Randomized Trial

Effectiveness and Safety of High-Voltage Pulsed Radiofrequency to Treat Patients with Primary Trigeminal Neuralgia: A Multicenter, Randomized, Double-Blind, Controlled Study Protocol

Yitong Jia, MD[1], Yuesong Pan, MD[2], Hao Ren, MD[1], Nan Ji, MD[3], and Fang Luo, MD[1]

From: [1]Department of Anesthesiology and Pain Management, Beijing Tiantan Hospital, Capital Medical University, China; [2]Clinical Trial and Research Center for Stroke, Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, China; [3]Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, China

Address Correspondence:
Luo Fang, MD
Department of Anesthesiology and Pain Management
Beijing Tiantan Hospital
Dongcheng District
Beijing 100050, PR China
E-mail: luofangwt@yahoo.com

Disclaimer: This study was supported by Beijing Municipal Administration of Hospitals Clinical Medicine Development of Special Funding Support (No. XMLX201707) and Foundation for the Excellent Medical Staff of Beijing (No. 2011-3-034 and No. 2014-3-035). YJ, YP, and HR contributed equally to this work. NJ and FL contributed equally in designing the project.
Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

Manuscript received: 06-11-2017
Revised manuscript received: 02-25-2018
Accepted for publication: 04-03-2018

Free full manuscript: www.painphysicianjournal.com

Background: Trigeminal neuralgia (TN) is a neurological syndrome characterized by paroxysmal, lightning-like, severe pain in the facial area innervated by the trigeminal nerve. Patients who do not respond well to drug treatment can undergo a nerve block, a traditional conservative treatment. Pulsed radiofrequency (PRF) is a nondestructive pain intervention technique. However, its treatment effectiveness for TN has rarely been reported and remains controversial among scholars. A recent single-center preliminary clinical study showed that high-voltage PRF was significantly effective in the treatment of TN. However, whether high-voltage PRF is a viable pain treatment option for TN patients who are unresponsive to drug treatment must still be confirmed with standardized clinical studies by utilizing conservative nerve block treatment as a control.

Objective: To compare the effectiveness and safety of high-voltage PRF and nerve block for primary TN patients who have failed to respond to pharmacological treatment and who are seeking a better non-surgical treatment option.

Study Design: Prospective, multicenter, randomized, double-blind, controlled clinical trial.

Setting: Three interventional pain management centers in Beijing, China.

Methods: The study will include 134 consecutive patients with primary TN who have failed to respond to drug treatment. The patients will be randomly assigned to 2 groups, the nerve block group and the PRF group. The nerve block group will be slowly injected with 1.4 mL of a mixture of dexamethasone and lidocaine after 360 s of sham PRF treatment, and 0.5 mL of normal saline will be administered before the needle is withdrawn. The PRF group will undergo 360 s of 42°C PRF treatment at the highest output voltage that the patients can tolerate, after which the patients will be injected with the same concentration and volume of lidocaine and normal saline that the nerve block group receives. The Barrow Neurological Institute (BNI) pain intensity scale will be used to assess the degree of pain relief before and after the treatment.

Results: The effectiveness and safety of high-voltage PRF and nerve block to treat TN will be analyzed to determine significant differences in pain relief and functional improvement. The primary efficacy outcome measure is the response rate at one-year post-operation (BNI I-III/total number of cases*100%). Secondary efficacy outcome measures include the response rate at postoperative day 1, week 1, week 2, month 1, month 3, month 6 and year 2, the patient satisfaction score (PSS) at various time points, the dosage of antiepileptic drugs (milligrams per day), and information regarding patients with a BNI score of IV or V who switch to other therapies.

Limitations: The effects of the waveform, treatment duration, frequency and other parameters of PRF deserve further investigation.

Conclusions: This is the first multicenter, double-blind, randomized controlled study to compare the efficacy and safety of PRF and nerve block to treat TN patients who have failed to respond to drug treatment. Moreover, the value of PRF in TN treatment may need to be clinically clarified with evidence-based medical support and other advanced studies.

Key words: Trigeminal neuralgia, effectiveness, safety, pulsed radiofrequency

Pain Physician 2018: 21:469-481

Trigeminal neuralgia (TN) is characterized by paroxysmal, recurrent, electric shock-like severe pain within the facial region innervated by the trigeminal nerve. The preferred treatment for TN is antiepileptic drug therapy. However, no new breakthroughs have been made in drug treatment for TN in recent years. TN patients who do not respond to drug therapy can choose nerve block treatment with local anesthetic and steroid. Moreover, these patients can elect to undergo a novel, nondestructive treatment known as pulsed radiofrequency (PRF).

The one-year response rate of one-time nerve block treatment for TN is low. Multiple repeated treatments are often needed to achieve a certain clinical effectiveness (1-3). Therefore, traditional nerve block treatment raises several concerns such as puncture operation-associated risks, local anesthetic drugs and steroid-associated side effects. PRF is a new type of neuromodulation technique. The initially proposed PRF parameters are a pulse frequency of 2 Hz, an output voltage of 45 V, an output frequency of 500 kHz, a continuous current action of 20 ms, and an intermission period of 480 ms. Within these parameters, the heat can be dissipated, the temperature during treatment will not exceed 42°C, and the heat will not cause target tissue injury (4-7). The nature of PRF offers attractive clinical prospects. Up to now, the efficacy of PRF in the treatment of TN is not yet unanimously recognized by all researchers. In 2003, Van Zundert et al (8) first reported that PRF treatment in 5 TN patients achieved satisfactory efficacy. In 2015, Nader et al(1) reported a TN patient underwent PRF treatment and achieved 100% pain relief for over 6 months without any side effects. In contrast, a prospective, randomized, controlled study by Erdine et al (9) in 2007 reported no effectiveness of PRF for the treatment of TN. Moreover, Elawamy et al (10) compared the effectiveness of PRF, continuous radiofrequency (CRF) and CRF combined PRF for idiopathic TN and found that PRF achieved the least effective rate. Nowadays, PRF is not yet recommended as a therapeutic method in TN treatment guidelines because of limited data from clinical studies.

