

Retrospective Study

# Effect of Repeated High-voltage Long-duration Pulsed Radiofrequency on Herpetic Neuralgia

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**Background:** Pulsed radiofrequency (PRF) is a commonly used, minimally invasive method to treat herpes zoster neuralgia, but the intensity of standard voltage PRF is limited, resulting in patients not getting a lasting therapeutic effect. The therapeutic effect of repeated high-voltage long-duration PRF on acute herpes zoster neuralgia has not been studied.

**Objective:** How to effectively reduce the incidence of postherpetic neuralgia is a serious challenge for clinicians. The purpose of this study was to investigate the clinical efficacy of repeated high-voltage long-duration pulsed radiofrequency therapy for patients with acute herpetic neuralgia and its preventive effect on postherpetic neuralgia.

**Study Design:** This is a retrospective study.

**Setting:** The study was carried out in the Pain Department of the affiliated Hospital of Jiaxing College in Jiaxing, China.

**Methods:** Eighty-one patients with acute herpetic neuralgia, who underwent minimally invasive treatment in the Pain Department of Jiaxing First Hospital from January 2020 through December 2020 were retrospectively analyzed. Patients were divided into 3 groups (n = 27 each group) according to treatment method: standard voltage PRF (group S); high-voltage long-duration PRF (group H), and repeated high-voltage long-duration PRF (group R). Pain was assessed according to Numeric Rating Scale (NRS-11) scores and analgesic drug doses were recorded. Blood galectin-3 (gal-3) and interleukin (IL)-6 levels among the 3 groups were compared before treatment and at one, 2, and 4 weeks posttreatment. The incidence of postherpetic neuralgia (PHN) and complications in the 3 groups were recorded.

**Results:** Pain intensity, blood levels of gal-3 and IL-6, and the dose of orally administered gabapentin capsules and morphine were reduced in all patients after treatment. Compared to group S, patients in group R exhibited lower NRS-11 scores, blood levels of gal-3 and IL-6, and dosages of oral gabapentin capsules after treatment. The incidence of PHN was significantly lower at weeks 4, 8, and 12. No adverse reactions occurred in the 3 groups posttreatment.

**Limitations:** Our small sample size is a limitation; we look forward to increasing the sample size in follow-up studies and exploring relevant conclusions in randomized controlled trials.

**Conclusion:** Repeated high-voltage long-duration PRF therapy was an effective treatment for acute herpetic neuralgia and may prevent the occurrence of PHN.

**Key words:** Pulsed radiofrequency, dorsal root ganglion, herpes zoster, postherpetic neuralgia

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**H**erpes zoster is caused by infection of the dorsal root ganglion (DRG) or cranial nerve by the varicella zoster virus and is mostly encountered

in middle-aged and elderly individuals with weakened immunity. Neuralgia is one of the most common and serious symptoms of herpes zoster (1). It has been reported

that the incidence of postherpetic neuralgia (PHN) is approximately 9%–34% (2,3). PHN can significantly affect quality of life, physical function, and mental health (4,5).

Long-term oral drug therapy (e.g., anticonvulsants, opioids, nonsteroidal anti-inflammatory drugs and other analgesics) not only decreases the curative effect, but also increases the risk for side effects from these drugs, such as gastrointestinal discomfort, nausea, dizziness, and others. Although nerve blocks or epidural injections can improve blood circulation and analgesia in herpes zoster, local anesthetics and glucocorticoids have no significant effect on the prevention of PHN (6,7). The curative effect of spinal cord stimulation (SCS) in the early treatment of herpes zoster neuralgia can effectively reduce the incidence of PHN (8); however, the placement of electrodes in the spinal canal, the risk of infection with epidurals and implants over time, electrode displacement, and even the risk for fracture, has limited its clinical application. Moreover, patients can incur expensive medical costs.

Pulsed radiofrequency (PRF) has demonstrated short-term efficacy. The puncture needles are safer and less expensive than those used in SCS because they do not enter the spinal canal; therefore, it is the most commonly used minimally invasive method for the treatment of herpes zoster neuralgia. However, poor long-term efficacy remains a major problem for clinicians.

