion that enters the external environment through the nasal mucosa¹⁸. The characteristic clinical symptoms of CH, such as tearing, runny nose, nasal congestion, and nasal oedema, are manifestations of parasympathetic excitations in the SPG, and ptosis and pupil diminution are manifestations of sympathetic inhibition in the SPG. Therefore, the pathogenesis of CH is considered to be related to the SPG¹⁹.

In recent years, there have been a series of reports on the treatment of CH via the SPG. One type of SPG treatment is destructive, which blocks pain signalling by denaturing SPG proteins, such as radiofrequency ablation techniques^{20 21} and local injection of absolute alcohol^{22 23}. The other type is non-destructive, such as nerve block^{12 19}, PRF¹⁵, and nerve electrical stimulation^{24 25}.

SPG nerve blocks include cotton swab nasal infiltration²⁶ and needle injection^{16 17}. The puncture approach of the SPG includes the sphenopalatine foramen approach²⁷, the supra-zygomatic approach²², the infrazygomatic crest approach²³, or the mandibular notch approach²⁸. Puncture can be performed with the assistance of nasal endoscopy^{16 17}, fluoroscopy^{20 21}, or CT^{9 15}. The commonly used nerve block drugs include local anaesthetics and steroid hormones, etc. Previous reports on nerve block for the treatment of CH are mostly case series analyses or case reports. Costa et al. conducted a randomized double-blinded placebo-controlled study of patients with

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3 nitroglycerine-induced CH, and the patients were treated with 10% cocaine, 10%
4 lidocaine, or saline placebo²⁶. The results showed that short-term treatment effects
5 were significant in the cocaine and lidocaine groups, and there were no related acute
6 side effects. However, the main drawbacks of nerve block treatment for CH are the
7 limited effect of pain relief in a single treatment, the short duration of treatment
8 efficacy. Therefore, nerve block needs to be implemented repeatedly. The puncture
9 approach in our study is the infrazygomatic crest approach²³, also known as the
10 translateral approach, and the injection is a mixture of the steroid hormone
11 triamcinolone acetonide and local anaesthetics in the control group.

12 PRF is a non-destructive, minimally invasive, and percutaneous interventional pain
13 management technique²⁹. Compared with radiofrequency ablation, the puncture site
14 and localization approach are consistent between the two. However, to treat the pain,
15 PRF regulates the nerve function through an electric field effect, while radiofrequency
16 ablation destroys the nerve through a thermal effect. Our previous study found that
17 after PRF treatment of 16 CH patients who had not responded to drug and nerve block,
18 11 patients with ECH and 1 patient with CCH had complete remission, though
19 treatments for 2 patients with ECH and 2 patients with CCH were not effective¹⁵.
20 Bendersky et al. also reported that PRF treatment failed to achieve satisfactory pain
21 relief in 3 patients with CCH³⁰. Therefore, it is currently believed that PRF treatment
22 may be more effective for ECH than CCH. However, the incidence of CCH is low,
23 and the number of CCH cases is small, and the existing study are not sufficient to
24 reach a convincing conclusion.

25 CT images are clear and intuitive, providing the clinician with a more accurate
26 guidance for puncture. The CT-guided SPG puncture technique was first applied in
27 clinical practice by Kastler et al²³. It was confirmed that puncture complications can
28 be reduced, and the puncture success rate and treatment satisfaction can be improved
29 with CT guidance. In the past, we have reported that the success rate of the puncture
30 was 100% for CH patients with CT-guided SPG puncture and PRF treatment, and
31 surgery-related complications, such as nosebleeds and cheek haematomas, were
32 successfully avoided¹⁵. In this study, both the NB and the PRF groups undergo
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3 CT-guided SPG puncture to ensure the accuracy of the puncture and to avoid the
4 effects of inaccurate puncture on the outcome.
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7 This study compares the efficacy of SPG nerve block and PRF in the treatment of
8 ECH in a multicentre, prospective, randomized, controlled, and blinded-endpoint
9 study, explores whether PRF can replace nerve block as a minimally invasive and safe
10 treatment option, and provides reliable evidence for treatment strategies for patients
11 with ECH who are not responding to conservative drug treatment. Of course, the
12 limitations of this study including that the participants in this study and the doctors
13 who conducted the interventions are not kept blinded to the trial, the follow-up period
14 of this study is only 1 year, and the lack of exploration of optimal parameters for PRF
15 treatment of ECH, which will be investigated through in-depth clinical research in the
16 future.
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24 **Author's contributions**

25
26 JL and HR contributed equally to this work and should be considered co-first authors.
27
28 JL and HR wrote the protocol and this manuscript. FL is the principal investigator of
29
30 the whole study. FL BW and DW are the site principal investigator of each research
31
32 centre. FL JL and HR contributed to the conception and design of the research
33
34 protocol. All authors approved the final version to be published.
35

36 **Acknowledgements**

37
38
39 Funding: This work will be supported by the Beijing Municipal Administration of
40
41 Hospitals Clinical Medicine Development of Special Funding Support (grant No.
42
43 XMLX201707) and the Foundation for the Excellent Medical Staff of Beijing (grant
44
45 No. 2014-3-035).

46 **Competing interests** None declared.
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49 **Figure 1**

50 Flow diagram of the study.
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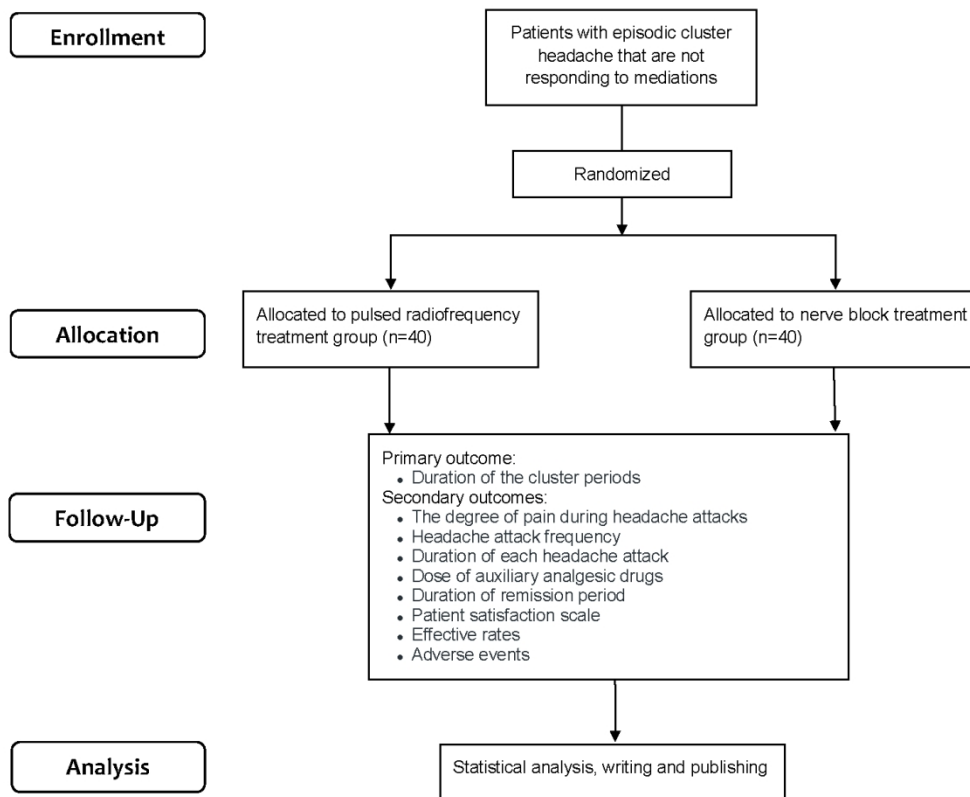


Figure 1/Flow diagram of the study.

205x169mm (192 x 191 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
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	5
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	5
Protocol version	#3	Date and version identifier	5
Funding	#4	Sources and types of financial, material, and other support	14
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	14
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	5

1	sponsor contact			
2	information			
3				
4	Roles and	#5c	Role of study sponsor and funders, if any, in study design;	5
5	responsibilities:		collection, management, analysis, and interpretation of	
6	sponsor and funder		data; writing of the report; and the decision to submit the	
7			report for publication, including whether they will have	
8			ultimate authority over any of these activities	
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12	Roles and	#5d	Composition, roles, and responsibilities of the coordinating	5
13	responsibilities:		centre, steering committee, endpoint adjudication	
14	committees		committee, data management team, and other individuals or	
15			groups overseeing the trial, if applicable (see Item 21a for	
16			data monitoring committee)	
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20	Background and	#6a	Description of research question and justification for	3-4
21	rationale		undertaking the trial, including summary of relevant studies	
22			(published and unpublished) examining benefits and harms	
23			for each intervention	
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27	Background and	#6b	Explanation for choice of comparators	3
28	rationale: choice of			
29	comparators			
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32	Objectives	#7	Specific objectives or hypotheses	4
33				
34				
35	Trial design	#8	Description of trial design including type of trial (eg, parallel	4
36			group, crossover, factorial, single group), allocation ratio,	
37			and framework (eg, superiority, equivalence, non-inferiority,	
38			exploratory)	
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42	Study setting	#9	Description of study settings (eg, community clinic,	4
43			academic hospital) and list of countries where data will be	
44			collected. Reference to where list of study sites can be	
45			obtained	
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48	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable,	5
49			eligibility criteria for study centres and individuals who will	
50			perform the interventions (eg, surgeons, psychotherapists)	
51				
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54	Interventions:	#11a	Interventions for each group with sufficient detail to allow	6-8
55	description		replication, including how and when they will be	
56			administered	
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1	Interventions:	#11b	Criteria for discontinuing or modifying allocated	7-8
2	modifications		interventions for a given trial participant (eg, drug dose	
3			change in response to harms, participant request, or	
4			improving / worsening disease)	
5				
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8	Interventions:	#11c	Strategies to improve adherence to intervention protocols,	7-8
9	adherence		and any procedures for monitoring adherence (eg, drug	
10			tablet return; laboratory tests)	
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12				
13	Interventions:	#11d	Relevant concomitant care and interventions that are	7-8
14	concomitant care		permitted or prohibited during the trial	
15				
16				
17	Outcomes	#12	Primary, secondary, and other outcomes, including the	8-9
18			specific measurement variable (eg, systolic blood pressure),	
19			analysis metric (eg, change from baseline, final value, time	
20			to event), method of aggregation (eg, median, proportion),	
21			and time point for each outcome. Explanation of the clinical	
22			relevance of chosen efficacy and harm outcomes is strongly	
23			recommended	
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28	Participant timeline	#13	Time schedule of enrolment, interventions (including any	8
29			run-ins and washouts), assessments, and visits for	
30			participants. A schematic diagram is highly recommended	
31			(see Figure)	
32				
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35	Sample size	#14	Estimated number of participants needed to achieve study	9
36			objectives and how it was determined, including clinical and	
37			statistical assumptions supporting any sample size	
38			calculations	
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42	Recruitment	#15	Strategies for achieving adequate participant enrolment to	6
43			reach target sample size	
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46	Allocation: sequence	#16a	Method of generating the allocation sequence (eg,	6
47	generation		computer-generated random numbers), and list of any	
48			factors for stratification. To reduce predictability of a random	
49			sequence, details of any planned restriction (eg, blocking)	
50			should be provided in a separate document that is	
51			unavailable to those who enrol participants or assign	
52			interventions	
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57	Allocation	#16b	Mechanism of implementing the allocation sequence (eg,	6
58	concealment		central telephone; sequentially numbered, opaque, sealed	
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1	mechanism		envelopes), describing any steps to conceal the sequence until interventions are assigned	
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3				
4	Allocation:	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
5	implementation			
6				
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9	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
10				
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14	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6
15	emergency			
16	unblinding			
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20	Data collection plan	#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	8-9
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31	Data collection plan:	#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	8-9
32	retention			
33				
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38	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	8-9
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46	Statistics: outcomes	#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	9-10
47				
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51	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9-10
52	analyses			
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54				
55	Statistics: analysis	#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)	9-10
56	population and			
57	missing data			
58				
59				

1	Data monitoring:	#21a	Composition of data monitoring committee (DMC); summary	8-9
2	formal committee		of its role and reporting structure; statement of whether it is	
3			independent from the sponsor and competing interests; and	
4			reference to where further details about its charter can be	
5			found, if not in the protocol. Alternatively, an explanation of	
6			why a DMC is not needed	
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11	Data monitoring:	#21b	Description of any interim analyses and stopping guidelines,	8-9
12	interim analysis		including who will have access to these interim results and	
13			make the final decision to terminate the trial	
14				
15				
16	Harms	#22	Plans for collecting, assessing, reporting, and managing	9
17			solicited and spontaneously reported adverse events and	
18			other unintended effects of trial interventions or trial conduct	
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21	Auditing	#23	Frequency and procedures for auditing trial conduct, if any,	8-9
22			and whether the process will be independent from	
23			investigators and the sponsor	
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27	Research ethics	#24	Plans for seeking research ethics committee / institutional	5
28	approval		review board (REC / IRB) approval	
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31	Protocol	#25	Plans for communicating important protocol modifications	n/a
32	amendments		(eg, changes to eligibility criteria, outcomes, analyses) to	
33			relevant parties (eg, investigators, REC / IRBs, trial	
34			participants, trial registries, journals, regulators)	
35				
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37	Consent or assent	#26a	Who will obtain informed consent or assent from potential	5-6
38			trial participants or authorised surrogates, and how (see	
39			Item 32)	
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43	Consent or assent:	#26b	Additional consent provisions for collection and use of	5-6
44	ancillary studies		participant data and biological specimens in ancillary	
45			studies, if applicable	
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48	Confidentiality	#27	How personal information about potential and enrolled	5-6
49			participants will be collected, shared, and maintained in	
50			order to protect confidentiality before, during, and after the	
51			trial	
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55	Declaration of	#28	Financial and other competing interests for principal	14
56	interests		investigators for the overall trial and each study site	
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59	Data access	#29	Statement of who will have access to the final trial dataset,	5-6
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		and disclosure of contractual agreements that limit such access for investigators	
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4	Ancillary and post	#30 Provisions, if any, for ancillary and post-trial care, and for	5-6
5	trial care	compensation to those who suffer harm from trial	
6		participation	
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9	Dissemination policy:	#31a Plans for investigators and sponsor to communicate trial	5
10	trial results	results to participants, healthcare professionals, the public,	
11		and other relevant groups (eg, via publication, reporting in	
12		results databases, or other data sharing arrangements),	
13		including any publication restrictions	
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17	Dissemination policy:	#31b Authorship eligibility guidelines and any intended use of	14
18	authorship	professional writers	
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21	Dissemination policy:	#31c Plans, if any, for granting public access to the full protocol,	5
22	reproducible	participant-level dataset, and statistical code	
23	research		
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27	Informed consent	#32 Model consent form and other related documentation given	5-6
28	materials	to participants and authorised surrogates	
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31	Biological specimens	#33 Plans for collection, laboratory evaluation, and storage of	n/a
32		biological specimens for genetic or molecular analysis in the	
33		current trial and for future use in ancillary studies, if	
34		applicable	
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BMJ Open

Multicentre, prospective, randomized, controlled, blinded-endpoint study to evaluate the efficacy and safety of pterygopalatine ganglion pulsed radiofrequency treatment for episodic cluster headache: study protocol

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-026608.R1
Article Type:	Protocol
Date Submitted by the Author:	07-Dec-2018
Complete List of Authors:	Li, Jin; Beijing Tiantan Hospital, Capital Medical University, Department of Anesthesiology and Pain Management Ren, Hao; Beijing Tiantan Hospital, Capital Medical University, Department of Anesthesiology and Pain Management Wang, Baoguo; Beijing Sanbo Brian Hospital, Capital Medical University, Department of Anesthesiology Wu, Dasheng; Jilin Province People's Hospital, Department of Pain Management Luo, Fang; Beijing Tiantan Hospital, Capital Medical University, Department of Pain Management
Primary Subject Heading:	Anaesthesia
Secondary Subject Heading:	Anaesthesia
Keywords:	Cluster headache, Pulsed radiofrequency, Randomized controlled trial, Protocol

SCHOLARONE™
Manuscripts

Title:

Multicentre, prospective, randomized, controlled, blinded-endpoint study to evaluate the efficacy and safety of pterygopalatine ganglion pulsed radiofrequency treatment for episodic cluster headache: study protocol

Authors:

Jin Li, M.D., Department of Anesthesiology and Pain Management, Beijing Tiantan Hospital, Capital Medical University, Beijing, China.