As early as 2006, Teixeira and Sluijter (11) first proposed the concept of high voltage PRF with adjusting the output voltage from standardized 45 V to 60 V on patients with discogenic pain and achieved a very significant fall in the numeric rating scale (NRS) scores over the first 3 months. Our previous studies found that the output voltage of PRF for the treatment of TN under computed tomography (CT) guidance is positively correlated with its efficacy (12-14). In 2014, we have investigated the efficacy of PRF with standard voltage for TN and the effective rate was only 35% (12). However, our subsequent study confirmed that among refractory TN patients who were unresponsive to drugs and nerve block, the one-year response rate (69%) with high-voltage PRF treatment was significantly higher than that with standard voltage (19%) (15). High-voltage PRF would allow a significant number of patients to avoid undergoing other surgical treatments that are associated with greater side effects and risks. However, it remains unclear whether it is a viable therapeutic choice for TN patients in whom pharmacological treatment is ineffective. Thus, standardized clinical studies that utilize nerve blocks as a control are required to provide stronger evidence. Therefore, the aim of this study is to design a multicenter, randomized, double-blind, controlled study to compare the long-term pain relief effectiveness of CT-guided high-voltage PRF treatment and traditional nerve block treatment on Gasserian ganglion for TN patients in whom conservative drug treatment is ineffective. We seek to determine whether high-voltage PRF could be a minimally invasive, safe, effective and durable treatment option for primary TN patients.

Objective

This is a prospective, multicenter, randomized, double-blind, controlled clinical study designed to compare the efficacy and safety of high-voltage PRF and nerve block for primary TN patients who have failed to respond to drug treatment and are seeking a better non-surgical treatment option.

Setting

The study will enroll patients from Beijing Tiantan Hospital, Beijing Friendship Hospital, and Beijing Ditan Hospital, China. All researchers will be trained using the same training protocol. All researchers are required to have clinical experience with both therapies and to have practiced both therapies clinically for over one year before participating in this study.

Approval of the Study Protocol

All procedures in the trial are in accordance with the World Medical Association's "Helsinki Declaration (version 19 October 2013)". The study plan (protocol version 1.0) is approved by the Ethics Committee of Beijing Tiantan Hospital, Capital Medical University, China (KY2017-004-01). The study strategy has been registered at ClinicalTrails.Gov (NCT03131466).

Informed Consent

All enrolled TN patients have the right to be informed of the study's objective, experimental procedure, benefits of the study and possible risks. All patients will sign written informed consent. Each patient will be given sufficient time to consider whether to participate in the study. Patients who participate in the study will be freely allowed to obtain more information, withdraw their consent, or discontinue participation without restrictions at any time.

Study Population

One hundred thirty-four patients who meet the inclusion criteria will be enrolled in the study. The patients will be randomly divided into 2 groups. The high-voltage PRF group will undergo 42°C high-voltage PRF treatment, and the nerve block group will undergo nerve block treatment with steroid and local anesthesia.

Pre-Enrollment Evaluation

The pre-enrollment evaluation will determine the demographic and preoperative data of patients, including age (years), gender (male or female), duration of disease (months), pain distribution (V1, V2, V3, V1-2, V2-3, V1-3), pain laterality (left / right), dosage of antiepileptic drugs (milligrams per day), Barrow Neurological Institute (BNI) pain intensity score (Table 1), and patient satisfaction score (PSS) (9). The BNI pain intensity score (16) includes 2 elements, the pain intensity element defined into 4 levels: none, occasional, some, and severe while the element of the situation of medication usage classified into no medication, reduced medication, and continued medication use (17). PSS scores will be used to evaluate patient satisfaction: 0 point indicates unsatisfactory, while 10 points indicate very satisfactory.

Inclusion Criteria

- Primary TN patients who meet the criteria of the International Classification of Headache Disorders (18).
- Age 18 to 75 years.
- Have responded poorly to drug treatment or are unable to tolerate the side effects of drug therapy.
- BNI pain intensity score of IV-V (16).
- Be supposed to undergo neurosurgical intervention according to TN treatment guidelines (19).
- Have signed informed consent.

Exclusion Criteria

- Coagulation disorders or bleeding disorders.
- Abnormal electrocardiogram or chest x-ray results.
- Severe cardiopulmonary dysfunction.
- Infection at the puncture site.
- History of mental illness.
- History of narcotic drug abuse.
- Allergy to local anesthetic drugs or steroids.
- Unable to cooperate with the treatment.
- Have undergone invasive treatments such as radiofrequency thermocoagulation, chemical ablation, balloon compression surgery, gamma knife treatment, peripheral denervation or microvascular decompression.

Subject Eligibility and Identification

After each patient signs the informed consent, the researchers will complete the eligibility checklists according to the items listed on the case report form (CRF). If the patient does not meet any of the inclusion criteria, he or she will not be enrolled in the clinical study, and exclusion will be noted.

Study Interventions

Procedure

Patients will lie in a supine position with their neck slightly extended on the CT scan bed and will be continuously monitored for blood pressure, heart rate, electrocardiogram and pulse oximetry. The negative plate of a PMG-230 Pain Management Generator (Baylis Medical Inc., Montreal, Canada) will be affixed to the patient's supper back, and the puncture treatment and other procedures will be conducted under aseptic conditions. Hartel's anterior approach will be used, and the puncture point will be approximately 3 cm outside the commissure of the mouth on the affected side. Anesthesia will be locally applied, and the 5-mm active tip

Table 1. *BNI pain intensity scoring criteria.*

BNI Pain Intensity Score	Definition
I	No pain, no medication required
II	Occasional pain, no medication required
IIIa	No pain, completely controlled with medication
IIIb	Some pain, can be adequately controlled with medication
IV	Some pain, can't be adequately controlled with medication
V	Severe pain, no pain relief

BNI: barrow neurological institute

of the 10-cm long, 21-gauge radiofrequency treatment trocar (PMF-21-100-5, Baylis Medical Inc., Montreal, Canada) will be inserted under the guidance of three-dimensional reconstruction using a thin-layer (2 mm/layer) CT scan (SOMATOM SIEMENS Company, Munich, Germany) of the skull base until the trocar accurately punctures the foramen ovale (Fig. 1).