PRF is an intermittent pulse current emitted by a radiofrequency instrument that acts on the pathological DRG and around nerve fibers to regulate disordered electrical signals, down-regulate substance P levels in the DRG, and up-regulate substance P levels in the spinal cord (9), thus exerting an analgesic effect. Because the electrode tip temperature does not exceed 42°C, the extent of energy transmission does not destroy the anatomical basis of pain impulse transmission nor does it destroy motor nerve function. Therefore, compared with traditional continuous radiofrequency, there is no thermal damage to the nerve and it does not aggravate the original neuropathic pain. However, due to the low therapeutic field intensity (40 V) and short duration (180–300 seconds) of standard voltage PRF, its effect intensity is limited; as such, patients cannot achieve lasting therapeutic effects, and the incidence of PHN cannot be significantly reduced.

Teixeira et al (10) found that PRF field intensity was positively correlated with treatment effect (10). Wan et al (11,12) adopted a technique using a PRF mode with high voltage long duration; more specifically, manually adjusting the field intensity and gradually increasing

the field intensity (maximum 90 V) according to patient tolerance, with a duration of 900 seconds (11,12). The Numeric Rating Scale (NRS-11) score for patients with herpetic neuralgia at one, 4, 8, and 12 weeks postsurgery decreased, and their quality of life improved. The above PRF treatment mode was a single operation, which could not reach the nerve regulation time of 1–2 weeks—provided by SCS for patients with herpes zoster neuralgia—and failed to significantly reduce the incidence of PHN. PRF causes virtually no damage to the body and is reproducible. It is accepted that the occurrence of PRF treatment for patients with herpes zoster neuralgia should be once every 3 days, for a total of 3 treatments, which is close to the nerve regulation time for SCS. However, whether it can significantly improve the long-term treatment effect in patients and reduce the incidence of PHN has not been clarified. This study aimed to investigate the clinical efficacy of repeated high-voltage long-duration PRF in the treatment of patients with acute herpetic neuralgia and its preventive effect on the occurrence of PHN.

## METHODS

### Inclusion Criteria and Exclusion Criteria

The present study was approved by the Medical Ethics Committee of the First Hospital of Jiaxing (Jiaxing, Zhejiang Province, China, approval number LS2020-133). Informed consent was obtained from each patient. For this retrospective analysis, inclusion criteria were as follows: acute herpes zoster neuropathy, with neck, thoracic, and lumbar ganglion involvement; duration  $\leq$  one month; and NRS-11 score  $>$  3. Individuals with an infection or tumor(s) at the puncture site, severe cardiovascular and cerebrovascular diseases, liver and kidney dysfunction, abnormal coagulation function, poor glycemic control in those with diabetes, long-term use of immunosuppressants or systemic failure, psychiatric diseases, and refusal to cooperate with the surgeon were excluded. Eighty-one patients with acute herpes zoster neuropathic pain who were treated at the authors' hospital from January 2020 through December 2020 were enrolled.

Patients were divided into 3 groups according to treatment method. There were no statistical differences in baseline data (gender, age, disease history) among the 3 groups. Four patients underwent PRF to the peripheral branches of the trigeminal nerve, 3 failed to be followed up 12 weeks posttreatment, and one had insufficient medical records. After excluding

these patients, the medical records of 81 patients were analyzed and divided into 3 groups (n = 27 each) according to treatment method: standard voltage PRF (group S), high voltage long-duration PRF (group H), and repeated high-voltage long-duration PRF (group R) (Fig. 1). None of the patients had a history of epidurals or nerve blocks before treatment.

