Randomized Controlled Study

The Efficacy and Safety of the Application of Pulsed Radiofrequency, Combined With Low-Temperature Continuous Radiofrequency, to the Gasserian Ganglion for the Treatment of Primary Trigeminal Neuralgia: Study Protocol for a Prospective, Open-Label, Parallel, Randomized Controlled Trial

Hao Ren, MD, Chunmei Zhao, MD, Xiaodi Wang, MD, Ying Shen, MD, Lan Meng, MD, and Fang Luo, MD

From: Department of Pain Management, Beijing Tiantan Hospital, Capital Medical University, Beijing, China

Address Correspondence: Fang Luo, MD Department of Pain Management, Beijing Tiantan Hospital, Capital Medical University, No. 119 W. Rd, S. 4th Ring Rd, Fengtai District Beijing 100070, Republic of China E-mail: luofangwt@yahoo.com

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Background: Trigeminal neuralgia is a very painful condition, and radiofrequency therapy is reserved for patients who are resistant or intolerant to pharmacologic therapy. Continuous radiofrequency (CRF) and pulsed radiofrequency (PRF) both have advantages and disadvantages. Recently, studies have found that PRF combined with low-temperature (< 65°C) CRF increases the efficacy of treatment, without leading to a significant increase in complications caused by nerve lesions. However, these reports have some limitations.

Objectives: We plan to conduct a randomized, controlled study to compare the efficacy of applying high-voltage PRF, with and without low-temperature CRF, to the Gasserian ganglion for the treatment of trigeminal neuralgia.

Study Design: A study protocol for a prospective, open-label, parallel, randomized controlled trial (clinicaltrials.gov; NCT04174443).

Setting: The Department of Pain Management, Beijing Tiantan Hospital, Capital Medical University in Beijing, China.

Methods: One hundred forty-six patients with primary trigeminal neuralgia will be randomly assigned to 1 of 2 groups using an allocation ratio of 1:1. In the high-voltage PRF combined with low-temperature CRF group, 2 Hz of PRF will be applied under the following conditions: a voltage of 70 V, temperature of 42°C, pulse width of 20 ms, and treatment time of 600 s. Low-temperature CRF will then be performed at 60°C, with a treatment time of 270 s. In the high-voltage PRF group, only high-voltage PRF will be performed, using the same treatment parameters. Follow-up process will last for a duration of 1 year.

Results: The primary outcome will be the effectiveness of the treatment after 12 months, which is the percentage of patients with a modified Barrow Neurological Institute Pain Intensity Score (BNI) between I and III. The secondary outcome will include the following: BNI score, Numeric Rating Scale, dose of carbamazepine or oxcarbazepine, patient satisfaction score, quality of life, numbness, side effects, and adverse reactions. These will be recorded over a 1-year follow-up period.

Limitations: The open-label study design may influence the measurement of outcomes and introduce bias, for example, performance or ascertainment bias.

Conclusions: To our knowledge, this will be the first prospective, open-label, parallel, randomized controlled trial to compare the efficacy and safety of the application of high-voltage PRF, combined with and without low-temperature (60°C) CRF, for the patients who have failed to respond to pharmacologic treatments for primary trigeminal neuralgia. If proven effective, this will be an important, safe, minimally destructive alternative treatment modality for primary trigeminal neuralgia following an ineffective conservative treatment.

Key words: Trigeminal neuralgia, PRF, continuous radiofrequency, high-voltage PRF combined with low-temperature continuous radiofrequency, study protocol, Barrow Neurological Institute Pain Intensity Score, patient satisfaction score, quality of life, numbness

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Trigeminal neuralgia is a very painful condition, characterized by transient and paroxysmal electric, shock-like pain that occurs in areas supplied by the trigeminal nerve (1). The incidence rate of trigeminal neuralgia is approximately 12.6 cases per 100,000 person-years, that increases with age (2). Severe pain has a huge impact on patient's quality of life and often leads to psychological disturbances (3).

