Randomized Controlled Trial

Efficacy of Higher-Voltage Long-Duration Pulsed Radiofrequency for Spinal Zoster-Associated Pain: A Randomized Controlled Trial

Xixia Feng, MD[1,2], Xueyin Zhao, MD[3], Ruihao Zhou, MD[1], Lu Chen, MD[1], Guo Chen, MD[1], Tao Zhu, MD[1], and Ling Ye, MD[2]

From: [1]Department of Anesthesiology, West China Hospital, Sichuan University, Chengdu, Sichuan Province, China; [2]Department of Pain Management, West China Hospital/West China Tianfu Hospital, Sichuan University, Chengdu, Sichuan Province, China; [3]Southern Central Hospital of Yunnan Province (The First People's Hospital of Honghe State), Yunnan, China

Address Correspondence:
Ling Ye, MD
Department of Pain Management, West China Hospital/West China Tianfu Hospital, Sichuan University, Chengdu, Sichuan Province
P. R. China, 610041
E-mail: zerodq_hx@163.com

Disclaimer: This study was funded by Grant 2023HXFH036 from the 1·3·5 Project for Disciplines of Excellence-Clinical Research Fund, West China Hospital, Sichuan University, Grant 2024NSFSC0624 from the Science and Technology Department of Sichuan Province, and Grant 2023092 from the Health Commission of Chengdu. Parts of the study's results have been accepted for poster presentation at the 18th World Congress of Anesthesiologists.

Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article.

Article received: 03-22-2024
Revised article received: 07-21-2024
Accepted for publication: 08-21-2024

Free full article: www.painphysicianjournal.com

Background: High-voltage (65 V) long-duration pulsed radiofrequency (HL-PRF) is an effective method for managing zoster-associated pain (ZAP), though the limited efficacy of and high recurrence rates associated with the procedure present concerns.

Objectives: This study aimed to investigate the safety and effectiveness of a higher-voltage HL-PRF treatment based on the original procedure for ZAP in the spinal area.

Study Design: A prospective, randomized, controlled trial.

Setting: Department of Pain Management, West China Hospital of Sichuan University.

Methods: In this prospective trial, patients were randomly assigned to one of 2 groups. Group A received an initial voltage of 65 V, which was incrementally increased to the maximum tolerable level (≤ 100 V). Group B maintained a steady voltage of 65 V throughout the treatment. The optimal puncture site was determined based on the distribution of rash and pain. With the use of a 16-slice spiral computed tomography (CT) scanner, the needle entry point, angle, and depth were calculated and marked. Under CT guidance, the needle was advanced to the upper edge of the intervertebral foramen, after which the PRF treatment instrument was connected. Accurate needle placement was confirmed through sensory and motor tests that induced a tingling sensation in the symptomatic nerve root area. Pain levels, negative emotional states, quality of life, and sleep quality were measured using the Visual Analog Scale (VAS), Brief Pain Inventory (BPI), Generalized Anxiety Disorder-7 (GAD-7), Patient Health Questionnaire-9 (PHQ-9), and Pittsburgh Sleep Quality Index (PSQI), respectively. The primary endpoint was the pain score at 12 weeks after treatment. Additional data collected included medication use, hospitalization costs and duration, and any adverse reactions.

Results: Sixty patients were finally analyzed. The average voltage used in Group A was 85.79 ± 2.14V. As for the primary outcome, the 12-week VAS scores of Group A were significantly lower than those of Group B ($P < 0.05$), with scores on the BPI, GAD-7, PHQ-9, and PSQI having notable differences ($P < 0.05$). A significant difference in VAS score was also observed on the first day after the 2 treatments ($P < 0.05$). Pregabalin consumption was lower in Group A at 12 weeks ($P < 0.05$). No statistical differences in the areas of rescue analgesic use, adverse reaction incidence, or economic indicators were found between the groups.

Limitations: This study took place in a single-center setting and had a short follow-up period and a relatively small number of patients.

