Clinical Trial

Bipolar High-Voltage, Long-Duration Pulsed Radiofrequency Improves Pain Relief in Postherpetic Neuralgia

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Background: Postherpetic neuralgia (PHN) is often refractory to existing treatments. Treatment of the dorsal root ganglion (DRG) using monopolar pulsed radiofrequency (PRF), which is a non- or minimally neurodestructive technique, is not efficacious in all patients.

Objectives: This study aimed to determine the safety and clinical efficacy of bipolar high-voltage, long-duration PRF on the DRG in PHN patients.

Study Design: Self before-after controlled clinical trial.

Setting: Department of Pain Medicine, the First Affiliated Hospital of China Medical University.

Methods: Ninety patients diagnosed with PHN for > 3months were included. Bipolar high-voltage, long-duration PRF at 42°C for 900 seconds was applied after the induction of paresthesias covered the regions of hyperalgesic skin. The therapeutic effects were evaluated using a visual analog scale (VAS) and the 36-item Short Form health survey (SF-36) before treatment and one, 4, 8, and 12 weeks after PRF.

Results: The VAS scores at one, 4, 8, and 12 weeks after PRF treatment were significantly lower than before treatment ($P < 0.001$). The SF-36 scores, which included physical functioning, physical role, bodily pain, general health perceptions, vitality, social function, emotional role, and the mental health index, were significantly improved up to 12 weeks after PRF treatment ($P < 0.001$). No serious adverse effects were identified following treatment. The main adverse reactions included pain, tachycardia, and high blood pressure (especially when the field strength was enhanced).

Limitations: Single center study, relatively small number of patients, lack of a control group.

Conclusion: Bipolar high-voltage, long-duration PRF on the DRG is an effective and safe therapeutic alternative for PHN patients. This treatment could improve the quality of life of PHN patients.

Clinical Trial Registration: NO ChiCTR-OCS-14005461

Key words: Pulsed radiofrequency, postherpetic neuralgia, VAS, SF-36

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Postherpetic neuralgia (PHN) is a neuropathic pain syndrome that results from injury to the nervous system caused by varicella zoster virus (herpes zoster) infection (1,2). PHN is typically defined as chronic pain that persists for > 3 months after rash onset (3) and is often associated with severe pain. Because of its severity and chronicity, PHN can adversely limit a patient's ability to perform daily self-

care and seriously affect quality of life (4,5).

PHN involves multiple mechanisms, including neuroplasticity and sensitization of both peripheral and central neurons (6). Evidence (7) indicates that pharmacological agents and interventional procedures, including opioids, tricyclic antidepressants (TCAs), antiepileptic drugs, paravertebral block, and selective nerve root injection, may result in only partial pain relief. More effective treatments for PHN are lacking (8,9).

Pulsed radiofrequency (PRF) is a novel therapeutic strategy that has recently been used (10) by pain practitioners as a non- or minimally neurodestructive technique in which short bursts of high-frequency current are applied to nervous tissue. PRF is delivered in a pulse of 20 milliseconds (ms) followed by a silent period of 480 ms to avoid radiofrequency heat lesions (11). This novel therapeutic strategy has recently been used to treat PHN (12), and the monopolar automatic mode has typically been the conventional choice in previous studies. However, we previously demonstrated that the hyperalgesia of PHN typically involves more than one sensory root (13). Thus, the monopolar automatic mode may not sufficiently relieve pain. To obtain a wider pulse regime and provide personalized treatments, we investigated the use of bipolar high-voltage, long-duration PRF in PHN patients. Thus, the aim of this study was to provide a more effective PRF methodology for the treatment of PHN.

