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ORIGINAL RESEARCH

Outcomes of Twice Repeated High-Voltage Long-Duration Pulsed Radiofrequency Treatment in Subacute Postherpetic Neuralgia: a Retrospective Single-Center Analysis

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Background: The treatment of herpes zoster-related pain is challenging, and requires a variety of methods including pulse radio frequency modulation. Among them, single-time high-voltage long-term pulsed radiofrequency (HL-PRF) has been proved to be an effective treatment for subacute postherpetic neuralgia. However, it has the possibility of poor long-term curative effect and recurrence of neuralgia. In this study, we aim to identify the clinical efficacy and safety of twice repeated HL-PRF treatment in patients with subacute postherpetic neuralgia.

Design: We conducted a retrospective analysis of subacute postherpetic neuralgia patients who underwent HL-PRF treatment.

Setting: Pain Management Department of First Affiliated Hospital of Wannan Medical College.

Patients: We enrolled all patients with subacute postherpetic neuralgia, who underwent HL-PRF treatment from January 2023 to October 2023.

Measurements: The primary outcome variable was the visual Analog Scale (VAS) scores at 1, 4, 8, and 12 weeks after treatment. Secondary outcomes included Pittsburgh sleep quality index (PSQI), 36-item short-form health survey (SF-36) score, and total effective rate after treatment.

Results: A total of 63 patients were included in the analysis. Among them, 33 patients received single-time HL-PRF treatment (Group S) and 30 patients received twice repeated HL-PRF treatment (Group T). Pain scores, PSQI scores, and SF-36 score were reduced in both groups after treatment ($P < 0.001$). Compared to group S, the VAS scores, PSQI scores, anxiety scores, and depression scores were significantly lower at 1, 4, 8, and 12 weeks in group T. ($P < 0.001$). The total efficiency rate at 12 weeks after treatment of group T was statistically higher than that of group S (60.6% vs 86.7%, $P < 0.05$).

Conclusion: Twice repeated high-voltage long-duration PRF therapy demonstrates satisfactory efficacy in patients with subacute postherpetic neuralgia and is associated with no significant adverse reactions.

Keywords: herpes zoster, subacute postherpetic neuralgia, CT-guided, pulsed radiofrequency therapy, dorsal root ganglion

Introduction

Zoster-associated pain (ZAP) refers to the neuropathic pain persisting in patients with herpes zoster (HZ) before, during and after the rash heals.[1] Based on the duration of pain, ZAP is categorized into acute herpetic neuralgia (AHN) within the first month of herpes, subacute herpetic neuralgia (SHN) within three months after the acute phase, and postherpetic neuralgia (PHN), characterized by pain lasting for more than three months.[2,3]

Current treatments for ZAP involve both drug therapy and minimally invasive interventional therapy. AHN can be effectively alleviated by early antiviral, oral analgesics, and nerve block.[4,5] However, once PHN develops, the available

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treatment methods are limited, and the effective rate of cure is also significantly reduced.[6] Therefore, the AHN/SHN is the key period of minimally invasive interventional therapy. Minimally invasive interventional therapy includes pulsed radiofrequency (PRF) technology and spinal cord stimulation, aiming to reduce the need for analgesic drugs and control pain effectively.[7] Although the traditional standard PRF (RF parameters: 42°C, 40V, 2Hz, 20ms, 120s) is widely used to treat postherpetic neuralgia,[8] its therapeutic effect is limited due to low action intensity and short field effect time. In comparison, HL-PRF has shown greater efficacy.[9] Yet, the long-term efficacy of single PRF in the treatment of postherpetic neuralgia is suboptimal. Studies suggest that repetitive standard PRF may outperform single standard PRF, demonstrating better early analgesic effects and reducing the incidence of clinically meaningful ZAP within the first month after treatment.[10]

Therefore, our retrospective study aims to observe the clinical efficacy and safety of twice repeated HL-PRF treatment in patients with subacute postherpetic neuralgia and compare the outcomes with a single PRF treatment.