The stylet will be removed, and a radiofrequency electrode (PMK-21-100, Baylis Medical Inc., Montreal, Canada) will be inserted. Electrical stimulation (50 Hz) will be used to determine the sensory threshold. A prickling sensation in the area innervated by trigeminal nerve can be induced by 0.1 - 0.3 V covering the painful site. Additionally, 2Hz electrical stimulation will be used

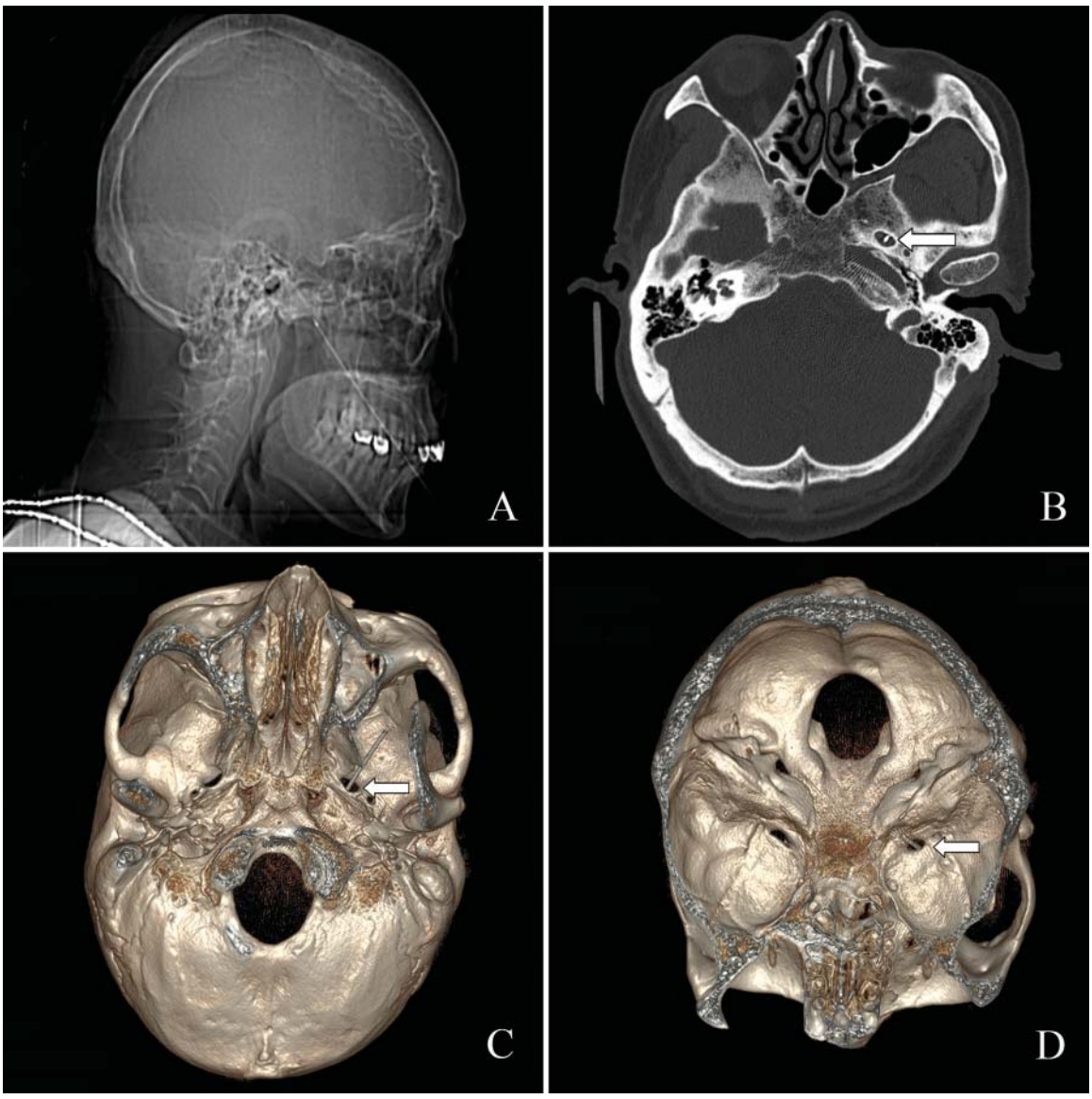

Fig. 1. *CT-guided puncture of the Gasserian ganglion. A) Location image. B) (the horizontal view) CT scan showing the tip of the trocar entering the foramen ovale.C) (skull base view) 3D CT reconstruction imaging showing that the trocar entering the foramen ovale. D) (interior skull base view) 3D CT reconstruction imaging showing that the trocar entering the foramen ovale.*

to test the motor threshold. 0.1 - 0.3 V can induce motion of mandible. The depth and direction of the trocar will be adjusted slightly corresponding to the patient's sensation and movement to ensure the accuracy of the puncture location.

The patients will be randomly divided into a nerve block group and a PRF group. In the nerve block group, a radiofrequency generator will be set at the sensory stimulating mode, and the lowest frequency of 0.2 V will be used for 360 s sham PRF treatment (20), after which 1.4 mL of a mixture of 2 mg of dexamethasone sodium phosphate and 1 mL of 1% plain lidocaine will be slowly injected through the radiofrequency treatment trocar. Before the trocar is removed, 0.5 mL of normal saline will be injected (21,22). In the PRF group, the pain treatment generator (15,23,24) will be set to manual PRF mode, and the upper temperature limit will be set to 42°C.The PRF output voltage will then be gradually increased to the highest voltage the patient can tolerate, and the patient will be treated for 360 s. After the treatment, 1.4 mL of a mixture of 0.4 mL of normal saline and 1 mL of 1% lidocaine will be injected through the trocar. Before the trocar is removed, 0.5 mL of normal saline will be injected.

Additional Interventions

If the Gasserian ganglion puncture is not successful or the treatment is not completed for other reasons, the patient will be considered a contravention of the project and will be excluded from the study. After treatment, the patient will be observed in the outpatient recovery room for approximately 6 h. The patient will be discharged from the hospital if he/she does not experience any discomfort. After treatment, the patients' doctors will decide whether to continue adjuvant antiepileptic drugs according to their condition, and the drug dosage will be adjusted based on the degree of pain.

Patients can be unblinded upon request or if they experience any emergency conditions. Unblinded patients and patients lost to follow-up will be considered withdrawn from the study. If the researchers determine that the treatment is ineffective or if the patients are not satisfied with the efficacy after one month, the patients can elect to switch to microvascular decompression, radiofrequency thermocoagulation, gamma knife treatment, or another more invasive treatment after unblinding. After one month of treatment, patients whose treatment is defined as effective by the researchers but later experience a relapse of pain can also be unblinded. These patients can then choose to undergo repeated nerve blocks, PRF or other more invasive therapies.