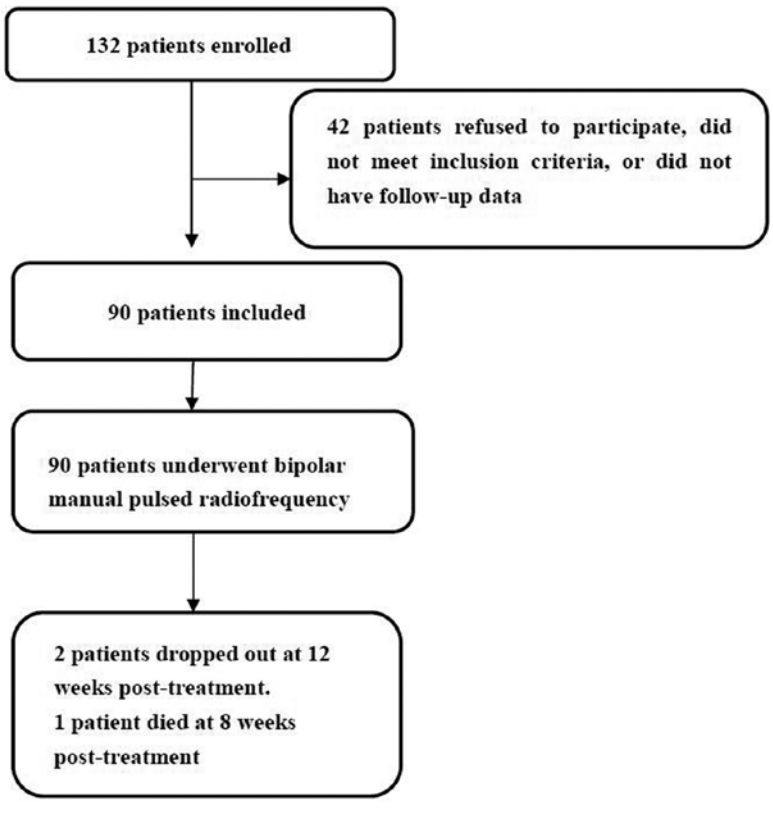

Fig. 1. *Study flowchart. All 90 patients were included in the treatment.*

Methods

Study Participants

From June 1, 2014, to December 1, 2014, 90 patients who had intractable PHN for > 3 months and had obtained minimal relief from various pharmacological agents and interventional procedures were enrolled in this study (Fig. 1). The study protocol was approved by the Human Ethics Committee of The First Affiliated Hospital of China Medical University (No: 2014-118-2). All patients read the informed consent form and provided written informed consent to participate. This trial was registered with chictr.org.cn, number ChiCTR-OCS-14005461.

Inclusion Criteria

Eligible patients were older than 60 years of age and had a PHN history > 3 months. Additional inclusion criteria comprised individuals with PHN who had been refractory to formal treatment, such as antiepileptic medicine, antidepressants, opioids, or physical treatments, according to the International Association for the Study of Pain guidelines (14), and a visual analog scale (VAS) score > 3 on a scale of 0 – 10.

Exclusion Criteria

The exclusion criteria included intolerance to the study procedures, uncooperative behavior (i.e., the patient did not provide an immediate response), or the intellectual inability to complete the self-evaluation questionnaires [VAS and 36-item Short Form health survey (SF-36)].