Conclusions: Using higher voltage in original HL-PRF treatments enhances pain relief, quality of life, and emotional well-being, in addition to reducing medication dependence. Multiple sessions might be preferable to a single treatment, with no additional cost or safety risks. Larger scale, long-term studies are needed to confirm these findings and guide clinical practice.

Key words: Zoster-associated pain, postherpetic neuralgia, pulsed radiofrequency, randomized controlled study

Pain Physician 2024: 27:E1073-E1083

Zoster-associated pain (ZAP) primarily encompasses both acute herpetic neuralgia and postherpetic neuralgia (PHN). Acute herpetic neuralgia refers to pain experienced from the onset of herpes zoster (HZ) until the lesions heal, while PHN is a chronic neuropathic pain condition that persists for more than one month after healing (1,2), although some studies define PHN as pain that endures for over 3 months after a rash resolves (3,4). The generally accepted categorization of ZAP includes the acute phase (within 30 days post-rash), the subacute phase (30-90 days post-rash), and the chronic phase (exceeding 90 days post-rash) (5). Patients with ZAP suffer from a spectrum of pain sensations, including persistent pain, radiating or tearing pain, and allodynia, sometimes accompanied by severe itching (6-8). The complex etiology of ZAP and the limited treatment options for it often result in prolonged, severe pain that significantly impacts patients' quality of life, contributing to psychological distress and social and economic burdens (6,9,10).

Pulsed radiofrequency (PRF) treatment has emerged as a promising, safe approach for ZAP management (11). Distinct from conventional radiofrequency (CRF) thermocoagulation, PRF administers brief, intermittent electrical pulses that maintain temperatures below 42°C, usually with output voltages of 45 V for periods ranging from 180 to 300 seconds. This approach significantly lowers the likelihood of tissue damage (12). Initial research has highlighted the potential of PRF to provide significant pain relief and possibly prevent the transition to PHN (13). Nonetheless, the effectiveness and long-term benefits of using standard PRF parameters have been subjects of debate, with some studies pointing out a notable rate of symptom recurrence (14). Evidence has shown that both the intensity of the PRF field and the duration of the treatment are directly linked to the success of the therapy. High-voltage PRF in particular has been associated with a 90% success rate in managing pain for cases of refractory infraorbital neuralgia across a one-year period (15). Moreover, the practice of administering repeated sessions of high-voltage, long-duration PRF (HL-PRF) therapy is emerging as a promising approach for the treatment of acute herpetic neuralgia, with the potential to prevent the development of PHN as well (16). This evolving strategy underscores the importance of optimizing PRF parameters to enhance therapeutic outcomes and sustain long-term benefits for patients suffering from such conditions.

With these considerations in mind, the study aims to investigate the analgesic efficacy of administering 2 sessions of higher-voltage long-duration PRF therapy to patients suffering from spinal ZAP, utilizing the original HL-PRF setting of 65 V as a reference point. This study will also evaluate the impact of this treatment on the patients' emotional states, quality of life, and sleep quality. Additionally, the safety profile of this approach and its economic ramifications will be assessed thoroughly to provide a comprehensive understanding of the procedure's potential benefits and drawbacks.

Methods

Study Design

The current study was designed as a prospective, randomized, controlled clinical trial and conducted from February 2022 to October 2022. The study protocol received approval from the Ethics Committee on Biomedical Research at West China Hospital of Sichuan University (approval number: 2021-1587) and was registered at Chictr.org.cn (registration number: ChiCTR2200056277). All patients provided informed consent after carefully reading the consent form.

Inclusion Criteria

Patients were eligible for inclusion based on the following criteria: (1) an age of 18 years or older with a diagnosis of ZAP; (2) a manifestation of ZAP that affected the unilateral spinal nerves (cervical, thoracic, lumbar, or sacral nerves); (3) a visual analog scale (VAS) score of 6 or greater; (4) refractoriness to conventional therapies by the standards of the International Association for the Study of Pain guidelines (17) (e.g., antiepileptic drugs, opioids, and antidepressants), or an inability to tolerate adverse drug reactions; and (5) the absence of a previous PRF treatment.

