Observational Study

# The Efficacy and Safety of Applying the Combination of Pulsed Radiofrequency and Platelet-Rich Plasma to the Gasserian Ganglion for the Treatment of Idiopathic Trigeminal Neuralgia: A Protocol for a Multi-Center, Prospective, Open-Label, Propensity Score Match Cohort Study

Tong Ren, MD[1], Lingjie Xia, MD[2], Yongjun Zheng, MD[3], Yixuan Yang, MD[4], Nan Ji, MD[1], and Fang Luo, MD[4]

From: [1]Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, Beijing, China; [2]Department of Pain Medicine, Henan Provincial People's Hospital, People's Hospital of Zhengzhou University, Zhengzhou, Henan, China; [3]Department of Pain Management, Huadong Hospital, Fudan University, Shanghai, China; [4]Department of Pain Management and Day Care Surgery, Beijing Tiantan Hospital, Capital Medical University, Beijing, China

Address Correspondence: Fang Luo, MD Department of Pain Management, Beijing Tiantan Hospital, Capital Medical University, Beijing 100070, China E-mail: 13611326978@163.com

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**Background:** Trigeminal neuralgia (TN) is one of the severest and most common forms of neuropathic pain, and the current standard treatments for TN still have some disadvantages and limitations. Pulsed radiofrequency (PRF) has great potential as a micro-destructive method in treating refractory TN, but the long-term outcomes of PRF have been reported to be unsatisfactory. Autologous platelet-rich plasma (PRP) can reduce inflammation and promote nerve repair and has been proven effective in a previously published case report. So far, there have been no reports on combining PRF with PRP for the treatment of TN.

**Objective:** We plan to conduct an open-label cohort study to compare the efficacy of PRF to that of PRF with PRP when each is applied to the Gasserian ganglion for the treatment of TN.

**Study Design:** A study protocol for a multicentric, prospective, observational, propensity score matching (PSM), parallel, cohort, non-randomized, and assessor-blinded trial.

**Setting:** Department of Pain Management, Beijing Tiantan Hospital, Capital Medical University in Beijing, China; Department of Pain Management, Henan Provincial People's Hospital, Henan, China; Department of Pain Management, Huadong Hospital, Fudan University, Shanghai.

**Methods:** A total of 270 patients with idiopathic TN will be assigned equally to one of 2 groups, based on their willingness. Both groups will receive 2 Hz of PRF, with the PRP group also receiving 2 mL of leukocyte-poor platelet-rich plasma (LP-PRP) mixture, which will be injected slowly into the Gasserian ganglion and the mandibular nerve. It is estimated that 81 patients who receive the combination of PRF and PRP will be matched with 81 PRF-alone controls after a propensity score match (PSM) to ensure balanced comparisons between the 2 groups.

**Results:** The primary outcome will be the response rate of the treatment after 12 months, which is the percentage of patients with a modified Barrow Neurological Institute (BNI) pain intensity score between I and III. The secondary outcome will include the following: BNI score, Numeric Rating Scale score, dose of carbamazepine, patient satisfaction score, score on the World Health Organization Quality of Life Questionnaire (WHOQOL-BREF), and adverse reactions. These data will be recorded over a one-year follow-up period.

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

**Conclusions:** To our knowledge, this trial will be the first multi-centric, prospective, observational

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study that has a relatively large sample size and compares the efficacy and safety of applied PRF to that of combined PRF and PRP for patients who have not responded to pharmacologic treatments for idiopathic TN. If the combination PRF-and-PRP treatment is proven effective, it will be an important, safe, minimally destructive alternative treatment modality for idiopathic TN that persists after ineffective conservative treatment.

**Key words:** Trigeminal neuralgia, platelet-rich plasma, pulsed radiofrequency, study protocol, analgesic effects

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Trigeminal neuralgia (TN), characterized by brief, recurrent paroxysms of lancinating pain in the distribution of at least one branch of the trigeminal nerve (fifth cranial nerve [CNV]), is one of the severest and most common forms of neuropathic pain (1,2). Epidemiological studies have reported that the incidence of TN is approximately between 2.1 and 27 cases per 100,000 person-years worldwide (1,2). Pain attacks can occur spontaneously or can be triggered by non-noxious stimuli, reducing the quality of life significantly (2,3). Furthermore, TN patients usually present with increased risks of anxiety, depression, and poor sleep, which may cause severe psychological disturbances (4).