Description of Interventions

The therapeutic target area was first determined by the region of skin

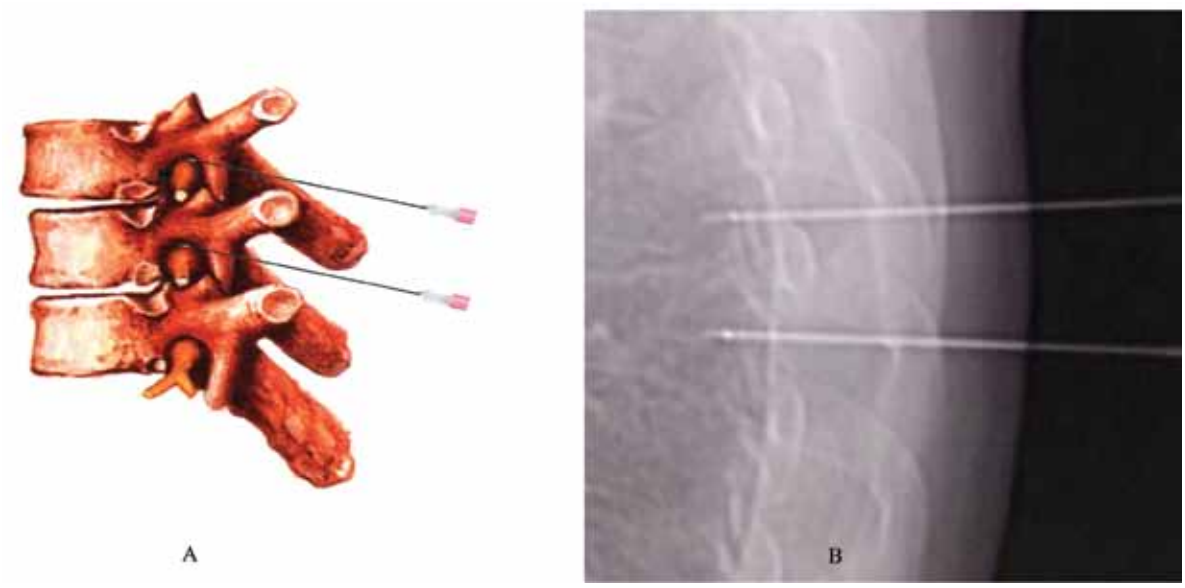

Fig. 2. *Schematic diagram (A) of PRF in the treatment of PHN through puncture position and x-ray photo (B). If the skin pigmentation occurred at the level of the xiphoid process, the T6 and T7 DRGs were selected as the PRF targets.*

pigmentation affected by herpes zoster, which is typically accompanied by hyperalgesia or allodynia (15). The lesion of one dorsal root ganglion (DRG) segment leads to the alteration of nearby DRGs (16) and is subsequently expanded down one adjacent segment. For example, if the skin pigmentation was present at the level of the xiphoid process, the T6 and T7 DRGs were then selected as the PRF targets.

The patients were positioned on the treatment bed in a prone or lateral position. Two 18-gauge (G) (21-G for cervical PHN), straight, sharp RF cannulas (Baylis Medical Company, Montreal, Canada) with a 10-mm exposed tip (5-mm for cervical PHN) were carefully inserted via computed tomography (CT) guidance until the needle tip reached the upper edge of the intervertebral foramen (in close proximity to the DRG) and were subsequently connected to a PRF element. The needle tip was slowly moved under the sensation testing mode (50 Hz, 0.1 – 0.3 V) from the superior margin of the intervertebral foramen downwards to the inferior margin. During this procedure, the patients were assessed for abnormal sensations (mainly soreness, numbness, thermalgia, and an occasional twitch-like or prickly sensation). When the induced paresthesias occurred over the skin areas with hyperalgesia, we considered that the electrode needle tips reached the target DRGs (Figs. 2, 3). All procedures were performed by the same investigator (Dr. Tao Song).

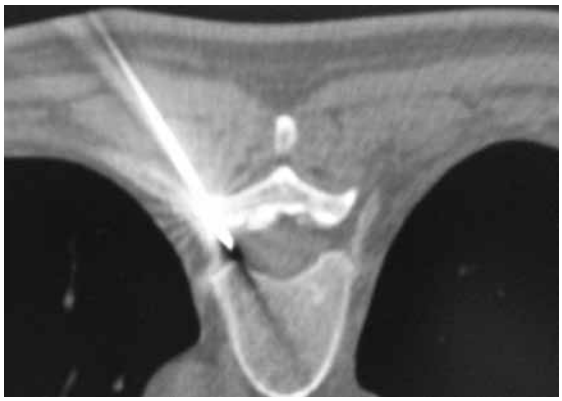

Fig. 3. *CT image of RF cannulas that reached the ideal DRG.*

After the ideal DRGs were attained, PRF treatment was performed using the Pain Management Generator (PM-230, Baylis Medical Company, Montreal, Canada). The manual PRF mode with the basic settings of 42°C, 2 Hz, 20 ms, and 900 s was used. The initial electric voltage was 40 V, which was then gradually increased until the patients could not tolerate the abnormal sensations (i.e., burning pain). All patients tolerated their individual maximal voltage (70 – 100 V) until the 900 s PRF was terminated.

Outcome Measures

VAS

The VAS scores were evaluated in the morning before treatment and one, 4, 8, and 12 weeks after PRF.

SF-36 Score Evaluation

The SF-36 health survey (17) was used to assess the health of the PHN patients. Patients needed only 6 – 9 minutes to complete the test. It assesses nearly all conceptual domains of the substantially longer generic patient-based assessments (PBAs), which have been used in other studies (18). The scores, including physical functioning, physical role, bodily pain, general health perceptions, vitality, social function, emotional role, and mental health index, were evaluated before treatment and one, 4, 8, and 12 weeks after PRF.

