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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

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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 ℃ 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

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.

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 months[3]. 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 treatment[4]. 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 CH[6].

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 effect[7]. 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 stimulation[8], SPG ablation[9], and SPG electrical stimulation[10-12] can relieve CH in some patients. Research has shown that high frequency stimulation of the SPG has preventive effects[6]. 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.

The percutaneous pulsed radiofrequency (PRF) technique is a non-destructive pain treatment technology[13]. 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 SPG 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 treatment[14]. In 2016, we reported the computed tomography (CT) -guided SPG PRF treatment in 13 patients with ECH who had not responded to drugs and nerve block, and found that SPG PRF could quickly, safely and effectively relieve the patients from their cluster periods[15]. 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 with nerve block as the control condition. Therefore, this study proposes a multicentre, prospective, randomized, controlled, blinded-endpoint study to compare the pain relief effects of CT-guided PRF and traditional nerve blockade of SPG for the treatment of ECH patients who are not responding to drug treatment.

METHODS

Trial design

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

Setting

Patients are selected from three research centres: XXX Hospital, XXX Hospital, XXX Hospital. All researchers were trained based on the same training protocol. All researchers are 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) 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 clinicaltrails.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

All enrolled patients 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 should be given enough time to consider whether they would like to participate in this study. Patients participating in the study 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.

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

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

PRF group: The pulse treatment generator is set to the pulsed radiofrequency automatic mode, with a temperature of 42 °C, pulse frequency of 2 Hz, pulse width of 20 ms, and treatment duration of 360 s[15].

NB group: A mixture of 40 mg triamcinolone + 2 ml of 1% bupivacaine + 2 ml of 2% mepivacaine + 1:100000 epinephrine is injected for nerve block treatment using a puncture needle[16 17].

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

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 are recorded.

The patients are 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 trained research assistants 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) are compared between the two groups of patients.

Efficiency at each time point will be calculated. Both complete relief and partial relief of pain are considered to be effective, and the effectiveness rate is calculated as follows: effectiveness rate = number of effective patients / total number of patients in this group × 100%. Complete pain relief: NRS = 0, discontinued administration of drugs. Partial relief of pain: postoperative pain levels during headache attacks, headache attack frequency, duration of each headache attack, and auxiliary analgesic

drug dosage are less than 50% of the preoperative levels. No remission of pain: the pain is no different from the preoperative level, or the degree of pain during headache attacks, the frequency of headache attacks, the duration of each headache attack, and the reduction in the use of adjuvant analgesics are still over 50% of the preoperative levels. The partial pain remission time, complete pain remission time, number of interventional treatments and treatment interval, and the number of cases receiving electrical stimulation of the SPG are recorded.

The details of the AEs are recorded during the surgery 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 surgery). For intraoperative AEs, the occurrences of puncture pain, headache, dizziness, nausea, vomiting, facial haematoma, and others are recorded. For postoperative AEs, headache, dizziness, facial numbness, and others are also recorded.

Sample size

This study adopts a one-sided superiority test, $\alpha = 0.025$, $\beta = 0.10$. After examining the literature, combined with the authors' published articles and clinical experience[15], 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. Shortening the duration of the cluster period by 20 days has clinical significance. The number of cases needed in each group is 36, calculated by PASS 11. Considering the 10% loss rate, 40 cases are required in each group, and a total of 80 cases are required for both groups.

Statistical analysis

The SAS9.4 statistical analysis system is used to analyse the data with the full analysis set and the per-protocol set. The Shapiro-Wilk test is used to check data for normal distribution. Normally distributed data are expressed as the means ± standard deviations. Parameters that do not meet the normal distribution are expressed as medians ± quartiles. The t-test is used for measurement data with normal distributions, the rank sum test is used for measurement data with non-normal distributions, and the

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 mucosa[18]. 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 SPG[19].

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], PRF[15], and nerve electrical stimulation[24 25].

SPG nerve blocks include cotton swab nasal infiltration[26] and needle injection[16 17]. The puncture approach of the SPG includes the sphenopalatine foramen approach[27], the supra-zygomatic approach[22], the infrazygomatic crest approach[23], or the mandibular notch approach[28]. 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

nitroglycerine-induced CH, and the patients were treated with 10% cocaine, 10% lidocaine, or saline placebo[26]. 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 is the infrazygomatic crest approach[23], also known as the translateral approach, and the injection is a mixture of the steroid hormone triamcinolone acetonide and local anaesthetics in the control group.

PRF is a non-destructive, minimally invasive, and percutaneous interventional pain management technique[29]. 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 effective[15]. Bendersky et al. also reported that PRF treatment failed to achieve satisfactory pain relief in 3 patients with CCH[30]. 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 convincing conclusion.

CT images are clear and intuitive, providing the clinician with a more accurate guidance for puncture. The CT-guided SPG puncture technique was first applied in clinical practice by Kastler et al[23]. It was confirmed that puncture complications can be reduced, and the puncture success rate and treatment satisfaction can be improved with CT guidance. In the past, we have reported that the success rate of the puncture was 100% for CH patients with CT-guided SPG puncture and PRF treatment, and surgery-related complications, such as nosebleeds and cheek haematomas, were successfully avoided[15]. In this study, both the NB and the PRF groups undergo

CT-guided SPG puncture to ensure the accuracy of the puncture and to avoid the effects of inaccurate puncture on the outcome.

This study compares the efficacy of SPG nerve block and PRF in the treatment of ECH in a multicentre, prospective, randomized, controlled, and blinded-endpoint study, explores whether PRF can replace nerve block as a minimally invasive and safe treatment option, and provides reliable evidence for treatment strategies for patients with ECH who are not responding to conservative drug treatment. Of course, the limitations of this study including that the participants in this study and the doctors who conducted the interventions are not kept blinded to the trial, the follow-up period of this study is only 1 year, and the lack of exploration of optimal parameters for PRF treatment of ECH, which will be investigated through in-depth clinical research in the future.

REFERENCES

1. Rozen TD, Fishman RS. Cluster Headache in the United States of America: Demographics, Clinical Characteristics, Triggers, Suicidality, and Personal Burden*. *Headache: The Journal of Head and Face Pain* 2012;52(1):99-113. doi: 10.1111/j.1526-4610.2011.02028.x

2. Weaver-Agostoni J. Cluster headache. *Am Fam Physician* 2013;88(2):122-8.

3. (IHS) HCCotIHS. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. *Cephalalgia* 2018;38(1):1-211. doi: 10.1177/0333102417738202

4. Hoffmann J, May A. Diagnosis, pathophysiology, and management of cluster headache. *The Lancet Neurology* 2018;17(1):75-83. doi: 10.1016/S1474-4422(17)30405-2

5. May A, Bahra A, Büchel C, et al. Hypothalamic activation in cluster headache attacks. *The Lancet* 1998;352(9124):275-78. doi: 10.1016/S0140-6736(98)02470-2

6. Schytz HW, Barløse M, Guo S, et al. Experimental activation of the sphenopalatine ganglion provokes cluster-like attacks in humans. *Cephalalgia* 2013;33(10):831-41. doi: 10.1177/0333102413476370

7. Penarrocha-Diago M, Boronat A, Penarrocha-Oltra D, et al. Clinical course of patients with episodic cluster headache treated with corticosteroids inproximity to the sphenopalatine ganglion: a preliminary study of 23 patients. *Med Oral Patol Oral Cir Bucal* 2012;17(3):e477-82.

8. Lepper A, Frese A, Summ O, et al. Hypothalamic dopaminergic stimulation in cluster headache. *Cephalalgia* 2013;33(14):1155-9. doi: 10.1177/0333102413487445

9. Loomba V, Upadhyay A, Kaveeshvar H. Radiofrequency Ablation of the Sphenopalatine Ganglion Using Cone Beam Computed Tomography for Intractable Cluster Headache. *Pain Physician* 2016;19(7):E1093-6.

10. Meng DW, Zhang JG, Zheng Z, et al. Chronic Bilateral Sphenopalatine Ganglion Stimulation for Intractable Bilateral Chronic Cluster Headache: A Case Report. *Pain Physician* 2016;19(4):E637-42.

