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Comparison of the Efficacy of Short-term Peripheral Nerve Stimulation and Pulsed Radiofrequency for Treating Herpes Zoster Ophthalmicus Neuralgia

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Objective: This study aimed to investigate the effect of therapy with peripheral nerve stimulation (PNS) and pulsed radiofrequency (PRF) combined or PNS and PRF separately in patients with herpes zoster ophthalmicus (HZO).

Materials and Methods: This cohort study included 106 cases of HZO. Three groups were identified according to the type of treatment received: combination therapy (PNS+PRF) (n = 38), PRF (n = 37), and PNS (n = 31). The observations at 0, 1, 2, and 4 weeks; 3 and 6 months; and 1 and 2 years after the operation were analyzed. Observations at each follow-up included baseline characteristics, Numerical Rating Scale (NRS) and the Pittsburgh Sleep Quality Index (PSQI), concomitant pain medication usage, relapse rate, and adverse events.

Results: The postoperative NRS of all 3 groups were significantly lower than preoperative scores. The PSQI of the 3 groups was significantly improved postoperatively, and the concomitant pain medication gradually decreased. Regarding long-term efficacy, the pain NRS and PSQI scores of the PNS+PRF and PNS groups were significantly lower than those of the PRF group ($P < 0.05$), and the relapse rate of the PRF group was higher than that of the PNS +PRF and PNS groups ($P < 0.05$). No significant difference was observed between the PNS+PRF and the PNS groups.

Conclusion: Both PNS and PRF treatment of HZO can decrease the pain score, yielding no serious complications. The combination of PNS and PRF or PNS alone resulted in more significant pain relief than treatment with PRF alone. Thus, PNS therapy may be a better treatment option for HZO.

Key Words: herpes zoster ophthalmicus, peripheral nerve stimulation, pulsed radiofrequency, pain

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Herpes zoster (HZ) infection occurs by reactivation of latent varicella-zoster virus in sensory ganglia. Pain is the major manifestation, usually accompanied by a vesicular rash. When the pain persists for > 3 months after the rash heals, it is called postherpetic neuralgia (PHN). One of the most important risk factors for PHN is age, which is also correlated with the severity of pain and the area and duration of the rash.[1] PHN is debilitating and causes psychological distress. The prevalence of HZ and PHN is 7.7% and 2.3%, respectively.[2]

Herpes zoster ophthalmicus (HZO) occurs when the HZ virus involves the ophthalmic division of the fifth cranial nerve. HZ of the ophthalmic nerve accounts for 10% to 20% of HZ cases, so the risk of developing HZO during a lifetime for an individual is 1%.[3] A predictive model evaluating the association between the occurrence of HZ and PHN shows that HZ is more likely to develop into PHN when the onset of HZ is closer to the head.[4] Therefore, HZO has a higher opportunity to develop PHN than other forms of HZ infections.

PHN is reported to negatively affect individuals, resulting in reduced sleep quality, decreased quality of life, work impairment, economic burden medical costs, and lost productivity. These burdens suggest the need for appropriate prevention and management of PHN.[5]

The pain management of HZO remains insufficient. Currently, there is no ideal method to cure PHN caused by HZO. In addition to medicinal therapy, other forms of interventional therapies have been shown to alleviate pain, such as nerve block,[6] peripheral nerve stimulation (PNS),[7] and pulsed radiofrequency (PRF).[8] To date, medication treatment for PHN heavily relies on opioid-based therapies, which potentially leads to dependence and abuse.[9] In comparison, nerve block is more effective; however, its duration is short.[10] Currently, PRF and PNS as neuroregulatory techniques are used in the treatment of HZO-related pain.

PNS functions by sending an electric current near the target nerve in patients to reduce their perception of pain.[11] Electrical stimulation of nerves inhibits pain input to the ascending pathway at the dorsal horn in the spinal cord.[12] PRF performed while maintaining the temperature at the tip of the electrode at 42°C ensures that neural structures are

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not damaged, which modulates nerve function.[13] PNS and PRF have demonstrated substantial therapeutic effects for pain treatment when applied separately. Ding et al[14] and Wan et al[15] have shown that PRF treatment of trigeminal PHN can relieve pain. However, the effect of combining PRF and PNS has not been reported. Therefore, in our study, we analyzed and compared the clinical effects of PNS combined with PRF, PRF alone, and PNS alone in the treatment of HZO.