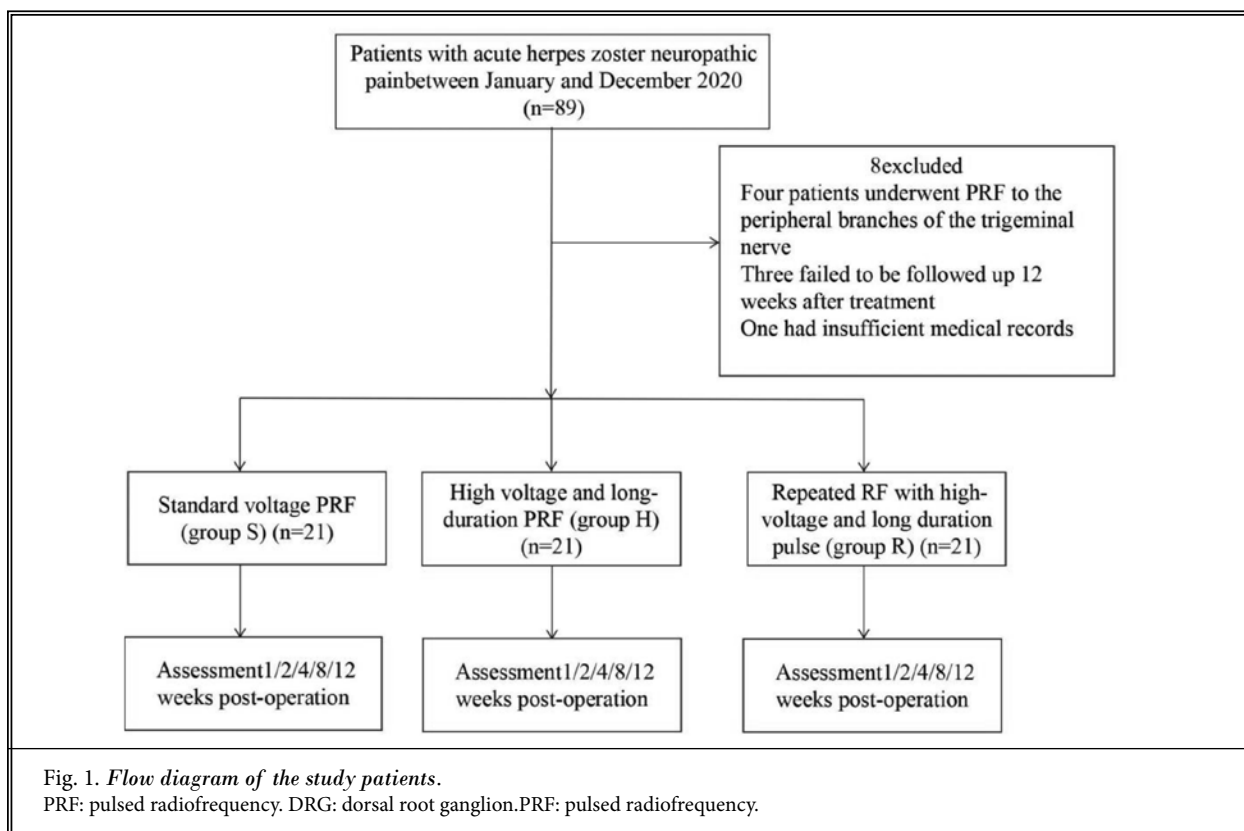
### Surgical Procedure

All patients generally underwent standard oral analgesic therapy (gabapentin capsules, nonsteroidal anti-inflammatory drugs, tramadol, or opioids) before admission; their pain was moderate to severe. PRF combined with a paraspinal injection was administered to the DRG at appropriate levels when conventional medication provided only temporary pain relief. All PRF combined with paraspinal injection procedures were performed by physicians with experience in pain management.

In the standard voltage PRF group (group S), patients were positioned prone on the computed tomography (CT) bed, with the segment with the most severe pain at the center, and the upper and lower segments

extended by one segment. DRG high-voltage long-duration PRF therapy was performed on the 3 segments in total each time. The upper edge of the ventral foramen was selected as the puncture point for CT positioning, the puncture path was determined (Fig. 2A), and disinfection towels were used. Local anesthesia (1.0% lidocaine hydrochloride) was used for infiltration, and an RF trocar puncture (20G, length 150 mm, active end length 10 mm) was slowly advanced under CT. Finally, the needle tip was placed in the upper ventral quadrant of the foramen, with root pain possibly occurring at the puncture point of the chest wall. Three-dimensional CT reconstruction was used to determine the position of the puncture needle in relation to the target (Fig. 2B).

The RF instrument (Baylis Medical Inc., Montreal, QC, Canada) was used for a sensory test with these parameters: voltage, 0.1–0.5 V and frequency 50 Hz. This can induce discomfort such as acid bilges, swelling, numbness, or tingling in the original pain area. Low-frequency current was used in the exercise test with these parameters: voltage, 0.1–0.5 V; frequency, 2 Hz. If vibrating and pulsating muscle fibers in the nerve root region of the lesion were replicated, it indicated that the