Methods

Study Design and Population

This is a single-center, retrospective observational investigation. This investigation was conducted at the Pain Management Department of First Affiliated Hospital of Wannan Medical College from January 2023 to October 2023. Approval was obtained from the Medical Ethics Committee of the First Affiliated Hospital of Wannan Medical College (Wuhu, Anhui Province, China, approval number: 2023-LSX-08). The treatment procedures were performed by 2 experienced attending physicians in the pain management department. We reviewed and extracted data from the electronic medical records of all patients who underwent HL-PRF treatment primarily for care of subacute postherpetic neuralgia.

Inclusion Criteria

1) Patients with PHN involving the thoracic and abdominal dermatomes; 2) Disease history ranging from 1 to 3 months; 3) Persistent intense pain with a Numeric Rating Scale (NRS) score > 3; 4) Pain not adequately controlled with standard pharmacotherapy (antiepileptic drugs, antidepressants, opioids); 5) Ages between 50 and 80.

Exclusion Criteria

1) Abnormal bleeding and coagulation function; 2) Patients with puncture site infection or tumor; 3) Severe organ dysfunction, including brain, heart, lung, kidney, and liver diseases; 4) Poor glycemic control in those with diabetes; or 5) Patients with intellectual inability to complete self-evaluation.

Clinical Procedure

Both treatment procedures were performed under CT guidance. Patients were positioned prone on a CT treatment bed, with 2 L/min of oxygen supplied through a nasal catheter and continuous monitoring of blood pressure, heart rate, pulse oxygen saturation, and electrocardiogram. Treatment was conducted based on the Fei et al technique.[11] The target nerve was selected according to the most severe pain site and lesion area of the patient, and the most painful site extended upward and downward in the middle and one site, respectively. Subsequently, PRF treatment of dorsal root ganglion was performed in three segments each time. After sterilization of the puncture site, 0.5% lidocaine was administered for local anesthesia. A 20-G radio-frequency needle (15-cm long with a 10-mm active tip; inomed Medizintechnik Company, Emmendingen, Germany) was slowly inserted toward the ventral side of the intervertebral foramen along the designated path until the needle tip reached the predefined depth. CT was rescanned to confirm the correct location of the needle tip (Figure 1). The sensory nerve was tested using the sensation-testing mode (50Hz, 0.1ms, 0.1–0.5V). Successful induction of discomfort, such as numbness, distension, soreness and pricking consistent with the usual pain site, was considered confirmation of the needle tip in correct place. PRF treatment was performed with the manual PRF mode (a frequency of 2Hz, a pulse width of 20ms, and a temperature of 42°C). The voltage gradually increased from 40V to the highest value that the patient could tolerate (usually up to 70V-90V) and maintained for 900s. After 15 minutes of observation, patient return to the ward with the stable vital signs.

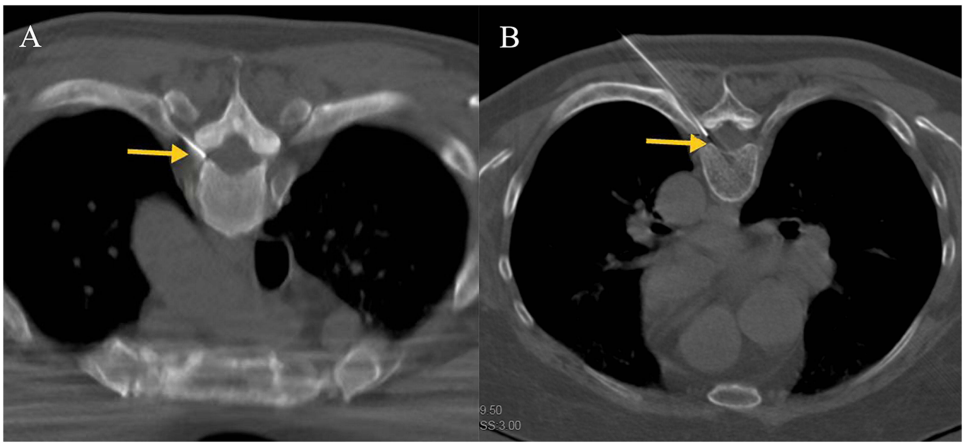

Figure 1 The yellow arrow points to the needle placed in the intervertebral foramen. (**A**). T3 spinal nerve; (**B**).T6 spinal nerve.

