Retrospective Study

Efficacy, Safety, and Predictors of Response to Pulsed Radiofrequency Therapy for Acute Zoster-Related Trigeminal Neuralgia Patients: A Multicenter Retrospective Study

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Background: The scarcity of an effective and safe therapy to relieve acute zoster-related trigeminal neuralgia (TN) and preventing it from developing into trigeminal postherpetic neuralgia is well known. Pulsed radiofrequency (PRF) is a novel and safe, minimally neuro-destructive technique for the treatment of acute zoster-related TN, which attains satisfactory pain relief. However, this result is only reported by a few single-center researches. In addition, no study has reported the predictive factors of the analgesic effect for PRF treatment on acute zoster-related TN patients.

Objectives: This study aimed to investigate the analgesic effect of computed tomography (CT)-guided PRF for acute zoster-related TN, and to explore determinants of the therapeutic efficacy of PRF based on clinical evidence at multiple centers.

Study Design: Retrospective, multicenter, observational clinical study.

Settings: The study was conducted at pain management centers in Beijing Tiantan Hospital, Beijing Red Cross Peace Orthopedic Hospital, and Beijing Puhua International Hospital.

Methods: We retrospectively analyzed the effects of PRF on gasserian ganglion or its corresponding peripheral nerve as treatment for 85 patients with acute zoster-related TN under CT guidance between January 2008 to March 2021. The response criterion was a Numeric Rating Scale score reduction of > 50% at 12 weeks postoperatively. Univariable and multivariable analyses were performed to identify the predictive factors for a PRF positive response.

Results: The medical records of a total of 85 acute zoster-related TN patients undergoing PRF treatment were identified and analyzed. The effective rate was 62.4% at 12 weeks postprocedure. Univariate analysis indicated that disease duration (P = 0.023), diabetes mellitus (P = 0.024), and treatment location (P = 0.013) were exposure factors for the analgesic efficacy of PRF treatment. On multivariable analysis, independent predictor of PRF positive response was the treatment location of the gasserian ganglion (odds ratio = 3.032; 95% confidence interval = 1.153-7.927; P = 0.024).

Limitations: This was a retrospective study with a small sample size. Optimal PRF treatment parameters, as well as pain subtypes, need to be investigated in future studies.

Conclusions: CT-guided PRF is an effective and safe treatment for acute zoster-related TN patients. Compared to peripheral nerve PRF, gasserian ganglion treatment may be more effective for patients with acute zoster-related TN.

Key words: Acute zoster-related trigeminal neuralgia, pulsed radiofrequency, efficacy, predictor, retrospective study

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Herpes zoster (HZ) is a viral infection caused by the reactivation of latent varicella zoster virus particles in the sensory ganglia, and is typically characterized as an acutely painful vesicular rash (1). Once intraganglionic spreading of the virus occurs, newly synthesized viral particles are transported

in both medical and peripheral directions, which causes neuronal damage (1). The annual incidence of HZ is approximately 3.4 cases per 1,000 persons (2). HZ has the potential to affect any sensory ganglion and its cutaneous nerve, while the trigeminal nerve is one of the most common cranial nerves involved (18.5%-22% of total cases) among maxillofacial manifestations (3). Acute zoster-related trigeminal neuralgia (TN) is presented as facial pain of < 3 months in the distribution(s) of the trigeminal nerve's divisions, and is associated with the clinical signs of acute HZ (4). If effective pain relief is not obtained in the acute phase of HZ, acute zoster-related TN may develop into trigeminal postherpetic neuralgia (TPHN). TPHN is defined as dermatomal pain persisting for over 3 months secondary to HZ-infected trigeminal nerve or its divisions (5). Patients with TPHN suffer moderate-to-severe facial pain, hyperalgesia, and allodynia with emotional distress and poor quality of life (6). Therefore, finding an effective method to treat acute zoster-related TN and to decrease the incidence of TPHN is of great importance (4).