Exclusion Criteria

Patients were excluded for the following reasons: (1) refusal to participate in the trial; (2) poor general condition precluding treatment (e.g., severe cardiac, cerebral, renal, or hepatic dysfunction; pregnancy or postpartum status; presence of pacemakers; or infection at the puncture site); (3) the presence of coagulation disorders or current anticoagulant use; (4) cognitive impairment that prevented completion of self-evaluation questionnaires; and (5) an allergy to research drugs or contrast agents.

Randomization and Blinding

A randomized number generation process was facilitated by an Excel spreadsheet. The allocation sequence was concealed using opaque, sequentially numbered envelopes. After giving informed consent, patients were handed these randomly distributed envelopes to determine their group assignment according to the pre-specified protocol within. Physicians administered PRF therapy at different voltage settings specific to each group. Both patients and outcome assessors were kept unaware of the group allocations throughout the follow-up period.

Description of PRF

All patients were escorted to the operating room and placed in a prone position for the continuous non-invasive monitoring of vital signs. The distribution of rash and pain delineated the targeted nerve segments and puncture areas. Using a 16-slice spiral computed tomography (CT) scanner, imaging was performed with slice thicknesses ranging from 0.75 to 3 mm. These CT images were instrumental in identifying the optimal puncture site. The distance from the needle entry point to the midline was measured, and the angle and depth of needle insertion were carefully calculated and marked. After thorough disinfection, draping, and administration of local anesthesia, a pair of 21-gauge, 10-cm-long RF cannulas with a 5-mm exposed tip were carefully inserted under CT guidance. The needle tip was advanced to the upper posterior superior edge of the intervertebral foramen, and the PRF generator (Radiofrequency Ablation for Pain Management, G4™ RF Generator; Cosman Medical) was then connected (Fig. 1). Sensory and motor function stimulation tests were conducted with currents of 50 Hz at 0.5 V and 2 Hz at less than one V, respectively. The position of the electrode was adjusted meticulously to evoke a tingling sensation in the nerve root area corresponding to the symptomatic region, confirming accurate needle placement. The impedance values were maintained within the optimal range of 300 to 400 Ω during the procedure to ensure proper needle placement and to monitor the tissue response.

The PRF therapy parameters were set as follows: a treatment temperature of 42°C, a frequency of 2 Hz, a pulse width of 20 ms, and a treatment duration of 900 seconds. The voltage of the experimental group (Group A) commenced at 65 V and was progressively increased to the maximum tolerable level for the patients, not exceeding 100 V. Meanwhile, the control group (Group B) received a voltage setting of 65 V. Upon the completion of the PRF therapy, a contrast agent was injected through the puncture needle to assess the nerve root diffusion. A pain-relief solution composed of 2 mL of a 2% lidocaine hydrochloride injection, 2 mL of a methyl cobalamin injection (0.5 mg/mL), one mL of a compound betamethasone injection (5 mg of betamethasone dipropionate and 2 mg of betamethasone sodium phosphate per mL), and 5 mL of saline was subsequently administered. The puncture site was then covered with a sterile dressing, and the patient was monitored for 10 minutes to confirm the stability