Outcomes

The primary outcome was Visual Analog Scale (VAS) scores before PRF treatment (baseline) and at 1, 4, 8, and 12 weeks afterwards. Secondary outcomes included differences between the groups in: Pittsburgh Sleep Quality Index (PSQI), Quality of life scores assessment (SF-36),[12] total efficiency rate, and adverse events.

The total efficiency rate was determined using the VAS score to evaluate the treatment effect of high-voltage, long-duration PRF at 12 weeks post-treatment. The treatment effect was categorized into four levels based on the VAS score reduction: excellent (VAS reduction ≥ 75%), good (VAS reduction between 50% and 75%), poor (VAS reduction between 25% and 50%), and ineffective (VAS reduction < 25%). The total efficiency rate (%) was calculated as the sum of the excellent and good categories divided by the total number of cases.

Adverse events referred to various postoperative complications recorded after PRF treatment, including nerve damage, hematoma, local infection, and other serious complications.

Data Analysis and Statistics

The analysis of all data was conducted using SPSS 26.0 (IBM Corporation, Armonk, NY, USA) and GraphPad Prism 9.0 (GraphPad Software, Inc). The measurement data were reported as the mean ± SD. To compare variable data at different time points, a repeated measures analysis of variance (RM-ANOVA) was utilized. A P-value <0.05 was considered statistically significant.

Results

Baseline Characteristics

Of 82 patients screened, 19 did not meet the inclusion criteria and were excluded, leaving 63 (32 female/31 male) patients for analysis (Figure 2). Of the 63 included patients, 33 underwent single-time HL-PRF treatment (Group S), and 30 underwent twice-repeated HL-PRF treatment (Group T). The treatment procedure for Group T was identical to that of Group S, except that Group T patients received an additional HL-PRF treatment on the day following the initial session.

The baseline characteristics of patients, including age, gender, weight, pain duration, preoperative VAS, preoperative PSQI, preoperative physical component summary (PCS), preoperative mental component summary (MCS), preoperative drug, and pain side, exhibited no significant differences between the two groups ($P > 0.05$, Table 1).

Analgesic Effect

VAS scores decreased in both groups at 1, 4, 8, and 12-weeks post-treatment compared to their pre-treatment scores ($P<0.001$). Group T showed significantly a greater reduction in VAS scores compared to Group S at all time points ($P<0.001$, Figure 3A).