11. Kohlmeier C, Behrens P, Boger A, et al. Improved surgical procedure using intraoperative navigation for the implantation of the SPG microstimulator in patients with chronic cluster headache. *Int J Comput Assist Radiol Surg* 2017;12(12):2119-28. doi: 10.1007/s11548-016-1512-2

12. Barloese MC, Jurgens TP, May A, et al. Cluster headache attack remission with sphenopalatine ganglion stimulation: experiences in chronic cluster headache patients through 24 months. *J Headache Pain* 2016;17(1):67. doi: 10.1186/s10194-016-0658-1

13. Sluijter ME. Non-thermal radiofrequency procedures in the treatment of spinal pain. Pain in Europe; 2nd Annual Congress of the European Federation of IASP Chapters. Barcelona, 1997:326.

14. Chua NH, Vissers KC, Wilder-Smith OH. Quantitative sensory testing may predict response to sphenopalatine ganglion pulsed radiofrequency treatment in cluster headaches: a case series. *Pain Pract* 2011;11(5):439-45. doi: 10.1111/j.1533-2500.2010.00445.x

15. Fang L, Jingjing L, Ying S, et al. Computerized tomography-guided sphenopalatine ganglion pulsed radiofrequency treatment in 16 patients with refractory cluster headaches: Twelve- to 30-month follow-up evaluations. *Cephalalgia* 2016;36(2):106-12. doi: 10.1177/0333102415580113

16. Felisati G, Arnone F, Lozza P, et al. Sphenopalatine endoscopic ganglion block: a revision of a traditional technique for cluster headache. *Laryngoscope* 2006;116(8):1447-50. doi: 10.1097/01.mlg.0000227997.48020.44

17. Pipolo C, Bussone G, Leone M, et al. Sphenopalatine endoscopic ganglion block in cluster headache: a reevaluation of the procedure after 5 years. *Neurol Sci* 2010;31 Suppl 1:S197-9. doi: 10.1007/s10072-010-0325-2

18. Ho KWD, Przkora R, Kumar S. Sphenopalatine ganglion: block, radiofrequency ablation and neurostimulation-a systematic review. *The journal of headache and pain* 2017;18(1):118. doi: 10.1186/s10194-017-0826-y

19. Piagkou M, Demesticha T, Troupis T, et al. The pterygopalatine ganglion and its role in various pain syndromes: from anatomy to clinical practice. *Pain Pract*

2012;12(5):399-412. doi: 10.1111/j.1533-2500.2011.00507.x

20. Narouze S, Kapural L, Casanova J, et al. Sphenopalatine ganglion radiofrequency ablation for the management of chronic cluster headache. *Headache* 2009;49(4):571-7. doi: 10.1111/j.1526-4610.2008.01226.x

21. Oomen KP, van Wijck AJ, Hordijk GJ, et al. Effects of radiofrequency thermocoagulation of the sphenopalatine ganglion on headache and facial pain: correlation with diagnosis. *J Orofac Pain* 2012;26(1):59-64.

22. Devoghel JC. Cluster headache and sphenopalatine block. *Acta Anaesthesiol Belg* 1981;32(1):101-7.

23. Kastler A, Cadel G, Comte A, et al. Alcohol percutaneous neurolysis of the sphenopalatine ganglion in the management of refractory cranio-facial pain. *Neuroradiology* 2014;56(7):589-96. doi: 10.1007/s00234-014-1354-y

24. Schoenen J, Jensen RH, Lanteri-Minet M, et al. Stimulation of the sphenopalatine ganglion (SPG) for cluster headache treatment. Pathway CH-1: a randomized, sham-controlled study. *Cephalalgia* 2013;33(10):816-30. doi: 10.1177/0333102412473667

25. Jurgens TP, Barloese M, May A, et al. Long-term effectiveness of sphenopalatine ganglion stimulation for cluster headache. *Cephalalgia* 2017;37(5):423-34. doi: 10.1177/0333102416649092

26. Costa A, Pucci E, Antonaci F, et al. The effect of intranasal cocaine and lidocaine on nitroglycerin-induced attacks in cluster headache. *Cephalalgia* 2000;20(2):85-91. doi: 10.1046/j.1468-2982.2000.00026.x

27. Barre F. Cocaine as an abortive agent in cluster headache. *Headache* 1982;22(2):69-73.

28. Zarembinski C, Graff-Radford S. An unusual challenge in performing sphenopalatine ganglion block with enlarged coronoid process: Jacob's disease. *Pain Med* 2014;15(2):329-32. doi: 10.1111/pme.12302

29. Vanneste T, Van Lantschoot A, Van Boxem K, et al. Pulsed radiofrequency in chronic pain. *Curr Opin Anaesthesiol* 2017;30(5):577-82. doi: 10.1097/aco.0000000000000502

30. Bendersky DC, Hem SM, Yampolsky CG. Unsuccessful pulsed radiofrequency of the sphenopalatine ganglion in patients with chronic cluster headache and subsequent successful thermocoagulation. *Pain Pract* 2015;15(5):E40-5. doi: 10.1111/papr.12288

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.

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Competing interests None declared.

Figure 1

Flow diagram of the study.

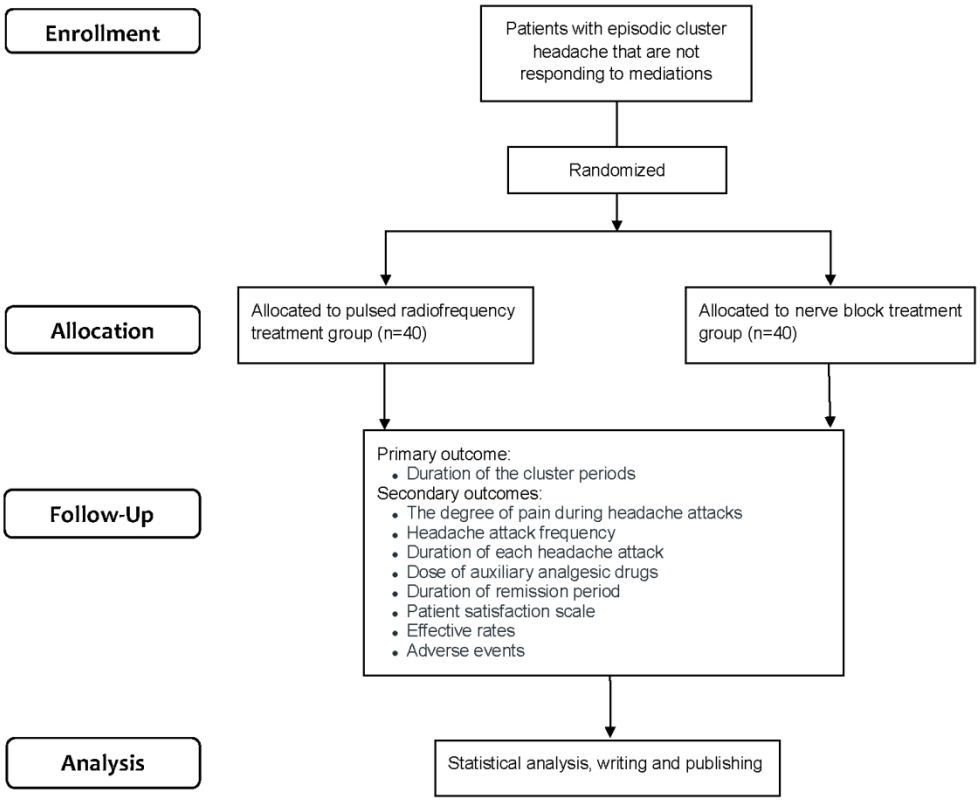

Figure 1/Flow diagram of the study.

205x169mm (192 x 191 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

sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	5
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	5
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3
Objectives	#7	Specific objectives or hypotheses	4
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-8

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

mechanism		envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6
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
Data collection plan: retention	#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
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
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
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9-10
Statistics: analysis population and missing data	#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

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

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

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

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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

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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 mediations. 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

the purpose of providing an additional treatment option for ECHs.

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

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

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 months[3]. 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 treatment[4]. 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 CH[6].

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 effect[7]. 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 stimulation[8], pterygopalatine ganglion ablation[9], and pterygopalatine ganglion electrical stimulation[10-13] 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 technology[14]. 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 treatment[15]. 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 periods[16]. 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 clinicaltrails.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 edition[3]

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.

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

Each research centre will have a research nurse who is responsible for implementing the allocation. According to a pre-generated random sequence, each enrolled patient will be given a sealed opaque random envelope based on the order of enrolment. After puncturing the pterygopalatine ganglion during the surgery, the research nurse will open the sealed envelope and assign the patient to the corresponding group according to the random number in the envelope, and the corresponding treatment will be 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 will be conducted by responsible physicians, who will be blinded to the allocation status of the patients. The data input will be completed by the data entry personnel, who are not from the research team, and the data analysis will be completed by the statisticians who are blinded to allocation information.