The current standard treatment for TN consists of sodium channel blockers such as carbamazepine. Although usually effective, these medications are associated with the need for titration, many side effects, and relapses of symptoms (5,6). If pharmacological intervention is not effective, surgical treatments will be utilized. Percutaneous procedures, which involve radiofrequency (RF) thermocoagulation, glycerol rhizotomy, and percutaneous balloon compression, are all recommended by TN treatment guidelines, but these procedures are not ideal treatments, since they cannot avoid the side effect of destroying the trigeminal nerve (7). Stereotactic radiosurgery involving a noninvasive gamma knife may have the lowest risk of short-term complications, but the post-procedure duration before pain relief can be expected is long, and the effectiveness is lower than that of percutaneous surgery (8). Open surgical treatment techniques, such as microvascular decompression (MVD), are nondestructive procedures that have been proven to be the most successful and durable surgical approaches, but the therapeutic option exists only for classical TN secondary to neurovascular impingement, and patients need to bear the risk of craniotomy and high treatment costs (9,10). Therefore, a minimally invasive interventional therapy between drug-based and surgical treatment is still worth developing (11,12).

In recent years, pulsed radiofrequency (PRF), a novel minimally invasive and micro-destructive technique, has been shown to be a promising treatment option for TN (13,14). PRF consists of a continuous high energy current of 20 ms and an intermission period of 480 ms. Since the heat of the electrode tip can be dissipated during this interval, this limits the temperature from exceeding 42°C and the induced target tissue injury is minimal (15,16). Although it is considerably effective in treating TN with an initial pain relief rate of 75.17% after the procedure, it was reported that the long-term outcomes of PRF were not satisfactory (17-19). Thus, there is an overwhelming need for finding a safe, more effective micro-destructive or nondestructive treatment option for TN.

Autologous platelet-rich plasma (PRP) is the processed liquid fraction of autologous peripheral blood with a platelet concentration above the baseline. PRP releases a variety of bioactive factors and adhesion proteins responsible for activating hemostatic cascade reaction, synthesizing new connective tissue and vascular reconstruction to initiate tissue repair processes (20-22). In recent years, PRP has become the focus of research and has been widely used in the treatment of chronic pain. Studies have shown that PRP can reduce inflammation and promote nerve repair, so it has also shown broad prospects as a neuropathic pain treatment (23-27).

In a case report by Dr. Arockia X. Doss, a 40-year-old

woman with TN underwent 5 injections of PRP to the distal branches of the trigeminal nerve in accordance with the Doss trigeminal neuralgia treatment (DTNT) protocol (28). For 6 months after the PRP injections, the patient had a normal social and work life with resolution of symptoms and no clinical features that suggested peripheral nerve damage (28). This paper indicates that PRP can be effective in TN treatment, but the document is a single case report on injections given to distal branches of the trigeminal nerve instead of the Gasserian ganglion and does not validate the routine use of PRP in treating TN (28). In 2023, a randomized controlled study showed that CT-guided PRF, when combined with PRP, could effectively treat postherpetic neuralgia (PHN) (29). However, the efficacy of the combination of PRF and PRP in treating TN was not reported. Because of ethical issues, we did not study the effects of pure PRP on TN due to the scarcity of existing data on the topic. We assume that a PRP-and-PRF combination acting on the Gasserian ganglion might have better therapeutic effects on TN than PRF alone, and we plan on conducting such a prospective trial to compare the clinical efficacy and safety of the 2 techniques (30).

### Objectives

Our objective is to investigate the efficacy and safety of the application of a PRF-and-PRP combination to the Gasserian ganglion for the treatment of idiopathic TN. We wish to find an effective, safe, and minimally destructive treatment that can be performed after ineffective conservative treatment.

## Methods

### Study Design

This will be a multi-centric, prospective, open-label, parallel, non-randomized, propensity score match cohort study.

### Study Setting

Patients with idiopathic TN who are receiving PRF, with or without accompanying PRP treatment, at the departments of pain management of 3 hospitals in China (Beijing Tiantan Hospital, Capital Medical University in Beijing, Henan Provincial People's Hospital in Henan, and Huadong Hospital, Fudan University in Shanghai) will be enrolled in the study. Approval from an ethics committee was obtained (KY-2023-263-03-1). All patients will be adequately informed of the study protocol and will sign written consent forms to take part in the trial. This study is scheduled to start on August 1, 2024, and is expected to occur over a duration of 2 years.

