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Comparison of Two Different Pulsed Radiofrequency Modes for Prevention of Postherpetic Neuralgia in Elderly Patients With Acute/Subacute Trigeminal Herpes Zoster

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ABSTRACT

Objective: Trigeminal postherpetic neuralgia (PHN) is often refractory to treatment. Pulsed radiofrequency (PRF) neuromodulation can help in preventing PHN after herpes zoster. This study aimed to compare the efficacy and safety of two different PRF modes on gasserian ganglion neuromodulation in elderly patients with acute/subacute trigeminal herpes zoster.

Materials and Methods: A total of 120 elderly patients with acute or subacute (within past three months) trigeminal herpes zoster were randomized to receive either a single cycle of high-voltage, long-duration PRF (HL-PRF group; $N = 60$) or three cycles of standard PRF (S-PRF group; $N = 60$). Patients were followed up for six months after treatment. Visual analog scale (VAS) pain score, 36-Item Short Form Health Survey (SF-36) score, and pregabalin at baseline and at different time points during follow-up were recorded.

Results: VAS and SF-36 scores declined significantly from baseline levels in both groups ($p < 0.001$). The scores were significantly lower in the HL-PRF group than in the S-PRF group at some time points ($p < 0.05$). The mean dose of pregabalin was significantly lower in the HL-PRF group than in the S-PRF group on days 3, 14, and 28 after treatment ($p < 0.05$). No serious adverse events occurred in either group.

Conclusion: HL-PRF neuromodulation of the gasserian ganglion appears to be more effective than S-PRF for preventing PHN in the elderly.

Clinical Trial Registration: ChiCTR2000038775.

Keywords: 36-Item Short Form Health Survey, pulsed radiofrequency, trigeminal herpes zoster, visual analog scale

Conflict of Interest: The authors declare that they have no conflict of interests.

INTRODUCTION

Postherpetic neuralgia (PHN) is the most common complication following herpes zoster. It presents as a persistent or paroxysmal stabbing or burning pain, usually beginning ≥3 months after complete healing of the skin lesions.[1-3] It is often refractory to pharmacological treatment.[4–7] The risk factors for PHN include older age, severe acute pain, severe rash, and immunocompromised state.[8,9] Trigeminal herpes zoster is more likely to convert to PHN and cause more severe pain than herpes zoster of spinal nerves,[10–12] and so every effort must be made to prevent the transition from acute trigeminal herpes zoster to trigeminal PHN, especially in the elderly.[12,13]

Pulsed radiofrequency (PRF) neuromodulation is an advanced non-neurodestructive method[13,14] for relief of neuralgic pain. Several previous studies have demonstrated that standard-mode PRF is effective in controlling PHN.[15–17] Our own research found that high-voltage, long-duration PRF (HL-PRF) is also effective and safe,[18,19] but it is not known whether it is more effective than the standard mode. This study aimed to determine which of the two modes is more effective for preventing PHN in elderly patients with acute/subacute trigeminal herpes zoster.

MATERIALS AND METHODS

Study Design and Setting

This randomized controlled clinical trial was conducted from February 14, 2019, to March 31, 2020, at the First Affiliated Hospital of China Medical University, Shenyang, China.

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Patients

Inclusion Criteria

1) Age >65 years; 2) history of trigeminal herpes zoster within the last three months; 3) persistent intense pain, with local skin hyperalgesia, numbness, or sensory abnormalities even after complete healing of skin lesions; 4) pain not controlled with standard pharmacotherapy (antiepileptic drugs, antidepressants, opioids) or physical treatments as recommended by the International Association for the Study of Pain[20]; and 5) 24-hour visual analog scale (VAS) pain score ≥5.

Exclusion Criteria

1) Severe coagulation disorder or current anticoagulant treatment; 2) severe liver or kidney dysfunction; 3) severe cardiopulmonary disease; 4) history of drug abuse; or 5) intellectual inability to complete self-evaluation by VAS or 36-Item Short Form Health Survey (SF-36).

Randomization and Sequence Generation

Out of the 157 patients who were screened, we excluded 37 patients (19 patients because they did not meet the inclusion criteria, 10 patients because they declined to participate, and 8 patients because of other reasons). The remaining 120 patients were randomly assigned (1:1) to receive either HL-PRF group ($N = 60$) or standard PRF (S-PRF group; $N = 60$). Figure 1 shows the patient selection and randomization process. The randomization was centrally controlled by the Human Ethics Committee (China Medical University, Shenyang, China) to ensure allocation concealment. An independent statistician used computer-generated randomization sequences to assign patients in blocks of two and four, stratified by site.