Medication is the primary treatment for most patients with trigeminal neuralgia (4). Surgical treatments including microvascular decompression (5), partial sensory rhizotomy (6), radiofrequency therapy (7,8), glycerol rhizolysis (9,10), balloon compression (10), and Gamma knife surgery (11), are reserved for patients who are resistant or intolerant to pharmacologic therapy (4). However, these treatment methods have both advantages and disadvantages; additionally, there is no one ideal surgical treatment yet (4). Continuous radiofrequency (CRF) is a percutaneous radiofrequency procedure that removes the need for endotracheal anesthesia and demands a rather short hospitalization (12-14). CRF also has a very low morbidity and virtually no mortality in comparison to microvascular decompression (7,15). Patients who cannot or prefer not to undergo microvascular decompression or recurrence after craniotomy can choose CRF instead (4,16). Temperature for the application of CRF is usually between 65° and 80°, and the Gasserian ganglion can thus be ablated through thermal effect (12,15,17,18). Higher temperatures appear to have a greater analgesic effect; however, they result in an increase in complications (15,19). The effectiveness of CRF is inconsistent, nonetheless, most studies suggest that CRF treatment is approximately 70% to 90% effective 1 year after the procedure (12,15,18). Although CRF is highly effective, it also results in many severe complications, such as facial numbness, masticatory weakness, and reduced corneal sensation (20,21). The quality of life of patients can be significantly reduced as a result of these complications.

Pulsed radiofrequency (PRF) is one of the most minimally destructive neuromodulation techniques, which can stimulate the Gasserian ganglion using pulsed current (22,23). The temperature of PRF treatment remains below 42°C, as the heat generated during the 20 ms of pulsed current has a silent time of 480 ms, during which the heat can dissipate (24). This alludes that it does not cause damage to neural tissue, unlike CRF that can cause nerve damage (22). Patients who receive effective PRF treatment tend to have a more significant improvement in their quality of life than those who receive CRF. However, pure PRF has limited efficacy and a shorter pain relief duration than CRF (16,25-28), even though adjustments have continuously been made to improve this. Our previous research established that the effectiveness of PRF treatment after 1 year could be increased from 41% to 69% by increasing the intraoperative output voltage manually (71.52 ± 7.97 V), instead of using a standard voltage (29). However, it was still difficult to meet the clinical requirements of efficacy and safety.

Recently, studies have proposed that PRF combined with low-temperature (<65°C) CRF could be applied to treat trigeminal neuralgia and may become a promising therapy, increasing the efficacy of treatment without significantly increasing complications due to nerve lesions. Ali Eissa et al (30) retrospectively analyzed the efficacy of PRF, combined with low-temperature (60°C–65°C) CRF, in 21 patients with trigeminal neuralgia. The effectiveness of treatment measured 1 week and 1 year after the procedure was 71.4% and 66.7%, respectively. In a randomized controlled study, patients with trigeminal neuralgia received PRF, CRF at 75°C, and PRF combined with low-temperature CRF at 60°C. The results showed that the effectiveness of treatment in the combined treatment group was 85%, which was higher than that of the single PRF group and CRF group. Side effects were also lower in the combined treatment group than in both PRF and CRF groups (31). In a retrospective study, PRF combined with CRF at 68°C was more effective than CRF alone (97.5% vs. 87.5%) after 1 year, along with fewer side effects and faster recovery times (32). The most recent randomized controlled trial found that PRF, combined with CRF at 60°C, for the treatment of recurrent trigeminal neuralgia after microvascular decompression, resulted in fewer side effects and complications with a similar effectiveness to CRF at 70°C (33). Currently, there is no consensus on the treatment parameters for PRF combined with CRF; including treatment time, temperature, and voltage. Different treatment parameters and outcome indicators may explain significant differences in efficacy reported in different studies.

However, these previous reports were either retrospective or prospective studies with a small sample size and did not disclose some important information such as randomization, blinding method, and sample size calculation. Moreover, to our knowledge, there has been no research on high-voltage PRF combined with low-temperature CRF. Therefore studies using a larger sample size and a more rigorous clinical design need to be carried

out to fully evaluate its efficacy. We hypothesize that high-voltage PRF combined with low-temperature CRF is more effective than high-voltage PRF alone. A randomized, controlled study will be conducted to compare the efficacy of high-voltage PRF, combined with and without low-temperature CRF, applied to the Gasserian ganglion for the treatment of trigeminal neuralgia.