Follow-up

Patients in both groups are required to complete a 1-year follow-up. The follow-up evaluations will include postoperative short-term (postoperative day 1, week 1, week 2, month 1, month 3 and month 6) and long-term (year 1 and year 2) BNI scores, PSS scores, antiepileptic drug dosages (milligrams per day), adverse events (AEs) and information regarding patients with a BNI score of IV and V who switch to other therapies.

Outcomes

Primary Outcome

The primary outcome parameter is the 1-year response rate of TN treatment with high-voltage PRF and traditional nerve block. The BNI score will be used to assess pain degree. The degree of pain relief will be evaluated as "excellent" (BNI pain score I-II), "good" (BNI pain score III), or "poor" (BNI pain score IV-V). The response rate will be calculated as [excellent and good pain relief (BNI I - III)]/ [total number of cases] *100%.

Secondary Outcomes

The secondary outcome parameters will include the postoperative response rates at day 1, week 1, week 2, month 1, month 3, month 6, and year 2, PSS scores at each follow-up time point within 2 years, dosage of adjuvant antiepileptic drugs, intraoperative and postoperative AEs, and data regarding patients with a BNI of IV or V who switch to other treatments.

Data Management and Analysis

Sample Size

Previous studies regarding Gasserian ganglion block have reported only cases with satisfactory results without examining the response rate. The 1-year response rate of 1-time treatment for TN using maxillary and mandibular blocks administered via a modified coronoid approach was 25% (3). Based on clinical experience, the response rate of Gasserian ganglion block under CT guidance is expected to be 40% higher than the response rate of maxillary and mandibular blocks. Previous studies have reported that the one-year response rate of high-voltage PRF on Gasserian ganglion under CT guidance to treat TN was 69% (15). With 134

patients in total (67 in each arm), we have 90% power to test the difference of 40% response rate in treated group and 69% response rate in the control group, with an $\alpha = 0.05$ and a drop-out rate of 10%.

Statistical Methods

All statistical analyses were performed with SAS 9.4. The Shapiro-Wilk test will be used to test whether all data follow a normal distribution. Data with a normal distribution will be expressed as the mean ± standard deviation. Data without a normal distribution will be expressed as the median and interquartile range.

A differential test will be used to compare the efficacy outcome indexes between the PRF group and the nerve block group. The outcome measures of the 2 groups will be compared at all the time points. Chi-square test and Fisher's exact test will be used for categorical variables. Student's t test will be used for continuous variables with a normal distribution, and the Mann-Whitney U test will be used for data without a normal distribution. In addition, the outcome measures in each group at all postoperative time points will be compared with the preoperative data in the same group. Categorical data will be analyzed using a paired chi-square test, while measurement data will be analyzed using paired t test or signed-rank test. Descriptive analyses will be used for all randomized and treated patients to evaluate safety indicators. A *P*-value of $\leq$ 0.05 will be considered statistically significant.

Intent-to-treat (ITT) and Per-Protocol (PP) Analyses

Intent-to-treat analysis and per-protocol analysis will be performed to analyze data. For patients who drop out from the study, the initial data or the last follow-up data will be utilized in accordance with specific conditions. Before unblinding the intervention measures, the responsible biometrician will determine whether the patient will be allocated to the PP analysis or ITT analysis.

Randomization and Allocation Concealment

The present study will enroll a total of 134 patients, and the patients will be randomized to 1 of the 2 study groups, each group with 67 patients (1:1 randomization). The randomization will be separately performed by the researchers at the 3 centers. After patients have been confirmed to meet the basic inclusion criteria, they will be randomly divided into 1 of the 2 research groups using a randomization sequence generated by SAS software.

Each research center will appoint a research nurse who will oversee the allocation. A random data table will be prepared beforehand. A sealed opaque randomized envelope will be given in the order of the consecutively enrolled patients. After the intraoperative puncture reaches Gasserian ganglion, the sealed envelope, which will contain the concealed randomized treatment protocol, will be opened by the research nurse, and the patient will be assigned to undergo the corresponding treatment. The research nurse will also be responsible for preparing the respective drugs to be used for intraoperative injection in the 2 groups.

Blinding

The patients and the pain doctors responsible for conducting the intervention treatment will be blinded to the group assignment. The sound of the radiofrequency generator will be turned off during the treatment. The research nurse will oversee operating the radiofrequency generator to perform PRF treatment or sham treatment based on the patient's grouping. After the treatment and before the trocar is removed, the pain doctor will slowly inject drugs prepared by the research nurse. Other than the research nurse, neither the personnel in the treatment room nor the patient will know the treatment assignment. The trained pain doctors will conduct blind evaluations at all postoperative time points.

Safety Assessments

During intraoperative and all postoperative follow-up time points (postoperative day 1, week 1, week 2, month 1, month 3, month 6 year 1 and year 2), the details of any AEs or adverse device effects reported by the subject will be documented in the CRF. The record will include the nature, start time, duration time, severity, relationship with the intervention treatment and prognosis of such events. The incidence of AEs will be reported by the subject and evaluated by the follow-up doctor. Intraoperative and postoperative AEs include vomiting, bradycardia, facial hematoma, transient diplopia, dysesthesia, masseter weakness, corneal anesthesia, keratitis and other incidences (Table 2). At each follow-up time point, the follow-up doctor will evaluate the degree of patients' AEs as "mild," "moderate," or "severe."

All AEs, regardless of their relationship with the study or severity, will first be treated by the researchers in a timely and appropriate manner until they are satisfactorily resolved. The AEs will be documented in the subject's CRF, and the study monitor will be informed

of the AEs. The severity and treatment of the AEs and their relationship with the study device/procedure will be reported. Severe AEs or adverse device effects that occur during the study, such as fatal or life-threatening events, must be immediately reported to the Institutional Review Board (IRB).

Results

Patient Flow

An illustration of the sequence of events during participation is shown in Table 3.

Recruitment

Recruitment will begin in April 2017 and will end in December 2018.We have completed interventions on 2 patients.