Study interventions

The patient will be in a supine position on a CT scan couch with their head turned to the contralateral side by approximately 50 degrees. Blood pressure, heart rate, electrocardiogram, and pulse oximetry will be continuously monitored. The negative plate of the PMG-230 pain treatment generator (Baylis Medical Inc., Montreal, Canada) will be applied to the upper abdominal skin of the patient. Aseptic drapes will be

routinely applied to the patient's face. The puncture point will be located under the zygomatic arch of the affected side, 3-4 cm in front of the tragus. After the administration of 1% lidocaine for local anaesthesia, a trocar needle with a length of 10 cm, 21-gauge will be inserted vertically into the puncture point. With an approximate depth of 4 cm, the trocar needle will reach the bone surface of the lateral pterygoid plate of the sphenoid. The trocar needle will be then withdrawn by 2 cm and reinserted towards the upper middle third of the pterygopalatine fossa until the tip of the needle glides over the leading edge of the lateral pterygoid plate of the sphenoid. The needle will be then inserted another 0.5 cm to enter the pterygopalatine fossa. We will use a CT scanner (medical X-ray CT scanner, model SOMATOM, SIEMENS, Munich, Germany) during the procedure to verify the position of the puncture needle in the pterygopalatine fossa. The orientation and depth of the puncture needle will be adjusted according to the CT image until the needle approaches the pterygopalatine ganglion. The stylet will be removed, and the electrode needle for PRF treatment (PMF-21-100-5, Baylis Medical Inc., Montreal, Canada) will be placed. The pain treatment generator will be connected with the RF needle, and the sensory threshold will be measured with 50 Hz electrical stimulation. Induction of sensory abnormality of the nasal roots via 0.1-0.3 V will indicate accurate puncture, and the depth and direction of the puncture needle will be appropriately adjusted according to the patient's response. When the needle is in place, the patients will receive PRF or nerve block treatment according to the random number in the envelope as follow.

PRF treatment: The pulse treatment generator will be set to the pulsed radiofrequency automatic mode, with a temperature of 42 °C, pulse frequency of 2 Hz, pulse width of 20 ms, and treatment duration of 360 s[16].

NB treatment: A mixture of 40 mg triamcinolone + 2 ml of 1% bupivacaine + 2 ml of 2% mepivacaine + 1:100000 epinephrine will be injected for nerve block treatment using a puncture needle[17 18].

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

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.

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

The details of the AEs will be recorded during the surgery 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 surgery). 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 experience[16], 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. Shortening the duration of the cluster period by 20 days has clinical significance. The number of cases needed in each group is 36, calculated by PASS 11. Considering the 10% loss rate, 40 cases are required in each group, and a total of 80 cases are required for both groups.

Statistical analysis

The SAS9.4 statistical analysis system will be used to analyse the data with the full analysis set and the per-protocol set. The Shapiro-Wilk test will be used to check data for normal distribution. Normally distributed data will be expressed as the means ± standard deviations. Parameters that do not meet the normal distribution will be expressed as medians ± quartiles. The t-test will be used for measurement data with normal distributions, the rank sum test will be used for measurement data with non-normal distributions, and the chi-square test will be used for count data. Efficacy analysis will be conducted via both intention-to-treat (ITT) analysis and the per-protocol analysis set in SAS. The t-test will be 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 will be used to compare the count data of efficacy outcome indicators between the PRF and NB groups. The chi-square test or exact probability analysis will be used to evaluate intraoperative and postoperative AEs.

DISCUSSION

The pterygopalatine ganglion 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 mucosa[19]. The characteristic clinical symptoms of CH, such as tearing, runny nose, nasal congestion, and nasal oedema, are manifestations of parasympathetic excitations in the pterygopalatine ganglion, and ptosis and pupil diminution are manifestations of sympathetic inhibition in the pterygopalatine ganglion. Therefore, the pathogenesis of CH is considered to be related to the pterygopalatine ganglion[20].

In recent years, there have been a series of reports on the treatment of CH via the pterygopalatine ganglion. One type of pterygopalatine ganglion treatment is destructive, which blocks pain signalling by denaturing pterygopalatine ganglion proteins, such as radiofrequency ablation techniques[21 22] and local injection of absolute alcohol[23 24]. The other type is non-destructive, such as nerve block[10 20], PRF[16], and nerve electrical

stimulation[13 25].

Pterygopalatine ganglion nerve blocks include cotton swab nasal infiltration[26] and needle injection[17 18]. The puncture approach of the pterygopalatine ganglion includes the sphenopalatine foramen approach[27], the supra-zygomatic approach[23], the infrazygomatic crest approach[24], or the mandibular notch approach[28]. 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 placebo[26]. 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 approach[24], 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 technique[29]. 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 effective[16]. Bendersky et al. also reported that PRF treatment failed to achieve satisfactory pain relief in 3 patients with CCH[30]. 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

convincing conclusion.

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

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

REFERENCES

1. Rozen TD, Fishman RS. Cluster Headache in the United States of America: Demographics, Clinical Characteristics, Triggers, Suicidality, and Personal Burden*. *Headache: The*

Journal of Head and Face Pain 2012;52(1):99-113. doi: 10.1111/j.1526-4610.2011.02028.x

2. Weaver-Agostoni J. Cluster headache. *Am Fam Physician* 2013;88(2):122-8.

3. (IHS) HCCotIHS. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. *Cephalalgia* 2018;38(1):1-211. doi: 10.1177/0333102417738202

4. Hoffmann J, May A. Diagnosis, pathophysiology, and management of cluster headache. *The Lancet Neurology* 2018;17(1):75-83. doi: 10.1016/S1474-4422(17)30405-2

5. May A, Bahra A, Büchel C, et al. Hypothalamic activation in cluster headache attacks. *The Lancet* 1998;352(9124):275-78. doi: 10.1016/S0140-6736(98)02470-2

6. Schytz HW, Barløse M, Guo S, et al. Experimental activation of the sphenopalatine ganglion provokes cluster-like attacks in humans. *Cephalalgia* 2013;33(10):831-41. doi: 10.1177/0333102413476370

7. Penarrocha-Diago M, Boronat A, Penarrocha-Oltra D, et al. Clinical course of patients with episodic cluster headache treated with corticosteroids inproximity to the sphenopalatine ganglion: a preliminary study of 23 patients. *Med Oral Patol Oral Cir Bucal* 2012;17(3):e477-82.

8. Lepper A, Frese A, Summ O, et al. Hypothalamic dopaminergic stimulation in cluster headache. *Cephalalgia* 2013;33(14):1155-9. doi: 10.1177/0333102413487445

9. Loomba V, Upadhyay A, Kaveeshvar H. Radiofrequency Ablation of the Sphenopalatine Ganglion Using Cone Beam Computed Tomography for Intractable Cluster Headache. *Pain Physician* 2016;19(7):E1093-6.

10. Barloese MC, Jurgens TP, May A, et al. Cluster headache attack remission with sphenopalatine ganglion stimulation: experiences in chronic cluster headache patients through 24 months. *J Headache Pain* 2016;17(1):67. doi: 10.1186/s10194-016-0658-1

11. Kohlmeier C, Behrens P, Boger A, et al. Improved surgical procedure using intraoperative navigation for the implantation of the SPG microstimulator in patients with chronic cluster headache. *Int J Comput Assist Radiol Surg* 2017;12(12):2119-28. doi: 10.1007/s11548-016-1512-2

12. Meng DW, Zhang JG, Zheng Z, et al. Chronic Bilateral Sphenopalatine Ganglion Stimulation for Intractable Bilateral Chronic Cluster Headache: A Case Report. *Pain Physician* 2016;19(4):E637-42.

13. Schoenen J, Jensen RH, Lanteri-Minet M, et al. Stimulation of the sphenopalatine ganglion (SPG) for cluster headache treatment. Pathway CH-1: a randomized, sham-controlled study. *Cephalalgia* 2013;33(10):816-30. doi: 10.1177/0333102412473667

14. Sluijter ME. Non-thermal radiofrequency procedures in the treatment of spinal pain. Pain in Europe; 2nd Annual Congress of the European Federation of IASP Chapters. Barcelona, 1997:326.