This study followed the ethical principles of the Declaration of Helsinki, and the study protocol was approved by the Human Ethics Committee of the First Affiliated Hospital of China Medical University (No: 2018-308). Informed consent forms were signed by all patients. This trial was registered with chictr.org.cn (No. ChiCTR2000038775).

Description of PRF

Treatment was administered with the patient in the supine position, with 2 L/min of oxygen supplied through a nasal catheter and continuous monitoring of heart rate, respiratory rate, and oxygen saturation (SaO_2). Computed tomography (CT) was used to determine the route of percutaneous insertion of the radiofrequency needle. After sterilization of the puncture site, 0.5% lidocaine was administered for local anesthesia. A 20-G radiofrequency needle (14.5-cm long, and with a 10-mm active tip; Baylis Medical Company, Montreal, Canada) was inserted and advanced slowly toward the foramen ovale along the designated path till the needle tip reached the predefined depth. CT was repeated to confirm the correct location of the needle tip. After the needle tip had advanced no more than 1.0 cm past the foramen ovale, electrical stimulation was performed. Sensory testing (50 Hz), 0.1–0.3 V is used to confirm that paresthesia covered the whole affected area. In case of unsatisfactory coverage, the place of the needle tip was adjusted. Because with HL-PRF the temperature may rise >42 °C, motor stimulation (2 Hz) 0.5 V is performed to ensure that no damage occurs to the motor innervation when the V3 division is targeted (Fig. 2).

PRF treatment was performed using the Pain Management Generator (PM-230; Baylis Medical Company, Montreal, Canada). In the HL-PRF group, treatment was initiated with the following

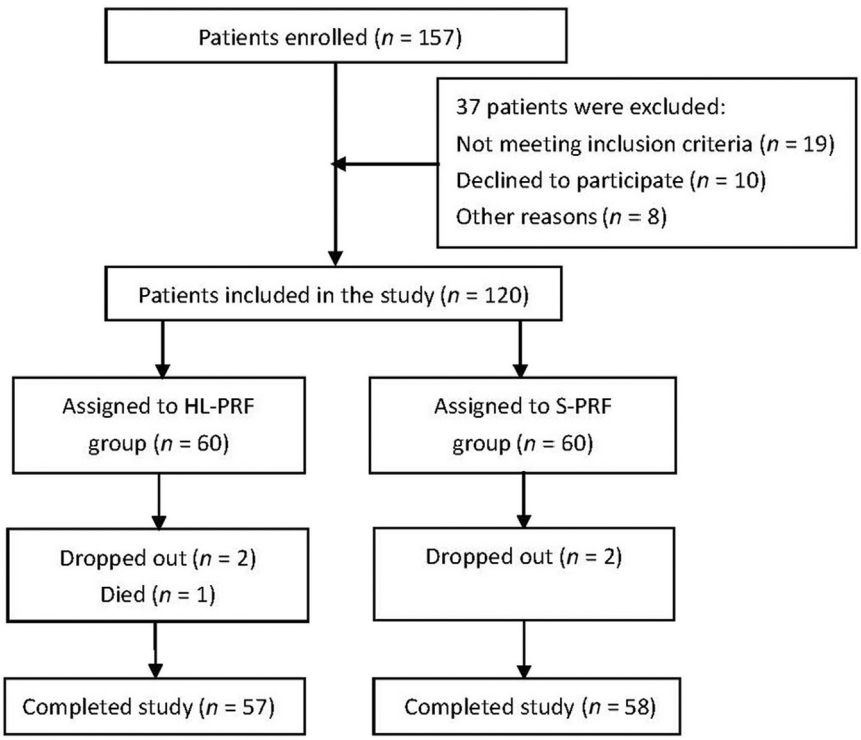

Figure 1. Study flowchart. One hundred and twenty randomized patients were included in the intention-to-treat analysis by use of repeated measures analysis of variance with mixed effects modeling.