MATERIALS AND METHODS

Objects

This study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Zhengzhou University, Zhengzhou, China (2020-KY-0301-001). This retrospective study included patients who were clinically diagnosed with HZO in the Pain Department at the First Affiliated Hospital of Zhengzhou University from January 2016 to January 2019. The detailed inclusion and exclusion criteria are as follows.

The inclusion criteria were (1) signs and symptoms consistent with the diagnosis of HZO (pain, rash limited to the periorbital region); (2) Numerical Rating Scale (NRS) score ≥ 4; (3) experience of persistent, severe and intractable pain and local skin hyperalgesia, numbness, and abnormal sensation; (4) history of ineffective conservative treatment (medicinal therapy); (5) age above 50 years; and (6) receipt of either PNS or PRF, or both treatments.

The exclusion criteria were (1) receipt of other treatment options at the time of PNS or PRF treatment; and (2) cases in which follow-up data were not fully available.

A total of 131 cases of HZO treated in the Pain Department of our hospital were identified from the selected time frame. Eight cases were excluded (2 cases did not meet the inclusion criteria, and 6 cases met the exclusion criteria). Seventeen of 123 patients were out of contact during the follow-up time. Finally, according to the treatment they chose, the patients were classified into 3 groups: PNS+PRF group (n = 38), where patients underwent both PNS and PRF treatment; PRF group (n = 37), where patients only underwent PRF; and PNS group (n = 31), where patients only underwent PNS, as shown in Figure 1.

Baseline Characteristics

The following baseline characteristics were collected before the operation for all patients: age, sex, course of the disease, affected facial side, and underlying diseases.

Surgical Technique

Implantation of the Electrode for Peripheral Nerve Electrical Stimulation

Patients were placed supine on the computed tomography (CT) imaging operating table. Electrocardiography, noninvasive blood pressure, and oxygen saturation monitoring were performed continuously during the operation. After routine disinfection and laying of towels, the puncture point was selected at 1 cm from the upper edge of the eyebrow arch upward. After applying local anesthesia with 0.5% lidocaine, the needle was inserted subcutaneously from the eyebrow arch to the medial border of the orbit. An 8-contact electrode was passed into the region through the needle. The electrode crosses the middle line to cover the distribution area of the supraorbital and supratrochlear nerve. The C-arm verified that the position was accurate, as shown in Figure 2, and then the needle was withdrawn. The test electrode (Model 3873; Medtronic) was connected to an extension multilead cable (Model 355531; Medtronic). To program the implantable electrode, an external cable was inserted into the neurostimulator (Model 37022; Medtronic). The program controller was adjusted to induce paresthesia in patients to reduce preoperative pain without discomfort in other positions. The test electrode was firmly fixed and covered with aseptic adhesive wound dressings. The stimulation parameters were as follows: pulse width was 450 μs, frequency was 40 to 60 Hz, voltage ranged from 0.1 to 5 V; the targets and if paresthesia mapping fit in the nerve distributions. The stimulation parameters were adjusted once a day to ensure effectiveness. The patient had the liberty to change the amplitude with steps of 0.1 V to provide individual pain relief. The electrode was implanted for 10 to 14 days. There was no consideration of permanent implantation.

PRF Operation on the Trigeminal Ganglion

Patients were placed in the supine position with a thin pillow under their shoulders on the operating table. CT was used to determine the route of percutaneous insertion. The