### Recruitment and Informed Consent

An experienced attending doctor will be responsible for enrolling patients with idiopathic TN at the departments of pain management of each participating study center. All patients will be informed in detail about the purpose of the study, the interventions, the benefits, the possible risks, and the corresponding responses. Patients will be given at least one hour to consider whether or not to participate in the study. They will sign the consent form voluntarily, and they have the right to withdraw from the study at any time without any risk. Every candidate enrolled in this study will be strictly evaluated, based on the inclusion and exclusion criteria.

### Patients

#### *Inclusion Criteria*

1. The diagnosis of TN has been established according to the criteria of the International Classification of Headache Disorders, third edition (ICHD-3) (1).
2. The patient is 18 to 75 years old.
3. The patient's pain has scored at least 7 on a Numeric Rating Scale (NRS-11) (NRS; range, 0-10; higher scores indicate severer pain) and could not be alleviated effectively by means of conservative medical therapy, such as carbamazepine or oxcarbazepine.
4. The patient has agreed to sign the consent form.

#### *Exclusion Criteria*

1. The patient presents with classic TN or secondary TN (e.g., multiple sclerosis).
2. An infection has appeared at the site of needle entry, or the patient has a systemic infection.
3. The patient has a history of psychiatric disease.
4. A disorder has been indicated in the results of the patient's routine blood tests, tests of hepatic, renal, or coagulation functioning, electrocardiograms, or chest x-rays.
5. The patient has a serious systemic disease such as uncontrolled hypertension, diabetes, or cardiac dysfunction (New York Heart Association grade II–III).
6. The patient has a history of abusing narcotics.

7. The patient has a history of receiving continuous radiofrequency (CRF) to the Gasserian ganglion or peripheral branches or of receiving glycerol rhizolysis, balloon compression, gamma knife, or any other neuro-destructive technique, such as neurotomy or nerve avulsion.
8. The patient has a history of receiving microvascular decompression.
9. The patient uses anticoagulants or an antiplatelet agent (e.g., acetylsalicylic acid).

### *Withdrawal Criteria*

1. The patient's vital organs show abnormal functioning.
2. The patient shows an allergic reaction to drugs or inability to tolerate adverse reactions.
3. The patient exhibits poor compliance.
4. The patient's condition exhibits aggravation or serious adverse reactions.
5. The patient expresses the desire for an alternative treatment.
6. The patient withdraws from the trial voluntarily for no known reason or is lost to follow-up during the study.
7. The PRP is produced at a concentration < 300% of the individual blood level.

## Study Interventions

### *PRP Preparation*

Twenty milliliters of blood will be withdrawn from the median cubital vein (22-gauge, one-inch needle) and used for preparation of autologous leukocyte-poor platelet-rich plasma (LP-PRP) (2 mL), depending on the baseline platelet count, and will not be used if produced at a concentration < 300% of the individual blood level. Under strict aseptic precautions, the process will be carried out at 22-26°C, and the blood will be collected in centrifuge test tubes, labeled with identification data (name and age), and gently mixed with acid citrate dextrose (ACD) as an anticoagulant in the ratio of 10:1.5. The tubes will then undergo the first centrifugation for separation (at the rate of 1,200 rpm over 10.6 minutes). When the blood is separated into the plasma, the buffy coat, and the upper layers of red blood cells, the plasma will be pipetted into other sterile tubes (without an anticoagulant) and subjected to a second round of centrifugation to activate the platelets (at the rate of 1,450 rpm for 15 minutes) (WG-YLJ-II, WEGO). Lastly, the platelets will settle down as PRP, the upper third or fourth supernatant will be discarded, and the lower PRP will be obtained, which will then be activated just before its injection by agitation through vigorous shaking.

### *Procedures*

All patients will lie in the supine position on the computed tomography (CT) scanning table. The patients' blood pressure, heart rate, heart activity, and oxygen saturation will be continuously monitored. The negative plate of the RF generator (PMG-230, Baylis Medical Inc.) will be placed on the skin of the abdomen. Local infiltration anesthesia with 1% lidocaine will be administered. A 100-mm trocar with a 5-mm non-insulated tip (PMF-21-100-5, Baylis Medical Inc.) will be used to puncture the foramen ovale on the affected side. Slice CT scanning (2 mm/layer) and 3-dimensional computerized reconstruction will be performed using a CT scanner (LightSpeed VCT 64, General Electric). The puncture point will be located 3 cm outside the corners of the mouth of the affected side, using the Hartel technique. Under CT guidance, the trocar will then be inserted through the ipsilateral foramen ovale and into the Gasserian ganglion. Three-dimensional reconstructed images will be used to determine the position of the needle tip and its relationship with the anatomical markers of the skull base. After the accurate puncturing of the foramen ovalis, the cannula needle core will be removed and connected to the RF electrode (PMK-21-100) and the RF generator. Electrical stimulation will be performed at 50 Hz to determine the sensory threshold and at 2 Hz to determine the motor threshold. The depth and direction of the puncture will be adjusted according to the patient' s response to ensure the accuracy of the puncture site. The RF generator will be set to manual PRF mode with a standard setting of 42°C and a maximum voltage (bearable without causing pain to conscious patients) and applied for 2 rounds of 120 seconds each.