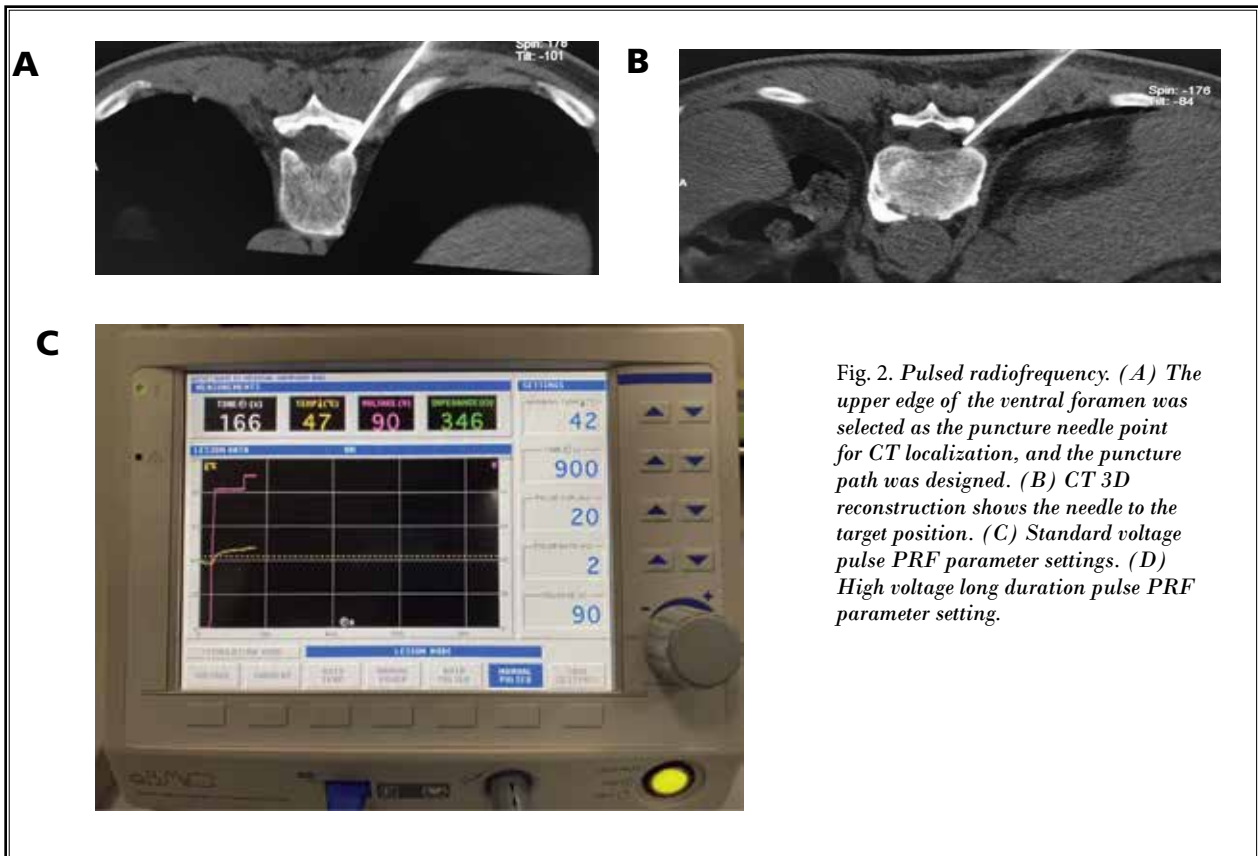


Fig. 2. Pulsed radiofrequency. (A) The upper edge of the ventral foramen was selected as the puncture needle point for CT localization, and the puncture path was designed. (B) CT 3D reconstruction shows the needle to the target position. (C) Standard voltage pulse PRF parameter settings. (D) High voltage long duration pulse PRF parameter setting.

puncture needle was located near the target. After confirming the position of the puncture needle, the temperature, time, pulse width, and frequency were set to 42°C, 300 seconds, 20 milliseconds, and 2 Hz, respectively (Fig. 2C). The formulation of the treatment solution (100 mg 2% lidocaine hydrochloride, 500 µg mecobalamin injection, one mL compound betamethasone injection, and 3 mL 30% iodohydrin) was added to dilute 15 mL 0.9% normal saline. The puncture site was compressed after needle extraction. After 15 minutes of observation, patients were returned to the ward with stable vital signs. Patients in group S were treated once every 3 days a total of 3 times (no PRF therapy was performed on the second and third times, only CT-guided paraspinal nerve block was performed, and the formulation of the treatment solution did not include compound betamethasone injection, as previously described).

In the high-voltage long-duration PRF group (group H), the surgical procedure was the same as that for group S. Sensory test and motion testing revealed that no blood, gas, or liquid was extracted from the needle after reaching the target position; as such, 2 mL of 1.0% lidocaine hydrochloride was injected into each

target for 5 minutes. The RF instrument was switched to manual pulse mode. The temperature, time, pulse width, and frequency were set to 42°C, 900 seconds, 20 milliseconds, and 2 Hz, respectively, with a field intensity of 90 V (Fig. 2D). At the end of PRF, the electrode needle core was removed, and no blood, gas, or liquid was drawn back from the needle. A 5 mL treatment solution was injected into each segment using the same formulation used in group S. The puncture site was compressed after needle extraction. After 15 minutes of observation, patients were returned to the ward with stable vital signs.