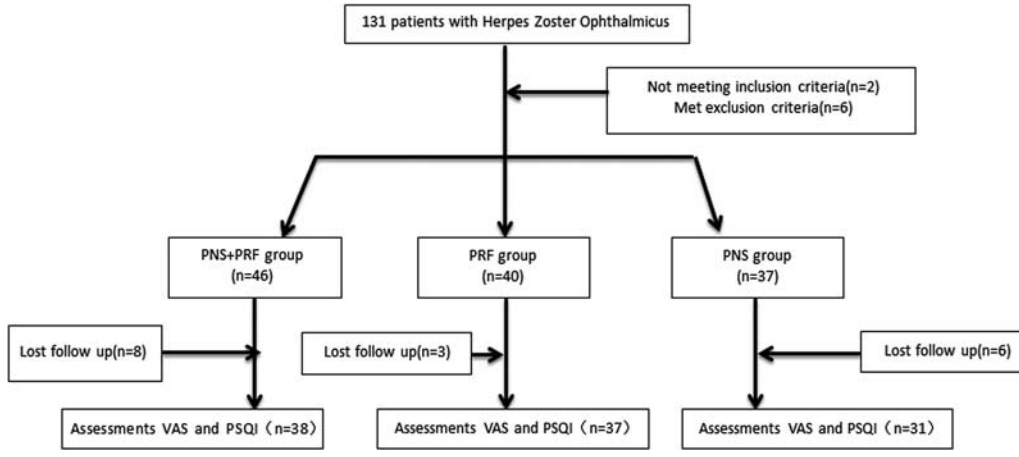

FIGURE 1. Work flow diagram of this study. PNS indicates peripheral nerve stimulation; PRF, pulsed radiofrequency; PSQI, Pittsburgh Sleep Quality Index; VAS, Visual Analog Scale.

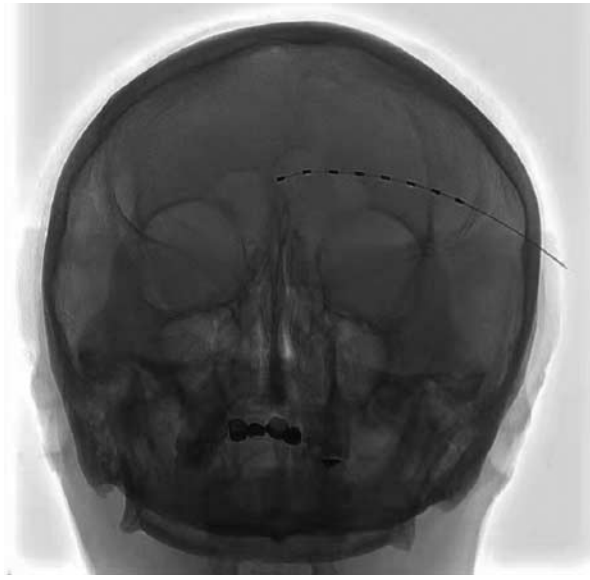

FIGURE 2. Image of the electrode (the electrode crosses the middle line to cover the distribution area of supraorbital and supratrochlear nerve).

Hartel anterior approach method was used to access the Gasserian ganglion. After successful local anesthesia with 0.5% lidocaine, the needle was used to puncture the foramen ovale. When the needle reached the predefined depth, a CT scan was performed at the proper location of the needle tip, as shown in Figure 3, which was connected to the PRF treatment instrument (Beiqi radiofrequency instrument R-2000; China) probe. The probe applied a pulse of electricity of <0.5 V to the treatment area. The pain or numbness induced under 0.5 V was confined to the pain area of the patient before the operation, ensuring that there was no pain or muscle contraction outside of the pain areas. Treatment with PRF was applied to the patients at 42°C, 2 Hz, and 20 ms for a duration of 600 seconds. The puncture point was compressed for 3 minutes to stop bleeding after the needle was removed. The combination therapy (PNS+ PRF) is shown in Figure 4.

Follow-up and Effect Evaluation

All patients were followed up at the outpatient department or by telephone. The primary outcome was the change in pain intensity after the operation as measured by the NRS (range from 0 to 10), where 0 represented no pain and 10 represented maximum pain.

Furthermore, sleep quality scores and concomitant medication usage were recorded in the 3 groups. The Pittsburgh Sleep Quality Index (PSQI)[16] was used to evaluate sleep quality (range from 0 to 21), where 0 represented the best sleep quality and 21 represented the worst sleep quality. Pregabalin and oxycontin could be used in combination if patients suffered severe pain. The average daily dosages (mg/d) were collected before and after treatment. Relapse was considered the patient appears pain worsening after a period of pain relieved, and the NRS score was >4 or became equal to or greater than the preoperative score during follow-up. The relapse rate is calculated by the following formula:

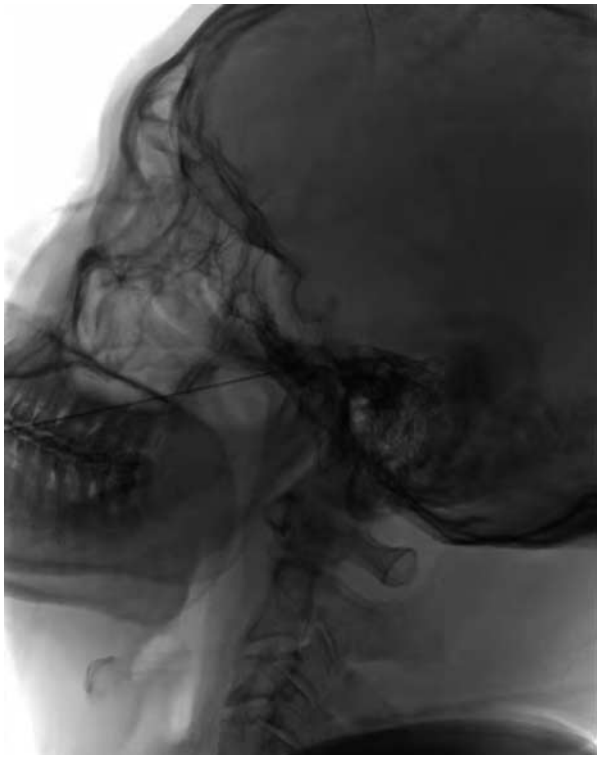

FIGURE 3. Image of the pulsed radiofrequency needle (the needle on the trigeminal ganglion).

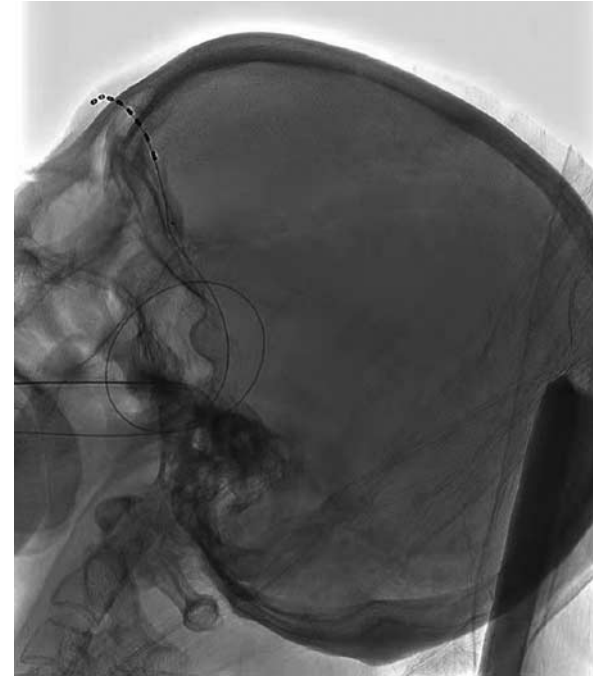

FIGURE 4. Image of the electrode and radiofrequency needle (the electrode crosses the middle line to cover the distribution area of supraorbital and supratrochlear nerve, the needle on the trigeminal ganglion).

TABLE 1. Clinical Data of the 3 Groups of Patients

Baseline Characteristics	Cases (N)	Treatment Group			Statistical Results
		PNS+PRF (n = 38)	PRF (n = 37)	PNS (n = 31)	
Age (mean ± SD) (y)	106	67.3 ± 10.1	69.3 ± 7.6	67.9 ± 9.2	0.35 ($F = 1.05$)
Sex					
Male	72	26	23	23	0.56 ($\chi^2 = 1.12$)
Female	34	12	14	8	
Course of the disease (pain)					
< 30 d	58	27	18	13	0.11 ($\chi^2 = 7.48$)
30-90 d	30	7	13	10	
> 90 d	18	4	6	8	
Affected facial side					
Left	51	16	22	13	0.23 ($\chi^2 = 2.93$)
Right	55	22	15	18	
Underlying diseases					
Yes	46	15	20	11	0.25 ($\chi^2 = 2.73$)
None	60	23	17	20	

PNS indicates peripheral nerve stimulation; PRF, pulsed radiofrequency.

$$\text{Relapse rate} = \frac{\text{Number of relapse case}}{\text{Total number of case}} \times 100\%$$

The observations of NRS, PSQI, and concomitant pain medication use were retrieved for the following time points: before surgery and 1 day; 1, 2, 4 weeks; 3, 6 months; 1 and 2 years after the operation. During follow-up visits/phone calls, patients were also asked if there were adverse events.