15. Chua NH, Vissers KC, Wilder-Smith OH. Quantitative sensory testing may predict response to sphenopalatine ganglion pulsed radiofrequency treatment in cluster headaches: a case series. *Pain Pract* 2011;11(5):439-45. doi: 10.1111/j.1533-2500.2010.00445.x

16. Fang L, Jingjing L, Ying S, et al. Computerized tomography-guided sphenopalatine ganglion pulsed radiofrequency treatment in 16 patients with refractory cluster headaches: Twelve- to 30-month follow-up evaluations. *Cephalalgia* 2016;36(2):106-12. doi:

10.1177/0333102415580113

17. Felisati G, Arnone F, Lozza P, et al. Sphenopalatine endoscopic ganglion block: a revision of a traditional technique for cluster headache. *Laryngoscope* 2006;116(8):1447-50. doi: 10.1097/01.mlg.0000227997.48020.44

18. Pipolo C, Bussone G, Leone M, et al. Sphenopalatine endoscopic ganglion block in cluster headache: a reevaluation of the procedure after 5 years. *Neurol Sci* 2010;31 Suppl 1:S197-9. doi: 10.1007/s10072-010-0325-2

19. Ho KWD, Przkora R, Kumar S. Sphenopalatine ganglion: block, radiofrequency ablation and neurostimulation-a systematic review. *The journal of headache and pain* 2017;18(1):118. doi: 10.1186/s10194-017-0826-y

20. Piagkou M, Demesticha T, Troupis T, et al. The pterygopalatine ganglion and its role in various pain syndromes: from anatomy to clinical practice. *Pain Pract* 2012;12(5):399-412. doi: 10.1111/j.1533-2500.2011.00507.x

21. Narouze S, Kapural L, Casanova J, et al. Sphenopalatine ganglion radiofrequency ablation for the management of chronic cluster headache. *Headache* 2009;49(4):571-7. doi: 10.1111/j.1526-4610.2008.01226.x

22. Oomen KP, van Wijck AJ, Hordijk GJ, et al. Effects of radiofrequency thermocoagulation of the sphenopalatine ganglion on headache and facial pain: correlation with diagnosis. *J Orofac Pain* 2012;26(1):59-64.

23. Devoghel JC. Cluster headache and sphenopalatine block. *Acta Anaesthesiol Belg* 1981;32(1):101-7.

24. Kastler A, Cadel G, Comte A, et al. Alcohol percutaneous neurolysis of the sphenopalatine

ganglion in the management of refractory cranio-facial pain. *Neuroradiology* 2014;56(7):589-96. doi: 10.1007/s00234-014-1354-y

25. Jurgens TP, Barloese M, May A, et al. Long-term effectiveness of sphenopalatine ganglion stimulation for cluster headache. *Cephalalgia* 2017;37(5):423-34. doi: 10.1177/0333102416649092

26. Costa A, Pucci E, Antonaci F, et al. The effect of intranasal cocaine and lidocaine on nitroglycerin-induced attacks in cluster headache. *Cephalalgia* 2000;20(2):85-91. doi: 10.1046/j.1468-2982.2000.00026.x

27. Barre F. Cocaine as an abortive agent in cluster headache. *Headache* 1982;22(2):69-73.

28. Zarembinski C, Graff-Radford S. An unusual challenge in performing sphenopalatine ganglion block with enlarged coronoid process: Jacob's disease. *Pain Med* 2014;15(2):329-32. doi: 10.1111/pme.12302

29. Vanneste T, Van Lantschoot A, Van Boxem K, et al. Pulsed radiofrequency in chronic pain. *Curr Opin Anaesthesiol* 2017;30(5):577-82. doi: 10.1097/aco.0000000000000502

30. Bendersky DC, Hem SM, Yampolsky CG. Unsuccessful pulsed radiofrequency of the sphenopalatine ganglion in patients with chronic cluster headache and subsequent successful thermocoagulation. *Pain Pract* 2015;15(5):E40-5. doi: 10.1111/papr.12288

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.

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Competing interests None declared.

Figure 1

Flow diagram of the study.

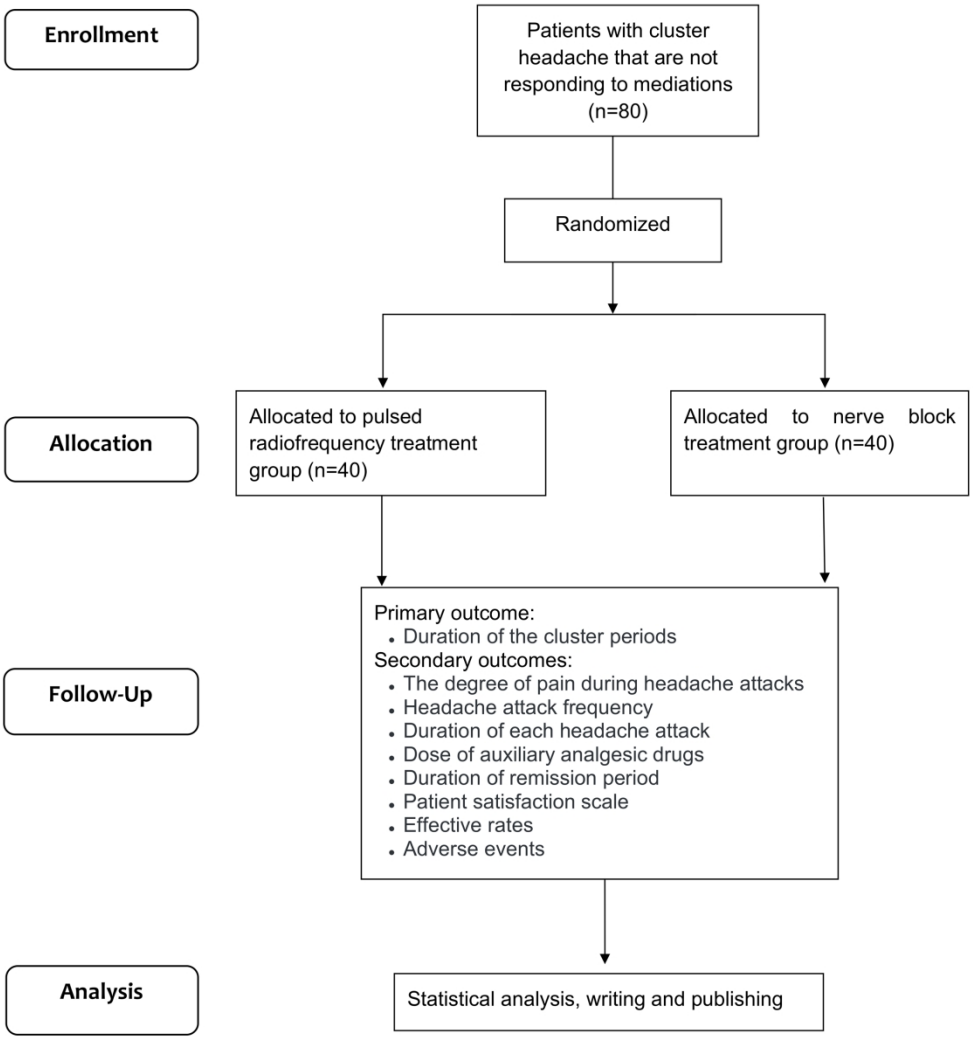

Figure 1/Flow diagram of the study.

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.

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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

sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	5
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	5
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3
Objectives	#7	Specific objectives or hypotheses	4
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-8

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

mechanism		envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6
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
Data collection plan: retention	#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
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
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
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9-10
Statistics: analysis population and missing data	#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

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

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

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

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Primary Subject Heading:	Anaesthesia
Secondary Subject Heading:	Anaesthesia
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Title:

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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 mediations. 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.

The randomised controlled trial design minimises risk of confounding bias.

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

The follow-up will be performed by telephone instead of hospital visit and telephone follow-up is already enough for obtaining the primary outcome.

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 months[3]. 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 treatment[4]. 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 CH[6].

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 effect[7]. 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 stimulation[8], pterygopalatine ganglion ablation[9], and pterygopalatine ganglion electrical stimulation[10-13] 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

urgent need for exploring 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 technology[14]. 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 treatment[15]. In 2016, we reported the computed tomography (CT) -guided pterygopalatine ganglion PRF treatment in 16 patients with CH 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[16]. However, to verify whether early intervention via PRF can be a treatment option for patients with CH 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 CH 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. CH 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 clinicaltrails.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 edition[3]

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.
Chronic cluster headache
A. Attacks fulfilling criteria for Cluster headache, and criterion B below
B. Occurring without a remission period, or with remissions lasting <3 months, for at least one year.