Patients in group H were treated at an interval of 3 days 3 consecutive times (the second and third times did not involve high-voltage long-duration PRF therapy; only a CT-guided paravertebral nerve block was performed. Also, the treatment solution did not include compound betamethasone in the injection, although the other drugs were the same as before).

In the repeated high-voltage long-duration PRF group (group R), the procedure was the same as for group H, but the difference was 3 consecutive days for treatments 1-3 (the second and third treatments were

high-voltage long-duration PRF, the procedure with the first, second, and third injection of the formulation did not include betamethasone, but the same drugs as the former).

During the treatment period, patients in both groups were given morphine hydrochloride instant release tablet 5 mg orally for breakthrough pain.

### Outcome measures

The analgesic effect of repeated high-voltage long-duration PRF on patients with acute herpetic neuralgia was evaluated according to their NRS-11 score and dosage of anticonvulsants and analgesics. For the purpose of analysis, the dosage of anticonvulsants and painkillers were converted to equivalent doses of gabapentin capsule (10,11) and oral morphine (12).

In previous studies, clinically significant PHN was defined as persistent pain according to NRS-11 with an intensity > 3 (13-15). The proportion of clinically significant PHN at 4, 8, and 12 weeks after the end of treatment was compared using the same criteria.

### Statistical Analysis

Data for continuous variables are expressed as mean  $\pm$  standard deviation (SD). Data normality was tested

using the Kolmogorov–Smirnov test. Results were compared using the Mann–Whitney U test or independent t test for continuous variables, and the  $\chi^2$  test or Fisher's exact test for categorical variables. Repeated measures analysis of variance (ANOVA) was used to assess blood gal-3 and IL-6 levels, as well as pain intensity and drug dose over time. All data were analyzed using SPSS version 21.0 (IBM Corporation). Differences with  $P < 0.05$  were considered to be statistically significant.

## RESULTS

### Demographic Data

All patients were treated with conventional antiviral therapy (topical acyclovir cream, 3–4 times per day combined with oral valacyclovir capsules, 0.3 g 3 times daily for 7–10 days of treatment) after the appearance of herpes zoster. All patients also received oral drug analgesia before PRF. No significant differences were found in terms of age, gender, treatment site, medical history, and analgesic drug types among the 3 groups. The mean NRS-11 scores before treatment were  $4.37 \pm 0.884$  for group S,  $4.70 \pm 0.823$  for group H, and  $4.67 \pm 1.038$  for group R; there were no significant differences among the 3 groups ( $P = 0.349$ ) (Table 1).

Table 1. Patient demographic data.

	Group S	Group H	Group R	P value
Age, years, mean $\pm$ SD	64.19 $\pm$ 11.007	64.96 $\pm$ 12.880	68.67 $\pm$ 10.232	0.311
Gender, n, male/female	10/17	11/16	11/16	0.950
Days from zoster onset, mean $\pm$ SD	21.52 $\pm$ 7.116	22.22 $\pm$ 7.239	20.15 $\pm$ 7.809	0.580
Involved dermatome, n				
Cervical, n	2	3	2	
Thoracic, n	19	17	18	0.974
Lumbosacral, n	6	7	7	
Underlying disease, n				
Malignant tumor, n	5	4	6	
Diabetes mellitus(DM), n	13	14	13	
Rheumatic immune disease, n	2	2	1	0.996
Two or more of these diseases, n	5	4	5	
None, n	2	3	2	
NRS before PRF, mean $\pm$ SD	4.37 $\pm$ 0.884	4.70 $\pm$ 0.823	4.67 $\pm$ 1.038	0.349
Analgesics at pre-PRF, n				
Tramadol only, n	3	4	3	
Tramadol with celecoxib	6	5	7	
Tramadol with opioid, n	5	5	4	0.999
Opioid only, n	4	5	5	
Tramadol, celecoxib and opioids, n	9	8	8	

NRS-11, numeric rating scale; PRF, pulsed radiofrequency

### Operation Related Data

Over time, the NRS-11 scores for the 3 groups decreased significantly. NRS-11 scores for group H at 4, 8, and 12 weeks posttreatment were significantly lower than those for group R at 2, 4, 8, and 12 weeks posttreatment ( $P = 0.016, 0.010, 0.001, 0.004, 0.000, 0.000, 0.000$ , respectively). Compared with group H, the NRS-11 score for group R was significantly lower at 4, 8, and 12 weeks posttreatment ( $P = 0.035, 0.002, \text{and } 0.042$ , respectively) (Fig. 3). Compared with group S, the incidence of PHN in group R was significantly lower at 4, 8, and 12 weeks posttreatment ( $P=0.005, 0.001, \text{and } 0.012$ , respectively) (Fig. 4).