Acute zoster-related pain is initially treated with medication including anticonvulsants, nonsteroidal anti-inflammatory drugs, tricyclic antidepressants, tramadol, opioid analgesics, and so on (7,8). Glucocorticoids reduce acute pain as an adjunct to antiviral therapy, but they do not reduce the incidence of postherpetic neuralgia (PHN) and cannot be used without antivirals (9). However, some patients with persistent and severe pain may respond poorly to oral drug treatments. A previous study (10) reported that nerve blocks with local anesthetics shorten the duration of zoster-related pain and reduce the incidence of PHN. However, there are a few studies (11,12) reporting the efficacy of nerve blocks in the treatment of acute zoster-related pain that usually required multiple treatments to achieve satisfactory results, which limit their clinical application. Capsaicin and 5% lidocaine patches are other options for treating acute zoster-related pain (11). Capsaicin patches may result in spontaneous burning pain or degradation of nociceptive nerve endings. Moreover, it has been demonstrated that capsaicin 0.025%-0.075% cream only has minor effects (12). Given the lack of high-quality studies, 5% lidocaine patches cannot be recommended as first-line pain medication for acute zoster-related pain therapy (13). Similarly, randomized clinical trials with high-quality evidence for the treatment of acute zoster-related TN in patients, who respond poorly to systemic analgesics, are scarce. Therefore, finding an effective and safe therapy to relieve acute zoster-related TN and preventing it from developing to TPHN is imperative for pain physicians.

Pulsed radiofrequency (PRF), a novel and minimally neuro-destructive technique, has been increasingly applied in various types of neuropathic pain (NP), such as cervical or lumbosacral radicular pain, occipital neuralgia, pudendal neuralgia, as well as TN (14-17). In addition, Kim et al (1) once performed PRF on the dorsal root ganglion (DRG) to treat acute zoster-related pain and attained satisfactory results. This procedure consists of pulsed energy waves followed by a 480 milliseconds heat dissipation interval, which assures that the temperature of the electrode does not exceed 42°C (14). Wan et al (4) reported that PRF treatment on patients with acute zoster-related TN could attain satisfactory pain relief and high safety within 6 months postoperatively. However, the patients in Wan et al's (4) study were recruited from a single center. In addition, there is a lack of studies reporting the predictive factors of the analgesic effect for PRF treatment on acute zoster-related TN patients.

Although PRF is a safe strategy with minimal risk of thermal injury or neuronal damage, its analgesic efficacy on acute zoster-related TN has not been guaranteed. Identification of determinants for the effectiveness of PRF could provide guidance for acute zoster-related TN treatment options. Therefore, the aim of our study was to investigate the analgesic effects of computed tomography (CT)-guided PRF for acute zoster-related TN, and to explore the predictive factors of therapeutic efficacy of PRF based on clinical evidence at multiple centers.

Methods

Patients

The study protocol was approved by the Medical Ethics Committee of Beijing Tiantan Hospital before the retrospective collection of the patient's data. Informed consent was waived due to the study's retrospective nature. A total of 3 hospitals, including Beijing Tiantan Hospital, Beijing Red Cross Peace Orthopedic Hospital, and Beijing Puhua International Hospital in Beijing, China, served as participating centers. Medical records were retrieved from hospital information systems (HIS) medical records, for patients with acute zoster-related TN, who had undergone PRF treatment between January 2008 to March 2021. Patients who met the follow-

ing criteria were eligible for the study: (1) age >18 years; (2) patients with acute zoster-related TN (with a history of HZ history < 90 days) who had undergone CT-guided PRF treatment of the gasserian ganglion or peripheral nerve (supraorbital nerve, infraorbital nerve, mental nerve, or multiple nerves combination); and (3) the preoperative Numeric Rating Scale (NRS-11) score (0: no pain; 10: the most imaginable severe pain) ≥ 5 with pharmacotherapy. The exclusion criteria were as follows: (1) patients with incomplete medical records (lack of baseline data or follow-up of < 12 weeks after PRF procedure); and (2) patients with unhealed herpes at the puncture site.