Statistical Analysis

Data analysis was performed using SPSS software (version 21.0). Age was tested by analysis of variance (ANOVA), and the χ^2 test was used to classify variables such as sex, course of the disease, affected facial side, underlying disease, relapse rate, and local pruritus for the 3 groups. Repeated-measures ANOVA was used for comparisons at different time points for each of the 3 groups. Single-factor ANOVA was used for comparison among the 3 groups at the same time point. P values <0.05 were considered statistically significant.

RESULTS

Preoperative Patient Characteristics

The characteristics were recorded preoperatively, including age, sex, course of disease, location, and underlying diseases, as shown in Table 1. No significant differences were found in these parameters among the 3 groups ($P > 0.05$).

NRS Scores Before and After Surgery

NRS scores were significantly lower than the preoperative values in the 3 groups at each observation time point after the operation ($P < 0.05$). The pain relief in the PNS+PRF group was significantly greater than that in the PNS group at 1 day after the operation ($P < 0.05$). The pain relief in the PRF group was significantly greater than that in the PNS group at 1 week after the operation. There was no significant difference in the short-term (2 wk) therapeutic effect among the 3 groups. However, regarding medium-term and long-term treatment effects (1, 3, 6 mo; 1, 2 y), the pain relief in the PNS+PRF and PNS groups was more significant than that in the PRF group. There was no significant difference between the PNS+PRF and the PNS groups ($P > 0.05$), as shown in Figure 5.

PSQI Scores Before and After Surgery

The postoperative PSQI scores were significantly lower than the preoperative values in all 3 groups at each observation time point ($P < 0.05$). Compared with that in the PRF group, the sleep quality of the PNS+PRF and PNS groups improved more significantly, and the difference was statistically significant ($P < 0.05$). There was no significant difference between the PNS+PRF and the PNS groups ($P > 0.05$), as shown in Figure 6.

Concomitant Pain Medication Use (Pregabalin and Oxycontin)

There was a significant difference in preoperative and postoperative pregabalin and oxycontin use in each of the 3 groups ($P < 0.05$). Medication usage gradually decreased, as shown in Figures 7 and 8. The dosage of oxycontin is zero

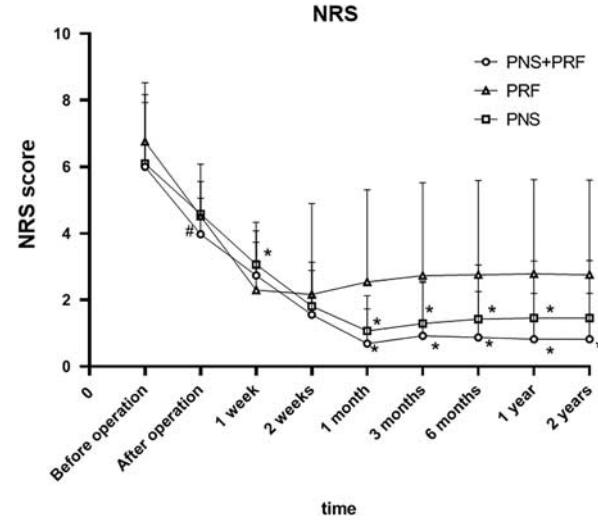

FIGURE 5. Comparison of NRS scores. *$P < 0.05$, versus the PRF group. #$P < 0.05$, versus the PNS group. NRS indicates Numerical Rating Scale; PNS, peripheral nerve stimulation; PRF, pulsed radiofrequency.

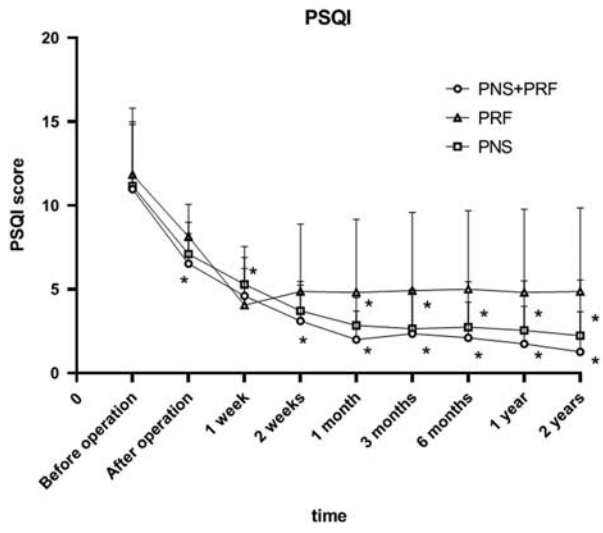

FIGURE 6. Comparison of PSQI scores. *$P < 0.05$, versus PRF group. PNS indicates peripheral nerve stimulation; PRF, pulsed radiofrequency; PSQI, Pittsburgh Sleep Quality Index.

after 1 month. There was no significant difference among the 3 groups at each time point.