Hao Ren, M.D., Department of Anesthesiology and Pain Management, Beijing Tiantan Hospital, Capital Medical University, Beijing, China.

Baoguo Wang, M.D., Department of Anesthesiology, Beijing Sanbo Brian Hospital, Capital Medical University, Beijing, China.

Dasheng Wu, M.D., Department of Pain Management, Jilin Province People's Hospital, Changchun, China.

Fang Luo, M.D., Department of Pain Management, Beijing Tiantan Hospital, Capital Medical University, Beijing, China.

Corresponding author contact details:

Fang Luo, M.D., Professor,

Department of Pain Management, Beijing Tiantan Hospital, Capital Medical University, Beijing 100050, China.

Phone: (86) 010 67096664.

Fax: (86) 010 67050177.

E-mail: luofangwt@yahoo.com.

Key words:

Cluster headache, Pulsed radiofrequency, Randomized controlled trial, Protocol

Word count :3311

ABSTRACT

Introduction Single-centre, small patient group case reports have shown that pterygopalatine ganglion pulsed radiofrequency treatment in patients with refractory cluster headache (CH) can quickly relieve pain without significant side effects. However, whether pterygopalatine ganglion pulsed radiofrequency treatment can be a treatment option for patients with CH that are not responding to drug treatment still requires evaluation in a properly designed randomized controlled trial.

Methods and analysis This is a multicentre, prospective, randomized, controlled, blinded-endpoint study. We will enrol 80 patients with episodic cluster headache (ECH) that are not responding to medications. The enrolled patients will be randomly divided into two groups: the nerve block (NB) group or the pulsed radiofrequency (PRF) group. All patients will undergo computed tomography (CT)-guided pterygopalatine ganglion puncture. A mixture containing steroids and local anaesthetics will be slowly injected into the patients in the NB group. The patients in the PRF group will be treated with PRF at 42 °C for 360 s. After treatment, the duration of cluster periods, degree of pain during headache attacks, headache attack frequency, duration of each headache attack, dose of auxiliary analgesic drugs, duration of remission period, patient satisfaction, effective rates at 1 day, 3 days, 1 week, 2 weeks, 1 month, 3 months, 6 months, and 1 year after surgery, and intraoperative and postoperative adverse events (AEs) will be compared between the two groups.

Ethics and dissemination This study was approved by the institutional ethics committee (Approval Number: KY 2018-027-02). The results of the study will be published in peer-reviewed journals, and the findings will be presented at scientific meetings.

Trial registration number NCT03567590; Pre-results.

Strength and limitations of this study

This study firstly compare the efficacy of pulsed radiofrequency of the pterygopalatine ganglion with a block with local anesthetic and corticosteroid for patients with episodic cluster headache (ECH) who are not responding to conservative drug treatment with

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4 the purpose of providing an additional treatment option for ECHs.

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6 The participants in this study and the doctors who conducted the interventions will be
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8 not kept blinded to the trial.

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10 The follow-up period of this study will be only 1 year, and long-term follow-up studies
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12 are still needed.
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For peer review only

INTRODUCTION

Cluster headache (CH) is a primary headache characterized by severe pain and has a considerable impact on quality of life. CH attacks are very painful, and the patients can even become suicidal. Therefore, CH is also known as "suicidal headache"^{1 2}. Severe unilateral pains occur in the orbital, frontal, and temporal areas during CH attacks and can last 15 minutes to 3 hours, with ipsilateral oculofacial autonomic symptoms. CH includes two categories: episodic cluster headache (ECH) and chronic cluster headache (CCH). ECH can involve several attacks in a day, and an attack period of 2 weeks to 3 months is called a "cluster period", which is followed by a pain-free "remission period" of ≥ 3 months³. During the cluster period, headaches often recur every day at a fixed period of time. Generally, CCH attacks occur less frequently than ECH on a daily basis and have no remission period.

Since the pathogenesis of CH remains unclear, there is a lack of targeted aetiological treatment⁴. It is currently believed that the pathogenesis of CH may involve the trigeminovascular system and the activation of parasympathetic system and ipsilateral hypothalamic grey matter^{4 5}. The pterygopalatine ganglion also be known as sphenopalatine ganglion (SPG) or ganglion pterygopalatinum which plays a very important role in the pathophysiology of CH⁶.

The clinical treatment of CH is still extremely difficult. For patients who do not respond to drug therapy, a pterygopalatine ganglion block via the application of local anaesthetics and steroid hormones has a certain effect⁷. Generally, a single pterygopalatine ganglion block is not sufficient to achieve satisfactory results; therefore, multiple pterygopalatine ganglion blocks are required, which increases the risk of puncture and steroid hormone-related side effects. In addition, multiple punctures also bring the risk of radiation exposure and increase medical costs. For intractable CH that does not respond to conservative treatment, deep brain stimulation⁸, pterygopalatine ganglion ablation⁹, and pterygopalatine ganglion electrical stimulation¹⁰⁻¹³ can relieve CH in some patients. Research has shown that high frequency stimulation of the pterygopalatine ganglion has preventive effects^{10 13}. However, the above methods all have problems, such as trauma caused by surgery, serious side effects, and high medical

costs. Therefore, there is an urgent need for exploring a new minimally invasive, safe, and effective technologies for the treatment of CH in clinical practice.

The percutaneous pulsed radiofrequency (PRF) technique is a minimally destructive pain treatment technology¹⁴. Different from the radiofrequency thermocoagulation, PRF uses the following parameters: pulse frequency of 2 Hz, output voltage of 45 V, output frequency of 500 kHz, continuous current action of 20 ms, intermittent time of 480 ms, and treatment temperature not exceeding 42 °C. This intervention technology does not cause local tissue damage, and there are few side effects.

In 2011, Chua et al. first reported the use of pterygopalatine ganglion PRF treatment in 3 patients with CH, of which 2 patients had complete remission of pain, 1 patient had partial remission of pain, and all had no neurological side effects or complications after treatment¹⁵. In 2016, we reported the computed tomography (CT) -guided pterygopalatine ganglion PRF treatment in 13 patients with ECH who had not responded to drugs and nerve block, and found that pterygopalatine ganglion PRF could quickly, safely and effectively relieve the patients from their cluster headache periods¹⁶. However, to verify whether early intervention via PRF can be a treatment option for patients with ECH who are not responding to drug therapy, we still need to obtain strong evidence via properly designed randomized controlled trial. Therefore, this study proposes a multicentre, prospective, randomized, controlled, blinded-endpoint study to compare the pain relief effects of CT-guided PRF and nerve blockade of pterygopalatine ganglion for the treatment of ECH patients who are not responding to drug treatment. Study outcomes at different timepoints will be assessed with standardized forms and procedures by responsible physicians blinded to the treatment allocation (blinded-endpoint).

METHODS

Trial design

This is a multicentre, prospective, randomized, controlled, blinded-endpoint study. ECH patients who are not responding to drug therapy will receive either CT-guided percutaneous puncture pterygopalatine ganglion nerve block or PRF, and efficacy and safety will be compared between the two groups of patients (Figure 1).

Setting

Patients will be selected from three research centres: Beijing Tiantan Hospital, Beijing Sanbo Brain Hospital, Jilin Province People's Hospital. All researchers will be trained based on the same training protocol and required to have more than 1 year of clinical experience with both treatment methods prior to participating in the study.

Ethics, trial registration and dissemination

This clinical study follows the relevant regulations of the Declaration of Helsinki (version 19 October 2013) of the World Medical Association. The research protocol (protocol version 1.0) has been approved by the Ethics Committee of the Beijing Tiantan Hospital (Approval Number: KY 2018-027-02). All patients will sign the informed consent at a screening visit. Before patient enrolment, the study design has been registered at clinicaltrials.gov (NCT03567590). This study, which has begun on July 5, 2018, will last for 3 years. The results of the study will be published in peer-reviewed journals, and the findings will be presented at scientific meetings.

Participants

Suitable participants will be screened in the pain management centre of each hospital to participate in the study.

Inclusion criteria comprise the following: (1) diagnosis of ECH is confirmed according to the diagnostic criteria of the International Classification of Headache Disorders 3rd edition (ICHD-3)³(Table 1); (2) patient's age is between 18 and 60 years; (3) patients seek treatment in the pain clinics of hospitals participating in the study within 5 days of the onset of the cluster period; pain conditions of patients remain the same after preventive therapy of available drugs in our hospital such as verapamil, topiramate, lithium or steroid, or the reduction rates are less than 50% in pain degree during headache attacks, headache attack frequency, duration of each headache attack, and auxiliary analgesic drug dosage.

Table 1. Diagnostic criteria for episodic cluster headache in the International Classification of Headache Disorders 3rd edition³

Cluster Headache

- A.** At least five attacks fulfilling criteria **B–D**
- B.** Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15–180 minutes (when untreated)
- C.** Either or both of the following:
 - 1.** at least one of the following symptoms or signs, ipsilateral to the headache:
 - a.** conjunctival injection and/or lacrimation; **b.** nasal congestion and/or rhinorrhea; **c.** eyelid oedema; **d.** forehead and facial sweating; **e.** miosis and/or ptosis
 - 2.** a sense of restlessness or agitation
- D.** Occurring with a frequency between one every other day and eight per day
- E.** Not better accounted for by another ICHD-3 diagnosis.

Episodic Cluster Headache

- A.** Attacks fulfilling criteria for Cluster headache and occurring in bouts (cluster periods)
- B.** At least two cluster periods lasting from seven days to one year (when untreated) and separated by pain-free remission periods of ≥ 3 months.

Exclusion criteria include the following: (1) abnormalities in blood measurements, liver and kidney function, blood glucose, coagulation, electrocardiogram, and chest radiograph; (2) infection at the puncture site; (3) previous mental illness; (4) previous history of narcotic drug abuse; (5) preceding anticoagulant or antiplatelet therapy; (6) implantable pulse generator; (7) previous history of invasive treatments such as pterygopalatine ganglion radiofrequency thermocoagulation and chemical destruction; and (8) pregnant or breastfeeding patients.

Recruitment and informed consent

All enrolled patients will have the right to be informed of the purpose of the study, the experimental procedures, the participants' benefits, and possible risks, and then sign the informed consent. All patients will be given enough time to consider whether they would like to participate in this study. Patients participating in the study will also have the right to freely obtain more information at any time and can freely withdraw their consent form or can withdraw from the study without restrictions at any stage.

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4 Once the patient signs the informed consent, the researchers will complete the
5 eligibility checklists based on the items listed on the case report form and record the
6 enrolment failure.
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9 **Interventions**

10 Randomization and allocation concealment

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12 All participants will be randomly divided into two groups in a 1:1 ratio. The researchers
13 will perform randomization in three centres. After confirming that the enrolled patient
14 satisfies the baseline inclusion/exclusion criteria, the patient will be randomly assigned
15 to one of the two study groups. The random sequence will be generated using SAS 9.1.3
16 (SAS Institute Inc., Cary, NC U.S.A.) software.
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20 Each research centre will have a research nurse who is responsible for implementing
21 the allocation. According to a pre-generated random sequence, each enrolled patient
22 will be given a sealed opaque random envelope based on the order of enrolment. After
23 puncturing the pterygopalatine ganglion during the surgery, the research nurse will
24 open the sealed envelope and assign the patient to the corresponding group according
25 to the random number in the envelope, and the corresponding treatment will be then
26 performed on the patient.
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29 **Blinding**

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31 This study is an open-label study. In this study, participants and doctors could not all
32 be blinded to the study. The telephone follow-up at different time points after surgery
33 will be conducted by responsible physicians, who will be blinded to the allocation status
34 of the patients. The data input will be completed by the data entry personnel, who are
35 not from the research team, and the data analysis will be completed by the statisticians
36 who are blinded to allocation information.
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39 **Study interventions**

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41 The patient will be in a supine position on a CT scan couch with their head turned to
42 the contralateral side by approximately 50 degrees. Blood pressure, heart rate,
43 electrocardiogram, and pulse oximetry will be continuously monitored. The negative
44 plate of the PMG-230 pain treatment generator (Baylis Medical Inc., Montreal, Canada)
45 will be applied to the upper abdominal skin of the patient. Aseptic drapes will be
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4 routinely applied to the patient's face. The puncture point will be located under the
5 zygomatic arch of the affected side, 3-4 cm in front of the tragus. After the
6 administration of 1% lidocaine for local anaesthesia, a trocar needle with a length of 10
7 cm, 21-gauge will be inserted vertically into the puncture point. With an approximate
8 depth of 4 cm, the trocar needle will reach the bone surface of the lateral pterygoid plate
9 of the sphenoid. The trocar needle will be then withdrawn by 2 cm and reinserted
10 towards the upper middle third of the pterygopalatine fossa until the tip of the needle
11 glides over the leading edge of the lateral pterygoid plate of the sphenoid. The needle
12 will be then inserted another 0.5 cm to enter the pterygopalatine fossa. We will use a
13 CT scanner (medical X-ray CT scanner, model SOMATOM, SIEMENS, Munich,
14 Germany) during the procedure to verify the position of the puncture needle in the
15 pterygopalatine fossa. The orientation and depth of the puncture needle will be adjusted
16 according to the CT image until the needle approaches the pterygopalatine ganglion.
17 The stylet will be removed, and the electrode needle for PRF treatment (PMF-21-100-
18 5, Baylis Medical Inc., Montreal, Canada) will be placed. The pain treatment generator
19 will be connected with the RF needle, and the sensory threshold will be measured with
20 50 Hz electrical stimulation. Induction of sensory abnormality of the nasal roots via
21 0.1-0.3 V will indicate accurate puncture, and the depth and direction of the puncture
22 needle will be appropriately adjusted according to the patient's response. When the
23 needle is in place, the patients will receive PRF or nerve block treatment according to
24 the random number in the envelope as follow.

25
26 PRF treatment: The pulse treatment generator will be set to the pulsed radiofrequency
27 automatic mode, with a temperature of 42 °C, pulse frequency of 2 Hz, pulse width of
28 20 ms, and treatment duration of 360 s¹⁶.

29
30 NB treatment: A mixture of 40 mg triamcinolone + 2 ml of 1% bupivacaine + 2 ml of
31 2% mepivacaine + 1:100000 epinephrine will be injected for nerve block treatment
32 using a puncture needle^{17 18}.

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34 After the operation, the patients will be delivered to the outpatient recovery room and
35 they will be discharged if no adverse signs are noted within 2 hours. Verapamil,
36 topiramate, lithium or steroid will be discontinued if patients take these

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4 medications prior to the procedure. The doctor will use rizatriptan to abort individual
5 attacks as needed. Participants will be treated with salvage therapy of other more
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medications prior to the procedure. The doctor will use rizatriptan to abort individual attacks as needed. Participants will be treated with salvage therapy of other more invasive therapies such as pterygopalatine ganglion ablation, electrical stimulation of the pterygopalatine ganglion, and deep brain stimulation if the pain and the dosage of auxiliary drugs have no difference from the preoperative level.

Patient and Public Involvement

Patients or public were not involved in the development of the research question, design or outcome measures of this study. The study recruitment will be conducted by research posters and physicians' presentations. Participants screening and enrollment will be performed by medically trained physicians. The trial outcomes of this study will be disseminated to all participants in newsletter on request. The burden of the intervention is not assessed by patients themselves. All participants will be provided with the detailed cost of the relevant intervention.

Variables and measurements

Prior to the intervention, the age, gender, the side of the headache (left or right), previous duration of cluster periods, current numeric rating scale (NRS, 0 points for no pain and 10 points for the most severe pain) score during headache attacks, headache attack frequency, duration of each headache attack, dose of auxiliary analgesics, and previous duration of remission period of the enrolled patients and a prospective evaluation (with diary) of the patients will be recorded.

The patients will be followed up by telephone at 1 day, 3 days, 1 week, 2 weeks, 1 month, 3 months, 6 months, and 1 year after surgery by responsible physicians who are blinded to the allocation status of the patients. The primary outcome is the duration of the cluster periods. The duration of the cluster period is defined as the total duration of the headache, including the pain attack time before and after treatment. The secondary outcomes include the degree of pain during headache attacks (NRS scores), headache attack frequency, duration of each headache attack, dose of auxiliary analgesic drugs, duration of remission period, patient satisfaction scale (0 point for unsatisfactory, and 10 points for very satisfied), effective rates, and intraoperative and postoperative adverse events (AEs) will be compared between the two groups of patients.