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.

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

Each research centre will have a research nurse who is responsible for implementing the allocation. According to a pre-generated random sequence, each enrolled patient will be given a sealed opaque random envelope based on the order of enrolment. After puncturing the pterygopalatine ganglion during the procedure, the research nurse will open the sealed envelope and assign the patient to the corresponding group according to the random number in the envelope, and the corresponding treatment will be 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 procedure will be conducted by responsible physicians, who will be blinded to the allocation status of the patients. The data input will be completed by the data entry personnel, who are not from the research team, and the data analysis will be completed by the statisticians who are blinded to allocation information.

Study interventions

The patient will be in a supine position on a CT scan couch with the head turned to the

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

PRF treatment: The pulse treatment generator will be set to the pulsed radiofrequency automatic mode, with a temperature of 42 °C, pulse frequency of 2 Hz, pulse width of 20 ms, and treatment duration of 360 s[16].

NB treatment: A mixture of 40 mg triamcinolone + 2 ml of 1% bupivacaine + 2 ml of 2% mepivacaine + 1:100000 epinephrine will be injected for nerve block treatment

using a puncture needle[17 18].

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

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

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 experience[16], 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.

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

Statistical analysis

The SAS9.4 statistical analysis system will be used to analyse the data with the full analysis set and the per-protocol set. The Shapiro-Wilk test will be used to check data for normal distribution. Normally distributed data will be expressed as the means ± standard deviations. Parameters that do not meet the normal distribution will be expressed as medians ± quartiles. The t-test will be used for measurement data with normal distributions, the rank sum test will be used for measurement data with non-normal distributions, and the chi-square test will be used for count data. Efficacy analysis will be conducted via both intention-to-treat (ITT) analysis and the per-protocol analysis set in SAS. The t-test will be 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 will be used to compare the count data of efficacy outcome indicators between the PRF and NB groups. The chi-square test or exact probability analysis will be used to evaluate intraoperative and postoperative AEs.

DISCUSSION

The pterygopalatine ganglion 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 mucosa[19]. The characteristic clinical symptoms of CH, such as tearing, runny nose, nasal congestion, and nasal oedema, are manifestations of parasympathetic excitations in the pterygopalatine ganglion, and ptosis and pupil diminution are manifestations of sympathetic inhibition in the pterygopalatine ganglion. Therefore, the pathogenesis of CH is considered to be related to the pterygopalatine ganglion[20].

In recent years, there have been a series of reports on the treatment of CH via the pterygopalatine ganglion. One type of pterygopalatine ganglion treatment is destructive, which blocks pain signalling by denaturing pterygopalatine ganglion proteins, such as radiofrequency ablation techniques[21 22] and local injection of absolute alcohol[23 24]. The other type is non-destructive, such as nerve block[10 20], PRF[16], and nerve electrical stimulation[13 25].

Pterygopalatine ganglion nerve blocks include cotton swab nasal infiltration[26] and needle injection[17 18]. The puncture approach of the pterygopalatine ganglion includes the sphenopalatine foramen approach[27], the supra-zygomatic approach[23], the infrazygomatic crest approach[24], or the mandibular notch approach[28]. 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 placebo[26]. 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 approach[24], 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 technique[29]. 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 effective[16]. Bendersky et al. also reported that PRF treatment failed to achieve satisfactory pain relief in 3 patients with CCH[30]. 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 convincing conclusion.

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

This study will compare the efficacy of pterygopalatine ganglion nerve block and PRF in the treatment of CH in a multicentre, prospective, randomized, controlled, and blinded-endpoint study, and will provide reliable evidence for treatment strategies for patients with CH who are not responding to conservative drug treatment. Of course, the limitations of this study including that the participants in this study and the doctors who conducted the interventions will be not kept blinded to the trial. In order to obtain greater scientific value, double-blind researches need to be carried out in the future. Other limitations include the follow-up period of this study will be only 1 year, and the lack of exploration of optimal parameters for PRF treatment of CH, which will be 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

pattern.

REFERENCES

1. Rozen TD, Fishman RS. Cluster Headache in the United States of America: Demographics, Clinical Characteristics, Triggers, Suicidality, and Personal Burden*. *Headache: The Journal of Head and Face Pain* 2012;52(1):99-113. doi: 10.1111/j.1526-4610.2011.02028.x

2. Weaver-Agostoni J. Cluster headache. *Am Fam Physician* 2013;88(2):122-8.

3. (IHS) HCCotIHS. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. *Cephalalgia* 2018;38(1):1-211. doi: 10.1177/0333102417738202

4. Hoffmann J, May A. Diagnosis, pathophysiology, and management of cluster headache. *The Lancet Neurology* 2018;17(1):75-83. doi: 10.1016/S1474-4422(17)30405-2

5. May A, Bahra A, Büchel C, et al. Hypothalamic activation in cluster headache attacks. *The Lancet* 1998;352(9124):275-78. doi: 10.1016/S0140-6736(98)02470-2

6. Schytz HW, Barløse M, Guo S, et al. Experimental activation of the sphenopalatine ganglion provokes cluster-like attacks in humans. *Cephalalgia* 2013;33(10):831-41. doi: 10.1177/0333102413476370

7. Penarrocha-Diago M, Boronat A, Penarrocha-Oltra D, et al. Clinical course of patients with episodic cluster headache treated with corticosteroids inproximity to the sphenopalatine ganglion: a preliminary study of 23 patients. *Med Oral Patol Oral Cir Bucal* 2012;17(3):e477-82.

8. Lepper A, Frese A, Summ O, et al. Hypothalamic dopaminergic stimulation in cluster headache. *Cephalalgia* 2013;33(14):1155-9. doi: 10.1177/0333102413487445

9. Loomba V, Upadhyay A, Kaveeshvar H. Radiofrequency Ablation of the Sphenopalatine Ganglion Using Cone Beam Computed Tomography for Intractable Cluster Headache. *Pain Physician* 2016;19(7):E1093-6.

10. Barloese MC, Jurgens TP, May A, et al. Cluster headache attack remission with sphenopalatine ganglion stimulation: experiences in chronic cluster headache patients through 24 months. *J Headache Pain* 2016;17(1):67. doi: 10.1186/s10194-016-0658-1

11. Kohlmeier C, Behrens P, Boger A, et al. Improved surgical procedure using intraoperative navigation for the implantation of the SPG microstimulator in patients with chronic cluster headache. *Int J Comput Assist Radiol Surg* 2017;12(12):2119-28. doi: 10.1007/s11548-016-1512-2

12. Meng DW, Zhang JG, Zheng Z, et al. Chronic Bilateral Sphenopalatine Ganglion Stimulation for Intractable Bilateral Chronic Cluster Headache: A Case Report. *Pain Physician* 2016;19(4):E637-42.

13. Schoenen J, Jensen RH, Lanteri-Minet M, et al. Stimulation of the sphenopalatine ganglion (SPG) for cluster headache treatment. Pathway CH-1: a randomized, sham-controlled study. *Cephalalgia* 2013;33(10):816-30. doi: 10.1177/0333102412473667

14. Sluijter ME. Non-thermal radiofrequency procedures in the treatment of spinal pain. Pain in Europe; 2nd Annual Congress of the European Federation of IASP Chapters. Barcelona, 1997:326.