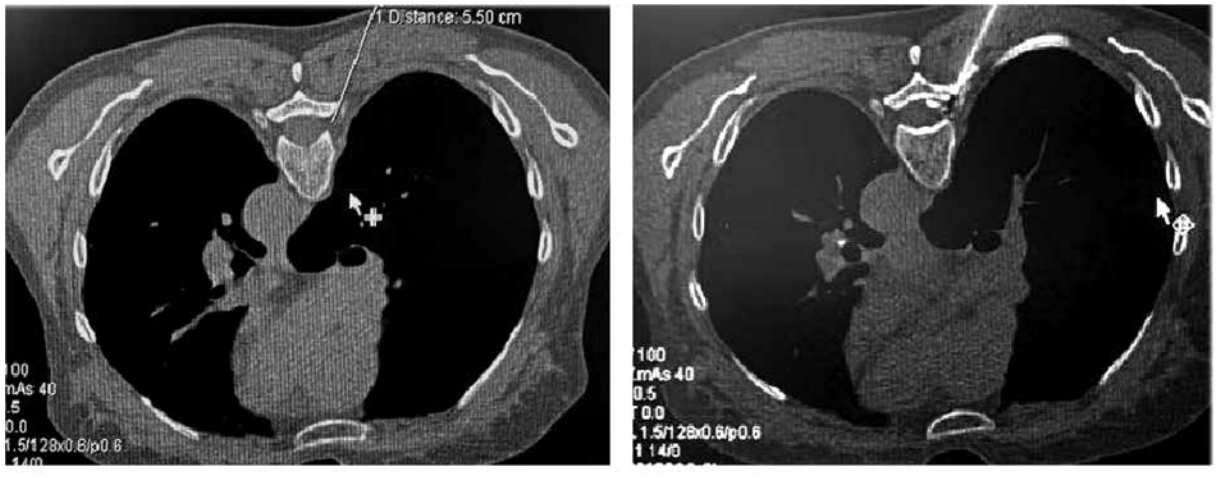

Fig. 1. *Representative CT images of positioning and placement during PRF treatment. (A) CT images of positioning during treatment. (B) CT images of placement during treatment.*

of the vital signs before being transferred to the ward. Follow-up took place one week later, at which point a second PRF treatment was administered.

Drug Administration

Patients in both groups were given pregabalin therapy, with an initial dose of 75 mg taken orally twice daily. The dosage was adjusted based on the intensity of pain and the patient's tolerance to adverse drug reactions. When a patient's VAS score exceeded 5 points, pregabalin dosage was increased and, conversely, reduced if adverse reactions were intolerable. The maximum daily dosage was capped at 300 mg. When this VAS score exceeded a threshold of 5 points consistently, oral oxycodone was prescribed for rescue analgesia. The prescribed regimen was one tablet, administered 3 times daily. Treatment was discontinued once the patient's continuous VAS score was maintained at 3 points or below.

Outcome Measures

Pain Assessment

The pain level of patients was assessed using the VAS score at multiple time intervals: pre-treatment (T_1), one day after initial treatment (T_2), immediately before the second treatment (T_3), and subsequently at one day (T_4), one week (T_5), 4 weeks (T_6), and 12 weeks (T_7) after the second treatment had concluded. The primary outcome measure focused on the VAS score at the 12-week mark following the second treatment.

Quality of Life Rating

Each patient's quality of life was evaluated using interference items pertaining to life quality as outlined in the Brief Pain Inventory (BPI) (18) (Supplementary Table S1). This instrument covers 7 dimensions: general activities, mood, walking ability, normal work (including housework), relations with other people, sleep, and enjoyment of life. The overall score was derived from the aggregated scores of 7 questions. Assessments were performed prior to the commencement of the treatment (T_1) and then at intervals of one (T_5), 4 (T_6), and 12 weeks (T_7) following the second treatment session.

Negative Emotions Assessment

Levels of anxiety were measured using the Generalized Anxiety Disorder-7 (GAD-7) scale (19) (Supplementary Table S2), and degrees of depression were assessed with the Patient Health Questionnaire-9 (PHQ-9) scale (20)(Supplementary Table S3). Each item on the scales was scored from 0 to 3, with the total score being the sum of the individual item scores from both scales. These evaluations occurred before treatment (T_1), and at one (T_5), 4 (T_6), and 12 weeks (T_7) after the second treatment.

Sleep Quality Evaluation

The Pittsburgh Sleep Quality Index (PSQI) (21) (Supplementary Table S4), which comprises 18 items across 7 components, was used to evaluate patients' sleep quality. A higher total score indicated poorer sleep quality. Assessments were conducted before treatment (T_1), and at one (T_5), 4 (T_6), and 12 weeks (T_7) after the second treatment.