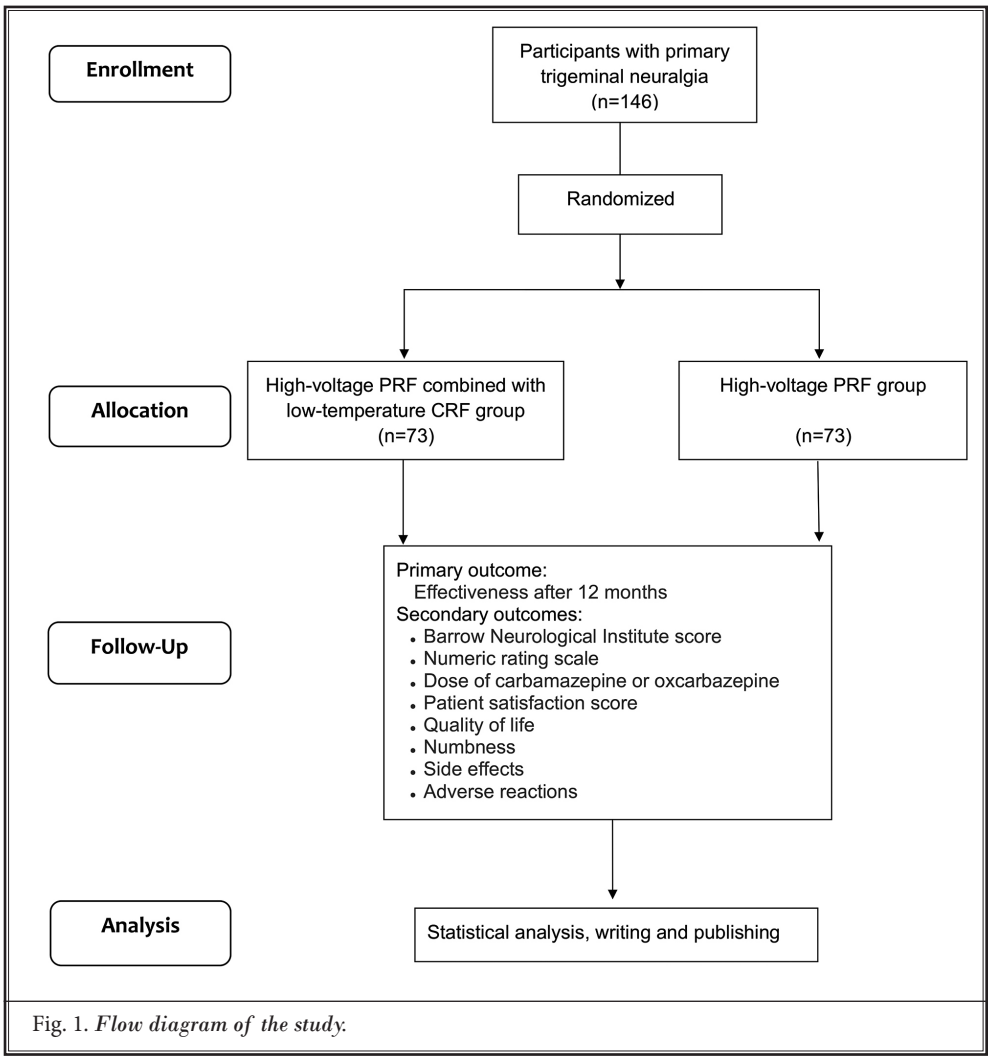

Fig. 1. *Flow diagram of the study.*

Objectives

To investigate the efficacy and safety of the application of high-voltage PRF combined with low-temperature (60°C) CRF to the Gasserian ganglion for the treatment of primary trigeminal neuralgia. We wish to find an effective, safe, and minimally destructive treatment, which can be performed after ineffective conservative treatment.

Methods

Trial Design

This will be a prospective, open-label, parallel, randomized controlled trial (Fig. 1).

Setting

Patients will be recruited from the Department of Pain Management, Beijing Tiantan Hospital, Capital Medical University in Beijing, China. All research members involved in this study will have a prior clinical experience of performing both treatments for at least 1 year. They will be trained according to the same treatment protocol before participating in the study. This study is scheduled to start in October 2020 and is expected to conclude in a duration of 3 years.