Side Effects

Side effects, including bleeding at the puncture site, infection, and increased pain, were recorded at one, 4, 8, and 12 weeks after treatment.

Table 1. *Baseline characteristics of the study participants.*

Patient Characteristics	
Number of patients (N)	87
M/F (n)	42/45
Mean age (years)	62.13 ± 12.79
Weight (kilograms)	67.43 ± 9.62
Left/Right	41/46
Pain duration (months)	12.51 ± 6.52

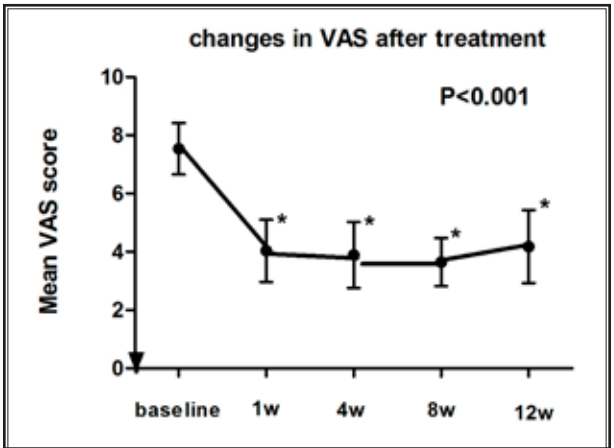

Fig. 4. *Significantly decreased mean VAS scores after PRF. *P < 0.001 indicates pre VAS vs. post VAS.*

Statistical Analysis

The efficacy end points were analyzed using an intention to treat analysis that included the VAS and SF-36 scores (i.e., the mean changes from baseline to week 12).We used a linear mixed model with a Toeplitz covariance structure (smallest Akaike information criterion) for the analysis of repeated measures structure; an analysis of the primary and secondary endpoints of the full analysis set, which contained unbalanced data, was conducted. A P value < 0.05 was deemed statistically significant. The analysis was performed using SPSS 18.0 software (SPSS Inc., Chicago, IL, USA). Safety analyses were conducted for the incidence of side effects.

Results

Patient Demographics

Ninety patients underwent bipolar high-voltage, long-duration PRF treatment. One patient died at 7 weeks post-treatment because of myocardial disease and 2 patients dropped out at 4 weeks after treatment (i.e., could not be contacted via telephone). The remaining 87 patients' demographic characteristics are shown in Table 1.

VAS

The mean VAS score before PRF was 7.41 ± 1.03. PRF treatment induced significant pain relief at one week (3.48 ± 1.29; P < 0.001; Fig. 4), and the effects were maintained during the subsequent 12 weeks of follow-up evaluations: 3.57 ± 1.10, 3.68 ± 0.96, and 3.95 ± 1.11 at 4, 8, and 12 weeks, respectively (all P < 0.001 compared with before treatment). Sixty patients (69.0%) were satisfied with the curative effect, and 7 patients (8.0%) experienced excellent pain relief (VAS ≤ 2). There were no significant differences in the VAS scores between one, 4, 8, and 12 weeks after PRF.

SF-36

The index scores in general health, social function, emotional role, mental health index, bodily pain, physical function, and physical role exhibited significant improvements in the PRF group after treatment (P < 0.001; Fig. 5).There was no significant change in the SF-36 scores between one and 12 weeks post-treatment.

Side Effects

The main adverse reactions included pain, tachycardia, and high blood pressure (especially when the field strength was enhanced). Drugs were administered