### *Groups*

The PRF group will receive only the PRF treatment. In the combination-PRF-and-PRP group, after the RF electrode is removed, 2 mL of the LP-PRP mixture will be injected slowly into each patient's Gasserian ganglion and mandibular nerve. Additional analgesics will be administered for patients' comfort during and after the procedure. If the patients are not satisfied with the outcome after one month, other treatment options will be available.

### *Follow-Up*

The patients will be discharged from the hospital 30 minutes after the procedure. Regular outpatient and telephone follow-ups will be conducted. Outpatient follow-ups will be performed at one and 2 weeks and at one, 3, 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. The follow-up will be conducted by a single trained doctor at each study center who will not be involved in the patient's enrollment and treatment processes.

## 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 case report forms will be recorded by the researchers in charge of enrollment and follow-up. The data and safety monitoring committee (DSMC) will monitor safety and the validity of data every 6 months to make recommendations on whether to continue the study.

## Study Outcomes

Demographic and baseline information will be collected and will include the following: BNI scores, age, gender, BMI, disease duration, laterality, affected nerve branches, NRS-11 scores, current profession, physical demands, doses of carbamazepine given, satisfaction, scores on the World Health Organization Quality of Life Questionnaire (WHOQOL-BREF), and adverse reactions.

### *Primary Outcome*

The response rate to the treatment after 12 months is the primary outcome. Patients with BNI scores of I to III will be considered to have responded to the treatment.

### *Secondary Outcomes*

- BNI score: BNI scores will be evaluated after one and 2 weeks and after one, 3, 6, and 12 months following the procedure.
- NRS-11 score: NRS-11 scores will be evaluated after one and 2 weeks and after one, 3, 6, and 12 months following the procedure.
- Anticonvulsant consumption: Doses of carbamazepine will be recorded after one and 2 weeks and after one, 3, 6, and 12 months following the procedure.
- Satisfaction: Patient satisfaction scores on the 5-point Likert scale (1: poor, 2: fair, 3: good, 4: very good, 5: excellent) will be evaluated after one, 6, and 12 months following the procedure.
- Quality of life: Scores on the WHOQOL-BREF will be evaluated after one, 6, and 12 months following the procedure.
- Adverse reactions: Nausea, vomiting, and facial hematoma during and after the procedure and headache, dizziness, and cerebrospinal fluid leakage occurring within 2 weeks of the procedure will be recorded.

### *Propensity Score Match*

This study is an open-label trial, so neither the researchers nor the patients will be blinded. Patients will be assigned to one of the 2 groups according to whether they agree to undergo a pure PRF treatment or a combination of PRF and PRP.

Gender, age, BMI, BNI score, disease duration, laterality, affected nerve branches, NRS scores, current profession, and physical demands will be included in the matching process as covariates. A one-to-one matching ratio will be applied, and the caliper width will be set at 0.2. As a result, patients who received the PRF-and-PRP combination (n = 81) will be propensity score matched (PSM) with (n = 81) PRF-only controls to ensure balanced comparison between the 2 groups. Ethical considerations will be observed diligently throughout the study, which will be conducted in accordance with the principles outlined in the Declaration of Helsinki.

## Sample Size

The main purpose of this study will be to compare the effectiveness of PRF alone to the PRF-and-PRP combination. The findings will be evaluated one year after the procedure. The effectiveness experienced by the PRF-and-PRP group after one year is estimated to be 90%, and the observed effectiveness experienced by the high-voltage PRF group was 69% (29). (The $\alpha$ is 0.05, and the power is 90%.) The Power Analysis and Sample Size (PASS) software program V.15.0 (NCSS Corporation) was used to compute the sample size. The results showed that 73 patients would be required in each group. However, when we account for 10% loss to follow-up and an additional 40% loss after propensity score matching, 135 patients will be recruited into each group. Therefore, the total sample size of this study will be 270 patients.