Oral Medication Usage

The consumption of pregabalin and oxycodone tablets was monitored and recorded before treatment (T_1) and at one (T_5), 4 (T_6), and 12 weeks (T_7) following the second treatment.

Economic Indicators

Treatment expenses and duration regarding hospitalization were calculated and recorded.

Safety Assessment

Based on prior pathological studies and clinical experience (22,23), PRF might lead to recoverable nerve damage, such as numbness. This study closely monitored and documented any adverse reactions during the study period, including local bleeding, hematoma, allergic reactions, dizziness, headache, nausea, vomiting, and nerve damage.

Statistical Analysis

Sample Size Calculation

In alignment with the methodologies of previous studies (24), the VAS score at 12 weeks after PRF treatment was designated as the primary outcome measure. With a one-to-one case ratio between groups, a significance level (α) of 0.05, and a power of 0.80, the required sample size was calculated using PASS 15 software (NCSS, LLC), which determined that 21 patients per group would be necessary. Anticipating a potential dropout and refusal rate of 20%, the final sample size for each group was set at 28, totaling a minimum of 56 patients for the study.

Data Analysis

IBM Statistics SPSS 26.0 (IBM Corporation) was employed for the statistical analysis. Continuous variables conforming to a normal distribution were reported as means ± SDs, while those not following a normal distribution were presented as medians with interquartile ranges (IQRs). For the purposes of analysis, we utilized t-tests or the Mann-Whitney U test as appropriate. Categorical data were expressed in terms of frequencies and percentages and analyzed using the chi-square (χ^2) tests. A *P* value less than 0.05 was considered indicative of a statistically significant difference.

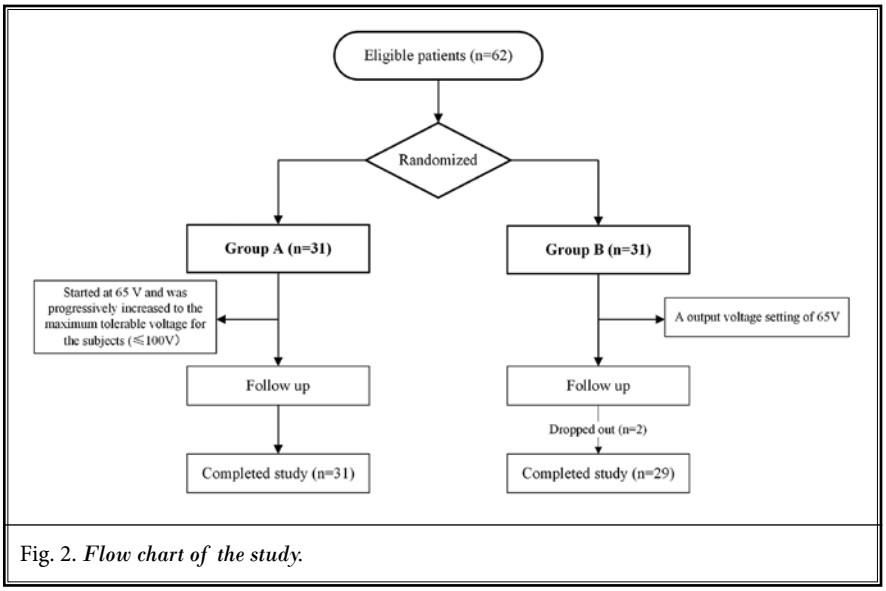

Fig. 2. *Flow chart of the study.*

Results

A total of 62 patients were enrolled in this study. However, 2 patients were excluded from the final analysis because one experienced a change in condition and another withdrew from the study. Consequently, 60 patients were included in the final analysis, with 31 in Group A and 29 in group B (Fig. 2). The demographic characteristics, such as age, gender, body mass index (BMI), disease duration, affected side, and spinal segments involved (cervical, thoracic, lumbar, sacral) before treatment, were comparable between the groups (Table 1). The output voltage for group B was set to 65 V, whereas the voltages used for Group A ranged from a minimum of 80 V to a maximum of 95 V, with an average of 85.79 ± 2.14 V.