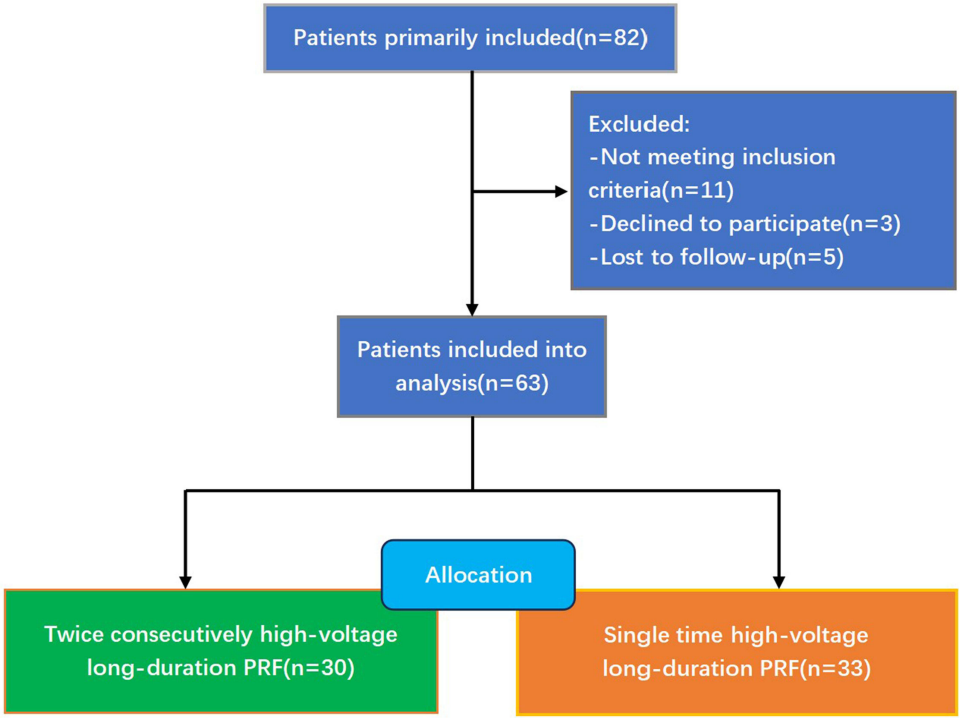

Figure 2 Study flowchart.

The total efficiency rate at 12 weeks post-treatment was significantly higher in Group T compared to Group S (86.7% vs 60.6%, $P < 0.05$, Table 2).

Sleep Quality

Sleep quality was assessed using PSQI. PSQI scores decreased in both groups at 1, 4, 8, and 12 weeks post-treatment ($P<0.001$). Group T showed a significantly greater reduction in PSQI scores compared to Group S at all time points ($P<0.001$, Figure 3B).

Table 1 Participants' Characteristics

	Group S	Group T
Patients (n)	33	30
Age (year)	66.43±6.67	66.03±7.09
Gender (M/F, %)	16 (48.5)/17 (51.5)	16 (53.3)/14 (46.7)
Weight (Kg)	63.70±9.16	62.70±9.55
Pain duration (day)	33.57±8.74	34.93±8.42
Preoperative VAS	6.10±1.27	6.03±1.38
Preoperative PSQI	17.87±0.86	17.93±0.74
Preoperative PCS	35.30±1.54	35.50±1.41
Preoperative MCS	36.03±1.33	35.83±1.29
Preoperative drug		
Tramadol (mg/day)	131.67±42.51	136.67±45.36
Pregabalin (mg/day)	230.00±81.05	220.00±90.12
Gabapentin (g/day)	1.40±0.33	1.49±0.37
Pain side (n, %)		
Right	14 (42.4)	14 (46.7)
Left	19 (57.6)	16 (53.3)