Baseline Data

Baseline demographics and clinical features will be documented including age (years), gender (male or female), duration of disease (months), pain distribution (V1, V2, V3, V1-2, V2-3, V1-3), pain laterality (left / right), dose of adjuvant antiepileptic drugs (milligrams per day), BNI score at baseline, and PSS. Significant differences will be assessed between the groups. Baseline data will be presented as shown in Table 4.

Data Analysis

The duration of this study is proposed to be from April 2017 to December 2019 and will include the selection of 134 patients (67 patients in each group). The SAS 9.4 statistical analysis system will be used to analyze the follow-up data, and the obtained results will be presented as shown in Table 5.

Efficacy

BNI, PSS, and the dosage of adjuvant antiepileptic drugs at postoperative day 1, week 1, week 2, month 1, month 3, month 6, year 1 and year 2 will be illustrated for the two groups, and significant differences will be compared between the 2 groups. In addition, the response rates of both groups will be calculated and compared.

Table 2. *Complications following intervention template.*

	PRF group (n = 67)	Nerve block group (n = 67)	*P* value
No complications			
Vomiting			
Bradycardia			
Facial hematoma			
Transient diplopia			
Facial numbness			
Dysesthesia			
Masseter weakness			
Trigeminal motor dysfunction			
Corneal anesthesia			
Keratitis			
Cranial nerve palsies			
Meningitis			
Intracranial hematoma			
Carotid-cavernous fistula			
Mortality			

Data described number (%), PRF: pulsed radiofrequency

Safety

The incidence of the AEs associated with the device and/or the procedure during the operation and throughout the entire postoperative follow-up period of the 2 groups will be compared. All study-related AEs will be monitored, and details about AEs including the nature, severity, duration, treatment, and relationship to the study procedure will be reported. The occurrence of all AEs will be identified by the study principal investigators.

Discussion

According to the TN treatment guidelines published by the American Academy of Neurology (AAN) and the European Federation of Neurological Societies (EFNS) (25), patients who have a poor response to carbamazepine or oxcarbazepine treatment are recommended to undergo surgical treatment. However, some patients do not want to receive surgical treatment or have contraindications for surgical treatment.

Surgical treatment includes nerve-damaging minimally invasive interventional therapies such as percutaneous retrogasserian glycerol injection, radiofrequency thermocoagulation, balloon decompression, and stereotactic radiosurgery (SRS). Moreover, it also includes neurosurgical microvascular decompression (MVD) (19,26). Unfortunately, evidence regarding the efficacy of interventional procedures is limited, and all inter-

Table 3. *Content for the schedule of enrollment, interventions and assessments.*

	Study Period									
	Enrolment	Allocation	Postoperative follow-up							Close out
Time point	Preoperative	0 d	1 d	1 wk	2 wk	1 mo	3 mo	6 mo	1 yr	2 yr
Enrollment										
Eligibility screen	X									
Informed consent	X									
Allocation		X								
Interventions										
Pulsed radiofrequency		X								
Nerve block		X								
Assessments										
Age	X									
Gender	X									
Duration of disease	X									
Pain distribution	X									
Pain laterality	X									
Dosage of antiepileptic drugs	X		X	X	X	X	X	X	X	X
BNI score	X		X	X	X	X	X	X	X	X
Patient satisfactory score	X		X	X	X	X	X	X	X	X
50 Hz stimulating voltage		X								
2 Hz stimulating voltage		X								
Tissue resistance		X								
RF output voltage		X								
Surgery duration		X								
Adverse events		X	X	X	X	X	X	X	X	X
Other treatments						X	X	X	X	X

BNI: barrow neurological institute; RF: radiofrequency

Table 4. *Demographic characteristics and preoperative data template.*

		PRF group	Nerve block group	*P* value
Age	Mean ± standard deviation			
Gender	Male			
	Female			
Duration of disease (months)	Mean ± standard deviation			
Pain distribution	V1			
	V2			
	V3			
	V1-2			
	V2-3			
	V1-3			
Pain laterality	Left			
	Right			
Dosage of antiepileptic drugs (milligrams per day)	Mean ± standard deviation			
BNI score	Mean ± standard deviation			
PSS	Mean ± standard deviation			

PRF: pulsed radiofrequency. * indicates significant difference between groups ($P < 0.05$).

Table 5. *The effectiveness and safety assessment between 2 groups (template).*

	Time points	PRF group	Nerve block group	*P* value
BNI	1 day			
Effective rate (%)				
PSS				
Dosage of antiepileptic drugs (milligrams per day)				
Adverse event rate (%)				
BNI	1 week			
Effective rate (%)				
PSS				
Dosage of antiepileptic drugs (milligrams per day)				
Adverse event rate (%)				
BNI	2 weeks			
Effective rate (%)				
PSS				
Dosage of antiepileptic drugs (milligrams per day)				
Adverse event rate (%)				
BNI	1 month			
Effective rate (%)				
PSS				
Dosage of antiepileptic drugs (milligrams per day)				
Adverse event rate (%)				
BNI	2 months			
Effective rate (%)				
PSS				
Dosage of antiepileptic drugs (milligrams per day)				
Adverse event rate (%)				

ventions have their own shortcomings. For example, after percutaneous radiofrequency thermocoagulation is performed, the region innervated by the trigeminal nerve may present hypesthesia, masseter muscle weakness and other discomfortable symptoms (27), which significantly influence patient quality of life. The treatment of TN with SRS has a slower onset, and the therapeutic effect is correlated with dose. Although increasing the dose can improve efficacy, it simultaneously increases the risk of facial numbness (28). MVD is one of the most effective therapeutic methods for TN patients (29-32). However, it will be ineffective without neurovascular compression (NVC). Moreover, MVD is not suitable for patients with advanced age, complications or weakness (33). Therefore, despite the existence of a variety of treatment options, the long-term efficacy of TN remains unsatisfactory.

With the acceleration of aging of the global population, the number of TN patients is increasing, particularly including the number of elderly TN patients. Thus, it is urgent to explore minimally invasive, safe, effective, and persistent non-surgical treatment options such as intranasal spray, subcutaneous injections, nerve blocks, botulinum toxin injection and PRF. Future studies should focus on improving the efficacy of non-surgical treatment options and providing scientific and medical evidence to support innovative non-surgical technologies as choices before surgery and for patients who are reluctant to undergo surgical treatment.