Relapse Rate

Among 38 cases in the PNS+PRF group, 1 case relapsed (2.6%). There were 37 cases in the PRF group, and 11 cases recurred (30%). There were 31 cases in the PNS group, and 4 cases relapsed (12.9%). The relapse rate in the PRF group was higher than that in the other 2 groups ($P < 0.001$), as shown in Table 2.

Adverse Events

No serious adverse events were observed in this study. Only adverse events with a frequency of ≥ 1 count were included; therefore, only skin pruritus was reported in this section. In the PNS+PRF group, local skin pruritus occurred in 12 cases (31%). Local skin pruritus occurred in 5 cases

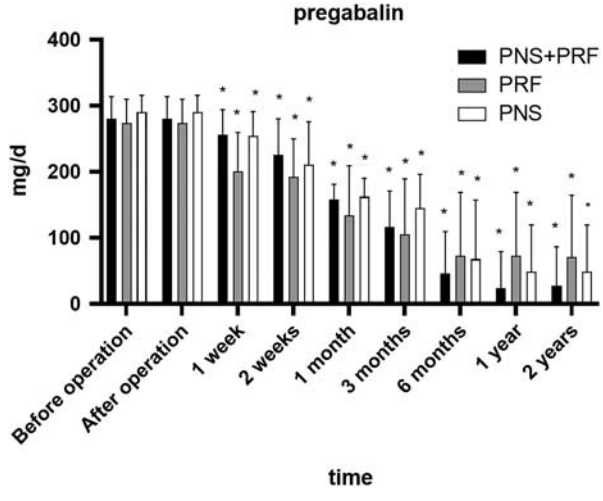

FIGURE 7. The dosage of pregabalin. *$P < 0.05$, versus before the operation. PNS indicates peripheral nerve stimulation; PRF, pulsed radiofrequency.

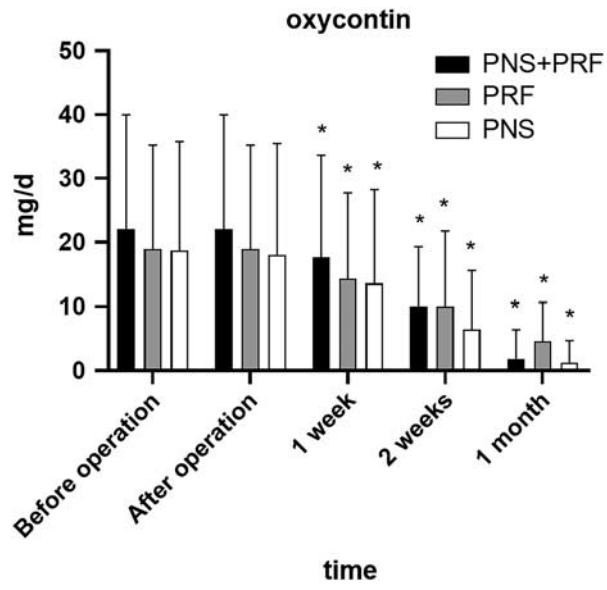

FIGURE 8. The dosage of oxycontin. *$P < 0.05$, versus before the operation. PNS indicates peripheral nerve stimulation; PRF, pulsed radiofrequency.

in the PRF group (13%) and 7 cases (22%) in the PNS group. There was no significant difference among the 3 groups ($P > 0.05$), as shown in Table 2.

DISCUSSION

HZO-induced pain is a type of classic neuropathic pain and is characterized by severe burning and lancinating pain often associated with allodynia and hyperalgesia. Acute pain results from viral replication, leading to the dehydration and apoptosis of cells and dead neurons together with cutaneous inflammation.[17,18] The most frequent complication of HZ is PHN, a leading cause of suicide in elderly patients with chronic pain.[3] The pain mechanism of PHN is related to the significant reduction in related peripheral innervation[19] and central sensitization.[20] The unsatisfactory management of PHN is due to the difficulty in determining the etiology due to the complexity of the PHN mechanism.