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4 Efficiency at each time point will be calculated. Both complete relief and partial relief
5 of pain will be considered to be effective, and the effectiveness rate will be calculated
6 as follows: effectiveness rate = number of effective patients / total number of patients
7 in this group \times 100%. Complete pain relief: NRS = 0, discontinued administration of
8 drugs. Partial relief of pain: postoperative pain levels during headache attacks,
9 headache attack frequency, duration of each headache attack, and auxiliary analgesic
10 drug dosage are less than 50% of the preoperative levels. No remission of pain: the pain
11 is not different from the preoperative level, or the degree of pain during headache
12 attacks, the frequency of headache attacks, the duration of each headache attack, and
13 the reduction in the use of adjuvant analgesics are still over 50% of the preoperative
14 levels. The partial pain remission time, complete pain remission time, number of
15 interventional treatments and treatment interval, and the number of cases receiving
16 electrical stimulation of the pterygopalatine ganglion will be recorded.

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29 The details of the AEs will be recorded during the surgery and at various time points
30 during the postoperative follow-up (1 day, 3 days, 1 week, 2 weeks, 1 month, 3 months,
31 6 months, and 1 year after surgery). For intraoperative AEs, the occurrences of puncture
32 pain, headache, dizziness, nausea, vomiting, facial haematoma, and others will be
33 recorded. For postoperative AEs, headache, dizziness, facial numbness, and others will
34 be also recorded.

40 41 **Sample size**

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43 This study will adopt a one-sided superiority test, $\alpha = 0.025$, $\beta = 0.10$. After examining
44 the literature, combined with the authors' published articles and clinical experience¹⁶,
45 the duration of the cluster period of the PRF group is approximately 15.5 days, and the
46 standard deviation is 9.3 days, while the cluster duration of the NB group is
47 approximately 45 days, and the standard deviation is approximately 15 days.
48 Shortening the duration of the cluster period by 20 days has clinical significance. The
49 number of cases needed in each group is 36, calculated by PASS 11. Considering the
50 10% loss rate, 40 cases are required in each group, and a total of 80 cases are required
51 for both groups.

52 53 54 55 56 57 58 59 60 **Statistical analysis**

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4 The SAS9.4 statistical analysis system will be used to analyse the data with the full
5 analysis set and the per-protocol set. The Shapiro-Wilk test will be used to check data
6 for normal distribution. Normally distributed data will be expressed as the means \pm
7 standard deviations. Parameters that do not meet the normal distribution will be
8 expressed as medians \pm quartiles. The t-test will be used for measurement data with
9 normal distributions, the rank sum test will be used for measurement data with non-
10 normal distributions, and the chi-square test will be used for count data. Efficacy
11 analysis will be conducted via both intention-to-treat (ITT) analysis and the per-
12 protocol analysis set in SAS. The t-test will be used to compare the measurement data
13 of efficacy outcome indicators between the RFP group and the NB group, such as
14 duration of cluster periods, pain degree during headache attacks, frequency of headache
15 attacks, the duration of each headache attack, the dose of auxiliary analgesics, duration
16 of remission period, and patient satisfaction. The chi-square test will be used to
17 compare the count data of efficacy outcome indicators between the PRF and NB groups.
18 The chi-square test or exact probability analysis will be used to evaluate intraoperative
19 and postoperative AEs.

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36 The pterygopalatine ganglion is one of the four major parasympathetic ganglia of the
37 head and neck. It is the largest group of neurons within the calvarium outside of the
38 brain and is the only ganglion that enters the external environment through the nasal
39 mucosa¹⁹. The characteristic clinical symptoms of CH, such as tearing, runny nose,
40 nasal congestion, and nasal oedema, are manifestations of parasympathetic excitations
41 in the pterygopalatine ganglion, and ptosis and pupil diminution are manifestations of
42 sympathetic inhibition in the pterygopalatine ganglion. Therefore, the pathogenesis of
43 CH is considered to be related to the pterygopalatine ganglion²⁰.

44 In recent years, there have been a series of reports on the treatment of CH via the
45 pterygopalatine ganglion. One type of pterygopalatine ganglion treatment is destructive,
46 which blocks pain signalling by denaturing pterygopalatine ganglion proteins, such as
47 radiofrequency ablation techniques^{21 22} and local injection of absolute alcohol^{23 24}. The
48 other type is non-destructive, such as nerve block^{10 20}, PRF¹⁶, and nerve electrical
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3 stimulation^{13 25}.

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5 Pterygopalatine ganglion nerve blocks include cotton swab nasal infiltration²⁶ and
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Pterygopalatine ganglion nerve blocks include cotton swab nasal infiltration²⁶ and
needle injection^{17 18}. The puncture approach of the pterygopalatine ganglion includes
the sphenopalatine foramen approach²⁷, the supra-zygomatic approach²³, the
infrazygomatic crest approach²⁴, or the mandibular notch approach²⁸. Puncture can be
performed with the assistance of nasal endoscopy^{17 18}, fluoroscopy^{21 22}, or CT^{9 16}. The
commonly used nerve block drugs include local anaesthetics and steroid hormones, etc.
Previous reports on nerve block for the treatment of CH are mostly case series analyses
or case reports. Costa et al. conducted a randomized double-blinded placebo-controlled
study of patients with nitroglycerine-induced CH, and the patients were treated with 10%
cocaine, 10% lidocaine, or saline placebo²⁶. The results showed that short-term
treatment effects were significant in the cocaine and lidocaine groups, and there were
no related acute side effects. However, the main drawbacks of nerve block treatment
for CH are the limited effect of pain relief in a single treatment, the short duration of
treatment efficacy. Therefore, nerve block needs to be implemented repeatedly. The
puncture approach in our study will be the infrazygomatic crest approach²⁴, also known
as the translateral approach, and the injection will be a mixture of the steroid hormone
triamcinolone acetonide and local anaesthetics in the control group.

PRF is a minimally destructive, minimally invasive, and percutaneous interventional
pain management technique²⁹. Compared with radiofrequency ablation, the puncture
site and localization approach are consistent between the two. However, to treat the
pain, PRF regulates the nerve function through an electric field effect, while
radiofrequency ablation destroys the nerve through a thermal effect. Our previous study
found that after PRF treatment of 16 CH patients who had not responded to drug and
nerve block, 11 patients with ECH and 1 patient with CCH had complete remission,
though treatments for 2 patients with ECH and 2 patients with CCH were not effective¹⁶.
Bendersky et al. also reported that PRF treatment failed to achieve satisfactory pain
relief in 3 patients with CCH³⁰. Therefore, it is currently believed that PRF treatment
may be more effective for ECH than CCH. However, the incidence of CCH is low, and
the number of CCH cases is small, and the existing study are not sufficient to reach a

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4 convincing conclusion.

5 CT images are clear and intuitive, providing the clinician with a more accurate guidance
6 for puncture. The CT-guided pterygopalatine ganglion puncture technique was first
7 applied in clinical practice by Kastler et al²⁴. It was confirmed that puncture
8 complications can be reduced, and the puncture success rate and treatment satisfaction
9 can be improved with CT guidance. In the past, we have reported that the success rate
10 of the puncture was 100% for CH patients with CT-guided pterygopalatine ganglion
11 puncture and PRF treatment, and surgery-related complications, such as nosebleeds and
12 cheek haematomas, were successfully avoided¹⁶. In this study, both the NB and the PRF
13 groups will undergo CT-guided pterygopalatine ganglion puncture to ensure the
14 accuracy of the puncture and to avoid the effects of inaccurate puncture on the outcome.
15 Minimizing the scope of CT scans for example just performing a scan of the
16 pterygopalatine fossa during the procedure by experienced physician puncture will be
17 a way to reduce the dose of radiation exposure.
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30 This study will compare the efficacy of pterygopalatine ganglion nerve block and PRF
31 in the treatment of ECH in a multicentre, prospective, randomized, controlled, and
32 blinded-endpoint study, and will provide reliable evidence for treatment strategies for
33 patients with ECH who are not responding to conservative drug treatment. Of course,
34 the limitations of this study including that the participants in this study and the doctors
35 who conducted the interventions will be not kept blinded to the trial. In order to obtain
36 greater scientific value, double-blind researches need to be carried out in the future.
37 Other limitations include the follow-up period of this study will be only 1 year, and the
38 lack of exploration of optimal parameters for PRF treatment of ECH, which will be
39 investigated through in-depth clinical research later. Furthermore, the variability of the
40 duration of the episodes of patients with ECH makes it difficult to establish the response
41 pattern, research on CCH needs to be carried out in the future.
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Author's contributions

JL and HR contributed equally to this work and should be considered co-first authors. JL and HR wrote the protocol and this manuscript. FL is the principal investigator of the whole study. FL BW and DW are the site principal investigator of each research centre. FL JL and HR contributed to the conception and design of the research protocol. All authors approved the final version to be published.

Acknowledgements

Funding: This work will be supported by the Beijing Municipal Administration of Hospitals Clinical Medicine Development of Special Funding Support (grant No. XMLX201707) and the Foundation for the Excellent Medical Staff of Beijing (grant No. 2014-3-035).

Competing interests None declared.

Figure 1

Flow diagram of the study.

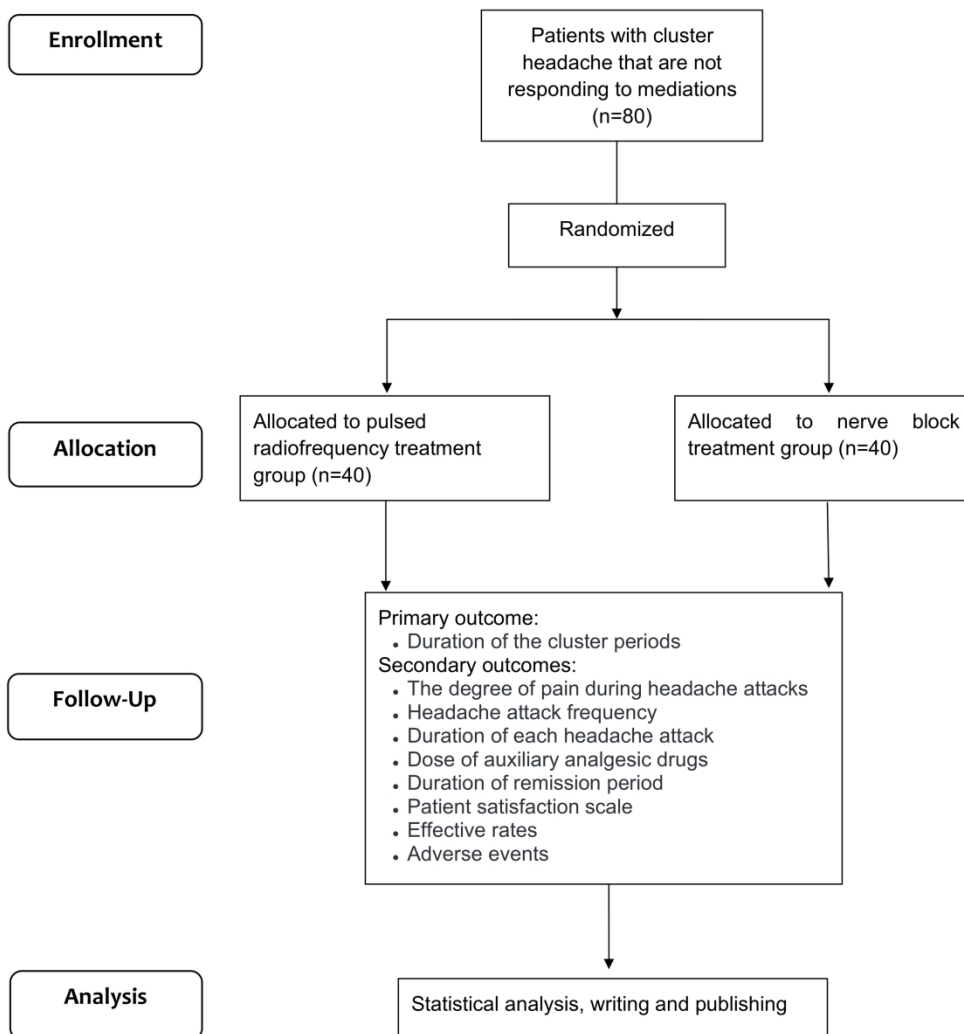


Figure 1/Flow diagram of the study.

206x218mm (300 x 300 DPI)

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		Reporting Item	Page Number
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	5
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	5
Protocol version	#3	Date and version identifier	5
Funding	#4	Sources and types of financial, material, and other support	14
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	14
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	5

1	sponsor contact			
2	information			
3				
4	Roles and	#5c	Role of study sponsor and funders, if any, in study design;	5
5	responsibilities:		collection, management, analysis, and interpretation of	
6	sponsor and funder		data; writing of the report; and the decision to submit the	
7			report for publication, including whether they will have	
8			ultimate authority over any of these activities	
9				
10				
11				
12	Roles and	#5d	Composition, roles, and responsibilities of the coordinating	5
13	responsibilities:		centre, steering committee, endpoint adjudication	
14	committees		committee, data management team, and other individuals or	
15			groups overseeing the trial, if applicable (see Item 21a for	
16			data monitoring committee)	
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19				
20	Background and	#6a	Description of research question and justification for	3-4
21	rationale		undertaking the trial, including summary of relevant studies	
22			(published and unpublished) examining benefits and harms	
23			for each intervention	
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26				
27	Background and	#6b	Explanation for choice of comparators	3
28	rationale: choice of			
29	comparators			
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32	Objectives	#7	Specific objectives or hypotheses	4
33				
34				
35	Trial design	#8	Description of trial design including type of trial (eg, parallel	4
36			group, crossover, factorial, single group), allocation ratio,	
37			and framework (eg, superiority, equivalence, non-inferiority,	
38			exploratory)	
39				
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41				
42	Study setting	#9	Description of study settings (eg, community clinic,	4
43			academic hospital) and list of countries where data will be	
44			collected. Reference to where list of study sites can be	
45			obtained	
46				
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48	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable,	5
49			eligibility criteria for study centres and individuals who will	
50			perform the interventions (eg, surgeons, psychotherapists)	
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54	Interventions:	#11a	Interventions for each group with sufficient detail to allow	6-8
55	description		replication, including how and when they will be	
56			administered	
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1	Interventions:	#11b	Criteria for discontinuing or modifying allocated	7-8
2	modifications		interventions for a given trial participant (eg, drug dose	
3			change in response to harms, participant request, or	
4			improving / worsening disease)	
5				
6				
7				
8	Interventions:	#11c	Strategies to improve adherence to intervention protocols,	7-8
9	adherence		and any procedures for monitoring adherence (eg, drug	
10			tablet return; laboratory tests)	
11				
12				
13	Interventions:	#11d	Relevant concomitant care and interventions that are	7-8
14	concomitant care		permitted or prohibited during the trial	
15				
16				
17	Outcomes	#12	Primary, secondary, and other outcomes, including the	8-9
18			specific measurement variable (eg, systolic blood pressure),	
19			analysis metric (eg, change from baseline, final value, time	
20			to event), method of aggregation (eg, median, proportion),	
21			and time point for each outcome. Explanation of the clinical	
22			relevance of chosen efficacy and harm outcomes is strongly	
23			recommended	
24				
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26				
27				
28	Participant timeline	#13	Time schedule of enrolment, interventions (including any	8
29			run-ins and washouts), assessments, and visits for	
30			participants. A schematic diagram is highly recommended	
31			(see Figure)	
32				
33				
34				
35	Sample size	#14	Estimated number of participants needed to achieve study	9
36			objectives and how it was determined, including clinical and	
37			statistical assumptions supporting any sample size	
38			calculations	
39				
40				
41				
42	Recruitment	#15	Strategies for achieving adequate participant enrolment to	6
43			reach target sample size	
44				
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46	Allocation: sequence	#16a	Method of generating the allocation sequence (eg,	6
47	generation		computer-generated random numbers), and list of any	
48			factors for stratification. To reduce predictability of a random	
49			sequence, details of any planned restriction (eg, blocking)	
50			should be provided in a separate document that is	
51			unavailable to those who enrol participants or assign	
52			interventions	
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57	Allocation	#16b	Mechanism of implementing the allocation sequence (eg,	6
58	concealment		central telephone; sequentially numbered, opaque, sealed	
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1	mechanism		envelopes), describing any steps to conceal the sequence until interventions are assigned	
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4	Allocation:	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
5	implementation			
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9	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
10				
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14	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6
15	emergency			
16	unblinding			
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20	Data collection plan	#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	8-9
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31	Data collection plan:	#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	8-9
32	retention			
33				
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38	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	8-9
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46	Statistics: outcomes	#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	9-10
47				
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51	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9-10
52	analyses			
53				
54				
55	Statistics: analysis	#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)	9-10
56	population and			
57	missing data			
58				
59				