Procedure

All PRF procedures were conducted by experienced physicians. Patients were placed in the supine position on the CT scanner bed and administered 3L per minute of oxygen. Heart rate, blood pressure, oxygen saturation, and respiratory rate were monitored continuously. CT was used to determine the percutaneous insertion route. The electrode plate of the radiofrequency apparatus was attached on the ipsilateral shoulder. After sterilization and local anesthesia with 1% lidocaine at the puncture site, PRF of the peripheral nerves or gasserian ganglion was performed.

The puncture point of the supraorbital nerve, infraorbital nerve, and mental nerve were in the supraorbital orifice, infraorbital foramen, and mental foramen, respectively. For patients undergoing PRF of the gasserian ganglion, the Hartel anterior approach was used, and the puncture site was positioned approximately 3 cm beside the corner of the mouth (Fig. 1). A 21-gauge sterilized radiofrequency needle (a 10-cm trocar with a 5-mm active tip, PMF-21-100-5, Baylis Medical Inc.) was inserted along the predefined path under the guidance of 3-dimensional CT. Once the needle reached the proper location, the stylet of the trocar was withdrawn, and the radiofrequency treatment electrode (PMK-21-100, Baylis Medical Inc.) was inserted and connected to the radiofrequency generator (PMG-230, Baylis Medical Inc.).

Electrical stimulation was done (sensory [50 Hz] and motor [2 Hz]) to assure coverage of affected area. The needle position was adjusted until movement and sensation determined that the affected area was covered. When accurate position was achieved, PRF treatment was applied for 900 seconds. The parameters of PRF treatment were set at 42 °C, 45V, 2 Hz with 20 milliseconds current (18).

Data Collection

Preoperative data, surgical records, and immediate efficacy were retrieved from the clinical electronical database. Baseline characteristics included age, gender, pain duration, pain laterality (left/right), presurvey NRS-11, previous treatments, and comorbidities, such as hypertension, diabetes mellitus (DM), and stroke. Intraoperative data included operation time, output voltage, treatment location, and local tissue resistance. Long-term outcomes were obtained from patient databases, which were routinely updated for medical quality control at all 3 participating centers. The effective rate was defined as cases with a reduction in pain intensity (NRS-11) >50% per total number of cases 100% in 12 weeks postoperatively. The patients were routinely contacted on day 1, week 1, week 2, month 1, month 3, month 6, and every year postoperatively. According to the standard treatment protocol of acute zoster-related TN at the study centers, once the NRS-11 score decreased to 0 without oral analgesics, patient follow-up was stopped. In addition, postoperative complications, such as facial numbness, facial swelling, ecchymosis, decreased masticatory muscle strength, infection or hematoma at puncture site, intracranial hemorrhage, or intracranial infection, were also recorded by the HIS medical record system or telephone follow-up.

Statistical Analysis

Patient data were assessed for normality using the Kolmogorov-Smirnov test. Continuous data following normal distributions were presented as means ± standard deviations and were analyzed using the t test. Nonnormally distributed continuous data were shown as medians and interquartile ranges and analyzed by the Mann-Whitney U test. Categorical data were described as numbers (percentages) and were tested using the chi square test or Fisher's exact test (when the expected values were < 5). All tests were 2-tailed, and the level of significance was set at $P < 0.05$. Binary logistic regression analysis was performed to assess the predictors of efficacy of PRF therapy for patients with acute zoster-related TN. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. All data were analyzed using IBM SPSS Statistics software (Version 26, IBM Corporation, Armonk, NY, United States).