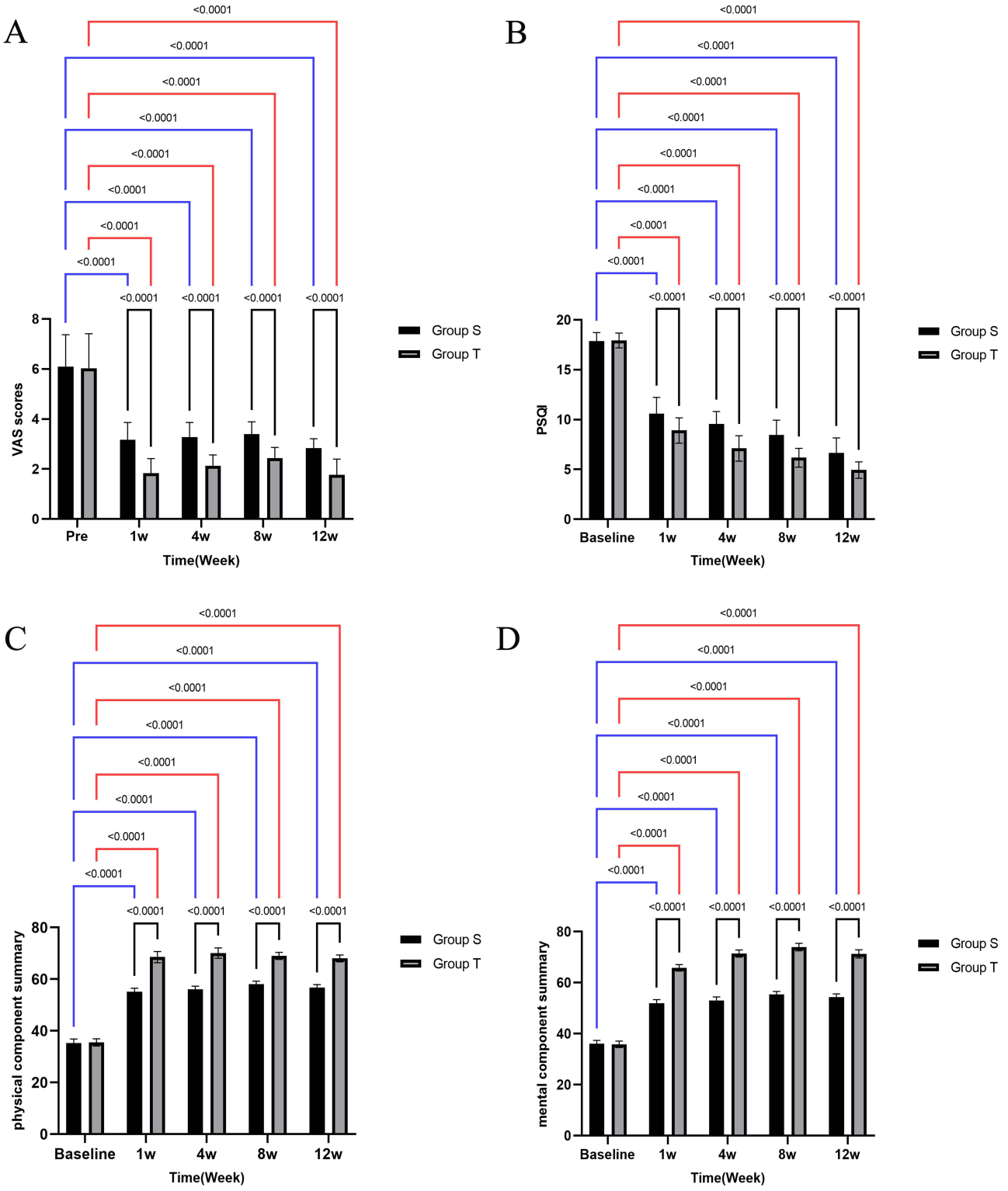

Figure 3 (**A**) The comparison of VAS pain scores pre-treatment and post-treatment in both groups; (**B**) The comparison of PSQI pre-treatment and post-treatment in both groups; (**C** and **D**). The comparison of quality of life scores (SF-36) pre-treatment and post-treatment in both treatment groups. Results are presented as means ± SD.
Abbreviations: PCS, physical component summary; MCS, mental component summary.

Table 2 The Comparison of Total Efficiency Rate Post-Treatment in Two Groups (%)

Group	n	Excellent	Good	Poor	Ineffective	Total Efficiency Rate
S	33	9	11	9	4	60.6
T	30	14	12	3	1	86.7*

Notes: *Compared with Group S, $p < 0.05$.

Quality of Life

The quality of life was evaluated by SF-36. Both groups showed a significant increase in PCS and MCS at 1, 4, 8, and 12 weeks post-treatment compared to pre-treatment ($P < 0.001$). Group T showed more pronounced PCS and MCS increases compared to Group S ($P < 0.001$, Figure 3C and D).

Adverse Events

No serious adverse reactions related to the treatment were recorded in either group. Among them, 2 patients had pain at the puncture point, and 1 patient had a little blood leakage at the puncture point.

Discussion

ZAP is a common and complex complication of herpes zoster, impairing patients emotionally and physically and reducing quality of life. Therefore, exploring more effective treatments for postherpetic neuralgia is important for improving ZAP patients' wellbeing. As a minimally invasive treatment, PRF has recently emerged as a safe and effective option for managing ZAP clinically. PRF is a non-invasive technique that can be repeatedly applied without causing nerve tissue damage. However, few studies have examined repeated HL-PRF for ZAP. Therefore, we retrospectively analyzed the clinical efficacy and safety of twice repeated HL-PRF treatment in patients with subacute postherpetic neuralgia. Our results demonstrate that twice repeated HL-PRF therapy has a satisfactory efficacy in patients with subacute postherpetic neuralgia.