1	Data monitoring:	#21a	Composition of data monitoring committee (DMC); summary	8-9
2	formal committee		of its role and reporting structure; statement of whether it is	
3			independent from the sponsor and competing interests; and	
4			reference to where further details about its charter can be	
5			found, if not in the protocol. Alternatively, an explanation of	
6			why a DMC is not needed	
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11	Data monitoring:	#21b	Description of any interim analyses and stopping guidelines,	8-9
12	interim analysis		including who will have access to these interim results and	
13			make the final decision to terminate the trial	
14				
15				
16	Harms	#22	Plans for collecting, assessing, reporting, and managing	9
17			solicited and spontaneously reported adverse events and	
18			other unintended effects of trial interventions or trial conduct	
19				
20				
21	Auditing	#23	Frequency and procedures for auditing trial conduct, if any,	8-9
22			and whether the process will be independent from	
23			investigators and the sponsor	
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27	Research ethics	#24	Plans for seeking research ethics committee / institutional	5
28	approval		review board (REC / IRB) approval	
29				
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31	Protocol	#25	Plans for communicating important protocol modifications	n/a
32	amendments		(eg, changes to eligibility criteria, outcomes, analyses) to	
33			relevant parties (eg, investigators, REC / IRBs, trial	
34			participants, trial registries, journals, regulators)	
35				
36				
37	Consent or assent	#26a	Who will obtain informed consent or assent from potential	5-6
38			trial participants or authorised surrogates, and how (see	
39			Item 32)	
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43	Consent or assent:	#26b	Additional consent provisions for collection and use of	5-6
44	ancillary studies		participant data and biological specimens in ancillary	
45			studies, if applicable	
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48	Confidentiality	#27	How personal information about potential and enrolled	5-6
49			participants will be collected, shared, and maintained in	
50			order to protect confidentiality before, during, and after the	
51			trial	
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55	Declaration of	#28	Financial and other competing interests for principal	14
56	interests		investigators for the overall trial and each study site	
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59	Data access	#29	Statement of who will have access to the final trial dataset,	5-6
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		and disclosure of contractual agreements that limit such access for investigators	
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4	Ancillary and post	#30 Provisions, if any, for ancillary and post-trial care, and for	5-6
5	trial care	compensation to those who suffer harm from trial	
6		participation	
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9	Dissemination policy:	#31a Plans for investigators and sponsor to communicate trial	5
10	trial results	results to participants, healthcare professionals, the public,	
11		and other relevant groups (eg, via publication, reporting in	
12		results databases, or other data sharing arrangements),	
13		including any publication restrictions	
14			
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17	Dissemination policy:	#31b Authorship eligibility guidelines and any intended use of	14
18	authorship	professional writers	
19			
20			
21	Dissemination policy:	#31c Plans, if any, for granting public access to the full protocol,	5
22	reproducible	participant-level dataset, and statistical code	
23	research		
24			
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27	Informed consent	#32 Model consent form and other related documentation given	5-6
28	materials	to participants and authorised surrogates	
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31	Biological specimens	#33 Plans for collection, laboratory evaluation, and storage of	n/a
32		biological specimens for genetic or molecular analysis in the	
33		current trial and for future use in ancillary studies, if	
34		applicable	
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BMJ Open

Multicentre, prospective, randomized, controlled, blinded-endpoint study to evaluate the efficacy and safety of pterygopalatine ganglion pulsed radiofrequency treatment for cluster headache: study protocol

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-026608.R2
Article Type:	Protocol
Date Submitted by the Author:	14-Jan-2019
Complete List of Authors:	Li, Jin; Beijing Tiantan Hospital, Capital Medical University, Department of Anesthesiology and Pain Management Ren, Hao; Beijing Tiantan Hospital, Capital Medical University, Department of Anesthesiology and Pain Management Wang, Baoguo; Beijing Sanbo Brian Hospital, Capital Medical University, Department of Anesthesiology Wu, Dasheng; Jilin Province People's Hospital, Department of Pain Management Luo, Fang; Beijing Tiantan Hospital, Capital Medical University, Department of Pain Management
Primary Subject Heading:	Anaesthesia
Secondary Subject Heading:	Anaesthesia
Keywords:	Cluster headache, Pulsed radiofrequency, Randomized controlled trial, Protocol

SCHOLARONE™
Manuscripts

Title:

Multicentre, prospective, randomized, controlled, blinded-endpoint study to evaluate the efficacy and safety of pterygopalatine ganglion pulsed radiofrequency treatment for cluster headache: study protocol

Authors:

Jin Li, M.D., Department of Anesthesiology and Pain Management, Beijing Tiantan Hospital, Capital Medical University, Beijing, China.

Hao Ren, M.D., Department of Anesthesiology and Pain Management, Beijing Tiantan Hospital, Capital Medical University, Beijing, China.

Baoguo Wang, M.D., Department of Anesthesiology, Beijing Sanbo Brian Hospital, Capital Medical University, Beijing, China.

Dasheng Wu, M.D., Department of Pain Management, Jilin Province People's Hospital, Changchun, China.

Fang Luo, M.D., Department of Pain Management, Beijing Tiantan Hospital, Capital Medical University, Beijing, China.

Corresponding author contact details:

Fang Luo, M.D., Professor,

Department of Pain Management, Beijing Tiantan Hospital, Capital Medical University, Beijing 100050, China.

Phone: (86) 010 67096664.

Fax: (86) 010 67050177.

E-mail: luofangwt@yahoo.com.

Key words:

Cluster headache, Pulsed radiofrequency, Randomized controlled trial, Protocol

Word count :3311

ABSTRACT

Introduction Single-centre, small patient group case reports have shown that pterygopalatine ganglion pulsed radiofrequency treatment in patients with refractory cluster headache (CH) can quickly relieve pain without significant side effects. However, whether pterygopalatine ganglion pulsed radiofrequency treatment can be a treatment option for patients with CH that are not responding to drug treatment still requires evaluation in a properly designed randomized controlled trial.

Methods and analysis This is a multicentre, prospective, randomized, controlled, blinded-endpoint study. We will enrol 80 patients with cluster headache that are not responding to medications. The enrolled patients will be randomly divided into two groups: the nerve block (NB) group or the pulsed radiofrequency (PRF) group. All patients will undergo computed tomography (CT) -guided pterygopalatine ganglion puncture. A mixture containing steroids and local anaesthetics will be slowly injected into the patients in the NB group. The patients in the PRF group will be treated with PRF at 42 °C for 360 s. After treatment, the duration of cluster periods, degree of pain during headache attacks, headache attack frequency, duration of each headache attack, dose of auxiliary analgesic drugs, duration of remission period, patient satisfaction, effective rates at 1 day, 3 days, 1 week, 2 weeks, 1 month, 3 months, 6 months, and 1 year after procedure, and intraoperative and postoperative adverse events (AEs) will be compared between the two groups.

Ethics and dissemination This study was approved by the institutional ethics committee (Approval Number: KY 2018-027-02). The results of the study will be published in peer-reviewed journals, and the findings will be presented at scientific meetings.

Trial registration number NCT03567590; Pre-results.

Strength and limitations of this study

This is a multicentered, prospective, randomized, controlled, blinded-endpoint study to compare the efficacy of pulsed radiofrequency with a block with local anesthetic plus corticosteroid for cluster headache patients for the first time.

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4 The randomised controlled trial design minimises risk of confounding bias.

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6 The participants in this study and the doctors who conducted the interventions will not
7
8 be blinded to the treatment procedure.

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10 The follow-up will be performed by telephone instead of hospital visit and telephone
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12 follow-up is already enough for obtaining the primary outcome.
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For peer review only

INTRODUCTION

Cluster headache (CH) is a primary headache characterized by severe pain and has a considerable impact on quality of life. CH attacks are very painful, and the patients can even become suicidal. Therefore, CH is also known as "suicidal headache"^{1 2}. Severe unilateral pains occur in the orbital, frontal, and temporal areas during CH attacks and can last 15 minutes to 3 hours, with ipsilateral oculofacial autonomic symptoms. CH includes two categories: episodic cluster headache (ECH) and chronic cluster headache (CCH). ECH can involve several attacks in a day, and an attack period of 2 weeks to 3 months is called a "cluster period", which is followed by a pain-free "remission period" of ≥ 3 months³. During the cluster period, headaches often recur every day at a fixed period of time. Generally, CCH attacks occur less frequently than ECH on a daily basis and have no remission period.

Since the pathogenesis of CH remains unclear, there is a lack of targeted aetiological treatment⁴. It is currently believed that the pathogenesis of CH may involve the trigeminovascular system and the activation of parasympathetic system and ipsilateral hypothalamic grey matter^{4 5}. The pterygopalatine ganglion also known as sphenopalatine ganglion (SPG) or ganglion pterygopalatinum which plays a very important role in the pathophysiology of CH⁶.

The clinical treatment of CH is still extremely difficult. For patients who do not respond to drug therapy, a pterygopalatine ganglion block via the application of local anaesthetics and steroid hormones has a certain effect⁷. Generally, a single pterygopalatine ganglion block is not sufficient to achieve satisfactory results; therefore, multiple pterygopalatine ganglion blocks are required, which increases the risk of puncture and steroid hormone-related side effects. In addition, multiple punctures would also increase medical costs. For intractable CH that does not respond to conservative treatment, deep brain stimulation⁸, pterygopalatine ganglion ablation⁹, and pterygopalatine ganglion electrical stimulation¹⁰⁻¹³ can relieve CH in some patients. Research has shown that tonic stimulation of the pterygopalatine ganglion has preventive effects^{10 13}. However, the above methods all have problems, such as trauma caused by surgery, serious side effects, and high medical costs. Therefore, there is an

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4 urgent need for exploring new minimally invasive, safe, and effective technologies for
5 the treatment of CH in clinical practice.

6
7 The percutaneous pulsed radiofrequency (PRF) technique is a minimally destructive
8 pain treatment technology¹⁴. Different from the radiofrequency thermocoagulation,
9 PRF uses the following parameters: pulse frequency of 2 Hz, output voltage of 45 V,
10 output frequency of 500 kHz, continuous current action of 20 ms, intermittent time of
11 480 ms, and treatment temperature not exceeding 42 °C. This intervention technology
12 does not cause local tissue damage, and there are few side effects.

13
14 In 2011, Chua et al. first reported the use of pterygopalatine ganglion PRF treatment in
15 3 patients with CH, of which 2 patients had complete remission of pain, 1 patient had
16 partial remission of pain, and all had no neurological side effects or complications after
17 treatment¹⁵. In 2016, we reported the computed tomography (CT) -guided
18 pterygopalatine ganglion PRF treatment in 16 patients with CH who had not responded
19 to drugs and nerve block, and found that pterygopalatine ganglion PRF could quickly,
20 safely and effectively relieve the patients from their cluster headache¹⁶. However, to
21 verify whether early intervention via PRF can be a treatment option for patients with
22 CH who are not responding to drug therapy, we still need to obtain strong evidence via
23 properly designed randomized controlled trial. Therefore, this study proposes a
24 multicentre, prospective, randomized, controlled, blinded-endpoint study to compare
25 the pain relief effects of CT-guided PRF and nerve blockade of pterygopalatine
26 ganglion for the treatment of CH patients who are not responding to drug treatment.
27 Study outcomes at different timepoints will be assessed with standardized forms and
28 procedures by responsible physicians blinded to the treatment allocation (blinded-
29 endpoint).

30 **METHODS**

31 **Trial design**

32 This is a multicentre, prospective, randomized, controlled, blinded-endpoint study. CH
33 patients who are not responding to drug therapy will receive either CT-guided
34 percutaneous puncture pterygopalatine ganglion nerve block or PRF, and efficacy and
35 safety will be compared between the two groups of patients (Figure 1).
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Setting

Patients will be selected from three research centres: Beijing Tiantan Hospital, Beijing Sanbo Brain Hospital, Jilin Province People's Hospital. All researchers will be trained based on the same training protocol and required to have more than 1 year of clinical experience with both treatment methods prior to participating in the study.

Ethics, trial registration and dissemination

This clinical study follows the relevant regulations of the Declaration of Helsinki (version 19 October 2013) of the World Medical Association. The research protocol (protocol version 1.0) has been approved by the Ethics Committee of the Beijing Tiantan Hospital (Approval Number: KY 2018-027-02). All patients will sign the informed consent at a screening visit. Before patient enrolment, the study design has been registered at clinicaltrials.gov (NCT03567590). This study, which has begun on July 5, 2018, will last for 3 years. The results of the study will be published in peer-reviewed journals, and the findings will be presented at scientific meetings.

Participants

Suitable participants will be screened in the pain management centre of each hospital to participate in the study.

Inclusion criteria comprise the following: (1) diagnosis of CH is confirmed according to the diagnostic criteria of the International Classification of Headache Disorders 3rd edition (ICHD-3)³(Table 1); (2) patient's age is between 18 and 60 years; (3) patients seek treatment in the pain clinics of hospitals participating in the study within 5 days of the onset of the cluster period; pain conditions of patients remain the same after preventive therapy of available drugs in our hospital such as verapamil, topiramate, lithium or steroid, or the reduction rates are less than 50% in pain degree during headache attacks, headache attack frequency, duration of each headache attack, and auxiliary analgesic drug dosage.

Table 1. Diagnostic criteria for cluster headache in the International Classification of Headache Disorders 3rd edition³

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4	Cluster Headache
5	A. At least five attacks fulfilling criteria B–D
6	B. Severe or very severe unilateral orbital, supraorbital and/or temporal pain
7	lasting 15–180 minutes (when untreated)
8	C. Either or both of the following:
9	1. at least one of the following symptoms or signs, ipsilateral to the
10	headache:
11	a. conjunctival injection and/or lacrimation; b. nasal congestion
12	and/or rhinorrhea; c. eyelid oedema; d. forehead and facial
13	sweating; e. miosis and/or ptosis
14	2. a sense of restlessness or agitation
15	D. Occurring with a frequency between one every other day and eight per day
16	E. Not better accounted for by another ICHD-3 diagnosis.
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23	Episodic Cluster Headache
24	
25	A. Attacks fulfilling criteria for Cluster headache and occurring in bouts
26	(cluster periods)
27	B. At least two cluster periods lasting from seven days to one year (when
28	untreated) and separated by pain-free remission periods of ≥ 3 months.
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32	Chronic cluster headache
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34	A. Attacks fulfilling criteria for Cluster headache, and criterion B below
35	B. Occurring without a remission period, or with remissions lasting < 3
36	months, for at least one year.
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Exclusion criteria include the following: (1) abnormalities in blood measurements, liver and kidney function, blood glucose, coagulation, electrocardiogram, and chest radiograph; (2) infection at the puncture site; (3) previous mental illness; (4) previous history of narcotic drug abuse; (5) preceding anticoagulant or antiplatelet therapy; (6) implantable pulse generator; (7) previous history of invasive treatments such as pterygopalatine ganglion radiofrequency thermocoagulation and chemical destruction; and (8) pregnant or breastfeeding patients.