Results

Patient Characteristics

Between January 2008 to March 2021, 92 patients

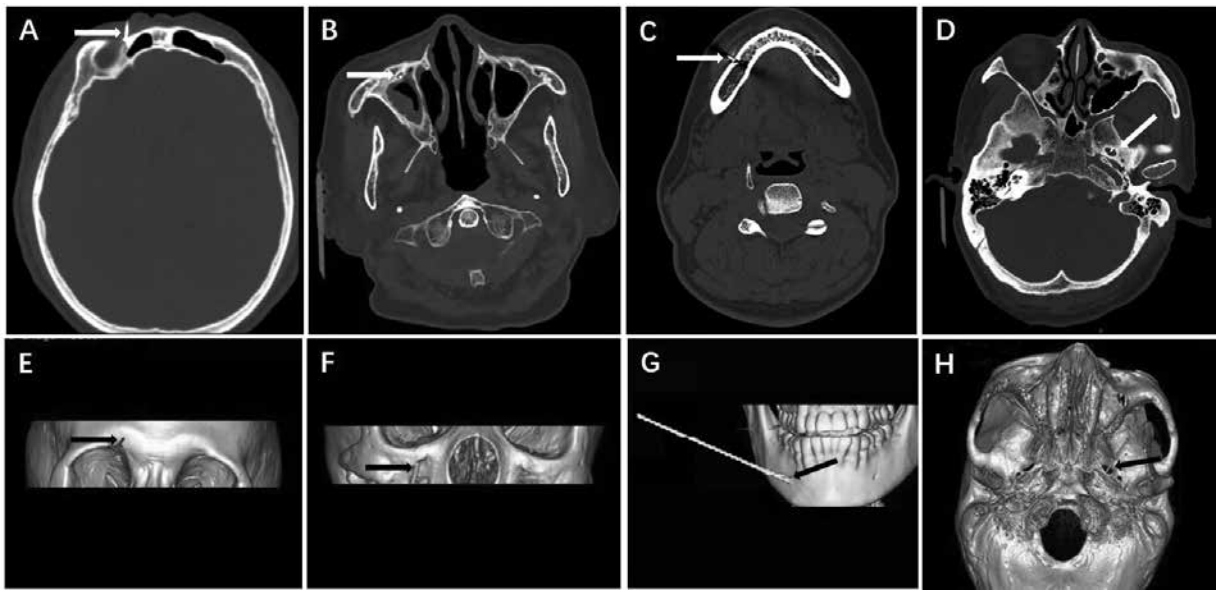

Fig. 1. *CT-guided pulsed radiofrequency treatment.* A-D: *CT scan showed the path and position of the needle located in the right supraorbital nerve, the right infraorbital nerve, the right mental nerve, and the left foramen ovale, respectively, shown by the white arrow;* E-H: *3D-CT showed the path and position of the needle located in the right supraorbital nerve, the right infraorbital nerve, the right mental nerve, and the left foramen ovale, respectively, shown by the black arrow.*
CT, computed tomography; 3D, 3-dimensional.

with acute zoster-related TN underwent CT-guided PRF at the department of pain management of the 3 study centers. Among these patients, 7 were excluded according to the exclusion criteria. In total, 85 patients were included in this study, including 41 men and 44 women (Fig. 2). Detailed characteristics of the 85 enrolled patients are shown in Table 1. The median age of patients was 57 years (range 23-82 years). The median disease duration was 45 days. The median preoperative NRS-11 score was 7.

Treatment Efficacy

Among 85 patients, 61 patients (71.2%) responded positively immediately after PRF treatment. When evaluated 4 weeks after treatment, 55 patients (64.7%) experienced effective pain relief. Moreover, 53 patients (62.4%) experienced effective pain relief 12 weeks postoperatively. NRS-11 pain scores decreased significantly immediately postoperatively, and at months 1 and 3 postoperatively ($P < 0.05$).

Side Effects

During the operation, transient bradycardia occurred in 3 patients (3.53%) while puncturing through the foramen ovale, which resolved spontaneously without treatment. Five patients (5.9%) suffered facial ecchymosis, which resolved within 2 weeks postoperatively. There were no other perioperative complications, such as increased numbness and decreased strength of masticatory muscles.

Univariate Analysis

The univariate analysis of exposure factors is shown in Table 2. Significant differences were associated with disease duration ($P = 0.023$), DM ($P = 0.024$), and treatment location ($P = 0.013$). No significant differences were found for other risk factors, including age, gender, laterality, branch affected, and so on ($P > 0.05$).