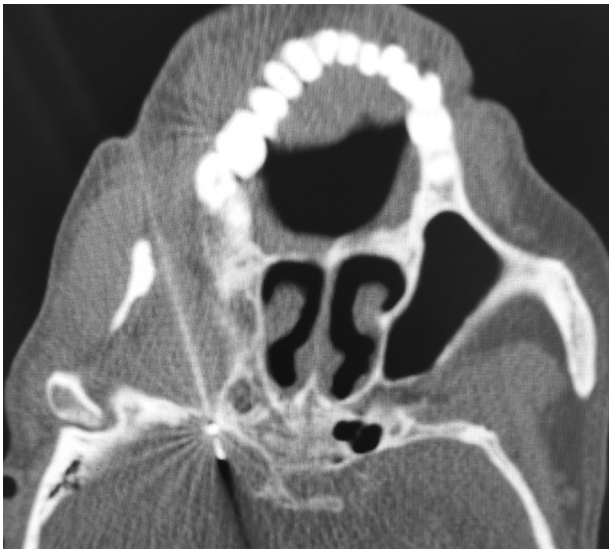

Figure 2. Representative computed tomography (CT) image of pulsed radiofrequency (PRF) needle puncturing arrived at gasserian ganglion.

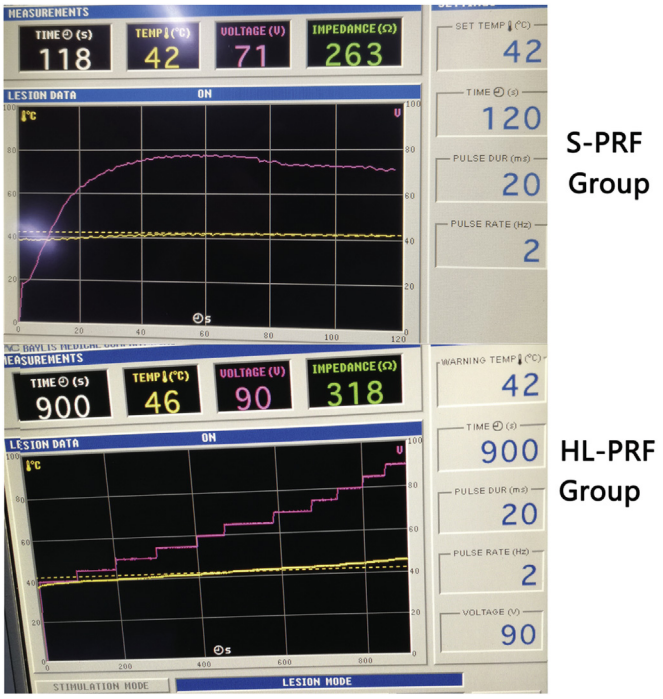

Figure 3. Representative image of two different pulsed radiofrequency (PRF) modes. [Color figure can be viewed at www.neuromodulationjournal.org]

parameters: 42 °C, 2 Hz, 20 msec, and 900 sec duration. The initial voltage output of 40 V was gradually increased until the patient could not tolerate the abnormal sensation (ie, burning pain). The maximal voltage output ranged from 60 V to 100 V. Treatment was terminated after 900 sec. In the S-PRF group, treatment was with the following settings: 42 °C, 2 Hz, 20 msec, and 120 sec duration. Three cycles were administered in auto-standard mode (Fig. 3).

Blinding

All PRF procedures were performed by the same investigator (Dr 1). The follow-up assessments were performed by two other investigators (Dr 2 and Dr 3) who were blinded to the PRF mode. The PRF instrument was operated by a nurse who did not participate in any other therapeutic or follow-up activities or trial discussions.

Post-PRF Drugs

After PRF, patients received pregabalin according to the pain severity. The initial dose was 50 mg every 12 hours. The dose was gradually increased if VAS scores were ≥3 or if the frequency of acute pain flares was >6 per day. Other medications were avoided.

Primary Outcome

Visual Analog Scale

The VAS scores were recorded before treatment and on the mornings of days 3, 7, and 14, and months 1, 3, and 6 after treatment.

Secondary Outcome

SF-36 Score

The SF-36[21,22] was used to assess the health of patients. The questionnaire, which can be completed in just 6–9 min, assesses nearly all conceptual domains of the substantially longer generic self-administered questionnaires that have been used in other studies.[23] The scores for each domain—bodily pain, general health, mental health, physical function, physical role, role-emotional, social function, and vitality—were recorded before treatment and on day 7 and months 1, 3, and 6 after treatment.