15. Chua NH, Vissers KC, Wilder-Smith OH. Quantitative sensory testing may predict response to sphenopalatine ganglion pulsed radiofrequency treatment in cluster headaches: a case series. *Pain Pract* 2011;11(5):439-45. doi: 10.1111/j.1533-2500.2010.00445.x

16. Fang L, Jingjing L, Ying S, et al. Computerized tomography-guided sphenopalatine ganglion pulsed radiofrequency treatment in 16 patients with refractory cluster headaches: Twelve- to 30-month follow-up evaluations. *Cephalalgia* 2016;36(2):106-12. doi: 10.1177/0333102415580113

17. Felisati G, Arnone F, Lozza P, et al. Sphenopalatine endoscopic ganglion block: a revision of a traditional technique for cluster headache. *Laryngoscope* 2006;116(8):1447-50. doi: 10.1097/01.mlg.0000227997.48020.44

18. Pipolo C, Bussone G, Leone M, et al. Sphenopalatine endoscopic ganglion block in cluster headache: a reevaluation of the procedure after 5 years. *Neurol Sci* 2010;31 Suppl 1:S197-9. doi: 10.1007/s10072-010-0325-2

19. Ho KWD, Przkora R, Kumar S. Sphenopalatine ganglion: block, radiofrequency ablation and neurostimulation-a systematic review. *The journal of headache and pain* 2017;18(1):118. doi: 10.1186/s10194-017-0826-y

20. Piagkou M, Demesticha T, Troupis T, et al. The pterygopalatine ganglion and its role in various pain syndromes: from anatomy to clinical practice. *Pain Pract* 2012;12(5):399-412. doi: 10.1111/j.1533-2500.2011.00507.x

21. Narouze S, Kapural L, Casanova J, et al. Sphenopalatine ganglion radiofrequency ablation for the management of chronic cluster headache. *Headache* 2009;49(4):571-7. doi: 10.1111/j.1526-4610.2008.01226.x

22. Oomen KP, van Wijck AJ, Hordijk GJ, et al. Effects of radiofrequency thermocoagulation of the sphenopalatine ganglion on headache and facial pain: correlation with diagnosis. *J Orofac Pain* 2012;26(1):59-64.

23. Devoghel JC. Cluster headache and sphenopalatine block. *Acta Anaesthesiol Belg* 1981;32(1):101-7.

24. Kastler A, Cadel G, Comte A, et al. Alcohol percutaneous neurolysis of the sphenopalatine ganglion in the management of refractory cranio-facial pain. *Neuroradiology* 2014;56(7):589-96. doi: 10.1007/s00234-014-1354-y

25. Jurgens TP, Barloese M, May A, et al. Long-term effectiveness of sphenopalatine ganglion stimulation for cluster headache. *Cephalalgia* 2017;37(5):423-34. doi: 10.1177/0333102416649092

26. Costa A, Pucci E, Antonaci F, et al. The effect of intranasal cocaine and lidocaine on nitroglycerin-induced attacks in cluster headache. *Cephalalgia* 2000;20(2):85-91. doi: 10.1046/j.1468-2982.2000.00026.x

27. Barre F. Cocaine as an abortive agent in cluster headache. *Headache* 1982;22(2):69-73.

28. Zarembinski C, Graff-Radford S. An unusual challenge in performing sphenopalatine ganglion block with enlarged coronoid process: Jacob's disease. *Pain Med* 2014;15(2):329-32. doi: 10.1111/pme.12302

29. Vanneste T, Van Lantschoot A, Van Boxem K, et al. Pulsed radiofrequency in chronic pain. *Curr Opin Anaesthesiol* 2017;30(5):577-82. doi: 10.1097/aco.0000000000000502

30. Bendersky DC, Hem SM, Yampolsky CG. Unsuccessful pulsed radiofrequency of the sphenopalatine ganglion in patients with chronic cluster headache and subsequent successful thermocoagulation. *Pain Pract* 2015;15(5):E40-5. doi: 10.1111/papr.12288

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.

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Competing interests None declared.

Figure 1

Flow diagram of the study.

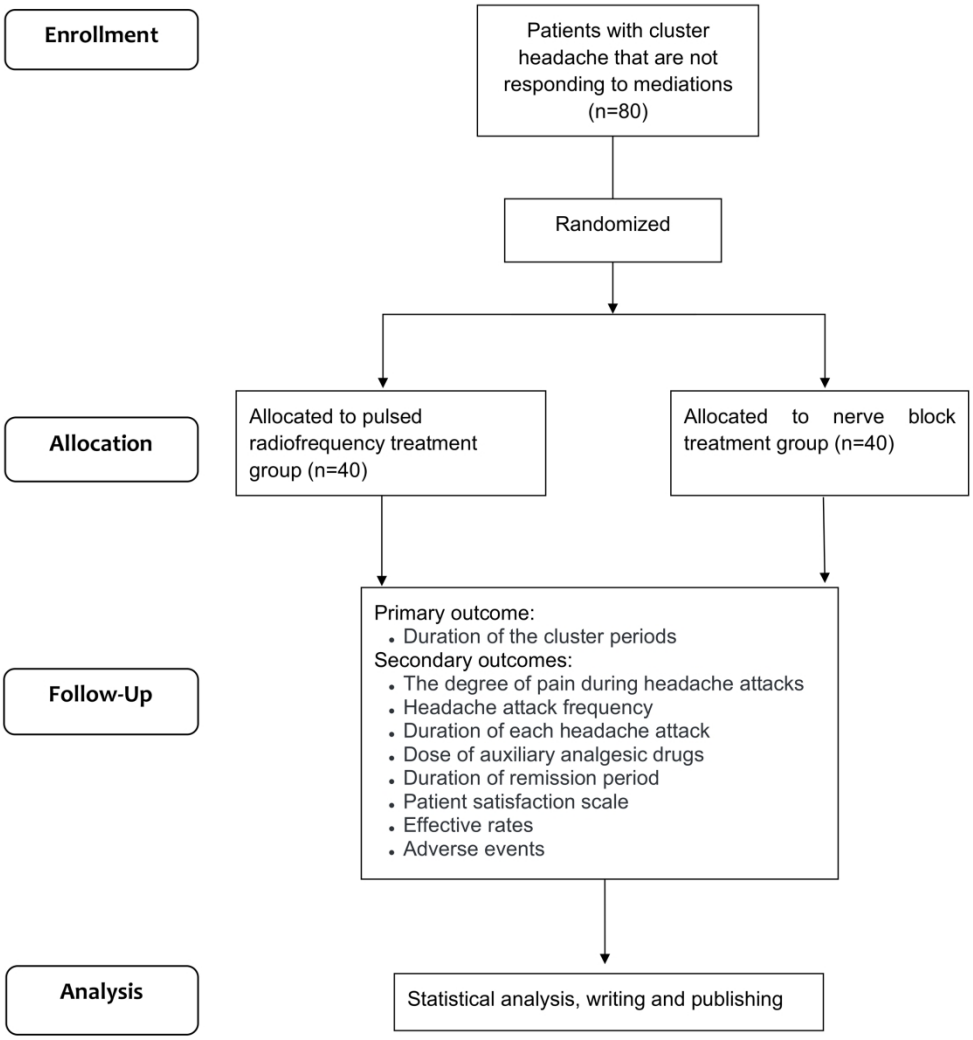

Figure 1/Flow diagram of the study.

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

sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	5
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	5
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3
Objectives	#7	Specific objectives or hypotheses	4
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-8

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

mechanism		envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6
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
Data collection plan: retention	#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
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
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
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9-10
Statistics: analysis population and missing data	#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

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

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

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

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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

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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.

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

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

The follow-up will be performed by telephone instead of hospital visits; telephone follow-up is sufficient to assess the primary outcome.

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 months[3]. 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 treatment[4]. 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 CH[6].

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 effectiveness[7]. 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 stimulation[8], pterygopalatine ganglion ablation[9], and pterygopalatine ganglion electrical stimulation[10-13] 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

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

The technique of percutaneous pulsed radiofrequency (PRF) is a minimally destructive pain-treatment technology[14]. In contrast to 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 whom 2 patients had complete remission of pain, 1 patient had partial remission of pain, and all patients were free of neurological side effects and complications after treatment[15]. In 2016, we reported computed tomography (CT)-guided pterygopalatine ganglion PRF treatment in 16 patients with CH who had not responded to drugs and nerve block (NB); we found that pterygopalatine ganglion PRF could quickly, safely and effectively relieve the patients from their cluster headache periods[16]. However, to verify whether early intervention via PRF is a viable treatment option for patients with CH who are not responding to drug therapy, we still need to obtain strong evidence through a 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 block of the pterygopalatine ganglion for CH 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 investigation is a multicentre, prospective, randomized, controlled, blinded-endpoint study. CH patients who are not responding to drug therapy will receive either CT-guided percutaneous puncture pterygopalatine ganglion NB 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 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 edition[3]

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 rhinorrhoea; **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
Chronic Cluster Headache
A. Attacks fulfilling criteria for cluster headache and criterion B below
B. Occurring without a remission period, or with remissions lasting <3 months, for at least one year

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

Recruitment and informed consent

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

which they will 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 will be allowed to freely withdraw their consent form or withdraw from the study without restrictions at any stage.

Once each patient signs the informed consent, the researchers will complete the eligibility checklists based on the items listed on the case report form; records will be made of any candidates who fail to enrol.

Interventions

Randomization and allocation concealment

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

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

Blinding

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

Study interventions

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

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 s[16].