In recent years, PRF has been increasingly used to treat clinical chronic pain disorders as a neuromodulation treatment, including discogenic pain (11,34,35), postherpetic neuralgia (36), chronic lumbosacral radicular pain (37-39), and phantom limb pain (40-42), etc. Neuromodulation treatment is also the focus of future studies for TN. A limited number of clinical observational studies suggest that refractory TN patients

Table 5 con't. *The effectiveness and safety assessment between 2 groups (template).*

	Time points	PRF group	Nerve block group	*P* value
BNI	3 months			
Effective rate (%)				
PSS				
Dosage of antiepileptic drugs (milligrams per day)				
Adverse event rate (%)				
BNI	6 months			
Effective rate (%)				
PSS				
Dosage of antiepileptic drugs (milligrams per day)				
Adverse event rate (%)				
BNI	1 year			
Effective rate (%)				
PSS				
Dosage of antiepileptic drugs (milligrams per day)				
Adverse event rate (%)				
BNI	2 years			
Effective rate (%)				
PSS				
Dosage of antiepileptic drugs (milligrams per day)				
Adverse event rate (%)				

* indicates significant difference between groups ($P < 0.05$). # Denotes values are expressed as median and interquartile range, otherwise as mean ± standard deviation.

in whom pharmacological treatment and nerve block are ineffective achieve higher success rates after PRF treatment (8,43). Clinical studies providing stronger evidence are required to further clarify the value of PRF for the treatment of TN.

Previous studies have reported that nerve block treatment of TN often requires multiple punctures and injection of local anesthetic drugs and steroids (1,3). While, one-time PRF treatment may provide a longer period of pain relief in TN patients (8). However, there is currently no report that has compared the efficacy of nerve block and PRF in TN patients in whom drug treatment is ineffective. Among the growing number of studies on improving the efficacy of PRF technology for TN treatment (12,13,15,43,44), high-voltage PRF is a particularly promising option for the treatment of refractory TN (15,44). By comparing the differences in efficacy between high-voltage PRF and nerve block treatment for TN, the present study can provide TN patients who have poor responses to drug treatment with a more effective treatment option with fewer side effects. The results of this study may help to optimize treatment guidelines for TN.

Previous reports have revealed that puncture of Gasserian ganglion was often performed under the guidance of C-arm imaging (9), which is not as intuitive as the guidance of reconstructed three-dimensional CT (12). Serious complications including death hematomas could happen in the procedure of foramen ovale puncturing under the guidance of fluoroscopy (45,46). However, patients in both groups in this study will undergo puncture under CT guidance, which will significantly improve the success rate of the puncture and avoid the effect of inaccurate puncture positioning on the results. Bhatjiwale et al reported that the use of the straight RF needle on a patient with ophthalmic division (V1) medically uncontrolled neuralgia obtained satisfactory efficacy with no obvious complications (47). Our previous studies also demonstrated that the punctures of Gasserian ganglion with the sharp trocar under the guidance of reconstructed 3-dimensional CT were relatively safe without reported complications (12,13,15).

There is no doubt that the curved blunt needle with an injectable side port may cause less tissue injury during the procedure and it deserves further investigations when blunt needles are commercially available in our country. Although the prognosis indicators of this study are subjective, our use of a randomized, double-blind, controlled design in which both the patients and follow-up doctors are blinded to the treatment allocation will prevent bias. Therefore, the present trial results will offer valuable scientific evidence.

The results of this study are expected to be obtained in 2019, and scientific reports will be published thereafter.

Study Limitations

The present study examines the effectiveness and safety of only 1 year after treatment. However, longer follow-up would provide more significant results. Consistent with similar studies, the present study examines only the degree of pain relief, satisfaction, side effects and other subjective indicators but lacks objective evaluation methods. Electrophysiological examination may provide further information regarding changes in neurological function, which is worth studying in the future. In 2010, Tanaka et al (48) found that increasing the treatment duration of PRF from 120 to 360 seconds showed a significant antiallodynic effect without nerve injury in rats. Recently, PRF treatment was applied for 360 seconds in several clinical studies (49,50). In this study, we also selected to investigate the treatment duration of 360 seconds with PRF. In a prospective double blind randomized study, van Kleef et al (6) evaluated the efficacy of radiofrequency lesion at 67°C and the results showed a 67°C radiofrequency lesion could effectively alleviated cervicobrachial pain. Heavner et al (51) found that PRF at 60°C did not cause egg white coagulation in vitro, while above 60°C, PRF produced thermocoagulation similar to CRF (51). Ali Eissa et al reported that the combination of PRF at 45°C for 12 minutes followed by CRF at 60°C for 2 minutes and 65°C for 2 minutes could achieve excellent pain relief and reduced consumption of analgesics for idiopathic TN patients 12 months after the procedure in a retrospective study (49). In 2017, Elawamy et al (10) compared the effect for idiopathic TN after CRF, PRF, and combined CRF and PRF treatment of the Gasserian ganglion and demonstrated that the best efficacy were observed in the CRF and PRF group, that is, the PRF for 10 minutes at 42°C followed by CRF for 270 seconds at 60°C, and with no complications for 2 year follow-up. Recently, it seems that the PRF combined with 60°C CRF treatment may become a novel technique for the trigeminal neuralgia patients but the clinical studies include small numbers of patients which deserves further investigation. However, the effects of the waveform, treatment duration, pulse width, frequency and other parameters on the efficacy of PRF still need to be studied. We aim to investigate the effectiveness and safety of high-voltage PRF to treat patients with primary trigeminal neuralgia under CT guidance which may restrict access clinically. The punctures under the more common used C-arm imaging guidance deserve to be evaluated in the future. Furthermore, the cost-effectiveness of nerve block and PRF, which is an important issue in clinical practice, is also worth evaluating.

Conclusion

This is the first multicenter, randomized, double-blind, controlled study to compare the effectiveness and safety of PRF and nerve block for the treatment of TN patients who have poor responses to drug treatment. The value of PRF for the clinical treatment of TN needs to be confirmed by conducting evidence-based medical studies and other advanced studies.