Mean Dose of Rescue Medication

The mean doses of pregabalin required on days 0, 3, 7, 14, and 28 after treatment were calculated in both groups.

Adverse Events

Occurrence of adverse events (ie, bleeding at puncture site, infection, new cranial nerve injury symptoms of hypoesthesia of face or weakness of masseter muscle, intracranial hemorrhage, cerebrospinal fluid leak) was recorded on days 1, 7, and 14 after treatment.

Statistical Analysis

Sample size calculation was based on the findings of our previous study,[19] where the effective rate of semilunar ganglion neuromodulation was 90% in the test group vs 52% in the control group. To detect a difference of this magnitude with a power of 0.8 and type-I error of 0.05, we estimated that at least 28 patients would be required per group. To allow for a potential dropout rate of 5%, we decide to enroll 60 patients per group.

Normality of distribution of continuous variables was confirmed by the Kolmogorov–Smirnov test. Continuous variables were summarized as means ± standard deviation. Mean values at different time points were compared using the repeated-measures analysis of variance. Categorical variables were summarized as percentages and compared using the Fisher exact test. Statistical analysis was performed using SPSS 19.0 (IBM Corp, Armonk, NY). Statistical significance was at $p < 0.05$.

Table 1. Baseline Characteristics of the Participants (Mean ± Standard Deviation).

Patients	S-PRF group (N = 58)	HL-PRF group (N = 57)
Age (years)	69.96 ± 13.66	70.54 ± 14.02
Female/male, N	35/23	36/21
Weight (kg)	68.19 ± 10.67	67.64 ± 12.47
Disease duration (days)	65.14 ± 18.53	67.28 ± 19.64
Average pain scores	7.61 ± 2.49	7.39 ± 2.43
HZ distribution, N (I/II/III branch)	15/18/25	12/17/28
Presence of ocular complications, N	4	5

HL-PRF, high-voltage, long-duration PRF; S-PRF, standard PRF.

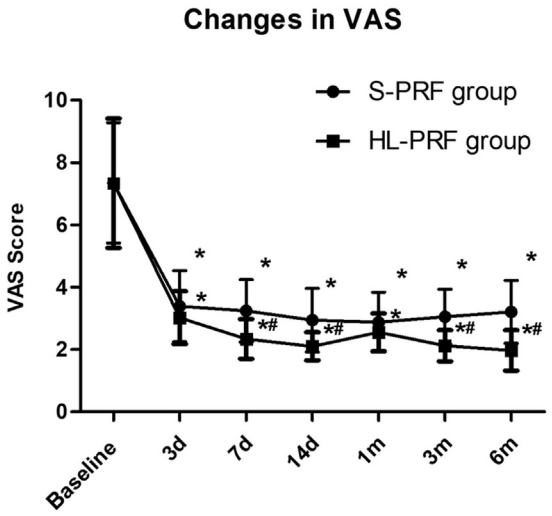

Figure 4. Significantly decreased mean visual analog scale (VAS) scores after treatment. *$p < 0.001$ indicates pre VAS vs post VAS. #$p < 0.05$ indicates high-voltage, long-duration PRF (HL-PRF) group vs standard PRF (S-PRF) group.

Table 2. Changes of VAS Scores Before and After Treatment.

VAS scores	S-PRF group (N = 58)	HL-PRF group (N = 57)
Baseline	7.35 ± 1.93	7.39 ± 2.08
3 days after PRF	3.39 ± 1.14*	3.02 ± 0.85*
7 days after PRF	3.24 ± 1.00*	2.34 ± 0.64*,†
14 days after PRF	2.94 ± 1.02*	2.10 ± 0.45*,†
1 month after PRF	2.88 ± 0.96*	2.55 ± 0.61*
3 months after PRF	3.05 ± 0.89*	2.12 ± 0.54*,†
6 months after PRF	3.21 ± 1.01*	1.97 ± 0.65*,†

HL-PRF, high-voltage, long-duration PRF; PRF, pulsed radiofrequency; S-PRF, standard PRF; VAS, visual analog scale.
*$p < 0.001$ indicates pre VAS vs post VAS
†$p < 0.05$ indicates HL-PRF group vs S-PRF group.