Compared with before treatment, the oral doses of gabapentin and morphine hydrochloride tablets in the 3 groups decreased at one, 2, 4, 8, and 12 weeks posttreatment, and were statistically significant ( $P < 0.05$ ). Compared with group S, the oral dose of gabapentin capsules in group R decreased at 8 and 12 weeks posttreatment, and were statistically significant ( $P < 0.05$ ) (Fig. 5). Compared with before treatment, blood levels of gal-3 and IL-6 decreased at one, 2, and 4 weeks posttreatment, and were statistically significant ( $P < 0.05$ ). Compared with group S, the levels of gal-3 and IL-6 in group R and IL-6 in group H decreased at one week posttreatment. Compared with group H, the blood gal-3 level in group R decreased significantly one week posttreatment ( $P < 0.05$ ) (Fig. 6).

No patients had a posttreatment adverse reaction such as fever, chills, fatigue, or myalgia.

### DISCUSSION

Herpetic neuralgia is a type of neuropathic pain that occurs spontaneously and is accompanied by allodynia and hypoalgesia in the affected area. After herpes zoster infection, the virus damages sensory neurons, resulting in changes in the composition, distribution, and function of the transmembrane ion channels. These damaged sensory neurons generate abnormal electrical impulses that are transmitted to the spinal cord and induce spontaneous pain.

PRF is a discontinuous pulsed current. In patients with herpes zoster, application of PRF to the DRG reduces signal transduction to the central nervous system by the modulation of nociceptive fibers. Thus, further neuropathic processes can be blocked before serious neuropathy occurs. PRF can microscopically affect the synaptic activity and cytokine levels of the nerves. The PRF field intensity using the standard voltage is low, the time course is short, and the action intensity is limited; as such, patients cannot achieve lasting treatment effects, and the occurrence of PHN cannot be significantly reduced.

Previous studies (11,12) have confirmed that high-voltage long-duration PRF treatment for patients with acute herpes zoster neuralgia can reduce their digital

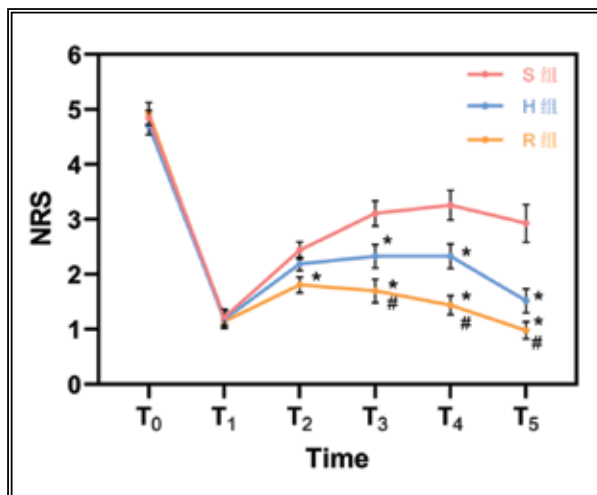


Fig. 3. Compared with group S, the NRS-11 score for group H and group R was significantly lower at 4, 8, and 12 weeks. Compared with group H, the NRS score for group R was significantly lower at 4, 8, and 12 weeks ( $P = 0.035, 0.002, \text{and } 0.042$ , respectively).