Table 1. *Demographic characteristics of the patients.*

Characteristics	Group A (n = 31)	Group B (n = 29)	*P* value
Gender, n (%)			
Men	15 (48.39%)	12 (41.38%)	0.59
Women	16 (51.61%)	17 (58.62%)	
Age (years), mean ± SDs	67.71±1.42	69.31±1.85	0.49
BMI (kg/m^2), mean ± SDs	25.20±3.62	23.70±3.18	0.09
Disease stage, n (%)			
Acute	2 (6.45%)	2 (6.90%)	0.88
Subacute	22 (70.97%)	22 (75.86%)	
Chronic	7 (22.58%)	5 (17.24%)	
Affected side, n (%)			
Left	13 (41.94%)	14 (48.28%)	0.62
Right	18 (58.06%)	15 (51.72%)	
Affected segments, n (%)			
Cervical	11 (35.48%)	10 (34.48%)	0.08
Thoracic	19 (61.29%)	14 (48.28%)	
Lumbar	0 (0.00%)	5 (17.24%)	
Sacral	1 (3.23%)	0 (0.00%)	

Abbreviations: BMI, body mass index

Pain Assessment

The baseline of VAS scores was not significantly different between the groups. However, following treatment, VAS scores significantly decreased in both groups at each subsequent time point ($P < 0.001$; Fig. 3). Moreover, Group A exhibited a greater decline in VAS scores at one week, 4 weeks, and 12 weeks after the second treatment than did Group B ($P < 0.05$; Fig. 3; Table 2). Additionally, in both groups, there was a significant difference in VAS scores between the initial and second treatments after one day ($P < 0.05$; Fig. 3; Table 3).

Quality of Life Rating

There were no significant differences observed in the baseline of life quality between the 2 groups. Notable enhancements were seen in interpersonal relations at one week after the second treatment, as well as in general activities, sleep quality, and the total quality of life score at 12 weeks after the second treatment, improvements that were greater in Group A than in Group B ($P < 0.05$) (Table 4).

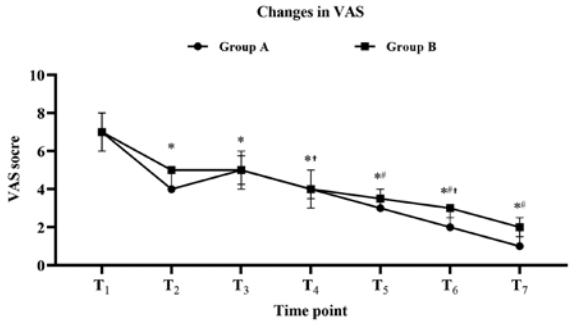

Fig. 3. *Evaluation of pain relief through VAS scores. (Significant reductions were observed in the VAS scores following treatment: *P < 0.05 indicates pre-treatment VAS score vs. post-treatment VAS scores. #P < 0.05 indicates Group A vs. Group B. †P < 0.05 indicates the day following the second treatment vs. the day following the first treatment.*
Abbreviations: VAS, Visual Analog Scale; T_1, before treatment; T_2, one day after the initial treatment; T_3, before the second treatment; T_4, one day after the second treatment; T_5, one week after the second treatment; T_6, 4 weeks after the second treatment; T_7, 12 weeks after the second treatment.)

Table 2. *Comparison of VAS scores between groups.*

Time Point	Group A (n = 31)	Group B (n = 29)	*P* value
T_1	7 (2)	7 (2)	0.36
T_2	4 (1)	5 (1)	0.18
T3	5 (2)	5 (1.5)	0.30
T_4	4 (1.5)	4 (0.5)	0.42
T_5	3 (1)	3.5 (1)	0.03
T_6	2 (1)	3 (0.5)	0.004
T_7	1 (1)	2 (1)	0.001

(Abbreviations: VAS, Visual Analog Scale; T_1, before treatment; T_2, one day after the initial treatment; T_3, before the second treatment; T_4, one day after the second treatment; T_5, one week after the second treatment; T_6, 4 weeks after the second treatment; T_7, 12 weeks after the second treatment.)