The pathogenesis of ZAP remains unclear. Studies have shown that the skin lesions of ZAP patients have class C fiber degeneration, which leads to the possible reorganization of pain signaling pathways in the central nervous system and a β Synaptic connection between fibers. The activation of fiber reflexes leads to the reduction of pain threshold, and the degree of degeneration of class C fibers is positively correlated with the degree of pain, which is one of the important causes of neuralgia.[13] Studies have found that PRF selectively inhibits the conduction of C fibers in normal rats and spinal nerve ligation neuropathic pain in model rats. For SNL model rats, PRF can induce long-term depression in the spinal cord and selectively inhibit the conduction of C fibers, resulting in analgesia.[14] Teixeira and Sluijter[15] showed that the field strength of pulsed RF was positively correlated with the treatment effect. Zhang et al[16] proves that the repeated HL-PRF treatment (interval of 3 days of treatment time, a total of 3 times) is more effective than standard pulsed radiofrequency in the treatment of acute herpetic neuralgia. In our study, we adjusted the treatment regimen, that is, HL-PRF treatments were performed two consecutive days. Our study demonstrated that twice repeated HL-PRF resulted in significantly lower VAS pain scores at all follow-up timepoints and higher total efficiency rate (86.7% vs 60.6%). The reason for the low total efficiency rate of single HL-PRF may be that its action time is not long enough, and neuralgia may recur within 3 months.

ZAP leads to sleep disorder. Insufficient sleep, in turn, elevates ZAP risk and may exacerbate pain in a vicious cycle. Our results showed that the PSQI score of the two groups at each time point after treatment was lower than that before treatment, while the PSQI score of twice repeated HL-PRF treatment was lower than that of single time HL-PRF treatment. It is suggested that twice repeated HL-PRF treatment can improve the sleep quality of patients better than single HL-PRF treatment. By modulating dorsal root ganglia, PRF may increase immune cell activity, improve neuroplasticity, reduce central sensitization, and enhance sleep. Twice repeated HL-PRF may be more effective in this regard by delivering prolonged and intense stimulation to the dorsal root ganglia.

Patients with ZAP often experience psychological distress, significantly impacting their quality of life. The severity and outcome of ZAP are significantly affected by various psychological and physiological factors, such as sleep disorders, psychological disorders, and hypothalamic pituitary adrenal axis dysfunction.[13] Studies have shown that insufficient sleep is closely related to the increased risk of ZAP.[17] ZAP impairs patients' quality of life and physical and mental health and potentially leads to depression and other mental illnesses. Some researchers[9,18] reported that patients in HL-PRF group obtained more significant pain relief and improvement in quality of life than in the standard-mode PRF group. Our results showed that patients received twice repeated HL-PRF possess better quality of life, both physical and psychological.

In this study, we adopted an HL-PRF treatment mode. Throughout the treatment procedure, we carefully controlled the temperature to ensure that it remained below 42 °C. This precautionary measure was implemented to mitigate any potential risks of nerve injury or tissue protein coagulation, thereby ensuring the safety of our patients. There was no incidence of serious complications such as infection, peripheral hematoma, or pneumothorax that observed among the study participants. Although this technique is considered relatively safe, and the use of CT in our study further mitigated the occurrence of serious complications, some complications may still occur. Pulsed radiofrequency belongs to invasive puncture treatment, and some patients may suffer from pain or bleeding at the puncture point during the treatment. Additionally, although rare, patients may develop allergic reactions to certain device materials or medications.

Limitations

This study has certain limitations. First, as a retrospective analysis, it cannot avoid information bias. Second, the sample size of this study is relatively small, and the follow-up time is short. In the future, multi-center and large sample studies are needed to further verify the findings. Finally, we did not include a separate standard PRF control group. The inclusion of a control group receiving standard PRF treatment would enhance the significance of this study.

Conclusions

Twice repeated high-voltage long-duration PRF therapy demonstrated satisfactory efficacy in subacute postherpetic neuralgia without significant adverse reactions.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

This retrospective study adhered to the World Medical Association Declaration of Helsinki. Data are presented in accordance with the Consolidated Standards of Reporting Trials (CONSORT) statement. This study was approved by the Ethics Committee of the First Affiliated Hospital of Wannan Medical College, No. 2 Zhe shan Street, Wuhu, Anhui, China (NO: 2023-LSX-08). Written informed consent was obtained from all patients before the study procedures.

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Disclosure

The authors declare no conflicts of interest in this work.

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