RESULTS

Patient Demographics

Demographic characteristics were comparable between the HL-PRF group and the S-PRF group (Table 1). While one patient in the HL-PRF group died within six months of enrollment and two patients each in the HL-PRF group and the S-PRF group dropped out during follow-ups; these five patients were not included in the final analysis (Fig. 1).

Visual Analog Scale

The pretreatment mean VAS scores were comparable in the two groups. The post-treatment VAS scores were significantly lower than baseline scores in both groups at all time points ($p < 0.001$; Fig. 4). The mean VAS scores were significantly lower in the HL-PRF group than in the S-PRF group at days 4 and 7 and months 3 and 6 after treatment ($p < 0.05$; Fig. 4 and Table 2).

SF-36

The pretreatment SF-36 scores were comparable in the two groups. The scores for each domain (bodily pain, general health, mental health, physical function, physical role, role-emotional, social function, and vitality) improved significantly from baseline level at all time points after treatment in both groups ($p < 0.001$; Fig. 5 and Table 3).

Bodily Pain

The scores for bodily pain indicated significantly greater improvement in the HL-PRF group than in the S-PRF group at six months after treatment ($p < 0.05$; Fig. 5a and Table 3).

General Health

The scores for general health indicated significantly greater improvement in the HL-PRF group than in the S-PRF group at seven days and at six months after treatment ($p < 0.05$; Fig. 5b and Table 3).

Mental Health

The scores for mental health indicated significantly greater improvement in the HL-PRF group than in the S-PRF group at three months after treatment ($p < 0.05$; Fig. 5c and Table 3).

Physical Function

The scores for physical function indicated significantly greater improvement in the HL-PRF group than in the S-PRF group at one and six months after treatment ($p < 0.05$; Fig. 5d and Table 3).

Physical Role

The scores for physical role indicated significantly greater improvement in the HL-PRF group than in the S-PRF group at three months after treatment ($p < 0.05$; Fig. 5e and Table 3).

Social Function

The scores for social function indicated significantly greater improvement in the HL-PRF group than in the S-PRF group at six months after treatment ($p < 0.05$; Fig. 5g and Table 3).