Multivariate Analysis

Multivariate logistic regression analysis was carried out to identify impact factors of the PRF therapeutic effect (Table 3). The results revealed that the treatment location of the gasserian ganglion was an independent predictor for excellent efficacy of PRF therapy, 12 weeks after the procedure (OR = 3.032; 95% CI = 1.153-7.927; $P = 0.024$). Disease duration (OR = 0.979; 95%

CI = 0.958-1.001; *P* = 0.059) and DM (OR = 0.365; 95% CI = 0.103-1.302; *P* = 0.120) were not independent impact factors for good analgesic efficacy of PRF treatment.

Discussion

Our study retrospectively reported the efficacy and safety of CT-guided PRF in patients with acute zoster-related TN. The results reveal that PRF is an effective therapy, without serious complications, with an effective rate of 64.7% and 62.4% at 1 month and 3 months, respectively. Our results are consistent with Wan et al's (4) single-center study, which demonstrated that high-voltage (60 V-90 V) PRF could significantly decrease VAS scores and improve the 36-Item Short Form Health Survey scores for acute zoster-related TN patients. Different from Wan et al's (4) research, in our study, we chose a standard parameter at the voltage of 45 V. However, the ideal PRF, including output voltage and other parameters for the treatment of acute zoster-related TN, remains to be verified.

In animal experiments, abnormal morphology of membranes, mitochondrial morphology, ultrastructural damage of axons and microtubules, as well as microfilament disintegration, were observed after performing the PRF treatment under an electron microscope (19). Recent studies (14,20) have reported that PRF relieves NP by selectively affecting the axons in small A δ and C fibers. Our study is consistent with previous research (21); there were no side effects regarding nerve damage after the procedure, which certified that PRF is a safe interventional technique that applies a discontinuous pulse current to the ganglion or peripheral nerve, and the heat could diffuse during the intermittent time without irreversible tissue damage. At our study centers, all patients received PRF treatment under CT guidance to ensure accurate positioning and safety. However, the problem of patient radiation exposure cannot be ignored. In recent years, ultrasonography has been successfully used for puncture guidance of