Patients

Inclusion criteria:

1. Diagnosed with trigeminal neuralgia according to the International Classification of Headache Disorders, 3rd edition (ICHD-3) criteria (1) (Table 1).
2. Aged 18 to 75 years (inclusive).
3. Suffering from severe trigeminal neuralgia that cannot be alleviated effectively by means of conservative medical therapy, such as carbamazepine, oxcarbazepine.
4. Numeric Rating Scale (NRS-11) score ≥ 7 before the procedure.

Table 1. *Diagnostic criteria for trigeminal neuralgia in the International Classification of Headache Disorders, 3rd edition (ICHD-3) (1).*

A. Recurrent paroxysms of unilateral facial pain in the distribution(s) of one or more divisions of the trigeminal nerve, with no radiation beyond, and fulfilling criteria B and C.
B. Pain has all of the following characteristics:
1. Lasting from a fraction of a second to 2 minutes.
2. Severe intensity.
3. Electric shock-like, shooting, stabbing, or sharp in quality.
C. Precipitated by innocuous stimuli within the affected trigeminal distribution.
D. Not better accounted for by another ICHD-3 diagnosis.

5. Agreed to sign the informed consent form.

Exclusion criteria:

1. Secondary trigeminal neuralgia such as trigeminal neuralgia attributed to a space-occupying lesion or multiple sclerosis.
2. Infection at the puncture site.
3. A history of psychiatric disease.
4. Disorder indicated in the results of routine blood tests, hepatic function, renal function, coagulation function, electrocardiogram, or chest x-ray.
5. Serious systemic diseases such as uncontrolled hypertension or diabetes, and cardiac dysfunction (New York Heart Association grade II–III).
6. A history of abuse of narcotics.
7. A history of receiving CRF to the Gasserian ganglion or peripheral branches, glycerol rhizolysis, balloon compression, Gamma knife, or any other neuroablative treatments.
8. A history of receiving microvascular decompression.

Recruitment and Informed Consent

An experienced attending doctor will enroll patients with primary trigeminal neuralgia at the Department of Pain Management, Beijing Tiantan Hospital, Capital Medical University. All the candidates will be informed in detail of the following information: the purpose of the study, interventions, benefits, possible risks, and corresponding responses. Candidates will be given at least 1 hour to consider whether or not to participate in the study. They will sign the informed consent form voluntarily and will have the right to withdraw from the study at any time without any risk. All of the candidates enrolled in this study will be strictly evaluated, based on the inclusion and exclusion criteria.

Randomization and Blinding

This will be an open-label trial, so neither the researchers nor the patients will be blinded. Patients will be randomly assigned to a high-voltage PRF combined with low-temperature CRF group, and a high-voltage PRF group at a ratio of 1:1. A simple random sample will be generated by IBM SPSS Statistics 25.0 (IBM Corporation, Armonk, NY). The allocations will be placed in opaque envelopes and sealed. These envelopes will then be placed in a safe, and the key will be safeguarded by the study nurse or the principal investigator. On the day of the procedure, the envelopes will be taken out sequentially according to the order of patients. All of the envelopes will be kept sealed until a puncture has been made in the correct area, and the patients are ready for the initiation of radiofrequency therapy.

Trial Interventions

All patients will lie in supine position on the computed tomography (CT) scanning table. Blood pressure, heart rate, electrocardiogram, and oxygen saturation will be continuously monitored. The negative plate of the radiofrequency generator (PMG-230, Baylis Medical Inc., Montreal, QC, Canada) will be placed on the skin of the abdomen. The puncture site will then be set approximately 3 cm from the corner of the mouth on the affected side, using the Hartel technique (34). Local infiltration anesthesia will be administered with 1% lidocaine. Slice CT scanning (2 mm/layer) and 3-dimensional computerized reconstruction will be performed using a CT scanner (LightSpeed 64 slice CT Scanner; General Electric Company, Boston, MA). Under CT guidance, a trocar (100 mm trocar with a 5-mm noninsulated tip, PMF-21-100-5, Baylis Medical Inc., Montreal, QC, Canada) will then be inserted through the ipsilateral foramen ovale to the Gasserian ganglion. The radiofrequency electrode (PMK-21-100, Baylis Medical Inc.) will then take the place of the core of the trocar. Sensory and motor electrical stimulation will be used to adjust the depth and direction of puncturing, to ensure accurate positioning. Fifty hertz of sensory electrical stimulation will induce tingling in the distribution of the trigeminal nerve at 0.1 to 0.3 V (35). Two hertz of motor electrical stimulation will induce mandibular movement at 0.1 to 0.3 V (35). After puncture has been made in the correct area, fentanyl (1 μg/kg) and midazolam (2 mg) will be given for conscious sedation. The patients will be assigned to either of the following groups, determined by the envelopes opened by the study nurse.