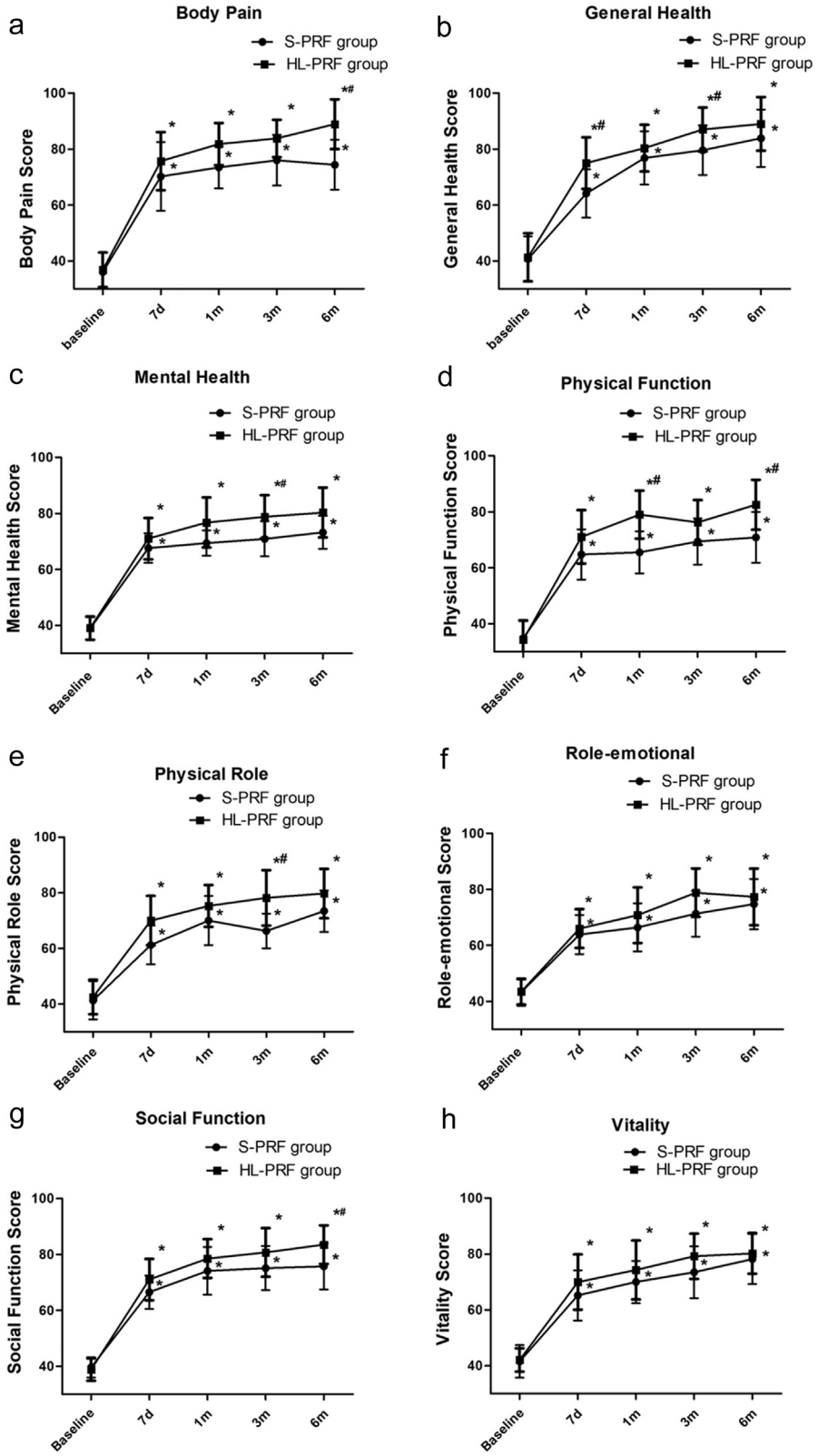

Figure 5. (a-h) Significantly improved mean SF-36 scores after treatment. *$p < 0.001$ indicates pre scores of SF-36 vs post scores. #$p < 0.05$ indicates high-voltage, long-duration PRF (HL-PRF) group vs standard PRF (S-PRF) group.

Table 3. Changes of Qualities of Life Scores Before and After Treatment.

		Baseline	After PRF treatment			
			Seven days	One month	Three months	Six months
Body pain	S-PRF group	36.06 ± 6.94	70.21 ± 12.29*	73.41 ± 7.54*	75.99 ± 9.07*	74.37 ± 8.90*
	HL-PRF group	36.84 ± 6.17	75.67 ± 10.39*	81.77 ± 7.54*	83.79 ± 6.69*	88.89 ± 8.81*,†
General health	S-PRF group	40.69 ± 8.14	64.10 ± 8.61*	76.80 ± 9.54*	78.60 ± 8.88*	83.84 ± 10.26*
	HL-PRF group	41.29 ± 8.60	74.98 ± 9.24*,†	80.32 ± 8.35*	87.00 ± 7.88*,†	89.97 ± 9.59*,†
Mental health	S-PRF group	38.92 ± 3.94	67.60 ± 5.29*	69.39 ± 4.54*	70.91 ± 6.27*	73.21 ± 5.90*
	HL-PRF group	37.99 ± 4.17	70.98 ± 9.24*	76.74 ± 8.94*	78.79 ± 7.69*,†	80.29 ± 8.89*
Physical function	S-PRF group	34.76 ± 6.09	64.75 ± 8.98*	65.46 ± 7.56*	69.38 ± 8.27*	70.84 ± 9.11*
	HL-PRF group	34.24 ± 7.00	71.01 ± 9.54*	78.98 ± 8.54*,†	76.21 ± 7.97*	82.48 ± 8.89*,†
Physical role	S-PRF group	41.29 ± 6.87	61.21 ± 6.98*	69.59 ± 8.84*	66.23 ± 6.27*	73.43 ± 7.50*
	HL-PRF group	42.49 ± 6.17	69.95 ± 8.90*	75.29 ± 7.54*	78.20 ± 9.97*,†	79.74 ± 8.85*
Role-emotional	S-PRF group	43.31 ± 4.96	63.80 ± 7.01*	66.39 ± 8.34*	71.26 ± 8.27*	74.69 ± 9.02*
	HL-PRF group	43.91 ± 4.55	65.98 ± 6.92*	70.74 ± 9.94*	78.79 ± 8.67*	77.27 ± 10.21*
Social function	S-PRF group	39.61 ± 3.65	66.45 ± 6.02*	74.08 ± 8.45*	75.05 ± 7.87*	75.69 ± 8.23*
	HL-PRF group	38.81 ± 4.01	70.98 ± 7.39*	78.50 ± 6.94*	80.70 ± 8.65*	83.45 ± 6.89*,†
Vitality	S-PRF group	41.55 ± 5.87	65.21 ± 8.98*	69.99 ± 7.54*	73.48 ± 9.27*	78.18 ± 8.90*
	HL-PRF group	42.19 ± 6.17	69.64 ± 9.90*	74.29 ± 10.54*	79.20 ± 8.07*	80.24 ± 7.29*