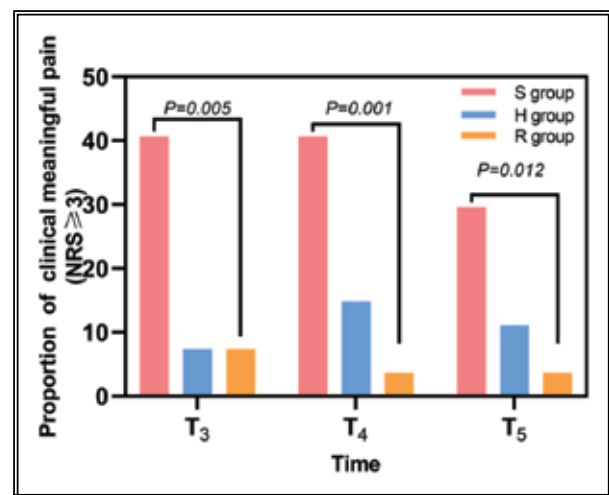
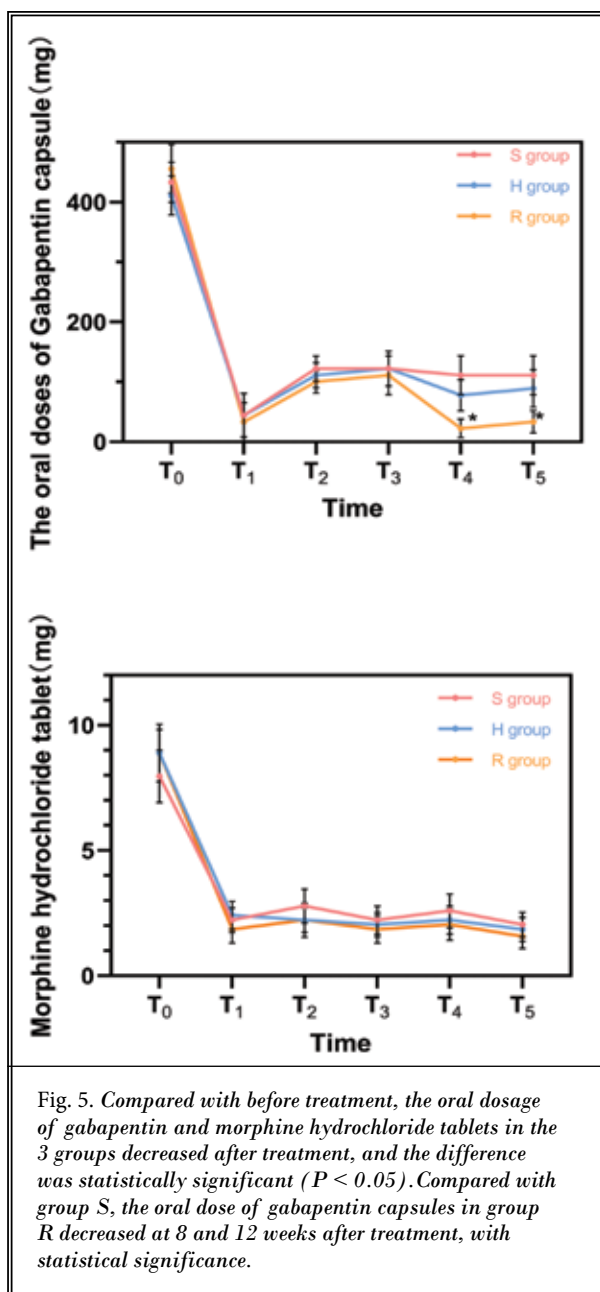
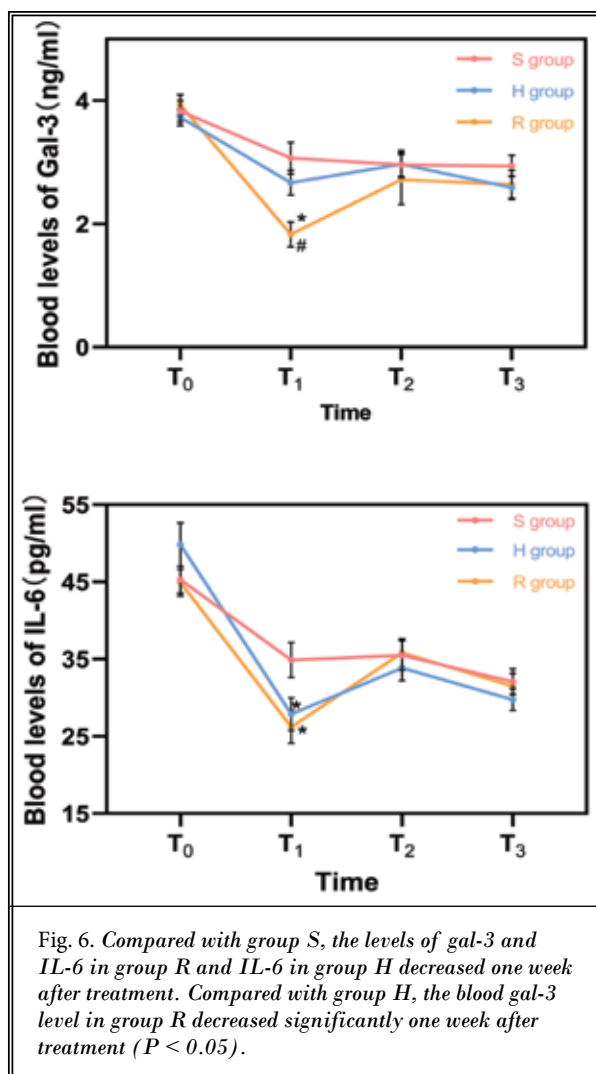