References

1. Nader A, Kendall MC, De Oliveria GS, Chen JQ, Vanderby B, Rosenow JM, Bendok BR. Ultrasound-guided trigeminal nerve block via the pterygopalatine fossa: An effective treatment for trigeminal neuralgia and atypical facial pain. *Pain Physician* 2013; 16:E537-E545.
2. Han KR, Chae YJ, Lee JD, Kim C. Trigeminal nerve block with alcohol for medically intractable classic trigeminal neuralgia: Long-term clinical effectiveness on pain. *Int J Med Sci* 2017; 14:29-36.
3. Elsheikh NA, Amr YM. Calcitonin as an additive to local anesthetic and steroid injection using a modified coronoid approach in trigeminal neuralgia. *Pain Physician* 2016; 19:457-464.
4. Tsou HK, Chao SC, Wang CJ, Chen HT, Shen CC, Lee HT, Tsuei YS. Percutaneous pulsed radiofrequency applied to the l-2 dorsal root ganglion for treatment of chronic low-back pain: 3-year experience. *J Neurosurg Spine* 2010; 12:190-196.
5. Kang KN, Park IK, Suh JH, Leem JG, Shin JW. Ultrasound-guided pulsed radiofrequency lesioning of the phrenic nerve in a patient with intractable hiccup. *Korean J Pain* 2010; 23:198-201.
6. Rehman SU, Khan MZ, Hussain R, Jamshed A. Pulsed radiofrequency modulation for lingual neuralgia. *Br J Oral Maxillofac Surg* 2012; 50:e4-e5.
7. Sluijter ME. Pulsed radiofrequency. Anesthesiology 2005; 103:1313; author reply 1313-1314.
8. Van Zundert J, Brabant S, Van de Kelft E, Vercruyssen A, Van Buyten JP. Pulsed radiofrequency treatment of the gasserian ganglion in patients with idiopathic trigeminal neuralgia. *Pain* 2003; 104:449-452.
9. Erdine S, Ozyalcin NS, Cimen A, Celik M, Talu GK, Disci R. Comparison of pulsed radiofrequency with conventional radiofrequency in the treatment of idiopathic trigeminal neuralgia. *Eur J Pain* 2007; 11:309-313.
10. Elawamy A, Abdalla EEM, Shehata GA. Effects of pulsed versus conventional versus combined radiofrequency for the treatment of trigeminal neuralgia: A prospective study. *Pain Physician* 2017; 20:E873-E881.
11. Teixeira A, Sluijter ME. Intradiscal high-voltage, long-duration pulsed radiofrequency for discogenic pain: A preliminary report. *Pain Med* 2006; 7:424-428.
12. Fang L, Ying S, Tao W, Lan M, Xiaotong Y, Nan J. 3d ct-guided pulsed radiofrequency treatment for trigeminal neuralgia. *Pain Pract* 2014; 14:16-21.
13. Luo F, Meng L, Wang T, Yu X, Shen Y, Ji N. Pulsed radiofrequency treatment for idiopathic trigeminal neuralgia: A retrospective analysis of the causes for ineffective pain relief. *Eur J Pain* 2013; 17:1189-1192.
14. Luo F, Lu J, Shen Y, Meng L, Wang T, Ji N. Effectiveness and safety of pulsed radiofrequency treatment guided by computed tomography for refractory neuralgia of infraorbital nerve: A pilot study. *Pain Physician* 2015; 18:E795-E804.
15. Fang L, Tao W, Jingjing L, Nan J. Comparison of high-voltage- with standard-voltage pulsed radiofrequency of gasserian ganglion in the treatment of idiopathic trigeminal neuralgia. *Pain Pract* 2015; 15:595-603.
16. Rogers CL, Shetter AG, Fiedler JA, Smith KA, Han PP, Speiser BL. Gamma knife radiosurgery for trigeminal neuralgia: The initial experience of the barrow neurological institute. *Int J Radiat Oncol Biol Phys* 2000; 47:1013-1019.
17. Lee JY. Measurement of trigeminal neuralgia pain: Penn facial pain scale. *Neurosurg Clin N Am* 2016; 27:327-336.
18. Cruccu G, Finnerup NB, Jensen TS, Scholz J, Sindou M, Svensson P, Treede RD, Zakrzewska JM, Nurmikko T. Trigeminal neuralgia: New classification and diagnostic grading for practice and research. *Neurology* 2016; 87:220-228.
19. Maarbjerg S, Di Stefano G, Bendtsen L, Cruccu G. Trigeminal neuralgia - diagnosis and treatment. Cephalalgia 2017:333102416687280.
20. Shanthanna H, Chan P, McChesney J, Paul J, Thabane L. Assessing the effectiveness of 'pulse radiofrequency treatment of dorsal root ganglion' in patients with chronic lumbar radicular pain: Study protocol for a randomized control trial. *Trials* 2012; 13:52.
21. Huang J, Ni Z, Finch P. Gasserian ganglion and retrobulbar nerve block in the treatment of ophthalmic postherpetic neuralgia: A case report. *Pain Pract* 2016; 17:961-967.
22. Candido KD, Germanovich A, Ghaly RF, Gorelick GH, Knezevic NN. Case report: Computed tomography scan-guided gasserian ganglion injection of dexamethasone and lidocaine for the treatment of recalcitrant pain associated with herpes simplex type 1 infection of the ophthalmic division of the trigeminal nerve. *Anesth Analg* 2011; 112:224-227.
23. Cho IT, Cho YW, Kwak SG, Chang MC. Comparison between ultrasound-guided interfascial pulsed radiofrequency and ultrasound-guided interfascial block with local anesthetic in myofascial pain syndrome of trapezius muscle. *Medicine (Baltimore)* 2017; 96:e6019.
24. Kim JH, Kim E, Kim BI. Pulsed radiofrequency treatment of the superior hypogastric plexus in an interstitial cystitis patient with chronic pain and symptoms refractory to oral and intravesical medications and bladder hydrodistension: A case report. *Medicine (Baltimore)* 2016; 95:e5549.
25. Cruccu G, Gronseth G, Alksne J, Argoff C, Brainin M, Burchiel K, Nurmikko T, Zakrzewska JM. Aan-efns guidelines on trigeminal neuralgia management. *Eur J Neurol* 2008; 15:1013-1028.
26. Wang DD, Raygor KP, Cage TA, Ward MM, Westcott S, Barbaro NM, Chang EF. Prospective comparison of long-term pain relief rates after first-time microvascular decompression and stereotactic radiosurgery for trigeminal neuralgia. *J Neurosurg* 2017:1-10.
27. Koning MV, Koning NJ, Koning HM, van Kleef M. Relationship between sensory stimulation and side effects in percutaneous radiofrequency treatment of the trigeminal ganglion. *Pain Pract* 2014; 14:581-587.
28. Kotecha R, Kotecha R, Modugula S, Murphy ES, Jones M, Kotecha R, Reddy CA, Suh JH, Barnett GH, Neyman G, Machado A, Nagel S, Chao ST. Trigeminal neuralgia treated with stereotactic radiosurgery: The effect of dose escalation on pain control and treatment outcomes. *Int J Radiat Oncol Biol Phys* 2016; 96:142-148.
29. Xia L, Zhong J, Zhu J, Wang YN, Dou NN, Liu MX, Visocchi M, Li ST. Effectiveness and safety of microvascular decompression surgery for treatment of trigeminal neuralgia: A systematic review. *J Craniofac Surg* 2014; 25:1413-1417.
30. Koopman JS, de Vries LM, Dieleman JP, Huygen FJ, Stricker BH, Sturkenboom MC. A nationwide study of three invasive treatments for trigeminal neuralgia. *Pain* 2011; 152:507-513.
31. Yang YM, Wang ZW, Cui Z, Jiang HZ, Sha C, Yuan QG, Xie HW, Wang DM.