HL-PRF, high-voltage, long-duration PRF; PRF, pulsed radiofrequency; S-PRF, standard PRF.
*$p < 0.001$ indicates pre scores of SF-36 vs post scores.
†$p < 0.05$ indicates HL-PRF group vs S-PRF group.

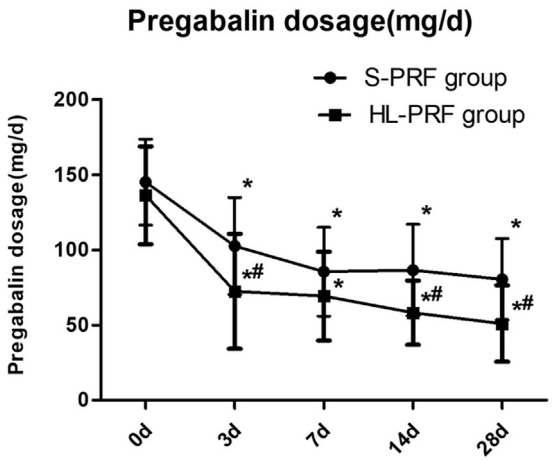

Figure 6. Significantly decreased mean dosages of pregabalin after treatment. *$p < 0.001$ indicates pre pregabalin dosage vs post dosage. #$p < 0.05$ indicates high-voltage, long-duration PRF (HL-PRF) group vs standard PRF (S-PRF) group.

Table 4. Changes of Pregabalin Doses Before and After Treatment.

	S-PRF group ($N = 58$)	HL-PRF group ($N = 57$)
0 day after PRF	145.07 ± 28.57	131.30 ± 32.53
3 days after PRF	102.51 ± 32.31*	72.47 ± 38.24*,†
7 days after PRF	85.44 ± 29.53*	69.25 ± 29.55*
14 days after PRF	86.56 ± 30.42*	58.16 ± 21.33*,†
28 days after PRF	80.42 ± 10.26*	50.99 ± 25.43*,†

HL-PRF, high-voltage, long-duration PRF; PRF, pulsed radiofrequency; S-PRF, standard PRF.
*$p < 0.001$ indicates pre pregabalin dosage vs post dosage.
†$p < 0.05$ indicates HL-PRF group vs S-PRF group.

Rescue Drug Dosage

The mean doses of the rescue drug (pregabalin) were significantly lower in the HL-PRF group than in the S-PRF group on days 3, 14, and 28 after treatment ($p < 0.05$; Fig. 6 and Table 4).

Adverse Events

No patient had bleeding at the puncture site, infection, new cranial nerve injury symptoms of hypoesthesia of face or weakness of masseter muscle, intracranial hemorrhage, or other serious adverse events after PRF treatment. Ecchymoses formed on the face in 7 patients in the S-PRF group and 11 patients in the HL-PRF group but subsided rapidly in all cases.

DISCUSSION

In this study, PRF neuromodulation of the gasserian ganglion effectively relieved trigeminal PHN in elderly patients and significantly improved their quality of life. The analgesia was better and the incidence of adverse events was lower with HL-PRF than with the standard-mode PRF. No serious adverse events occurred with either mode.

PHN is a severe neuropathic pain that occurs following herpes zoster. Immune system dysfunction due to aging, infection, malignant disease, or other conditions results in reactivation of latent virus and causes severe inflammation in the posterior root spinal neurons or cranial nerve ganglia. Massive viral replication can cause cell dehydration and apoptosis, chronic inflammatory cell infiltration, and other complicated pathological changes in the primary sensory neurons.[24] Patients typically present with spontaneous pain, allodynia, and hyperalgesia in the distribution of the affected nerve.[25] Because the etiology and mechanism of PHN remain unclear, there is still no effective treatment.[26–29]

The trigeminal nerve is the main orofacial sensory nerve. Activation and replication of latent herpes zoster virus in the gasserian ganglion result in PHN.[30] In the elderly, the risk of developing PHN

is higher after trigeminal herpes zoster than after a spinal nerve herpes zoster[31]; pain relief with drugs and other therapies is also less likely. Therefore, the need for an intervention to prevent progression to trigeminal PHN is very essential.