Recruitment and informed consent

All enrolled patients will have the right to be informed of the purpose of the study, the experimental procedures, the participants' benefits, and possible risks, and then sign

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4 the informed consent. All patients will be given enough time to consider whether they
5 would like to participate in this study. Patients participating in the study will also have
6 the right to freely obtain more information at any time and can freely withdraw their
7 consent form or can withdraw from the study without restrictions at any stage.
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11 Once the patient signs the informed consent, the researchers will complete the
12 eligibility checklists based on the items listed on the case report form and record the
13 enrolment failure.
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16 **Interventions**

17 **Randomization and allocation concealment**

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19 All participants will be randomly divided into two groups in a 1:1 ratio. The researchers
20 will perform randomization in three centres. After confirming that the enrolled patient
21 satisfies the baseline inclusion/exclusion criteria, the patient will be randomly assigned
22 to one of the two study groups. The random sequence will be generated using SAS 9.1.3
23 (SAS Institute Inc., Cary, NC U.S.A.) software.
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26
27 Each research centre will have a research nurse who is responsible for implementing
28 the allocation. According to a pre-generated random sequence, each enrolled patient
29 will be given a sealed opaque random envelope based on the order of enrolment. After
30 puncturing the pterygopalatine ganglion during the procedure, the research nurse will
31 open the sealed envelope and assign the patient to the corresponding group according
32 to the random number in the envelope, and the corresponding treatment will be then
33 performed on the patient.
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36 **Blinding**

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38 This study is an open-label study. In this study, participants and doctors could not all
39 be blinded to the study. The telephone follow-up at different time points after procedure
40 will be conducted by responsible physicians, who will be blinded to the allocation status
41 of the patients. The data input will be completed by the data entry personnel, who are
42 not from the research team, and the data analysis will be completed by the statisticians
43 who are blinded to allocation information.
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46 **Study interventions**

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48 The patient will be in a supine position on a CT scan couch with the head turned to the
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4 contralateral side by approximately 50 degrees. Blood pressure, heart rate,
5 electrocardiogram, and pulse oximetry will be continuously monitored. The negative
6 plate of the PMG-230 pain treatment generator (Baylis Medical Inc., Montreal, Canada)
7 will be applied to the upper abdominal skin of the patient. Aseptic drapes will be
8 routinely applied to the patient's face. The puncture point will be located under the
9 zygomatic arch of the affected side, 3-4 cm in front of the tragus. After the
10 administration of 1% lidocaine for local anaesthesia, a trocar needle with a length of 10
11 cm, 21-gauge will be inserted vertically into the puncture point. With an approximate
12 depth of 4 cm, the trocar needle will reach the bone surface of the lateral pterygoid plate
13 of the sphenoid. The trocar needle will be then withdrawn by 2 cm and reinserted
14 towards the upper middle third of the pterygopalatine fossa until the tip of the needle
15 glides over the leading edge of the lateral pterygoid plate of the sphenoid. The needle
16 will be then inserted another 0.5 cm to enter the pterygopalatine fossa. We will use a
17 CT scanner (medical X-ray CT scanner, model SOMATOM, SIEMENS, Munich,
18 Germany) during the procedure to verify the position of the puncture needle in the
19 pterygopalatine fossa. The orientation and depth of the puncture needle will be adjusted
20 according to the CT image until the needle approaches the pterygopalatine ganglion.
21 The stylet will be removed, and the electrode needle for PRF treatment (PMF-21-100-
22 5, Baylis Medical Inc., Montreal, Canada) will be placed. The pain treatment generator
23 will be connected with the RF needle, and the sensory threshold will be measured with
24 50 Hz electrical stimulation. Induction of sensory abnormality of the nasal roots via
25 0.1-0.3 V will indicate accurate puncture, and the depth and direction of the puncture
26 needle will be appropriately adjusted according to the patient's response. When the
27 needle is in place, the patients will receive PRF or nerve block treatment according to
28 the random number in the envelope as follow.

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52 PRF treatment: The pulse treatment generator will be set to the pulsed radiofrequency
53 automatic mode, with a temperature of 42 °C, pulse frequency of 2 Hz, pulse width of
54 20 ms, and treatment duration of 360 s¹⁶.

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58 NB treatment: A mixture of 40 mg triamcinolone + 2 ml of 1% bupivacaine + 2 ml of
59 2% mepivacaine + 1:100000 epinephrine will be injected for nerve block treatment
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4 using a puncture needle^{17 18}.

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6 After the operation, the patients will be delivered to the outpatient recovery room and
7 they will be discharged if no adverse signs are noted within 2 hours. Verapamil,
8 topiramate, lithium or steroid will be discontinued if patients take these
9 medications prior to the procedure. The doctor will use rizatriptan to abort individual
10 attacks as needed. Participants will be treated with salvage therapy of other more
11 invasive therapies such as pterygopalatine ganglion ablation, electrical stimulation of
12 the pterygopalatine ganglion, and deep brain stimulation if the pain and the dosage of
13 auxiliary drugs have no difference from the preoperative level.
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21 **Patient and Public Involvement**

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23 Patients or public were not involved in the development of the research question, design
24 or outcome measures of this study. The study recruitment will be conducted by research
25 posters and physicians' presentations. Participants screening and enrollment will be
26 performed by medically trained physicians. The trial outcomes of this study will be
27 disseminated to all participants in newsletter on request. The burden of the intervention
28 is not assessed by patients themselves. All participants will be provided with the
29 detailed cost of the relevant intervention.
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36 **Variables and measurements**

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38 Prior to the intervention, the age, gender, the side of the headache (left or right),
39 previous duration of cluster periods, current numeric rating scale (NRS, 0 points for no
40 pain and 10 points for the most severe pain) score during headache attacks, headache
41 attack frequency, duration of each headache attack, dose of auxiliary analgesics, and
42 previous duration of remission period of the enrolled patients and a prospective
43 evaluation (with diary) of the patients will be recorded.
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50 The patients will be followed up by telephone at 1 day, 3 days, 1 week, 2 weeks, 1
51 month, 3 months, 6 months, and 1 year after procedure by responsible physicians who
52 are blinded to the allocation status of the patients. The primary outcome is the duration
53 of the cluster periods. The duration of the cluster period is defined as the total duration
54 of the headache, including the pain attack time before and after treatment. The
55 secondary outcomes include the degree of pain during headache attacks (NRS scores),
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4 headache attack frequency, duration of each headache attack, dose of auxiliary
5 analgesic drugs, duration of remission period, patient satisfaction scale (0 point for
6 unsatisfactory, and 10 points for very satisfied), effective rates, and intraoperative and
7 postoperative adverse events (AEs) will be compared between the two groups of
8 patients.
9

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12
13 Efficiency at each time point will be calculated. Both complete relief and partial relief
14 of pain will be considered to be effective, and the effectiveness rate will be calculated
15 as follows: effectiveness rate = number of effective patients / total number of patients
16 in this group \times 100%. Complete pain relief: NRS = 0, discontinued administration of
17 drugs. Partial relief of pain: postoperative pain levels during headache attacks,
18 headache attack frequency, duration of each headache attack, and auxiliary analgesic
19 drug dosage are less than 50% of the preoperative levels. No remission of pain: the pain
20 is not different from the preoperative level, or the degree of pain during headache
21 attacks, the frequency of headache attacks, the duration of each headache attack, and
22 the reduction in the use of adjuvant analgesics are still over 50% of the preoperative
23 levels. The partial pain remission time, complete pain remission time, number of
24 interventional treatments and treatment interval, and the number of cases receiving
25 electrical stimulation of the pterygopalatine ganglion will be recorded.
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The details of the AEs will be recorded during the procedure and at various time points
during the postoperative follow-up (1 day, 3 days, 1 week, 2 weeks, 1 month, 3 months,
6 months, and 1 year after procedure). For intraoperative AEs, the occurrences of
puncture pain, headache, dizziness, nausea, vomiting, facial haematoma, and others
will be recorded. For postoperative AEs, headache, dizziness, facial numbness, and
others will be also recorded.

Sample size

This study will adopt a one-sided superiority test, $\alpha = 0.025$, $\beta = 0.10$. After examining
the literature, combined with the authors' published articles and clinical experience¹⁶,
the duration of the cluster period of the PRF group is approximately 15.5 days, and the
standard deviation is 9.3 days, while the cluster duration of the NB group is
approximately 45 days, and the standard deviation is approximately 15 days.

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4 Shortening the duration of the cluster period by 20 days has clinical significance. The
5 number of cases needed in each group is 36, calculated by PASS 11. Considering the
6 10% loss rate, 40 cases are required in each group, and a total of 80 cases are required
7 for both groups.
8
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10 11 **Statistical analysis**

12
13 The SAS9.4 statistical analysis system will be used to analyse the data with the full
14 analysis set and the per-protocol set. The Shapiro-Wilk test will be used to check data
15 for normal distribution. Normally distributed data will be expressed as the means \pm
16 standard deviations. Parameters that do not meet the normal distribution will be
17 expressed as medians \pm quartiles. The t-test will be used for measurement data with
18 normal distributions, the rank sum test will be used for measurement data with non-
19 normal distributions, and the chi-square test will be used for count data. Efficacy
20 analysis will be conducted via both intention-to-treat (ITT) analysis and the per-
21 protocol analysis set in SAS. The t-test will be used to compare the measurement data
22 of efficacy outcome indicators between the RFP group and the NB group, such as
23 duration of cluster periods, pain degree during headache attacks, frequency of headache
24 attacks, the duration of each headache attack, the dose of auxiliary analgesics, duration
25 of remission period, and patient satisfaction. The chi-square test will be used to
26 compare the count data of efficacy outcome indicators between the PRF and NB groups.
27 The chi-square test or exact probability analysis will be used to evaluate intraoperative
28 and postoperative AEs.
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44 **DISCUSSION**

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46 The pterygopalatine ganglion is one of the four major parasympathetic ganglia of the
47 head and neck. It is the largest group of neurons within the calvarium outside of the
48 brain and is the only ganglion that enters the external environment through the nasal
49 mucosa¹⁹. The characteristic clinical symptoms of CH, such as tearing, runny nose,
50 nasal congestion, and nasal oedema, are manifestations of parasympathetic excitations
51 in the pterygopalatine ganglion, and ptosis and pupil diminution are manifestations of
52 sympathetic inhibition in the pterygopalatine ganglion. Therefore, the pathogenesis of
53 CH is considered to be related to the pterygopalatine ganglion²⁰.
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4 In recent years, there have been a series of reports on the treatment of CH via the
5 pterygopalatine ganglion. One type of pterygopalatine ganglion treatment is destructive,
6 which blocks pain signalling by denaturing pterygopalatine ganglion proteins, such as
7 radiofrequency ablation techniques^{21 22} and local injection of absolute alcohol^{23 24}. The
8 other type is non-destructive, such as nerve block^{10 20}, PRF¹⁶, and nerve electrical
9 stimulation^{13 25}.

10
11 Pterygopalatine ganglion nerve blocks include cotton swab nasal infiltration²⁶ and
12 needle injection^{17 18}. The puncture approach of the pterygopalatine ganglion includes
13 the sphenopalatine foramen approach²⁷, the supra-zygomatic approach²³, the
14 infrazygomatic crest approach²⁴, or the mandibular notch approach²⁸. Puncture can be
15 performed with the assistance of nasal endoscopy^{17 18}, fluoroscopy^{21 22}, or CT^{9 16}. The
16 commonly used nerve block drugs include local anaesthetics and steroid hormones, etc.
17 Previous reports on nerve block for the treatment of CH are mostly case series analyses
18 or case reports. Costa et al. conducted a randomized double-blinded placebo-controlled
19 study of patients with nitroglycerine-induced CH, and the patients were treated with 10%
20 cocaine, 10% lidocaine, or saline placebo²⁶. The results showed that short-term
21 treatment effects were significant in the cocaine and lidocaine groups, and there were
22 no related acute side effects. However, the main drawbacks of nerve block treatment
23 for CH are the limited effect of pain relief in a single treatment, the short duration of
24 treatment efficacy. Therefore, nerve block needs to be implemented repeatedly. The
25 puncture approach in our study will be the infrazygomatic crest approach²⁴, also known
26 as the translateral approach, and the injection will be a mixture of the steroid hormone
27 triamcinolone acetonide and local anaesthetics in the control group.

28
29 PRF is a minimally destructive, minimally invasive, and percutaneous interventional
30 pain management technique²⁹. Compared with radiofrequency ablation, the puncture
31 site and localization approach are consistent between the two. However, to treat the
32 pain, PRF regulates the nerve function through an electric field effect, while
33 radiofrequency ablation destroys the nerve through a thermal effect. Our previous study
34 found that after PRF treatment of 16 CH patients who had not responded to drug and
35 nerve block, 11 patients with ECH and 1 patient with CCH had complete remission,
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4 though treatments for 2 patients with ECH and 2 patients with CCH were not effective¹⁶.
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6 Bendersky et al. also reported that PRF treatment failed to achieve satisfactory pain
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8 relief in 3 patients with CCH³⁰. Therefore, it is currently believed that PRF treatment
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10 may be more effective for ECH than CCH. However, the incidence of CCH is low, and
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12 the number of CCH cases is small, and the existing study are not sufficient to reach a
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14 convincing conclusion.

15
16 CT images are clear and intuitive, providing the clinician with a more accurate guidance
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18 for puncture. The CT-guided pterygopalatine ganglion puncture technique was first
19
20 applied in clinical practice by Kastler et al²⁴. It was confirmed that puncture
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22 complications can be reduced, and the puncture success rate and treatment satisfaction
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24 can be improved with CT guidance. In the past, we have reported that the success rate
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26 of the puncture was 100% for CH patients with CT-guided pterygopalatine ganglion
27
28 puncture and PRF treatment, and surgery-related complications, such as nosebleeds and
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30 cheek haematomas, were successfully avoided¹⁶. In this study, both the NB and the PRF
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32 groups will undergo CT-guided pterygopalatine ganglion puncture to ensure the
33
34 accuracy of the puncture and to avoid the effects of inaccurate puncture on the outcome.
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36 Minimizing the scope of CT scans for example just performing a scan of the
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38 pterygopalatine fossa during the procedure by experienced physician puncture will be
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40 a way to reduce the dose of radiation exposure.

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42 This study will compare the efficacy of pterygopalatine ganglion nerve block and PRF
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44 in the treatment of CH in a multicentre, prospective, randomized, controlled, and
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46 blinded-endpoint study, and will provide reliable evidence for treatment strategies for
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48 patients with CH who are not responding to conservative drug treatment. Of course, the
49
50 limitations of this study including that the participants in this study and the doctors who
51
52 conducted the interventions will be not kept blinded to the trial. In order to obtain
53
54 greater scientific value, double-blind researches need to be carried out in the future.
55
56 Other limitations include the follow-up period of this study will be only 1 year, and the
57
58 lack of exploration of optimal parameters for PRF treatment of CH, which will be
59
60 investigated through in-depth clinical research later. Furthermore, the variability of the
duration of the episodes of patients with CH makes it difficult to establish the response

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4 pattern.

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Author's contributions

JL and HR contributed equally to this work and should be considered co-first authors.

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4 JL and HR wrote the protocol and this manuscript. FL is the principal investigator of
5 the whole study. FL BW and DW are the site principal investigator of each research
6 centre. FL JL and HR contributed to the conception and design of the research protocol.
7
8 All authors approved the final version to be published.
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13 **Acknowledgements**

14
15 Funding: This work will be supported by the Beijing Municipal Administration of
16 Hospitals Clinical Medicine Development of Special Funding Support (grant No.
17 XMLX201707) and the Foundation for the Excellent Medical Staff of Beijing (grant
18 No. 2014-3-035).
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22 **Competing interests** None declared.
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26 Figure 1

27 Flow diagram of the study.
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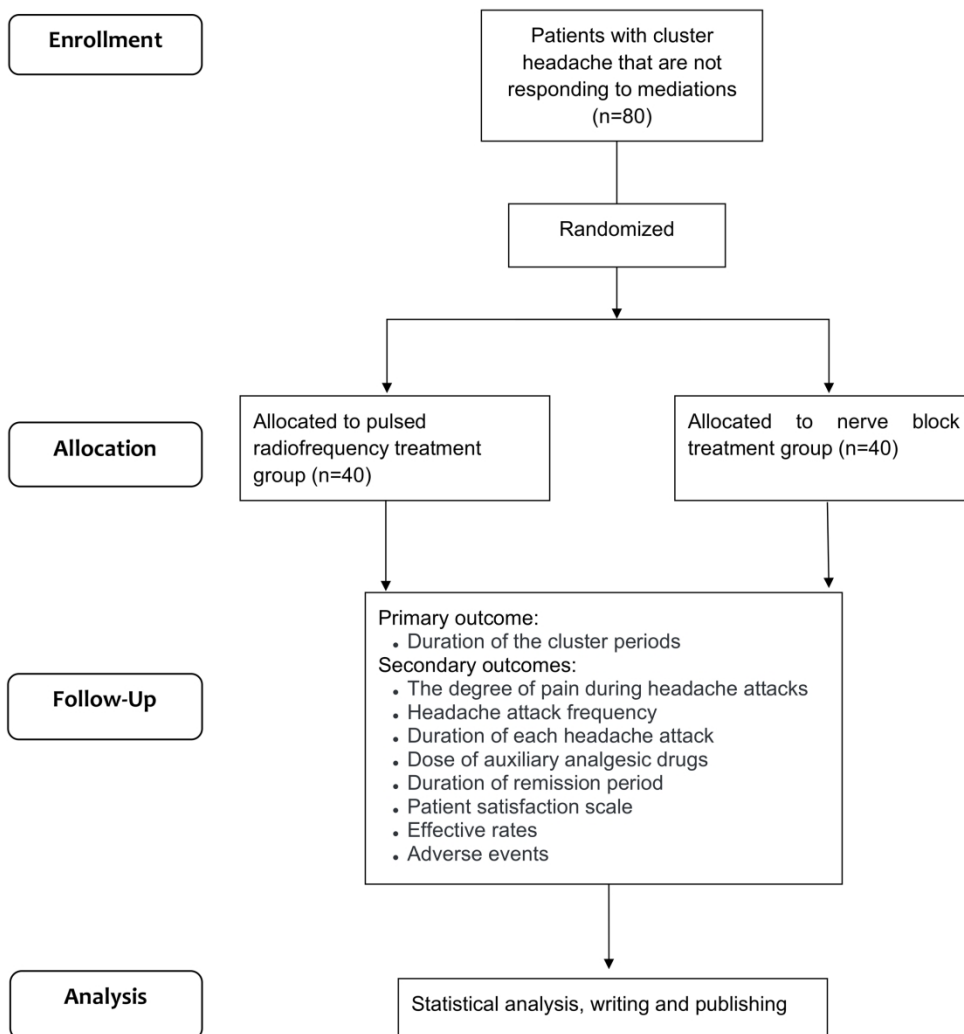


Figure 1/Flow diagram of the study.