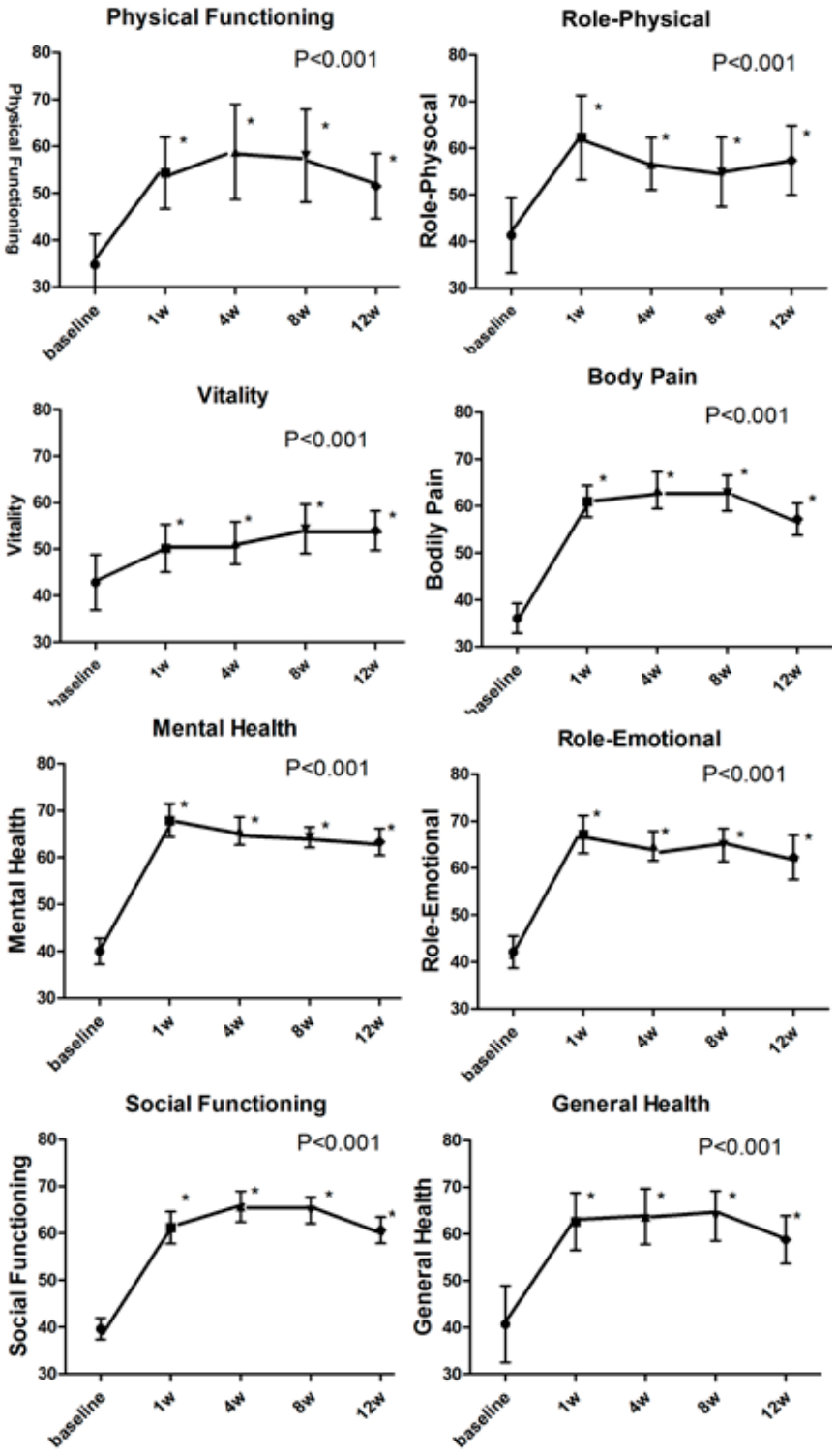

Fig. 5. *Mean SF-36 scores before and after PRF. The improvements in the quality of life were maintained for at least 12 weeks. *P < 0.001 indicates pre scores vs. post scores.*

to treat these symptoms, and the intensity was slowly increased to reduce the adverse reactions. No patients withdrew from the treatment because of an adverse reaction. There were no cases of infection, nerve injury, postoperative paresthesia, pain exacerbation, pneumothorax, or other serious adverse effects following the PRF treatment. Ecchymoma was identified in 5 patients; however, they rapidly recovered without adverse effects during the follow-up period.

Discussion

PHN is a refractory chronic pain. There is no definitive treatment algorithm devised for all PHN patients. PHN animal model studies (19,20) have demonstrated that the allodynia threshold of rats to mechanical stimulation significantly increased after PRF treatment compared with the control group. This finding suggested that PRF was effective for PHN; thus, PRF was investigated as a treatment method in the current study.