Wall and Sweet[11] reported for the first time that neuropathic pain can be relieved by nerve electrical stimulation. Subsequently, the application of peripheral nerve electrical stimulation is becoming increasingly often seen in the clinic. Some retrospective studies have analyzed the efficacy of PNS in the treatment of HZO. It is not only safe and effective,[21] but can also reduce the incidence of PHN.[22] Previous studies have shown that permanent implantation

TABLE 2. The Pruritus and Relapse of 3 Groups of Patients

		Treatment Group, n (%)		
Characteristics	Cases (N)	PNS+PRF (n = 38)	PRF (n = 37)	PNS (n = 31)
Local pruritus	24	12 (31)	5 (13)	7 (22)
Relapse	16	1 (2.6)*	11 (30)	4 (12.9)*

PNS indicates peripheral nerve stimulation; PRF, pulsed radiofrequency.
*$P < 0.05$, versus the PRF group.

of electrodes for electrical stimulation can relieve pain for a long time.[23] Studies have also shown that short-term implantation is able to reduce neuropathic pain effectively, and the effectiveness lasts for at least 12 months.[24] This is consistent with our results at 1 and 2 years, where pain reduction from PNS and combined PNS and PRF treatment were still significant.

Nerve electrical stimulation reduces pain mostly through the inhibition of Aδ spinothalamic tract cells.[25] Electrical stimulation of large diameter low-threshold non-nociceptive Aβ fibers results in excitation of inhibitory dorsal horn interneurons, which in turn inhibits nociceptive signaling from the Aδ and C nerve fibers into higher centers in the central nervous system.[26]

PRF is thought to reduce pain by eliciting an anti-inflammatory response. The high-frequency and high-voltage PRF produces voltage fluctuations in the treatment area. PRF causes nerves to undergo ultrastructural changes, such as abnormal membranes and morphology of mitochondria, and disruption and disorganization of microfilaments and microtubules.[27] PRF selectively affects small diameter C and Aδ nociceptive fibers,[28] and it has a higher effect on C fibers than Aδ fibers.[27]

Based on the difference in mechanisms of action of the 2 methods, we speculate that the direct inhibition of nociceptive pathway is the reason why the long-term effect in the PNS+PRF and PNS groups was more efficient than that in the PRF group. In both groups with PNS, pain was relieved, the incidence of sleep pain and awakening was reduced, the sleep quality was significantly improved, and medication usage was reduced.

Ding et al[14] and Wan et al[15] have demonstrated the efficacy of PRF in the treatment of postherpetic ophthalmic neuralgia. Other studies in the literature are in support of their conclusion.[29] A meta-analysis of PRF treatment for PHN showed that PRF has a high relapse rate, which potentially would require repeated treatment.[30] This conclusion is consistent with our results, where the combined PNS+PRF and PNS groups both had a lower relapse rate than the PRF group. Based on clinical experience, the radiofrequency parameter of this study was set to a temperature of 42°C, frequency of 2 Hz, and intensity of 600 seconds. Compared with the traditional 120 seconds, 600 seconds can produce a better curative effect. This study showed that the NRS score and PSQI score of patients with this parameter decreased significantly, and the immediate effect (1 d and 1 wk after operation) was more significant than that of the PNS group. The relapse rate of the PRF was much higher than that of the PNS+PRF and PNS groups, and the long-term effect was not statistically significant.

This study is a single-center retrospective study with a limited sample size. Retrospective case-control studies are more susceptible to selection bias than other epidemiologic studies as by design they require that both cases and controls are representative of the same population. A randomized, prospective controlled study with larger sample sizes is needed to obtain stronger statistical power.

CONCLUSIONS

PNS and PRF are safe and effective in the treatment of PHN. In our study, we compared the efficacy of PNS, PRF, and combination therapy with both modalities in patients with PHN. With treatment, all patient groups had significantly decreased NRS and PSQI scores and dosages of drugs without serious complications. The relapse rate of the PNS+PRF and PNS groups was lower than that of the PRF group, and the long-term pain relief effect of the PNS+PRF group was better. Therefore, peripheral electrical stimulation is recommended over PRF for the treatment of postherpetic ophthalmic neuralgia.

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