High-Voltage PRF Combined with Low-Temperature CRF Group

Two hertz of PRF will be administered at a voltage of 70 V, temperature of 42°C, pulse width of 20 ms, and treatment time of 600 s. (29,31) Then low-temperature CRF will be performed at 60°C, with a treatment time of 270 s (31,33).

High-Voltage PRF Group

Two hertz of PRF will be administered at a voltage of 70 V, temperature of 42°C, pulse width of 20 ms, and treatment time of 600 s (29,31).

Postoperative patients will remain in the hospital for 2 hours to monitor potential complications. The patients will continue to receive oral carbamazepine or oxcarbazepine treatment and the dose of the drug will be reduced gradually according to postoperative pain intensity until its withdrawal. After 1 month, the patients who do not respond well to high-voltage PRF combined with or without low-temperature CRF therapy (those with a modified Barrow Neurological Institute Pain Intensity Score [BNI] of IV and V) will undergo other treatments such as high-temperature CRF, balloon compression, Gamma knife surgery, or microvascular decompression.

Study Outcomes

Demographic and baseline information will be collected, and will include the following: age, gender, disease duration, laterality, affected nerve branches, NRS-11 scores, doses of carbamazepine or oxcarbazepine given, and scores on the World Health Organization Quality of Life Questionnaire (WHOQOL-BREF).

Primary Outcome

The modified BNI (Table 2) (11,36) will be used to evaluate the efficacy of treatment. Twelve months after the procedure, patients with BNI scores of I to III will be defined as having received effective treatment. The primary outcome will be the effectiveness of treatment after 12 months.

Secondary Outcome

- BNI score: BNI scores will be evaluated on day 1; after 1 and 2 weeks; and after 1, 2, 3, 6, and 12 months following the procedure.
- NRS-11 score: NRS-11 scores will be evaluated on day 1; after 1 and 2 weeks; and after 1, 2, 3, 6, and 12 months following the procedure.
- Dose of carbamazepine or oxcarbazepine will be recorded on day 1; after 1 and 2 weeks; and after 1, 2, 3, 6, and 12 months following the procedure.
- Patient satisfaction scores on the 5-point Likert scale (37) (1: poor, 2: fair, 3: good, 4: very good, 5: excellent) will be evaluated after 1, 6, and 12 months following the procedure.
- Quality of life: Scores on the WHOQOL-BREF (38) will be evaluated after 1, 6, and 12 months following the procedure.
- Numbness: BNI facial numbness scores (Table 3) (11) will be evaluated on day 1; after 1 and 2 weeks; and after 1, 2, 3, 6, and 12 months following the procedure.
- Anesthesia dolorosa: Whether the patient's facial sensation has decreased and/or is accompanied by pain will be recorded within 12 months of the procedure.
- Masticator weakness: Occlusal dysfunction or a lower degree of masseter muscle fullness on one side when biting hard will be evaluated within 12 months of the procedure.
- Corneal anesthesia: Whether touching the sclera with a sterile cotton swab causes the eyelids to close quickly will be evaluated within 12 months of the procedure.
- Keratitis: Eye dryness and pain, photophobia, lacrimation, excess mucus, and other conditions diagnosed as keratitis will be thoroughly investigated by an ophthalmologist and recorded within 12 months of the procedure.

Table 2. *The modified BNI score.*

Score	Pain Relief
I	No pain, off medications
II	Occasional pain, off medications
IIIa	No pain, continued use of medications
IIIb	Pain persists, but adequately controlled with medications
IV	Pain not adequately controlled with medications
V	No relief

Table 3. *The BNI facial numbness score.*

Score	Pain Relief
I	No facial numbness
II	Mild facial numbness, not bothersome
III	Facial numbness, somewhat bothersome
IV	Facial numbness, very bothersome

- Adverse reactions: Nausea, vomiting, and facial hematoma during and after the procedure, headache, dizziness, and cerebrospinal fluid leakage occurring within 2 weeks of the procedure will be recorded.