206x218mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

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		Reporting Item	Page Number
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	5
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	5
Protocol version	#3	Date and version identifier	5
Funding	#4	Sources and types of financial, material, and other support	14
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	14
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	5

1	sponsor contact			
2	information			
3				
4	Roles and	#5c	Role of study sponsor and funders, if any, in study design;	5
5	responsibilities:		collection, management, analysis, and interpretation of	
6	sponsor and funder		data; writing of the report; and the decision to submit the	
7			report for publication, including whether they will have	
8			ultimate authority over any of these activities	
9				
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12	Roles and	#5d	Composition, roles, and responsibilities of the coordinating	5
13	responsibilities:		centre, steering committee, endpoint adjudication	
14	committees		committee, data management team, and other individuals or	
15			groups overseeing the trial, if applicable (see Item 21a for	
16			data monitoring committee)	
17				
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19				
20	Background and	#6a	Description of research question and justification for	3-4
21	rationale		undertaking the trial, including summary of relevant studies	
22			(published and unpublished) examining benefits and harms	
23			for each intervention	
24				
25				
26				
27	Background and	#6b	Explanation for choice of comparators	3
28	rationale: choice of			
29	comparators			
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32	Objectives	#7	Specific objectives or hypotheses	4
33				
34				
35	Trial design	#8	Description of trial design including type of trial (eg, parallel	4
36			group, crossover, factorial, single group), allocation ratio,	
37			and framework (eg, superiority, equivalence, non-inferiority,	
38			exploratory)	
39				
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42	Study setting	#9	Description of study settings (eg, community clinic,	4
43			academic hospital) and list of countries where data will be	
44			collected. Reference to where list of study sites can be	
45			obtained	
46				
47				
48	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable,	5
49			eligibility criteria for study centres and individuals who will	
50			perform the interventions (eg, surgeons, psychotherapists)	
51				
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54	Interventions:	#11a	Interventions for each group with sufficient detail to allow	6-8
55	description		replication, including how and when they will be	
56			administered	
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1	Interventions:	#11b	Criteria for discontinuing or modifying allocated	7-8
2	modifications		interventions for a given trial participant (eg, drug dose	
3			change in response to harms, participant request, or	
4			improving / worsening disease)	
5				
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7				
8	Interventions:	#11c	Strategies to improve adherence to intervention protocols,	7-8
9	adherence		and any procedures for monitoring adherence (eg, drug	
10			tablet return; laboratory tests)	
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13	Interventions:	#11d	Relevant concomitant care and interventions that are	7-8
14	concomitant care		permitted or prohibited during the trial	
15				
16				
17	Outcomes	#12	Primary, secondary, and other outcomes, including the	8-9
18			specific measurement variable (eg, systolic blood pressure),	
19			analysis metric (eg, change from baseline, final value, time	
20			to event), method of aggregation (eg, median, proportion),	
21			and time point for each outcome. Explanation of the clinical	
22			relevance of chosen efficacy and harm outcomes is strongly	
23			recommended	
24				
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26				
27				
28	Participant timeline	#13	Time schedule of enrolment, interventions (including any	8
29			run-ins and washouts), assessments, and visits for	
30			participants. A schematic diagram is highly recommended	
31			(see Figure)	
32				
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34				
35	Sample size	#14	Estimated number of participants needed to achieve study	9
36			objectives and how it was determined, including clinical and	
37			statistical assumptions supporting any sample size	
38			calculations	
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41				
42	Recruitment	#15	Strategies for achieving adequate participant enrolment to	6
43			reach target sample size	
44				
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46	Allocation: sequence	#16a	Method of generating the allocation sequence (eg,	6
47	generation		computer-generated random numbers), and list of any	
48			factors for stratification. To reduce predictability of a random	
49			sequence, details of any planned restriction (eg, blocking)	
50			should be provided in a separate document that is	
51			unavailable to those who enrol participants or assign	
52			interventions	
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57	Allocation	#16b	Mechanism of implementing the allocation sequence (eg,	6
58	concealment		central telephone; sequentially numbered, opaque, sealed	
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60				

1	mechanism		envelopes), describing any steps to conceal the sequence until interventions are assigned	
2				
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4	Allocation:	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
5	implementation			
6				
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9	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
10				
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14	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6
15	emergency			
16	unblinding			
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19				
20	Data collection plan	#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	8-9
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31	Data collection plan:	#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	8-9
32	retention			
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38	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	8-9
39				
40				
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45				
46	Statistics: outcomes	#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	9-10
47				
48				
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51	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9-10
52	analyses			
53				
54				
55	Statistics: analysis	#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)	9-10
56	population and			
57	missing data			
58				
59				

1	Data monitoring:	#21a	Composition of data monitoring committee (DMC); summary	8-9
2	formal committee		of its role and reporting structure; statement of whether it is	
3			independent from the sponsor and competing interests; and	
4			reference to where further details about its charter can be	
5			found, if not in the protocol. Alternatively, an explanation of	
6			why a DMC is not needed	
7				
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10				
11	Data monitoring:	#21b	Description of any interim analyses and stopping guidelines,	8-9
12	interim analysis		including who will have access to these interim results and	
13			make the final decision to terminate the trial	
14				
15				
16	Harms	#22	Plans for collecting, assessing, reporting, and managing	9
17			solicited and spontaneously reported adverse events and	
18			other unintended effects of trial interventions or trial conduct	
19				
20				
21	Auditing	#23	Frequency and procedures for auditing trial conduct, if any,	8-9
22			and whether the process will be independent from	
23			investigators and the sponsor	
24				
25				
26				
27	Research ethics	#24	Plans for seeking research ethics committee / institutional	5
28	approval		review board (REC / IRB) approval	
29				
30				
31	Protocol	#25	Plans for communicating important protocol modifications	n/a
32	amendments		(eg, changes to eligibility criteria, outcomes, analyses) to	
33			relevant parties (eg, investigators, REC / IRBs, trial	
34			participants, trial registries, journals, regulators)	
35				
36				
37	Consent or assent	#26a	Who will obtain informed consent or assent from potential	5-6
38			trial participants or authorised surrogates, and how (see	
39			Item 32)	
40				
41				
42				
43	Consent or assent:	#26b	Additional consent provisions for collection and use of	5-6
44	ancillary studies		participant data and biological specimens in ancillary	
45			studies, if applicable	
46				
47				
48	Confidentiality	#27	How personal information about potential and enrolled	5-6
49			participants will be collected, shared, and maintained in	
50			order to protect confidentiality before, during, and after the	
51			trial	
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55	Declaration of	#28	Financial and other competing interests for principal	14
56	interests		investigators for the overall trial and each study site	
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59	Data access	#29	Statement of who will have access to the final trial dataset,	5-6
60				

		and disclosure of contractual agreements that limit such access for investigators	
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4	Ancillary and post	#30 Provisions, if any, for ancillary and post-trial care, and for	5-6
5	trial care	compensation to those who suffer harm from trial	
6		participation	
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9	Dissemination policy:	#31a Plans for investigators and sponsor to communicate trial	5
10	trial results	results to participants, healthcare professionals, the public,	
11		and other relevant groups (eg, via publication, reporting in	
12		results databases, or other data sharing arrangements),	
13		including any publication restrictions	
14			
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16			
17	Dissemination policy:	#31b Authorship eligibility guidelines and any intended use of	14
18	authorship	professional writers	
19			
20			
21	Dissemination policy:	#31c Plans, if any, for granting public access to the full protocol,	5
22	reproducible	participant-level dataset, and statistical code	
23	research		
24			
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26			
27	Informed consent	#32 Model consent form and other related documentation given	5-6
28	materials	to participants and authorised surrogates	
29			
30			
31	Biological specimens	#33 Plans for collection, laboratory evaluation, and storage of	n/a
32		biological specimens for genetic or molecular analysis in the	
33		current trial and for future use in ancillary studies, if	
34		applicable	
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BMJ Open

Multicentre, prospective, randomized, controlled, blinded-endpoint study to evaluate the efficacy and safety of pterygopalatine ganglion pulsed radiofrequency treatment for cluster headache: study protocol

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-026608.R3
Article Type:	Protocol
Date Submitted by the Author:	21-Jan-2019
Complete List of Authors:	Li, Jin; Beijing Tiantan Hospital, Capital Medical University, Department of Anesthesiology and Pain Management Ren, Hao; Beijing Tiantan Hospital, Capital Medical University, Department of Anesthesiology and Pain Management Wang, Baoguo; Beijing Sanbo Brian Hospital, Capital Medical University, Department of Anesthesiology Wu, Dasheng; Jilin Province People's Hospital, Department of Pain Management Luo, Fang; Beijing Tiantan Hospital, Capital Medical University, Department of Pain Management
Primary Subject Heading:	Anaesthesia
Secondary Subject Heading:	Anaesthesia
Keywords:	Cluster headache, Pulsed radiofrequency, Randomized controlled trial, Protocol

SCHOLARONE™
Manuscripts

Title:

Multicentre, prospective, randomized, controlled, blinded-endpoint study to evaluate the efficacy and safety of pterygopalatine ganglion pulsed radiofrequency treatment for cluster headache: study protocol

Authors:

Jin Li, M.D., Department of Anesthesiology and Pain Management, Beijing Tiantan Hospital, Capital Medical University, Beijing, China.

Hao Ren, M.D., Department of Anesthesiology and Pain Management, Beijing Tiantan Hospital, Capital Medical University, Beijing, China.

Baoguo Wang, M.D., Department of Anesthesiology, Beijing Sanbo Brian Hospital, Capital Medical University, Beijing, China.

Dasheng Wu, M.D., Department of Pain Management, Jilin Province People's Hospital, Changchun, China.

Fang Luo, M.D., Department of Pain Management, Beijing Tiantan Hospital, Capital Medical University, Beijing, China.

Corresponding author contact details:

Fang Luo, M.D., Professor,

Department of Pain Management, Beijing Tiantan Hospital, Capital Medical University, Beijing 100050, China.

Phone: (86) 010 67096664.

Fax: (86) 010 67050177.

E-mail: luofangwt@yahoo.com.

Key words:

Cluster headache, Pulsed radiofrequency, Randomized controlled trial, Protocol

Word count :3836

ABSTRACT

Introduction Single-centre reports on small groups of patients have shown that pterygopalatine ganglion pulsed radiofrequency treatment in patients with refractory cluster headache (CH) can quickly relieve pain without significant side effects. However, a randomized controlled trial is still necessary to evaluate whether pterygopalatine ganglion pulsed radiofrequency (PRF) treatment is a viable treatment option for patients with CH who are not responding to drug treatment.

Methods and analysis This investigation is a multicentre, prospective, randomized, controlled, blinded-endpoint study. We will enrol 80 patients with CH who are not responding to medication. The enrolled patients will be randomly divided into two groups: the nerve block (NB) group and the PRF group. All patients will undergo computed tomography (CT)-guided pterygopalatine ganglion puncture. A mixture containing steroids and local anaesthetics will be slowly injected into the patients in the NB group. The patients in the PRF group will be treated with PRF at 42 °C for 360 s. After treatment, the duration of cluster periods; degree of pain during headache attacks; frequency of headache attacks; duration of each headache attack; dose of auxiliary analgesic drugs; duration of remission; degree of patient satisfaction; effectiveness rates at 1 day, 3 days, 1 week, 2 weeks, 1 month, 3 months, 6 months, and 1 year after the procedure; and intraoperative and postoperative adverse events (AEs) will be compared between the two groups.

Ethics and dissemination This study was approved by the institutional ethics committee (Approval Number: KY 2018-027-02). The results of the study will be published in peer-reviewed journals, and the findings will be presented at scientific meetings.

Trial registration number NCT03567590; pre-results.

Strengths and limitations of this study

This multicentre, prospective, randomized, controlled, blinded-endpoint study will be the first investigation to compare the efficacy of pulsed radiofrequency to that of nerve block with local anaesthetic plus corticosteroids for cluster headache patients.

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4 The randomized controlled trial design minimizes the risk of confounding bias.

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6 The participants in this study and the doctors who conduct the interventions will not be
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8 blinded to the treatment procedure.

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10 The follow-up will be performed by telephone instead of hospital visits; telephone
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12 follow-up is sufficient to assess the primary outcome.
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For peer review only

INTRODUCTION

Cluster headache (CH), a primary headache characterized by severe pain, has a considerable impact on quality of life. CH attacks are very painful, and the patients can even become suicidal. Therefore, CH is also known as "suicidal headache"^{1 2}. Severe unilateral pain occurs in the orbital, frontal, and temporal areas during CH attacks and can last 15 minutes to 3 hours, accompanied by ipsilateral oculofacial autonomic symptoms. CH includes two categories: episodic cluster headache (ECH) and chronic cluster headache (CCH). ECH can involve several attacks in a day, and an attack period of 2 weeks to 3 months is called a "cluster period", which is followed by a pain-free "remission period" of ≥ 3 months³. During the cluster period, headaches often recur every day at a fixed time. Generally, CCH attacks occur less frequently than ECH attacks on a daily basis and have no remission period.

Since the pathogenesis of CH remains unclear, there is a dearth of targeted aetiological treatment⁴. It is currently believed that the pathogenesis of CH may involve the trigeminovascular system and the activation of the parasympathetic system and ipsilateral hypothalamic grey matter^{4 5}. The pterygopalatine ganglion, also known as the sphenopalatine ganglion (SPG) or ganglion pterygopalatinum, plays a very important role in the pathophysiology of CH⁶.

The clinical treatment of CH is still extremely difficult. For patients who do not respond to drug therapy, a pterygopalatine ganglion block via the application of local anaesthetics and steroid hormones has a certain degree of effectiveness⁷. Generally, a single pterygopalatine ganglion block is not sufficient to achieve satisfactory results; therefore, several such blocks are required, which increases the risk of puncture and steroid-hormone-related side effects. In addition, multiple punctures also increase medical costs. For intractable CH that does not respond to conservative treatment, deep brain stimulation⁸, pterygopalatine ganglion ablation⁹, and pterygopalatine ganglion electrical stimulation¹⁰⁻¹³ can provide relief in some patients. Research has shown that tonic stimulation of the pterygopalatine ganglion has preventive effects^{10 13}. However, the abovementioned methods all have problems, such as trauma caused by surgery, serious side effects, and high medical costs. Therefore, there is an urgent need for

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4 exploring new minimally invasive, safe, and effective technologies for the treatment of
5 CH in clinical practice.

6
7 The technique of percutaneous pulsed radiofrequency (PRF) is a minimally destructive
8 pain-treatment technology¹⁴. In contrast to radiofrequency thermocoagulation, PRF
9 uses the following parameters: pulse frequency of 2 Hz, output voltage of 45 V, output
10 frequency of 500 kHz, continuous current action of 20 ms, intermittent time of 480 ms,
11 and treatment temperature not exceeding 42 °C. This intervention technology does not
12 cause local tissue damage, and there are few side effects.