Table 3. *Comparison of VAS scores at one day after treatment for initial and repeat treatments.*

Groups	T_2	T_4	*P* value
Group A (n = 31)	4 (1)	4 (1.5)	0.003
Group B (n = 29)	5 (1)	4 (0.5)	< 0.001

(Abbreviations: VAS, Visual Analog Scale; T_2, one day after the initial treatment; T_4, one day after the second treatment.)

Table 4. *Comparison of items regarding life quality in BPI between groups.*

Quality of Life Rating	Group A (n = 31)	Group B (n = 29)	*P* value
T_1			
General activities	6 (2)	6 (2)	0.09
Mood	5 (3)	5 (2)	0.56
Walking ability	2 (3)	3 (4)	0.19
Normal work	5 (2)	6 (3)	0.30
Relations with others	3 (4)	3 (5)	0.87
Sleep	6 (2)	7 (1)	0.12
Enjoyment of life	5 (3)	5 (3)	0.41
Total score	31 (10)	35 (12)	0.45
T_5			
General activities	4 (2)	4 (2)	0.64
Mood	4 (2)	3 (1)	0.16
Walking ability	1 (2)	2 (3)	0.39
Normal work	4 (2)	4 (2)	0.86
Relations with others	2 (3)	0 (1)	0.03
Sleep	4 (1)	5 (1)	0.28
Enjoyment of life	3 (2)	3 (2)	0.94
Total score	22 (9)	22 (5)	0.74
T_6			
General activities	2 (1)	3 (1)	0.15
Mood	2 (1)	2 (0)	0.53
Walking ability	0 (0)	0 (1)	0.23
Normal work	2 (1)	3 (1)	0.26
Relations with others	0 (0)	0 (0)	0.30
Sleep	3 (1)	3 (1)	0.06
Enjoyment of life	2 (1)	2 (1)	0.89
Total score	12 (4)	13 (5)	0.23
T_7			
General activities	1 (1)	2 (1)	< 0.01
Mood	1 (1)	1 (1)	0.54
Walking ability	0 (0)	0 (0)	0.21
Normal work	1 (1)	2 (1)	0.11
Relations with others	0 (0)	0 (0)	0.96
Sleep	1 (1)	2 (1)	0.03
Enjoyment of life	0 (1)	1 (1)	0.23
Total score	5 (4)	7 (4)	0.02

Abbreviations: BPI, Brief Pain Inventory; T_1, before treatment; T_5, one week after the second treatment; T_6, 4 weeks after the second treatment; T_7, 12 weeks after the second treatment.

Negative Emotions Assessment

The evaluation of negative emotions, particularly anxiety and depression, revealed that the 2 groups had no significant differences in the levels of these emotion prior to any intervention or at one week following the second session of treatment. Nevertheless, at the 4-week and 12-week marks after the second treatment, the analysis demonstrated a statistically significant disparity in the 2 groups' anxiety and depression scores ($P < 0.05$; Fig. 4; Tables 5,6). The experimental group exhibited lower scores for these negative emotions than did to the control group.