Follow-Up

The patients will be discharged from the hospital after the procedure. Regular outpatient and telephone follow-ups will be conducted. Outpatient follow-ups will be performed at 1, 6, and 12 months following the procedure, and patients will be suggested to actively report pain recurrence and adverse reactions by telephone or instant messaging. Follow-up will be conducted by a single trained doctor who will not be involved in the patient's enrolment and treatment processes (Table 4).

Data Collection

Case report forms and standard operating procedure will be based on this research protocol. All the researchers will be systematically trained and will execute a test run before the recruitment process begins. The data required from the case report form will be recorded by the researchers in charge of enrolment and follow-up. The data and safety monitoring committee (DSMC) will monitor the safety and validity data every 6 months to make recommendations on whether or not to continue the study. Back-to-back and double-entry systems using Epidata 4.6 (EpiData Association, Denmark) will ensure the accuracy of data entry.

Safety

All adverse events will be recorded in detail and given appropriate treatment and follow-up until fully treated or in a stable condition. Serious adverse events will be reported to the ethics committee, competent authorities, and trial sponsors within 24 hours. The DSMC will regularly review all adverse events, and convene meetings when necessary, to assess the risks and benefits of the study. The DSMC has the right to terminate the study at any time.

Patient and Public Involvement

Neither patients nor the public will be involved in the formulation of research questions, designs, or outcome measurements. Recruitment will be conducted through research posters and physicians' presentations. Patients will be screened and enrolled by trained physicians. The results of this study will be distributed to all patients in the form of newsletters. All patients will be informed regarding relevant intervention in detail.

Sample Size

The main purpose of this study will be to compare the effectiveness of high-voltage PRF combined with and without low-temperature CRF, evaluated 1 year after the procedure. According to our previous report, the effectiveness of PRF combined with low-temperature CRF group after 1 year was 91%, and that of the high-voltage PRF group was 69% (29) (The α is 0.05, and the power is 90%). Power Analysis and Sample Size (PASS) V.15.0 software (NCSS Corporation, Kaysville, UT, USA) was used to compute the sample size. The results show that 65 patients will be required in each group. However, considering the dropout rate is likely to be 10%, 73 patients will be recruited in each group. Therefore the total sample size of this study will be 146 patients.

Statistical Analysis

During data entry, names will be replaced by an alphanumeric code, and no personal information will be revealed. The statistician will use both intention-to-treat and per protocol analysis for the dataset using IBM SPSS V25.0 (IBM Corporation). The normally distributed continuous variables will be presented as means ± standard deviations. The nonnormally distributed continuous variables will be presented as medians (interquartile range). Two-sample t-tests or the Mann-Whitney/Wilcoxon signed-rank test will be used for data measurement, according to their distributions. The $\chi 2$ test or the Fisher exact test will be used for categorical data. A repeated measures analysis of variance on ranks will be performed for the repeated data, and Bonferroni correction will be used to correct multiple comparisons. Safety assessment will be evaluated using descriptive analysis. A *P* value of less than an alpha level of 0.05 will be defined as statistically significant.

Ethics and Dissemination

This protocol was approved by the institutional review board of Beijing Tiantan Hospital (KY-2019-266-01) and registered on clinicaltrials.gov (NCT04174443). The trial complies with the guidelines of the Declaration of Helsinki on ethical principles and good clinical practice. All patients will sign the written informed consent prior to randomization. They will also be informed that they have the right to withdraw from the study at any time. The study results will be submitted for publica-

tion in peer-reviewed journals. The anonymized patient-level dataset will be shared on clinicaltrials.gov.

Discussion

This study intends to adopt a rigorously designed and implemented randomized controlled method to evaluate the efficacy and safety of the administration of high-voltage PRF, combined with low-temperature CRF, for the treatment of primary trigeminal neuralgia. The aim of this study is to explore a treatment with greater efficacy and fewer side effects for patients with primary trigeminal neuralgia, who have found pharmacologic therapy ineffective. This treatment, if proven effective, may then be used as an alternative to a more traumatic operation.