Fig. 4. Compared with group S, the incidence of PHN in group R was significantly lower at 4, 8, and 12 weeks after treatment. ( $P = 0.005, 0.001, \text{and } 0.012$ , respectively).



pain score and improve their quality of life. However, the time to regulate the nerve is short and its curative effect does not persist. PRF has no damage to the nerve, has repeatability, this study adopted the repeated high-voltage long-duration PRF treatment (interval of 3 days of treatment time, a total of 3 times), herpes zoster neuralgia, compared with the former 2 groups, the NRS-11 score and the dose of gabapentin capsules and morphine hydrochloride tablets were significantly



decreased in the repeated high-voltage long-term PRF group. The possible reason is that single or high-voltage PRF only temporarily stimulates the DRG a single time, while repeated high-voltage long duration PRF adopts repeated stimulation of the DRG many times so as to achieve a lasting analgesic effect.

Gal-3, a  $\beta$ -galactoside-binding protein, may mediate herpes zoster neuralgia via phagocytes and microglia. Gal-3 level is one of the criteria used to assess the severity of neuropathic pain. IL-6 is a cytokine that stimulates the proliferation, differentiation, and function of cells involved in the immune response. Additionally, it is involved in inflammatory and febrile responses and plays an important role in anti-infective responses. In this study, patients who underwent repeated high-voltage long-duration PRF (group R) had their levels

of gal-3 and IL-6 decrease significantly after one week of treatment compared with the groups S and H. This indicates that pain was relieved and immunity (the ability to consciously resist unhealthy influences) was improved. These results are consistent with those of previous studies. Nerve repair and recovery require a long time; therefore, long-term follow-up is required.

SCS reduces pain by inserting electrodes into the epidural space and using electrical currents to stimulate neurons in the posterior horn of the spinal cord to block pain signals. Yuhui Luo et al (16) and Zhiguang Lin et al (17) proved that spinal cord electrical stimulation can rapidly reduce pain and significantly change the sleep quality of patients. Liu B et al (18) demonstrated that both SCS and PRF effectively alleviated PHN in a retrospective analysis (18). Wu Y (19) proved that both acute and subacute pain can be alleviated by short-term spinal cord stimulation and DRG PRF. For herpetic neuralgia, SCS is more effective than PRF in patients over 65 years of age. An experiment conducted by Wang et al (20) proved that SCS and PRF were effective in alleviating the clinical symptoms of patients with PHN, and the levels of related pain factors were both lower than before treatment; however, the incidence of complications was high in the PRF group (20).

Our study proves that repeated high-voltage long-duration pulsed radiofrequency is more effective than standard pulsed radiofrequency in the treatment of acute herpetic neuralgia and could prevent the occurrence of PHN. The reason may be the high voltage,

the long duration, and that damaged nerves tend to repair quickly. This is similar to the efficacy of SCS, but the cost of repeated high-voltage long-duration PRF is lower than that of SCS, and is more minimally invasive and more suitable for the vast majority of patients. SCS requires electrodes to be placed in the spinal canal, so its risk of infection is higher than that of repeated high-voltage PRF. Moreover, repeated high-voltage long-duration PRF has strong repeatability, so repeated high-voltage long-duration PRF is a better choice for the treatment of herpetic neuralgia in the acute stage.

### Limitations

The current study has several limitations that should be addressed in future studies. First, patients were recruited from a single center and the sample size was relatively small. Second, this study was not randomized and was retrospective. Third, the follow-up duration was short. Future studies should include larger prospective sample sizes and longer follow-up periods. The present study provides only preliminary evidence that repeated high-voltage long-duration sessions are an effective method to relieve herpetic neuralgia in the acute phase and prevent the occurrence of PHN.

### CONCLUSION

In conclusion, repeated high-voltage long-duration PRF is an effective treatment to prevent the incidence of PHN.

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