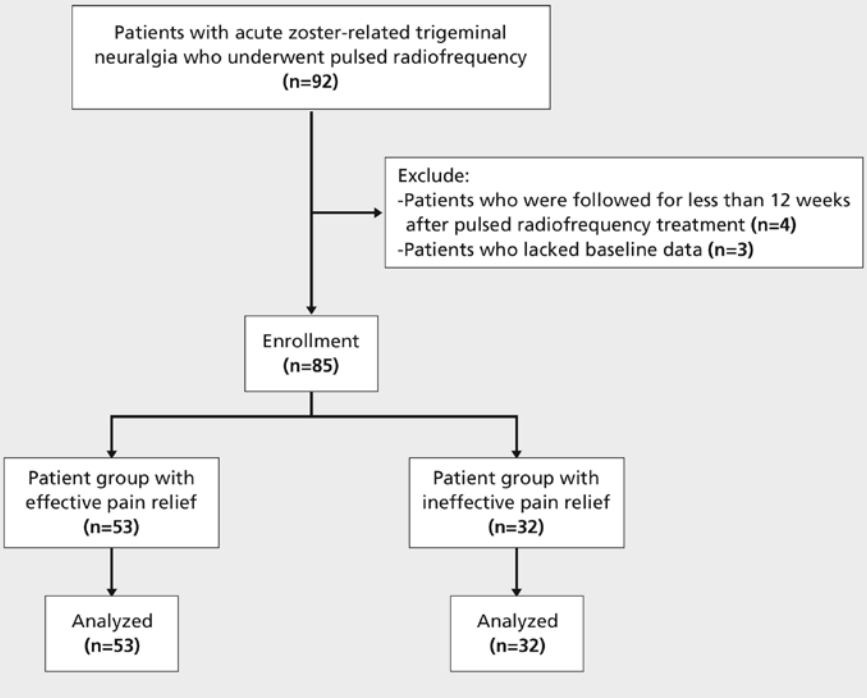

Fig. 2. *Flow diagram of the study populations.*

Table 1. *Baseline characteristics of the patients.*

Variable	n = 85
Age, Years, Median Score (IQR)	57 (49.5,65.5)
Gender, Men (%)	41 (48.2%)
Disease Duration, Days, Median Score (IQR)	45 (26.5,65.5)
Laterality, Right (%)	47 (55.3%)
Preoperative NRS-11, Median Score (IQR)	7 (6-8)
Branch Affected	
V1, n (%)	10 (11.8%)
V2, n (%)	6 (7.1%)
V3, n (%)	27 (31.8%)
V1 + V2, n (%)	19 (22.4%)
V2 + V3, n (%)	19 (22.4%)
V1 + V2 + V3, n (%)	4 (4.7%)
Comorbid Medical Disease	
Hypertension, n (%)	18 (21.2%)
Diabetes Mellitus, n (%)	14 (16.5%)
Coronary Heart Disease, n (%)	13 (15.3%)
Stroke, n (%)	9 (10.6%)
Hyperlipemia, n (%)	28 (32.9%)

Abbreviations: IQR, interquartile range; NRS-11, numeric rating scale; V1, ophthalmic division; V2, maxillary division; V3, mandibular division.

Table 2. *Comparison of the study population between the responsive group and the nonresponsive group.*

	Responsive Group (n = 53)	Nonresponsive Group (n = 32)	*P* value
Age, Median Score (IQR)	61 (49,66)	54.5 (51,65)	0.931
Gender, Men (%)	27 (50.9%)	14 (43.8%)	0.520
Disease Duration, Median Score (IQR)	39 (25,62.5)	55.5 (39,76)	0.023
Laterality, Right (%)	30 (56.6%)	17 (53.1%)	0.755
Branch Affected			
V1, n (%)	7 (13.2%)	3 (9.4%)	0.166
V2, n (%)	5 (9.4%)	1 (3.1%)	
V3, n (%)	16 (30.2%)	11 (34.4%)	
V1+ V2, n (%)	13 (24.5%)	6 (18.8%)	
V2+ V3, n (%)	12 (22.6%)	7 (21.9%)	
V1+ V2+ V3, n (%)	0 (0%)	4 (12.5%)	
Comorbid Medical Disease			
Hypertension, n (%)	12 (22.6%)	6 (18.8%)	0.670
Diabetes Mellitus {AU: Change to abbreviation "DM" or leave expansion for consistency?}, n (%)	5 (9.4%)	9 (28.1%)	**0.024**
Coronary Heart Disease, n (%)	8 (15.1%)	5 (15.6%)	1.000
Stroke, n (%)	7 (13.2%)	2 (6.3%)	0.473
Hyperlipemia, n (%)	19 (35.8%)	9 (28.1%)	0.463
Treatment Location			
Gasserian Ganglion	33 (62.3%)	11 (34.4%)	**0.013**
Peripheral Nerve	20 (37.7%)	21 (65.6%)	
Preoperative NRS-11, Median Score (IQR)	7 (6,8)	7 (6,8)	0.525

Abbreviation: IQR, interquartile range; V1, ophthalmic division; V2, maxillary division; V3, mandibular division; NRS-11, numeric rating scale.
Boldface value indicates $P < 0.05$.

Table 3. *Results of the binary logistic regression analysis.*

Characters	*P* value	OR	95% CI
Disease Duration	0.059	0.979	0.958-1.001
Diabetes Mellitus	0.120	0.365	0.103-1.302
Treatment Location of Gasserian Ganglion	**0.024**	3.032	1.153-7.927

Abbreviations: OR, odds ratios; CI, confidence intervals.
Boldface value indicates $P < 0.05$.

radiofrequency on the supraorbital nerve and infraorbital nerve, without the risk of radiation exposure (21-24). However, there is no research reporting the efficacy of PRF treatment on the gasserian ganglion under the guidance of ultrasound.