The DRG is an oval inflation of the dorsal root at the upper region of the intervertebral foramen (under the upper pedicle notch), which contains first class neurons of sensory afferents. Following herpes zoster infection, the virus damages sensory neurons, which causes alterations in the composition, distribution, and functional characteristics of the trans-membrane ion channels of sensory neurons. These damaged sensory neurons produce abnormal electric impulses, which are transmitted to the spinal cord and induce spontaneous pain (21,22). Cell dehydration, decreased cell number, chronic inflammatory cell infiltration, and other pathological changes may occur in the DRG (23). Previous research (24) has suggested that monopolar PRF treatment of the DRG can relieve symptoms of PHN. Thus, the current study investigated DRGs as the targets of PRF.

Kapural et al (25) suggested bipolar RF could target a broader region compared with the monopolar mode. Thus, the current study used bipolar PRF to expand the range as much as possible. A thicker RF trocar (18G Baylis cannula), with an approximately 1.2 mm diameter and a 10 mm working needle tip, was used to ensure the maximum pulsed range. Teixeira and Sluijter (26) demonstrated that the PRF effect was positively correlated with high-voltage in the treatment of discogenic pain. Furthermore, Luo et al (27) demonstrated that a higher output voltage and electrical field intensity produced improved analgesic effects for primary trigeminal neuralgia. Thus, in the current study, the voltage was gradually increased from 40 V to a maximum level according to the patient's individual level of tolerance (i.e., the level at which the patient was unable to tolerate the burning feeling, which represents thermal inductance from PRF). The absolute maximum was 100 V. Previous research (20) has demonstrated that increasing the exposure time to PRF current produced a significant anti-allodynic effect; thus, the longest RPF (900 s) for each patient was adopted in the current study. This treatment approach with the maximum range, intensity, and duration was effective, and the VAS scores were significantly decreased.

All patients had suffered from severe pain for > 3 months. Twenty-one patients did not experience improvement following previous neurotrophic drug use (such as antidepressants, anticonvulsants, or opioids) or previous intervertebral foramen injection (in our hospital or others) with glucocorticoids prior to RPF treatment. Thus, PHN was a very intractable pain in these patients. In stark contrast, following RPF, the VAS scores significantly decreased, and 7 patients experienced excellent pain relief (VAS $\leq$ 2) without additional analgesic drugs. These findings suggest that the effective pain relief in these patients was induced by bipolar high-voltage, long-duration PRF rather than other causes.

The pain of PHN is severe, and the lighting or tearing pain often induces feelings of uneasiness even when patients eat or sleep. This pain is associated with anxiety disorders or depression in many patients, as well as suicidal tendencies (28). These symptoms may be chronic and substantially affect the quality of life. The goal of PHN treatment is to ease pain, improve sleep, and improve the quality of life. The SF-36 is widely used to evaluate quality of life (29,30), and the current findings suggest that the quality of life scores of all patients were significantly improved at 4, 8, and 12 weeks after PRF treatment. Furthermore, the adverse reactions were minimal (e.g., pain, tachycardia, and high blood pressure), easily treated, and reduced when the intensity of therapy was slowly increased.

No neurological or other complications were identified in the current study. The likely reasons are as follows: 1. PRF employs a non- or minimally neurodestructive technique. 2. The puncture process is continuously guided by CT. 3. All procedures were performed by a highly experienced investigator.

Nevertheless, there were several limitations in our current study design, which should be addressed in future trials. First, this study comprised a prospective clinical trial that lacked a control group. Second, the patients were recruited from a single center, and

the sample size was relatively small. Third, the patients were only followed for 12 weeks after treatment. Future studies should include a large, prospective study across multiple sites with the inclusion of a non-intervention control group and a longer length of follow-up. Nevertheless, the current findings provide strong preliminary evidence that PRF is an effective pain relief method for PHN.

Conclusion

In summary, bipolar high-voltage, long-duration PRF on DRGs represents an effective and safe method for PHN patients. The benefits of PRF include minimal invasiveness that provides short-term pain relief and improves quality of life.

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