[anatomy and management of superior petrosal vein in microvascular decompression for trigeminal neuralgia]. *Zhonghua Yi Xue Za Zhi* 2017; 97:522-524.

32. Berger I, Nayak N, Schuster J, Lee J, Stein S, Malhotra NR. Microvascular decompression versus stereotactic radiosurgery for trigeminal neuralgia: A decision analysis. *Cureus* 2017; 9:e1000.
33. Ko AL, Ozpinar A, Lee A, Raslan AM, McCartney S, Burchiel KJ. Long-term efficacy and safety of internal neurolysis for trigeminal neuralgia without neurovascular compression. *J Neurosurg* 2015; 122:1048-1057.
34. Papadopoulos D, Kostopanagiotou G, Lemonis A, Batistaki C. Intradiscal combination of pulsed radiofrequency and gelified ethanol for the treatment of chronic discogenic low back pain. *Pain Med* 2014; 15:881-883.
35. Fukui S, Nitta K, Iwashita N, Tomie H, Nosaka S, Rohof O. Intradiscal pulsed radiofrequency for chronic lumbar discogenic low back pain: A one year prospective outcome study using discoblock for diagnosis. *Pain Physician* 2013; 16:E435-E442.
36. Wan CF, Liu Y, Dong DS, Zhao L, Xi Q, Yu X, Cui WY, Wang QS, Song T. Bipolar high-voltage, long-duration pulsed radiofrequency improves pain relief in postherpetic neuralgia. *Pain Physician* 2016; 19:E721-E728.
37. Vigneri S, Sindaco G, Gallo G, Zanella M, Paci V, La Grua M, Ravaioli L, Pari G. Effectiveness of pulsed radiofrequency with multifunctional epidural electrode in chronic lumbosacral radicular pain with neuropathic features. *Pain Physician* 2014; 17:477-486.
38. Chang MC, Cho YW, Ahn SH. Comparison between bipolar pulsed radiofrequency and monopolar pulsed radiofrequency in chronic lumbosacral radicular pain: A randomized controlled trial. *Medicine (Baltimore)* 2017; 96:e6236.
39. Bhatia A. Questions regarding "pulsed radiofrequency for chronic intractable lumbosacral radicular pain: A six-month cohort study". *Pain Med* 2016; 17:989.
40. West M, Wu H. Pulsed radiofrequency ablation for residual and phantom limb pain: A case series. *Pain Pract* 2010; 10:485-491.
41. Imani F, Gharaei H, Rezvani M. Pulsed radiofrequency of lumbar dorsal root ganglion for chronic postamputation phantom pain. *Anesth Pain Med* 2012; 1:194-197.
42. Wilkes D, Ganceres N, Solanki D, Hayes M. Pulsed radiofrequency treatment of lower extremity phantom limb pain. *Clin J Pain* 2008; 24:736-739.
43. Thapa D, Ahuja V, Dass C, Verma P. Management of refractory trigeminal neuralgia using extended duration pulsed radiofrequency application. *Pain Physician* 2015; 18:E433-E435.
44. Luo F, Wang T, Shen Y, Meng L, Lu J, Ji N. High voltage pulsed radiofrequency for the treatment of refractory neuralgia of the infraorbital nerve: A prospective double-blinded randomized controlled study. *Pain Physician* 2017; 20:271-279.
45. Sweet W, Poletti C. Complications of percutaneous rhizotomy and microvascular decompression operations for facial pain, in Schmideck H (ed). *Operative Neurosurgical Techniques: Indication, Methods, and Results (Ed 4)*. WB Saunders Co, Philadelphia, PA, 2000, pp 1595-1598.
46. Sweet WH, Wepsic JG. Controlled thermocoagulation of trigeminal ganglion and rootlets for differential destruction of pain fibers. 1. Trigeminal neuralgia. *J Neurosurg* 1974; 40:143-156.
47. Bhatjiwale MG, Bhatjiwale MM, Bhagat A. Ultra-extended euthermic pulsed radiofrequency for the treatment of ophthalmic neuralgia: A case report with elaboration of a new technique. *Surg Neurol Int* 2016; 7:S818-S823.
48. Tanaka N, Yamaga M, Tateyama S, Uno T, Tsuneyoshi I, Takasaki M. The effect of pulsed radiofrequency current on mechanical allodynia induced with resiniferatoxin in rats. *Anesth Analg* 2010; 111:784-790.
49. Ali Eissa AA, Reyad RM, Saleh EG, El-Saman A. The efficacy and safety of combined pulsed and conventional radiofrequency treatment of refractory cases of idiopathic trigeminal neuralgia: A retrospective study. *J Anesth* 2015; 29:728-733.
50. Kim JH, Yu HY, Park SY, Lee SC, Kim YC. Pulsed and conventional radiofrequency treatment: Which is effective for dental procedure-related symptomatic trigeminal neuralgia? *Pain Med* 2013; 14:430-435.
51. Heavner JE, Boswell MV, Racz GB. A comparison of pulsed radiofrequency and continuous radiofrequency on thermocoagulation of egg white in vitro. *Pain Physician* 2006; 9:135-137.