To our knowledge, this is the first study to propose predictive factors of PRF therapeutic efficacy for acute zoster-related TN. Among the preoperative data, such as age, gender, pain duration, pain laterality (left/right), presurgery NRS-11, previous treatments, comorbidities, and intraoperative data, such as treatment location, we found that treatment location was the only independent predictor of analgesic efficacy. The effective rate of patients receiving PRF treatment on the gasserian ganglion is higher than peripheral nerve therapy in our study. Our results show that choosing the gasserian ganglion as the therapeutic target attained a better effect than treating peripheral nerves. Previously, Ding et al (6) reported that gasserian ganglion PRF was more effective than peripheral nerve PRF for TPHN patients ($P < 0.05$). For acute zoster-related TN patients, whether there is a difference between the effect of PRF on the gasserian ganglion and peripheral nerve has not been reported before. Therefore, our research results have the potential to provide guidance for clinical treatment decision. However, the specific mechanism of it needs to be further confirmed by conducting relevant animal experiments.

In our univariate analysis results, the PRF treatment was more effective in the earlier stage ($P = 0.023$) (Table 2). Similarly, Kim et al (1) reported that the success rate was significantly higher in the early PRF group (within 90 days after zoster onset) than that in the PHN PRF group (82.7% vs 17.0%, $P < 0.0001$) where patients who underwent PRF on the DRG from the cervical level to the lumbosacral level. In this study, patients, who underwent PRF on the trigeminal nerve were excluded. In animal studies (25-27), early PRF application were more effective than late PRF application for the treatment of spinal nerve ligation. We hypothesized that longer duration of acute zoster-related TN caused more severe nerve pathophysiological changes; therefore, early PRF therapy in patients with shorter disease duration may achieve better analgesic efficacy than those with longer disease duration. However, the final multivariate regression analysis showed that disease duration of acute zoster-related TN had no association with postprocedure analgesic efficacy (OR= 0.979; 95% CI = 0.958-1.001; $P = 0.059$) (Table 3). As a result, studies with larger sample size need to be performed to fur-

ther explore the association between disease duration of acute zoster-related TN and therapeutic efficacy of CT-guided PRF.

A large cohort study (28,29) with 34,280 patients revealed that patients with DM had an increased risk of developing PHN in multivariable analyses (OR = 1.351; 95% CI = 1.246–1.467; $P < 0.001$). But the relation between DM and the therapeutic effect of PRF for HZ patients had not been reported yet. Our study found that patients without DM could attain better pain relief than those with DM ($P = 0.024$) (Table 2). Therefore, treatment of acute zoster-related TM in patients with DM must be approached with utmost caution. Nevertheless, our results show that DM has no association with postoperative pain relief in multivariate regression (OR = 0.365; 95% CI= 0.103-1.302; $P = 0.120$) (Table 3). Therefore, further studies are yet to be performed, to conclude if DM impacts the effectiveness of PRF treatment on acute zoster-related TM patients.

Our study has several limitations. First, this is a retrospective study with a relatively small sample size, which lacks a control group. Potential bias may exist in selection of information owing to the retrospective study design. Prospective controlled studies with larger sample size need to be conducted to further explore the predictive factors of the analgesic efficacy of PRF treatment in acute zoster-related TN. Second, PRF was performed at fixed treatment duration, output voltage, and operating temperature in our research. Optimal PRF treatment parameters need to be investigated in future studies. Third, sleep disturbance, quality of life, and psychological factors have not been analyzed in our study. Fourth, the study did not analyze what pain subtype was best alleviated by PRF therapy, such as allodynia, stabbing pain, or continuous ache or burn due to incomplete relevant content in the electronic medical records, which may need further improvement. All in all, this is the first study focusing on the predictive factors of the therapeutic efficacy of CT-guided PRF in patients with acute zoster-related TN.

Conclusions

This study found that CT-guided PRF is an effective and safe treatment for acute zoster-related TN patients. Treatment location had predictive value for treatment efficacy. Compared to peripheral nerve PRF, gasserian ganglion treatment may be more effective for patients with acute zoster-related TN.

Authors' Contributions

YJ, YS, LM, TW, and FL made substantial contributions to conception and design; YJ, YS, and FL have been involved in acquisition, analysis, and interpretation of data; YJ, LM, TW, and FL made substantial contributions to manuscript preparation, editing, and review; YS made contributions to English language editing; TW and FL have given final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved and FL is responsible as corresponding author.

Availability of Data and Materials

The datasets of the current study are available from the corresponding authors upon reasonable request.

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