13
14 In 2011, Chua et al. first reported the use of pterygopalatine ganglion PRF treatment in
15 3 patients with CH, of whom 2 patients had complete remission of pain, 1 patient had
16 partial remission of pain, and all patients were free of neurological side effects and
17 complications after treatment¹⁵. In 2016, we reported computed tomography (CT)-
18 guided pterygopalatine ganglion PRF treatment in 16 patients with CH who had not
19 responded to drugs and nerve block (NB); we found that pterygopalatine ganglion PRF
20 could quickly, safely and effectively relieve the patients from their cluster headache
21 periods¹⁶. However, to verify whether early intervention via PRF is a viable treatment
22 option for patients with CH who are not responding to drug therapy, we still need to
23 obtain strong evidence through a properly designed randomized controlled trial.
24 Therefore, this study proposes a multicentre, prospective, randomized, controlled,
25 blinded-endpoint study to compare the pain-relief effects of CT-guided PRF and nerve
26 block of the pterygopalatine ganglion for CH patients who are not responding to drug
27 treatment. Study outcomes at different timepoints will be assessed with standardized
28 forms and procedures by responsible physicians blinded to the treatment allocation
29 (blinded endpoint).

30 **METHODS**

31 **Trial design**

32 This investigation is a multicentre, prospective, randomized, controlled, blinded-
33 endpoint study. CH patients who are not responding to drug therapy will receive either
34 CT-guided percutaneous puncture pterygopalatine ganglion NB or PRF, and efficacy
35 and safety will be compared between the two groups of patients (Figure 1).
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Setting

Patients will be selected from three research centres: Beijing Tiantan Hospital, Beijing Sanbo Brain Hospital, Jilin Province People's Hospital. All researchers will be trained based on the same training protocol and required to have more than 1 year of clinical experience with each treatment method prior to participating in the study.

Ethics, trial registration and dissemination

This clinical study follows the relevant regulations of the Declaration of Helsinki (version 19 October 2013) of the World Medical Association. The research protocol (protocol version 1.0) has been approved by the Ethics Committee of the Beijing Tiantan Hospital (Approval Number: KY 2018-027-02). All patients will sign an informed consent at a screening visit. Before patient enrolment, the study design was registered at clinicaltrials.gov (NCT03567590). This study, which has begun on July 5, 2018, will last for 3 years. The results of the study will be published in peer-reviewed journals, and the findings will be presented at scientific meetings.

Participants

Suitable participants will be screened at the pain management centre of each hospital to participate in the study.

The inclusion criteria comprise the following: (1) the diagnosis of CH is confirmed according to the diagnostic criteria of the International Classification of Headache Disorders 3rd edition (ICHD-3)³ (Table 1); (2) the patient's age is between 18 and 60 years; (3) the patient seeks treatment in the pain clinics of hospitals participating in the study within 5 days of the onset of the cluster period; the patient's pain condition remains the same after preventive therapy with drugs available in our hospital such as verapamil, topiramate, lithium or steroids, or there is a reduction of less than 50% in the intensity and frequency of headache attacks, the duration of each attack, and the dosage of auxiliary analgesic drugs used.

Table 1. Diagnostic criteria for cluster headache in the International Classification of Headache Disorders 3rd edition³

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4	Cluster Headache
5	A. At least five attacks fulfilling criteria B–D
6	B. Severe or very severe unilateral orbital, supraorbital and/or temporal pain
7	lasting 15–180 minutes (when untreated)
8	C. Either or both of the following:
9	1. at least one of the following symptoms or signs, ipsilateral to the
10	headache:
11	a. conjunctival injection and/or lacrimation; b. nasal congestion
12	and/or rhinorrhoea; c. eyelid oedema; d. forehead and facial
13	sweating; e. miosis and/or ptosis
14	2. a sense of restlessness or agitation
15	D. Occurring with a frequency between one every other day and eight per day
16	E. Not better accounted for by another ICHD-3 diagnosis
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23	Episodic Cluster Headache
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25	A. Attacks fulfilling criteria for cluster headache and occurring in bouts
26	(cluster periods)
27	B. At least two cluster periods lasting from seven days to one year (when
28	untreated) and separated by pain-free remission periods of ≥ 3 months
29	
30	
31	
32	Chronic Cluster Headache
33	
34	A. Attacks fulfilling criteria for cluster headache and criterion B below
35	B. Occurring without a remission period, or with remissions lasting < 3
36	months, for at least one year
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41 The exclusion criteria include the following: (1) abnormalities in blood measurements,

42 liver and kidney function, blood glucose, coagulation, electrocardiography, or chest

43 radiography; (2) infection at the puncture site; (3) previous mental illness; (4) previous

44 history of narcotic drug abuse; (5) prior anticoagulant or antiplatelet therapy; (6) an

45 implantable pulse generator; (7) previous history of invasive treatments such as

46 pterygopalatine ganglion radiofrequency thermocoagulation and chemical destruction;

47 and (8) current pregnancy or breastfeeding.

48 **Recruitment and informed consent**

49 All enrolled patients will have the right to be informed of the purpose of the study, the

50 experimental procedures, the benefits to the participants, and the possible risks, after

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4 which they will sign the informed consent. All patients will be given enough time to
5 consider whether they would like to participate in this study. Patients participating in
6 the study will also have the right to freely obtain more information at any time and will
7 be allowed to freely withdraw their consent form or withdraw from the study without
8 restrictions at any stage.
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13 Once each patient signs the informed consent, the researchers will complete the
14 eligibility checklists based on the items listed on the case report form; records will be
15 made of any candidates who fail to enrol.
16
17

18 **Interventions**

19 **Randomization and allocation concealment**

20
21 All participants will be randomly divided into two groups in a 1:1 ratio. The researchers
22 will apply randomization at each of the three centres. After each enrolled patient is
23 confirmed to satisfy the baseline inclusion and exclusion criteria, the patient will be
24 randomly assigned to one of the two study groups. The random sequence will be
25 generated using SAS 9.1.3 (SAS Institute Inc., Cary, NC, U.S.A.) software.
26
27

28 Each research centre will have a research nurse responsible for implementing the
29 allocation. According to a pre-generated random sequence, each enrolled patient will
30 be given a sealed opaque envelope based on the order of enrolment. After the
31 pterygopalatine ganglion is punctured during the procedure, the research nurse will
32 open the sealed envelope and assign the patient to the corresponding group according
33 to the random number in the envelope, and the corresponding treatment will then be
34 performed on the patient.
35
36

37 **Blinding**

38 This study has an open-label design. In this investigation, participants and doctors could
39 not all be blinded to the study conditions. However, the telephone follow-ups at
40 different time points after the procedure will be conducted by responsible physicians
41 blinded to the allocation status of the patients. The data input will be completed by data-
42 entry personnel who are not on the research team, and the data analysis will be
43 completed by statisticians blinded to the allocation information.
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46 **Study interventions**

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4 The patient will be in a supine position on a CT scanner couch with the head turned
5 approximately 50 degrees to the contralateral side. Blood pressure, heart rate,
6 electrocardiography, and pulse oximetry will be continuously monitored. The negative
7 plate of the PMG-230 pain-treatment generator (Baylis Medical Inc., Montreal, Canada)
8 will be applied to the upper abdominal skin of the patient. Aseptic drapes will be applied
9 to the patient's face in a routine manner. The puncture point will be located under the
10 zygomatic arch of the affected side, 3-4 cm in front of the tragus. After the
11 administration of 1% lidocaine for local anaesthesia, a 21-gauge trocar needle with a
12 length of 10 cm will be inserted vertically into the puncture point. At an approximate
13 depth of 4 cm, the trocar needle will reach the bone surface of the lateral pterygoid plate
14 of the sphenoid. The trocar needle will be then withdrawn by 2 cm and reinserted
15 towards the upper part of the middle third of the pterygopalatine fossa until the tip of
16 the needle glides over the leading edge of the lateral pterygoid plate of the sphenoid.
17 The needle will then be inserted another 0.5 cm to enter the pterygopalatine fossa. We
18 will use a CT scanner (medical X-ray CT scanner, model SOMATOM, SIEMENS,
19 Munich, Germany) during the procedure to verify the position of the puncture needle
20 in the pterygopalatine fossa. The orientation and depth of the puncture needle will be
21 adjusted according to the CT image until the needle approaches the pterygopalatine
22 ganglion. The stylet will be removed, and the electrode needle for PRF treatment (PMF-
23 21-100-5, Baylis Medical Inc., Montreal, Canada) will be placed. The pain-treatment
24 generator will be connected to the radiofrequency needle, and the sensory threshold
25 will be measured with 50-Hz electrical stimulation. Induction of sensory abnormality
26 at the root of the nose by a stimulus of 0.1-0.3 V will indicate accurate puncture, and
27 the depth and direction of the puncture needle will be appropriately adjusted according
28 to the patient's response. When the needle is in place, the patients will receive PRF or
29 NB treatment according to the random number in the envelope. The treatments will be
30 as follows.

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PRF treatment: The pulse treatment generator will be set to the automatic pulsed radiofrequency mode, with a temperature of 42 °C, pulse frequency of 2 Hz, pulse width of 20 ms, and treatment duration of 360 s¹⁶.

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4 NB treatment: A mixture of 40 mg of triamcinolone + 2 ml of 1% bupivacaine + 2 ml
5 of 2% mepivacaine + 1:100,000 epinephrine will be injected for nerve-block treatment
6 using a puncture needle^{17 18}.

7
8
9 After the operation, the patients will be delivered to the outpatient recovery room, and
10 they will be discharged if no adverse signs are noted within 2 hours. Verapamil,
11 topiramate, lithium or steroid administration will be discontinued if patients take
12 these medications prior to the procedure. The doctor will use rizatriptan to abort
13 individual attacks as needed. Participants will be treated with salvage therapy using
14 other, more invasive therapies such as pterygopalatine ganglion ablation, electrical
15 stimulation of the pterygopalatine ganglion, and deep brain stimulation if the pain and
16 the necessary dosage of auxiliary drugs do not differ from their preoperative levels.

24 25 **Patient and public involvement**

26
27 Neither the patients nor members of the public were involved in the development of the
28 research question, design or outcome measures of this study. The study recruitment will
29 be conducted through research posters and physicians' presentations. Participant
30 screening and enrolment will be performed by trained physicians. The trial outcomes
31 of this study will be disseminated to all participants in a newsletter on request. The
32 burden of the intervention will not be assessed by patients themselves. All participants
33 will be informed in detail of the cost of the relevant intervention.

39 40 41 **Variables and measurements**

42
43 Prior to the intervention, the age, gender, headache lateralization (left or right), previous
44 duration of cluster periods, current numeric rating scale (NRS, from 0 points for no pain
45 to 10 points for the most severe pain) score during headache attacks, frequency of
46 headache attacks, duration of each headache attack, dose of auxiliary analgesics, and
47 previous duration of remission of the enrolled patients will be recorded, and a
48 prospective evaluation will be conducted by having the patients keep diaries.

49
50 The patients will be followed up by telephone at 1 day, 3 days, 1 week, 2 weeks, 1
51 month, 3 months, 6 months, and 1 year after the procedure by responsible physicians
52 who are blinded to the allocation status of the patients. The primary outcome is the
53 duration of the cluster periods. The duration of a cluster period is defined as the total
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4 duration of the headache, including the pain experienced before and after treatment.
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6 The secondary outcomes, which include the degree of pain during headache attacks
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8 (NRS scores), the frequency of headache attacks, the duration of each headache attack,
9
10 the dose of auxiliary analgesic drugs taken, the duration of remission, self-rated patient
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12 satisfaction (from 0 point for unsatisfied to 10 points for very satisfied), the
13
14 effectiveness rate of treatment, and intraoperative and postoperative adverse events
15
16 (AEs), will also be compared between the two groups of patients.

17
18 The effectiveness of the treatments at each time point will be calculated. Effectiveness
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20 will be defined as either complete or partial relief of pain, and the rate will be calculated
21
22 as follows: effectiveness rate = number of effectively treated patients / total number of
23
24 patients in this group $\times 100\%$. Complete pain relief will be defined as NRS = 0 and
25
26 discontinued administration of drugs. Partial pain relief will be defined as a
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28 postoperative reduction of more than 50% in the intensity, frequency, and duration of
29
30 headache attacks as well as auxiliary analgesic drug dosage. No remission of pain will
31
32 be defined as no change from the preoperative level of pain or as the postoperative
33
34 intensity, frequency, and duration of headache attacks as well as auxiliary analgesic
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36 drug dosage remaining over 50% of the preoperative levels. The partial pain remission
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38 time, complete pain remission time, number of interventional treatments, treatment
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40 intervals, and number of cases receiving electrical stimulation of the pterygopalatine
41
42 ganglion will be recorded.

43
44 Details regarding the AEs will be recorded during the procedure and at various time
45
46 points during the postoperative follow-up period (1 day, 3 days, 1 week, 2 weeks, 1
47
48 month, 3 months, 6 months, and 1 year after the procedure). For intraoperative AEs,
49
50 the occurrence of puncture pain, headache, dizziness, nausea, vomiting, facial
51
52 haematoma, and other effects will be recorded. For postoperative AEs, headache,
53
54 dizziness, facial numbness, and other effects will also be recorded.

54 **Sample size**

55
56 This study will apply a one-sided superiority test with $\alpha = 0.025$ and $\beta = 0.10$. Based
57
58 on a review of the literature, combined with the authors' published articles and clinical
59
60 experience¹⁶, the duration of the cluster period of the PRF group is approximately 15.5

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4 days, and the standard deviation is 9.3 days, while the cluster duration of the NB group
5 is approximately 45 days, with a standard deviation of approximately 15 days.
6 Shortening the duration of the cluster period by 20 days has clinical significance. The
7 number of cases needed in each group is 36 as calculated by PASS 11. Allowing for a
8 10% rate of loss to follow-up, 40 cases are required in each group, and a total of 80
9 cases are required for both groups together.
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15 **Statistical analysis**

16
17 The statistical analysis software SAS 9.4 will be used to analyse both the full data set
18 and the per-protocol set. The Shapiro-Wilk test will be used to test whether the data
19 follow the normal distribution. Normally distributed data will be expressed as the
20 means \pm standard deviations. Parameters that do not follow the normal distribution will
21 be expressed as medians \pm quartiles. Student's t-test will be used for measurement data
22 with normal distributions, the Wilcoxon rank sum test will be used for measurement
23 data with non-normal distributions, and the chi-squared test will be used for count data.
24 Effectiveness will be analysed via both intention-to-treat (ITT) analysis and the per-
25 protocol analysis set in SAS. Student's t-test will be used to compare measurement data
26 on the outcome indicators, such as duration of cluster periods, degree of during
27 headache attacks, frequency of headache attacks, duration per headache attack, dose of
28 auxiliary analgesics, duration of remission, and patient satisfaction, between the PRF
29 group and the NB group. The chi-squared test will be used to compare the count data
30 of efficacy outcome indicators between the PRF and NB groups. The chi-squared test
31 or Fisher's exact test will be used to evaluate intraoperative and postoperative AEs.
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46 **DISCUSSION**

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48 The pterygopalatine ganglion is one of the four major parasympathetic ganglia of the
49 head and neck. This ganglion is the largest group of neurons within the calvarium
50 outside the brain and is the only ganglion that enters the external environment through
51 the nasal mucosa¹⁹. The characteristic clinical symptoms of CH, such as tearing, runny
52 nose, nasal congestion, and nasal oedema, are manifestations of parasympathetic
53 excitation in the pterygopalatine ganglion, and ptosis and pupil diminution are
54 manifestations of sympathetic inhibition in the pterygopalatine ganglion. Therefore, the
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4 pathogenesis of CH is considered to be related to the pterygopalatine ganglion²⁰.

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6 In recent years, there have been a series of reports on the treatment of CH via the
7
8 pterygopalatine ganglion. One type of pterygopalatine ganglion treatment is destructive
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10 treatment, which blocks pain signalling by denaturing pterygopalatine ganglion
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12 proteins; treatments of this type include radiofrequency ablation techniques^{21 22} and
13
14 local injection of absolute alcohol^{23 24}. The other type is minimally destructive
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16 treatment, such as NB^{10 20}, PRF¹⁶, and electrical nerve stimulation^{13 25}.