With a discontinuous pulse current (20 ms, 2 Hz), PRF is a minimally invasive treatment[32] that could provide long-term analgesia.[33] Many clinical and experimental studies have shown that PRF can control neuropathic pain.[34] The gasserian ganglion plays a critical role in expressing various signaling molecules that modulate peripheral and central sensitization. Arici et al have previously shown that PRF neuromodulation of the gasserian ganglion can achieve good analgesia[35,36]; therefore, we chose the gasserian ganglion as the therapeutic target in this study.

In this study, other than voltage and time settings, the parameters were the same in the HL-PRF and S-PRF groups. Patients in both groups obtained significant pain relief and improvement of life quality. However, the improvement was greater in the HL-PRF. Ewertowska et al[37] have previously shown that increasing the magnitude of the electric field through high voltage might be more effective for pain relief.

We recognize several limitations in this study. First, this was a single-center study with a small sample. Second, the patients were only followed up for six months after treatment.

CONCLUSION

The HL-PRF mode for gasserian ganglion neuromodulation may be more effective than standard-mode PRF for reducing the incidence and severity of trigeminal PHN in elderly patients with acute or recent trigeminal herpes zoster. Both modes appear to be comparably safe.

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Authorship Statements

Cheng-Fu Wan was responsible for clinical experiment design, follow-up, data collection and analysis, and manuscript writing; and Tao Song was responsible for the clinical experiment design and manuscript review. Both authors approved the final version of the manuscript.

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COMMENTS

The management of postherpetic neuralgia is often difficult, because of minimal effect or intolerable side effects of pharmacological treatment. Herpes infection in the trigeminal nerves can evolve into postherpetic trigeminal neuralgia.

Conventional radiofrequency (RF) treatment of the Gasserian ganglion reduces pain, but may also induce analgesia dolorosa, a serious complication. Pulsed radiofrequency (PRF) treatment was compared to RF in a randomized controlled trial (Erdine S, Yucel A, Cimen A, Aydin S, Sav A, Bilir A. Effects of pulsed versus conventional radiofrequency current on rabbit dorsal root ganglion morphology. *Eur J Pain*. 2005;9(3):251–256.). The pain was reduced in both groups of 20 patients each, but the effect of PRF waned off 3 months after the intervention. In the RF group one patient developed anesthesia dolorosa, in the PRF group no side effects were reported.

In a search to combine the efficacy of RF with the safety of PRF, the effect of combining PRF with continuous radiofrequency was assessed in a trial that randomly allocated patients to short continuous radiofrequency, long continuous radiofrequency or pulsed and continuous radiofrequency. All groups experienced significant differences in pain compared to baseline, but there were no differences between groups. Over 50% of patients experienced mild facial dysesthesia twelve months after treatment but the incidence of facial dysesthesia did not differ between the three groups (Li X, Ni J, Yang L, et al. A prospective study of Gasserian ganglion pulsed radiofrequency combined with continuous radiofrequency for the treatment of trigeminal neuralgia. *J Clin Neurosci*. 2012;19(6):824–828.).

The use of high voltage PRF (HV PRF) was reported in a retrospective study (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(8):1189–1192.) and an RCT (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(7):595–603.) that found that PRF of the Gasserian resulted in a longer lasting effect than PRF at low voltage without compromising the safety. The authors of the current study published the comparative results of HV PRF with sham intervention. Patients in the HV PRF group had a significant pain reduction lasting up to 6 months (Wan C, Dong DS, Song T. High-voltage, long-duration pulsed radiofrequency on gasserian ganglion improves acute/subacute zoster-related trigeminal neuralgia: a randomized, double-blinded, controlled trial. *Pain Physician*. 2019;22(4):361–368.).

No serious adverse events were reported with HV PRF.

The voltage used depends on the patients, tolerance, therefore we see a wide variation in voltages, which makes it difficult to interpret. Moreover, it is not clear whether HV PRF induces tissue damage.

Up till now the results obtained in a difficult to treat population are encouraging and further research should be performed.

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