### Statistical Analysis

The analysis plan for this future study has been determined. Intention-to-treat analyses (ITT analyses) and per-protocol analyses (PP analyses) will be used for primary analysis. The ITT analysis set for the efficacy analysis will include all patients. A sensitivity analysis of the PP population will be performed. Means ± SD will be used to describe normally distributed continuous variables. Medians (interquartile range) will be used to describe abnormally distributed continuous variables. Numbers and proportions will be used to describe categorical data. 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. The primary outcome in prespecified subgroups will also be analyzed. Prespecified subgroup analysis include age (< 65 years vs. ≥ 65 years), gender (male vs. female), and duration of TN diagnosis (< 60 months vs. ≥ 60 months). Propensity score matching will be conducted using the method described by Thoemmes with the following parameters: nearest-neighbor matching (one-to-one) with a caliper of 0.2; exact matching for site of disease onset; and covariates of age at onset, disease duration, and the modified BNI pain score. Matching quality will be evaluated by comparing baseline characteristics between patients receiving PRF-and-PRP combinations and matched control patients receiving only PRF treatment.

### 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 review all adverse events regularly 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 the 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 about relevant intervention in detail.

### Ethics and Dissemination

This protocol was approved by the institutional review board of Beijing Tiantan Hospital (KY-2023-263-03-1) and registered on Clinicaltrials.gov (NCT06472323). The trial complies with the guidelines of the Declaration of Helsinki on ethical principles and good clinical practice. All patients will sign the written consent form, and 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 publication 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 non-randomized controlled method to evaluate the efficacy and safety of the administration of a PRF-and-PRP combination for the treatment of idiopathic TN. The aim of this study is to explore a treatment with greater efficacy and fewer side effects for patients who have idiopathic TN and have found pharmacologic therapy to be ineffective. This treatment, if proven effective, may then be used as an alternative to more traumatic procedures.

Due to the lack of previous large-scale studies on this subject and the need to consider ethical deliberations, patients must be strictly assigned to each group according to their willingness. Therefore, this trial is designed as a non-randomized study. We adopted propensity score matching, since patients with an equal (or similar enough) propensity score (PS) will have similar baseline covariate values and thus be sufficiently comparable for the creation of a balanced sample, which can compensate for the system errors caused by non-randomization. Blinding will be difficult to achieve in this trial, so this study has an open-label design. Open-label trials are also used extensively for the evaluation of non-pharmacological treatments, which are more challenging to blind than those of pharmacological treatments. However, to minimize the subjective influence, outcome assessment and statistical analysis will be implemented by a third party, who will be blinded to grouping.

The response rate of treatment after 12 months, the primary outcome of this study, will use BNI scores 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: First, the BNI score considers both pain

and medication. For the patients who do not respond to pharmacological therapy before the procedure, satisfactory pain relief can still be achieved through medication after the procedure. These patients will still have benefited from treatment. Second, the BNI score assesses the state of the patient, rather than a specific measured value. This feature makes the definition of the primary outcome clearer and more suitable for an open-label trial. Furthermore, we will also include the NRS-11 to evaluate the secondary outcomes.

Although it is safer to puncture the Gasserian ganglion with a curved blunt needle, these types of needles are not commercially available in our country. However, the puncturing of the Gasserian ganglion under the guidance of reconstructed 3-dimensional CT is relatively safe. The correct positioning of the needle tip is key to ensure efficacy and reduce complications. In this study, all the RF 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 expose patients to higher levels of radiation than does 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. We previously reported that the puncture success rate of RF therapy through the foramen ovale under CT guidance was 100% and that the punctures caused no severe complications. Moreover, sensory and motor stimulation will be used to indicate the distance of the needle from the Gasserian ganglion. Therefore, puncture inaccuracy is highly unlikely to interfere with the outcomes.

## Conclusion

This prospective study has several limitations. First, the open-label design may influence the measurement of outcomes and introduce biases, such as performance or ascertainment bias. Second, there is no uniform standard for the application of PRF and PRP injections at present. In our study, PRF will be administered for 240 seconds, and 2 mL of PRP will be administered. This program, along with the treatment voltage and temperature of PRF, has been guided by published literature and our clinical experience. However, different treatment parameters of PRF and different PRP preparation techniques may lead to different effects. Finally, we plan to continue the follow-up process for 12 months. There is also a limitation of scale, since idiopathic TN is not a common disease among patients, which is also one of the reasons for adopting a multicentric approach. Long-term efficacy assessment on a larger scale will be required in future research. Furthermore, the cost-effectiveness of PRP, which is an important issue in clinical practice, is also worth evaluating in the future.

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