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

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

Patient and public involvement

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

Variables and measurements

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

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 the procedure 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 a cluster period is defined as the total

duration of the headache, including the pain experienced before and after treatment. The secondary outcomes, which include the degree of pain during headache attacks (NRS scores), the frequency of headache attacks, the duration of each headache attack, the dose of auxiliary analgesic drugs taken, the duration of remission, self-rated patient satisfaction (from 0 point for unsatisfied to 10 points for very satisfied), the effectiveness rate of treatment, and intraoperative and postoperative adverse events (AEs), will also be compared between the two groups of patients.

The effectiveness of the treatments at each time point will be calculated. Effectiveness will be defined as either complete or partial relief of pain, and the rate will be calculated as follows: effectiveness rate = number of effectively treated patients / total number of patients in this group × 100%. Complete pain relief will be defined as NRS = 0 and discontinued administration of drugs. Partial pain relief will be defined as a postoperative reduction of more than 50% in the intensity, frequency, and duration of headache attacks as well as auxiliary analgesic drug dosage. No remission of pain will be defined as no change from the preoperative level of pain or as the postoperative intensity, frequency, and duration of headache attacks as well as auxiliary analgesic drug dosage remaining over 50% of the preoperative levels. The partial pain remission time, complete pain remission time, number of interventional treatments, treatment intervals, and number of cases receiving electrical stimulation of the pterygopalatine ganglion will be recorded.

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

Sample size

This study will apply a one-sided superiority test with $\alpha = 0.025$ and $\beta = 0.10$. Based on a review of the literature, combined with the authors' published articles and clinical experience[16], 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, with a standard deviation of approximately 15 days. Shortening the duration of the cluster period by 20 days has clinical significance. The number of cases needed in each group is 36 as calculated by PASS 11. Allowing for a 10% rate of loss to follow-up, 40 cases are required in each group, and a total of 80 cases are required for both groups together.

Statistical analysis

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

DISCUSSION

The pterygopalatine ganglion is one of the four major parasympathetic ganglia of the head and neck. This ganglion is the largest group of neurons within the calvarium outside the brain and is the only ganglion that enters the external environment through the nasal mucosa[19]. The characteristic clinical symptoms of CH, such as tearing, runny nose, nasal congestion, and nasal oedema, are manifestations of parasympathetic excitation in the pterygopalatine ganglion, and ptosis and pupil diminution are manifestations of sympathetic inhibition in the pterygopalatine ganglion. Therefore, the

pathogenesis of CH is considered to be related to the pterygopalatine ganglion[20].

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

Methods of pterygopalatine ganglion NB include cotton-swab nasal infiltration[26] and needle injection[17 18]. Puncture approaches to the pterygopalatine ganglion include the sphenopalatine foramen approach[27], the suprazygomatic approach[23], the infrazygomatic crest approach[24], and the mandibular notch approach[28]. Puncture can be performed with the assistance of nasal endoscopy[17 18], fluoroscopy[21 22], or CT[9 16]. The commonly used NB drugs include local anaesthetics and steroid hormones. The previous reports on NB for the treatment of CH are mostly case-series analyses and case reports. Costa et al. conducted a randomized double-blind placebo-controlled study of patients with nitroglycerine-induced CH; the patients were treated with 10% cocaine, 10% lidocaine, or a saline placebo[26]. 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, NB treatment for CH has certain drawbacks, the most important of which are the limited effect of pain relief in a single treatment and the short duration of treatment efficacy. Therefore, NB needs to be implemented repeatedly. The puncture approach in our study will be the infrazygomatic crest approach[24], 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, percutaneous interventional pain management technique[29]. This procedure uses the same puncture site and localization approach as radiofrequency ablation. However, to treat the pain, PRF regulates the 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

patients who had not responded to drugs or NB, 11 patients with ECH and 1 patient with CCH had complete remission, although treatment was ineffective for 2 patients with ECH and 2 patients with CCH[16]. Bendersky et al. also reported that PRF treatment failed to achieve satisfactory pain relief in 3 patients with CCH[30]. Therefore, it is currently believed that PRF treatment may be more effective for ECH than for CCH. However, given the low incidence of CCH and the small number of established cases, the existing studies are not sufficient to reach a convincing conclusion.

CT images are clear and intuitive, providing the clinician with accurate guidance for puncturing the surgical site. The CT-guided pterygopalatine ganglion puncture technique was first applied in clinical practice by Kastler et al.[24]. CT guidance was confirmed to reduce puncture complications and increase both the puncture success rate and treatment satisfaction. In the past, we have reported a 100% success rate of puncture for CH patients undergoing CT-guided pterygopalatine ganglion puncture and PRF treatment, and surgery-related complications, such as nosebleeds and cheek haematomas, were successfully avoided[16]. In the proposed study, both the NB and PRF groups will undergo CT-guided pterygopalatine ganglion puncture to ensure the accuracy of the puncture and to avoid the effects of inaccurate puncture on the outcome. During the procedure, the dose of radiation exposure will be controlled by minimizing the scope of CT scans, for example, scanning only the pterygopalatine fossa as needed by the experienced physician performing the puncture.

This study will compare the effectiveness of pterygopalatine ganglion NB and PRF for the treatment of CH in a multicentre, prospective, randomized, controlled, blinded-endpoint study; the results are expected to provide reliable evidence regarding treatment strategies for patients with CH who are not responding to conservative drug treatment. Of course, this study has some limitations; for example, the participants in the trial and the doctors who conduct the interventions will be not kept blinded to the treatment allocations. Double-blind studies need to be carried out in the future to achieve results of greater scientific value. Other limitations include the short follow-up period of only 1 year and the lack of exploration of optimal parameters for PRF treatment of CH, which will be investigated through in-depth clinical research later.

Furthermore, the variability in the duration of episodes in patients with CH makes it difficult to discern the response pattern.

REFERENCES

1. Rozen TD, Fishman RS. Cluster Headache in the United States of America: Demographics, Clinical Characteristics, Triggers, Suicidality, and Personal Burden*. *Headache: The Journal of Head and Face Pain* 2012;52(1):99-113. doi: 10.1111/j.1526-4610.2011.02028.x

2. Weaver-Agostoni J. Cluster headache. *Am Fam Physician* 2013;88(2):122-8.

3. (IHS) HCCotIHS. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. *Cephalalgia* 2018;38(1):1-211. doi: 10.1177/0333102417738202

4. Hoffmann J, May A. Diagnosis, pathophysiology, and management of cluster headache. *The Lancet Neurology* 2018;17(1):75-83. doi: 10.1016/S1474-4422(17)30405-2

5. May A, Bahra A, Büchel C, et al. Hypothalamic activation in cluster headache attacks. *The Lancet* 1998;352(9124):275-78. doi: 10.1016/S0140-6736(98)02470-2

6. Schytz HW, Barløse M, Guo S, et al. Experimental activation of the sphenopalatine ganglion provokes cluster-like attacks in humans. *Cephalalgia* 2013;33(10):831-41. doi: 10.1177/0333102413476370

7. Penarrocha-Diago M, Boronat A, Penarrocha-Oltra D, et al. Clinical course of patients with episodic cluster headache treated with corticosteroids inproximity to the sphenopalatine ganglion: a preliminary study of 23 patients. *Med Oral Patol Oral Cir Bucal* 2012;17(3):e477-82.

8. Lepper A, Frese A, Summ O, et al. Hypothalamic dopaminergic stimulation in cluster

headache. *Cephalalgia* 2013;33(14):1155-9. doi: 10.1177/0333102413487445

9. Loomba V, Upadhyay A, Kaveeshvar H. Radiofrequency Ablation of the Sphenopalatine Ganglion Using Cone Beam Computed Tomography for Intractable Cluster Headache. *Pain Physician* 2016;19(7):E1093-6.

10. Barloese MC, Jurgens TP, May A, et al. Cluster headache attack remission with sphenopalatine ganglion stimulation: experiences in chronic cluster headache patients through 24 months. *J Headache Pain* 2016;17(1):67. doi: 10.1186/s10194-016-0658-1

11. Kohlmeier C, Behrens P, Boger A, et al. Improved surgical procedure using intraoperative navigation for the implantation of the SPG microstimulator in patients with chronic cluster headache. *Int J Comput Assist Radiol Surg* 2017;12(12):2119-28. doi: 10.1007/s11548-016-1512-2

12. Meng DW, Zhang JG, Zheng Z, et al. Chronic Bilateral Sphenopalatine Ganglion Stimulation for Intractable Bilateral Chronic Cluster Headache: A Case Report. *Pain Physician* 2016;19(4):E637-42.