The trial design of this study is open-label (39), as blinding is considered rather difficult to achieve and strictly maintain. For instance, the difference in radiofrequency treatment time between the 2 groups will make it easy for the health care providers, present to ensure patient safety, to figure out which group the patient has been assigned to. Side effects are also a factor that may cause unintentional unblinding. Additionally, low-temperature CRF reduces the incidence of facial numbness compared with high-temperature CRF (30-32,40); however, PRF rarely causes facial numbness and other side effects of nerve damage. Therefore some of the patients may be able to determine their group if they experience facial numbness.

Table 4. *The schedule of enrollment, interventions, and assessments.*

	STUDY PERIOD											
	Enrollment	Allocation	Postallocation									Close-out
TIMEPOINT	Preoperative	Procedure	Immediately after the procedure	1 day	1 week	2 weeks	1 month	2 months	3 months	6 months	12 months	
ENROLLMENT:												
Eligibility screen	X											
Informed consent	X											
Allocation		X										
INTERVENTIONS:												
PRF + CRF		X										
PRF		X										
ASSESSMENTS:												
Demographic and baseline information	X	X										
BNI score				X	X	X	X	X	X	X	X	X
NRS-11 score				X	X	X	X	X	X	X	X	X
Dose of drugs				X	X	X	X	X	X	X	X	X
Patient satisfaction score							X			X	X	X
Quality of life							X			X	X	X
Numbness				X	X	X	X	X	X	X	X	X
Side effects				X	X	X	X	X	X	X	X	X
Adverse reactions			X	X	X	X						

Based on the considerations, we think that if blinding is attempted in this study, it will inevitably lead to inadvertent unblinding. Open-label trials are also extensively used for the evaluation of nonpharmacologic treatments, which are more challenging to blind than pharmacologic treatments (41,42).

BNI score, the primary outcome of this study, will be used to evaluate treatment outcomes and calculate efficacy instead of the NRS-11 or the Visual Analog Scale (VAS). Although the NRS-11 and VAS are the most widely used pain questionnaires, the BNI score has 2 main advantages (11,36): First, the BNI score considers both pain and medication. For the patients who do not respond to pharmacologic therapy before the procedure, satisfactory pain relief can still be achieved through medication after radiofrequency procedure. These patients will still have benefitted from radiofrequency treatment. Second, the BNI score assesses the state of the patient, rather than a specific measured value. This makes the definition of the primary outcome clearer and more suitable for an open-label trial (43). Furthermore, we will also be including the NRS-11 to evaluate secondary outcome.

Although it is safer to puncture Gasserian ganglion with a curved blunt needle (44,45), these types of needles are not commercially available in our country. However, the punctures of Gasserian ganglion under the guidance of reconstructed 3-dimensional CT are relatively safe. The correct positioning of the needle tip is key to ensure efficacy and reduce complications. In this study, all the radiofrequency procedures will be performed under CT guidance. CT will clearly show the relative position of the needle as well as bony landmarks, improving the success rate of the puncture. Although CT scans have a higher radiation exposure than a single C-arm scan, CT guidance will allow the puncture to be accomplished more quickly, reducing the risk of additional radiation exposure and potential damage caused by repeated adjustments of needle repositioning (46). We previously reported that the puncture success rate of radiofrequency therapy through the foramen ovale under CT guidance was 100%, and that the punctures caused no severe complications (8,27). Moreover, sensory and motor stimulation will be used to indicate the distance of the needle from the Gasserian ganglion (35). Therefore puncture inaccuracy is highly unlikely to interfere with outcomes.

Conclusions

There are several limitations of this prospective study. First, the open-label study design may influence the measurement of outcomes and introduce bias, for example performance or ascertainment bias. Second, there is no uniform standard for the treatment duration of PRF and CRF at present. In our study, high-voltage PRF will be administered for 600 s, and low-temperature CRF will be administered for 270 s. This program, along with the treatment voltage and temperature, has been guided by published literatures and our clinical experience. Different treatment parameters may, however, lead to different effects. Finally, we plan to continue the follow-up process for 12 months. Therefore long-term efficacy assessment will require further research.

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