17
18 Methods of pterygopalatine ganglion NB include cotton-swab nasal infiltration²⁶ and
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20 needle injection^{17 18}. Puncture approaches to the pterygopalatine ganglion include the
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22 sphenopalatine foramen approach²⁷, the suprazygomatic approach²³, the
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24 infrazygomatic crest approach²⁴, and the mandibular notch approach²⁸. Puncture can be
25
26 performed with the assistance of nasal endoscopy^{17 18}, fluoroscopy^{21 22}, or CT^{9 16}. The
27
28 commonly used NB drugs include local anaesthetics and steroid hormones. The
29
30 previous reports on NB for the treatment of CH are mostly case-series analyses and
31
32 case reports. Costa et al. conducted a randomized double-blind placebo-controlled
33
34 study of patients with nitroglycerine-induced CH; the patients were treated with 10%
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36 cocaine, 10% lidocaine, or a saline placebo²⁶. The results showed that short-term
37
38 treatment effects were significant in the cocaine and lidocaine groups, and there were
39
40 no related acute side effects. However, NB treatment for CH has certain drawbacks, the
41
42 most important of which are the limited effect of pain relief in a single treatment and
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44 the short duration of treatment efficacy. Therefore, NB needs to be implemented
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46 repeatedly. The puncture approach in our study will be the infrazygomatic crest
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48 approach²⁴, also known as the translateral approach, and the injection will be a mixture
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50 of the steroid hormone triamcinolone acetonide and local anaesthetics in the control
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52 group.

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54 PRF is a minimally destructive, minimally invasive, percutaneous interventional pain
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56 management technique²⁹. This procedure uses the same puncture site and localization
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58 approach as radiofrequency ablation. However, to treat the pain, PRF regulates the
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60 nerve function through an electric field, while radiofrequency ablation destroys the
nerve by thermal damage. Our previous study found that after PRF treatment of 16 CH

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4 patients who had not responded to drugs or NB, 11 patients with ECH and 1 patient
5 with CCH had complete remission, although treatment was ineffective for 2 patients
6 with ECH and 2 patients with CCH¹⁶. Bendersky et al. also reported that PRF treatment
7 failed to achieve satisfactory pain relief in 3 patients with CCH³⁰. Therefore, it is
8 currently believed that PRF treatment may be more effective for ECH than for CCH.
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13 However, given the low incidence of CCH and the small number of established cases,
14 the existing studies are not sufficient to reach a convincing conclusion.
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18 CT images are clear and intuitive, providing the clinician with accurate guidance for
19 puncturing the surgical site. The CT-guided pterygopalatine ganglion puncture
20 technique was first applied in clinical practice by Kastler et al.²⁴. CT guidance was
21 confirmed to reduce puncture complications and increase both the puncture success rate
22 and treatment satisfaction. In the past, we have reported a 100% success rate of puncture
23 for CH patients undergoing CT-guided pterygopalatine ganglion puncture and PRF
24 treatment, and surgery-related complications, such as nosebleeds and cheek
25 haematomas, were successfully avoided¹⁶. In the proposed study, both the NB and PRF
26 groups will undergo CT-guided pterygopalatine ganglion puncture to ensure the
27 accuracy of the puncture and to avoid the effects of inaccurate puncture on the outcome.
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29 During the procedure, the dose of radiation exposure will be controlled by minimizing
30 the scope of CT scans, for example, scanning only the pterygopalatine fossa as
31 needed by the experienced physician performing the puncture.
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43 This study will compare the effectiveness of pterygopalatine ganglion NB and PRF for
44 the treatment of CH in a multicentre, prospective, randomized, controlled, blinded-
45 endpoint study; the results are expected to provide reliable evidence regarding
46 treatment strategies for patients with CH who are not responding to conservative drug
47 treatment. Of course, this study has some limitations; for example, the participants in
48 the trial and the doctors who conduct the interventions will be not kept blinded to the
49 treatment allocations. Double-blind studies need to be carried out in the future to
50 achieve results of greater scientific value. Other limitations include the short follow-up
51 period of only 1 year and the lack of exploration of optimal parameters for PRF
52 treatment of CH, which will be investigated through in-depth clinical research later.
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4 Furthermore, the variability in the duration of episodes in patients with CH makes it
5 difficult to discern the response pattern.
6

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Author's contributions

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4 JL and HR contributed equally to this work and should be considered co-first authors.
5
6 JL and HR wrote the protocol and this manuscript. FL is the principal investigator of
7
8 the whole study. FL BW and DW are the site principal investigator of each research
9
10 centre. FL JL and HR contributed to the conception and design of the research protocol.
11
12 All authors approved the final version to be published.
13
14

15 **Acknowledgements**

16
17 Funding: This work will be supported by the Beijing Municipal Administration of
18
19 Hospitals Clinical Medicine Development of Special Funding Support (grant No.
20
21 XMLX201707) and the Foundation for the Excellent Medical Staff of Beijing (grant
22
23 No. 2014-3-035).
24

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27 **Competing interests** None declared.
28

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31 Figure 1

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Flow diagram of the study.

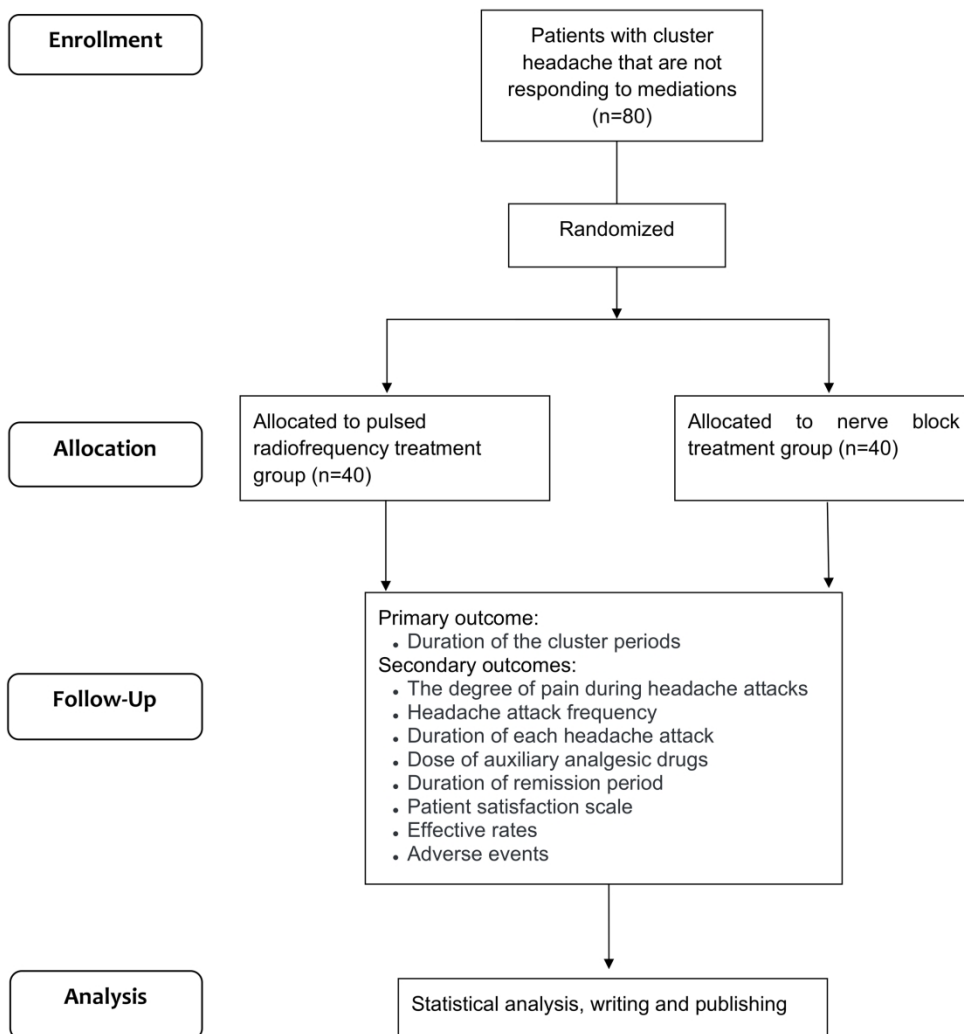


Figure 1/Flow diagram of the study.

206x218mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, Hróbjartsson A, Mann H, Dickersin K, Berlin J, Doré C, Parulekar W, Summerskill W, Groves T, Schulz K, Sox H, Rockhold FW, Rennie D, Moher D. SPIRIT 2013 Statement: Defining standard protocol items for clinical trials. *Ann Intern Med.* 2013;158(3):200-207

		Reporting Item	Page Number
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	5
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	5
Protocol version	#3	Date and version identifier	5
Funding	#4	Sources and types of financial, material, and other support	14
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	14
Roles and responsibilities:	#5b	Name and contact information for the trial sponsor	5

1	sponsor contact			
2	information			
3				
4	Roles and	#5c	Role of study sponsor and funders, if any, in study design;	5
5	responsibilities:		collection, management, analysis, and interpretation of	
6	sponsor and funder		data; writing of the report; and the decision to submit the	
7			report for publication, including whether they will have	
8			ultimate authority over any of these activities	
9				
10				
11				
12	Roles and	#5d	Composition, roles, and responsibilities of the coordinating	5
13	responsibilities:		centre, steering committee, endpoint adjudication	
14	committees		committee, data management team, and other individuals or	
15			groups overseeing the trial, if applicable (see Item 21a for	
16			data monitoring committee)	
17				
18				
19				
20	Background and	#6a	Description of research question and justification for	3-4
21	rationale		undertaking the trial, including summary of relevant studies	
22			(published and unpublished) examining benefits and harms	
23			for each intervention	
24				
25				
26				
27	Background and	#6b	Explanation for choice of comparators	3
28	rationale: choice of			
29	comparators			
30				
31				
32	Objectives	#7	Specific objectives or hypotheses	4
33				
34				
35	Trial design	#8	Description of trial design including type of trial (eg, parallel	4
36			group, crossover, factorial, single group), allocation ratio,	
37			and framework (eg, superiority, equivalence, non-inferiority,	
38			exploratory)	
39				
40				
41				
42	Study setting	#9	Description of study settings (eg, community clinic,	4
43			academic hospital) and list of countries where data will be	
44			collected. Reference to where list of study sites can be	
45			obtained	
46				
47				
48	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable,	5
49			eligibility criteria for study centres and individuals who will	
50			perform the interventions (eg, surgeons, psychotherapists)	
51				
52				
53				
54	Interventions:	#11a	Interventions for each group with sufficient detail to allow	6-8
55	description		replication, including how and when they will be	
56			administered	
57				
58				
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60				

1	Interventions:	#11b	Criteria for discontinuing or modifying allocated	7-8
2	modifications		interventions for a given trial participant (eg, drug dose	
3			change in response to harms, participant request, or	
4			improving / worsening disease)	
5				
6				
7	Interventions:	#11c	Strategies to improve adherence to intervention protocols,	7-8
8	adherence		and any procedures for monitoring adherence (eg, drug	
9			tablet return; laboratory tests)	
10				
11				
12				
13	Interventions:	#11d	Relevant concomitant care and interventions that are	7-8
14	concomitant care		permitted or prohibited during the trial	
15				
16				
17	Outcomes	#12	Primary, secondary, and other outcomes, including the	8-9
18			specific measurement variable (eg, systolic blood pressure),	
19			analysis metric (eg, change from baseline, final value, time	
20			to event), method of aggregation (eg, median, proportion),	
21			and time point for each outcome. Explanation of the clinical	
22			relevance of chosen efficacy and harm outcomes is strongly	
23			recommended	
24				
25				
26				
27				
28	Participant timeline	#13	Time schedule of enrolment, interventions (including any	8
29			run-ins and washouts), assessments, and visits for	
30			participants. A schematic diagram is highly recommended	
31			(see Figure)	
32				
33				
34				
35	Sample size	#14	Estimated number of participants needed to achieve study	9
36			objectives and how it was determined, including clinical and	
37			statistical assumptions supporting any sample size	
38			calculations	
39				
40				
41				
42	Recruitment	#15	Strategies for achieving adequate participant enrolment to	6
43			reach target sample size	
44				
45				
46	Allocation: sequence	#16a	Method of generating the allocation sequence (eg,	6
47	generation		computer-generated random numbers), and list of any	
48			factors for stratification. To reduce predictability of a random	
49			sequence, details of any planned restriction (eg, blocking)	
50			should be provided in a separate document that is	
51			unavailable to those who enrol participants or assign	
52			interventions	
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57	Allocation	#16b	Mechanism of implementing the allocation sequence (eg,	6
58	concealment		central telephone; sequentially numbered, opaque, sealed	
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60				

1	mechanism		envelopes), describing any steps to conceal the sequence until interventions are assigned	
2				
3				
4	Allocation:	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
5	implementation			
6				
7				
8				
9	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
10				
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14	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6
15	emergency			
16	unblinding			
17				
18				
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20	Data collection plan	#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	8-9
21				
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31	Data collection plan:	#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	8-9
32	retention			
33				
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38	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	8-9
39				
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46	Statistics: outcomes	#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	9-10
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51	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9-10
52	analyses			
53				
54				
55	Statistics: analysis	#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)	9-10
56	population and			
57	missing data			
58				
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1	Data monitoring:	#21a	Composition of data monitoring committee (DMC); summary	8-9
2	formal committee		of its role and reporting structure; statement of whether it is	
3			independent from the sponsor and competing interests; and	
4			reference to where further details about its charter can be	
5			found, if not in the protocol. Alternatively, an explanation of	
6			why a DMC is not needed	
7				
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11	Data monitoring:	#21b	Description of any interim analyses and stopping guidelines,	8-9
12	interim analysis		including who will have access to these interim results and	
13			make the final decision to terminate the trial	
14				
15				
16	Harms	#22	Plans for collecting, assessing, reporting, and managing	9
17			solicited and spontaneously reported adverse events and	
18			other unintended effects of trial interventions or trial conduct	
19				
20				
21	Auditing	#23	Frequency and procedures for auditing trial conduct, if any,	8-9
22			and whether the process will be independent from	
23			investigators and the sponsor	
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27	Research ethics	#24	Plans for seeking research ethics committee / institutional	5
28	approval		review board (REC / IRB) approval	
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31	Protocol	#25	Plans for communicating important protocol modifications	n/a
32	amendments		(eg, changes to eligibility criteria, outcomes, analyses) to	
33			relevant parties (eg, investigators, REC / IRBs, trial	
34			participants, trial registries, journals, regulators)	
35				
36				
37	Consent or assent	#26a	Who will obtain informed consent or assent from potential	5-6
38			trial participants or authorised surrogates, and how (see	
39			Item 32)	
40				
41				
42				
43	Consent or assent:	#26b	Additional consent provisions for collection and use of	5-6
44	ancillary studies		participant data and biological specimens in ancillary	
45			studies, if applicable	
46				
47				
48	Confidentiality	#27	How personal information about potential and enrolled	5-6
49			participants will be collected, shared, and maintained in	
50			order to protect confidentiality before, during, and after the	
51			trial	
52				
53				
54				
55	Declaration of	#28	Financial and other competing interests for principal	14
56	interests		investigators for the overall trial and each study site	
57				
58				
59	Data access	#29	Statement of who will have access to the final trial dataset,	5-6
60				

		and disclosure of contractual agreements that limit such access for investigators	
1			
2			
3			
4	Ancillary and post	#30 Provisions, if any, for ancillary and post-trial care, and for	5-6
5	trial care	compensation to those who suffer harm from trial	
6		participation	
7			
8			
9	Dissemination policy:	#31a Plans for investigators and sponsor to communicate trial	5
10	trial results	results to participants, healthcare professionals, the public,	
11		and other relevant groups (eg, via publication, reporting in	
12		results databases, or other data sharing arrangements),	
13		including any publication restrictions	
14			
15			
16			
17	Dissemination policy:	#31b Authorship eligibility guidelines and any intended use of	14
18	authorship	professional writers	
19			
20			
21	Dissemination policy:	#31c Plans, if any, for granting public access to the full protocol,	5
22	reproducible	participant-level dataset, and statistical code	
23	research		
24			
25			
26			
27	Informed consent	#32 Model consent form and other related documentation given	5-6
28	materials	to participants and authorised surrogates	
29			
30			
31	Biological specimens	#33 Plans for collection, laboratory evaluation, and storage of	n/a
32		biological specimens for genetic or molecular analysis in the	
33		current trial and for future use in ancillary studies, if	
34		applicable	
35			
36			

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