13. Schoenen J, Jensen RH, Lanteri-Minet M, et al. Stimulation of the sphenopalatine ganglion (SPG) for cluster headache treatment. Pathway CH-1: a randomized, sham-controlled study. *Cephalalgia* 2013;33(10):816-30. doi: 10.1177/0333102412473667

14. Sluijter ME. Non-thermal radiofrequency procedures in the treatment of spinal pain. Pain in Europe; 2nd Annual Congress of the European Federation of IASP Chapters. Barcelona, 1997:326.

15. Chua NH, Vissers KC, Wilder-Smith OH. Quantitative sensory testing may predict response to sphenopalatine ganglion pulsed radiofrequency treatment in cluster headaches: a

case series. *Pain Pract* 2011;11(5):439-45. doi: 10.1111/j.1533-2500.2010.00445.x

16. Fang L, Jingjing L, Ying S, et al. Computerized tomography-guided sphenopalatine ganglion pulsed radiofrequency treatment in 16 patients with refractory cluster headaches: Twelve- to 30-month follow-up evaluations. *Cephalalgia* 2016;36(2):106-12. doi: 10.1177/0333102415580113

17. Felisati G, Arnone F, Lozza P, et al. Sphenopalatine endoscopic ganglion block: a revision of a traditional technique for cluster headache. *Laryngoscope* 2006;116(8):1447-50. doi: 10.1097/01.mlg.0000227997.48020.44

18. Pipolo C, Bussone G, Leone M, et al. Sphenopalatine endoscopic ganglion block in cluster headache: a reevaluation of the procedure after 5 years. *Neurol Sci* 2010;31 Suppl 1:S197-9. doi: 10.1007/s10072-010-0325-2

19. Ho KWD, Przkora R, Kumar S. Sphenopalatine ganglion: block, radiofrequency ablation and neurostimulation-a systematic review. *The journal of headache and pain* 2017;18(1):118. doi: 10.1186/s10194-017-0826-y

20. Piagkou M, Demesticha T, Troupis T, et al. The pterygopalatine ganglion and its role in various pain syndromes: from anatomy to clinical practice. *Pain Pract* 2012;12(5):399-412. doi: 10.1111/j.1533-2500.2011.00507.x

21. Narouze S, Kapural L, Casanova J, et al. Sphenopalatine ganglion radiofrequency ablation for the management of chronic cluster headache. *Headache* 2009;49(4):571-7. doi: 10.1111/j.1526-4610.2008.01226.x

22. Oomen KP, van Wijck AJ, Hordijk GJ, et al. Effects of radiofrequency thermocoagulation of the sphenopalatine ganglion on headache and facial pain: correlation with diagnosis. *J*

Orofac Pain 2012;26(1):59-64.

23. Devoghel JC. Cluster headache and sphenopalatine block. *Acta Anaesthesiol Belg* 1981;32(1):101-7.

24. Kastler A, Cadel G, Comte A, et al. Alcohol percutaneous neurolysis of the sphenopalatine ganglion in the management of refractory cranio-facial pain. *Neuroradiology* 2014;56(7):589-96. doi: 10.1007/s00234-014-1354-y

25. Jurgens TP, Barloese M, May A, et al. Long-term effectiveness of sphenopalatine ganglion stimulation for cluster headache. *Cephalalgia* 2017;37(5):423-34. doi: 10.1177/0333102416649092

26. Costa A, Pucci E, Antonaci F, et al. The effect of intranasal cocaine and lidocaine on nitroglycerin-induced attacks in cluster headache. *Cephalalgia* 2000;20(2):85-91. doi: 10.1046/j.1468-2982.2000.00026.x

27. Barre F. Cocaine as an abortive agent in cluster headache. *Headache* 1982;22(2):69-73.

28. Zarembinski C, Graff-Radford S. An unusual challenge in performing sphenopalatine ganglion block with enlarged coronoid process: Jacob's disease. *Pain Med* 2014;15(2):329-32. doi: 10.1111/pme.12302

29. Vanneste T, Van Lantschoot A, Van Boxem K, et al. Pulsed radiofrequency in chronic pain. *Curr Opin Anaesthesiol* 2017;30(5):577-82. doi: 10.1097/aco.0000000000000502

30. Bendersky DC, Hem SM, Yampolsky CG. Unsuccessful pulsed radiofrequency of the sphenopalatine ganglion in patients with chronic cluster headache and subsequent successful thermocoagulation. *Pain Pract* 2015;15(5):E40-5. doi: 10.1111/papr.12288

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.

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Competing interests None declared.

Figure 1

Flow diagram of the study.

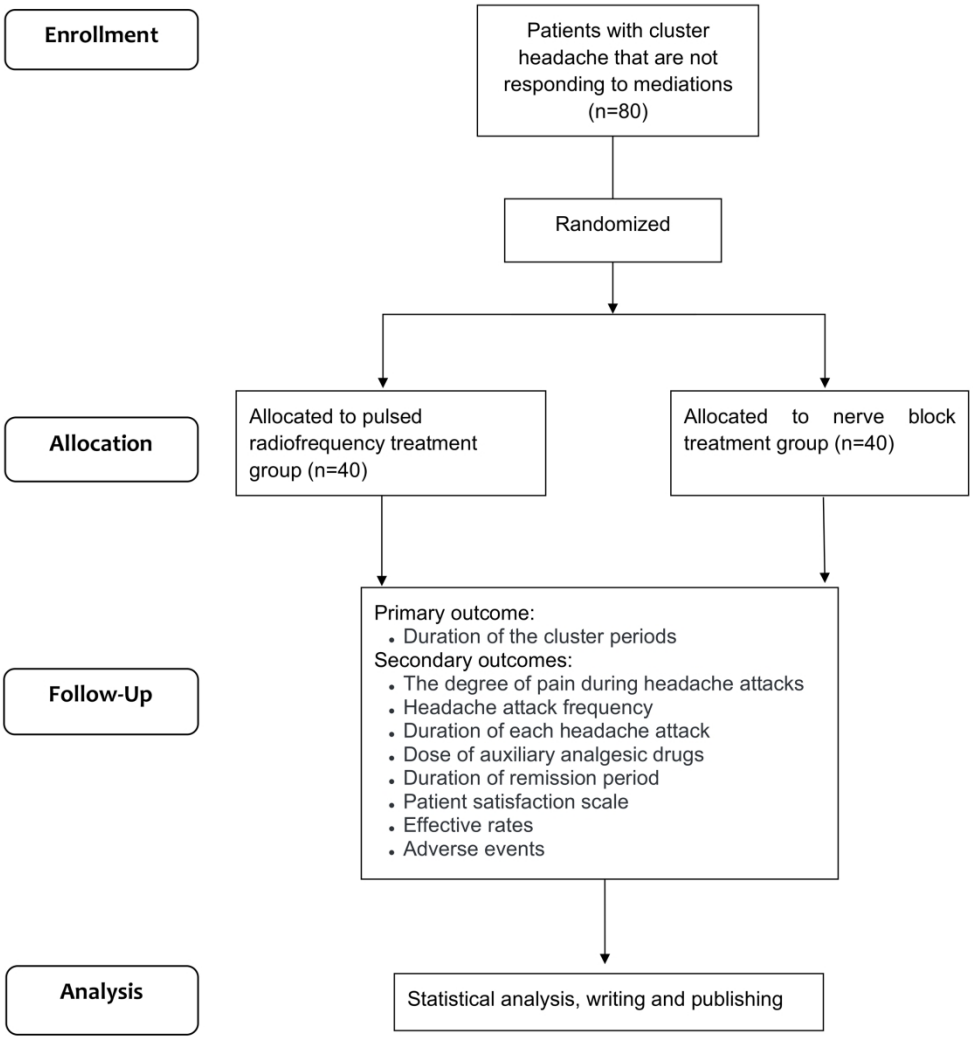

Figure 1/Flow diagram of the study.

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.

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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

sponsor contact information			
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	5
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	5
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3
Objectives	#7	Specific objectives or hypotheses	4
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	4
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-8

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

mechanism		envelopes), describing any steps to conceal the sequence until interventions are assigned	
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6
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
Data collection plan: retention	#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
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
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
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9-10
Statistics: analysis population and missing data	#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

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

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