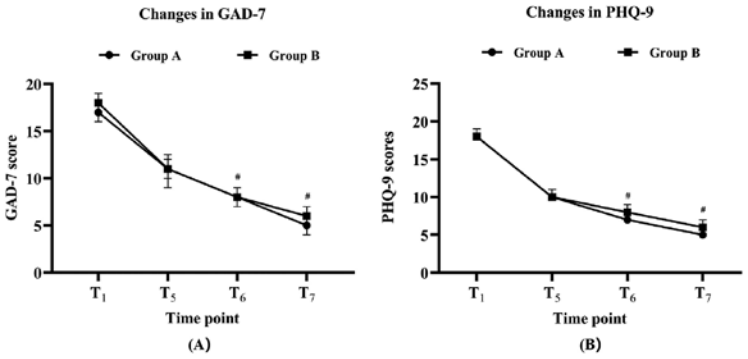

Fig. 4. *Evaluation of improvements in negative emotional states using GAD-7 and PHQ-9 scores.*
(A) Evaluation of improvements in anxiety by GAD-7. (B) evaluation of improvements in depression by PHQ-9. (Significant reductions were observed in both GAD-7 and PHQ-9 scores following treatment: $^{\#}P < 0.05$ indicates Group A vs. Group B.)
Abbreviations: GAD-7, Generalized Anxiety Disorder-7; PHQ-9, Patient Health Questionnaire-9; T_1, before treatment; T_5, one week after the second treatment; T_6, 4 weeks after the second treatment; T_7, 12 weeks after the second treatment.)

Sleep Quality Evaluation

Before treatment and at one week and 4 weeks after the second treatment, there was no significant difference in sleep improvement between the 2 groups ($P > 0.05$; Fig. 5; Table 7). However, at week 12, a statistically significant difference in sleep improvement could be observed ($P < 0.05$), and the score of the experimental group was lower than that of the control group.

Oral Medication Usage

All patients in both groups were administered oral medications, which included pregabalin and oxycodone tablets, before commencing their treatment regimens. The analysis of the consumption of these oral medications showed no statistically significant difference between the 2 groups prior to the treatment or one week following the second treatment. Nonetheless, statistically significant differences in pregabalin usage were observed after 4 weeks and again after 12 weeks after the treatment ($P < 0.05$; Supplementary Table S5), with Group A demonstrating lower levels of pregabalin consumption. Conversely, there was no statistically significant difference in the use of oxycodone tablets between the groups at any follow-up point during the study ($P > 0.05$; Supplementary Table S6).

Economic Indicators

Upon assessing the treatment expenditures, we found no substantial discrepancy in costs incurred by the 2 groups ($P > 0.05$; Supplementary Table S7). Similarly, the groups showed no significant difference in the duration of hospital stays ($P > 0.05$; Supplementary Table S7).

Table 5. *Comparison of GAD-7 scores between groups.*

Time Point	Group A (n = 31)	Group B (n = 29)	*P* value
T_1	17 (3)	18 (2)	0.12
T_5	11 (3)	11 (2.5)	0.12
T_6	8 (2)	8 (1)	0.03
T_7	5 (2)	6 (2)	< 0.01

Abbreviations: GAD-7, Generalized Anxiety Disorder-7; T_1, before treatment; T_5, one week after the second treatment; T_6, 4 weeks after the second treatment; T_7, 12 weeks after the second treatment.

Table 6. *Comparison of PHQ-9 scores between groups.*

Time Point	Group A (n = 31)	Group B (n = 29)	*P* value
T_1	18 (4)	18 (2)	0.39
T_5	10 (2)	10 (2)	0.35
T_6	7 (2)	8 (1.5)	< 0.01
T_7	5 (3)	6 (2)	< 0.01

Abbreviations: PHQ-9, Patient Health Questionnaire-9; T_1, before treatment; T_5, one week after the second treatment; T_6, 4 weeks after the second treatment; T_7, 12 weeks after the second treatment.

Safety Assessment

Throughout the study period, no severe adverse events attributable to the PRF treatments were recorded for any patient in either group. A minor subset of individuals, comprising 4 members of Group A and 2 of Group B, experienced a transient intensification of pain

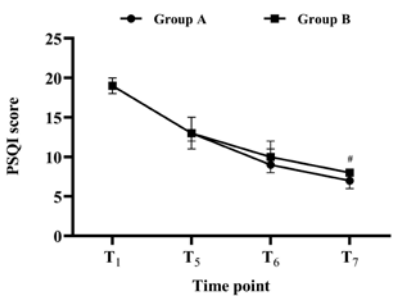

Fig. 5. *Evaluation of sleep quality improvement using PSQI.*
(Significant reductions were observed in the PSQI scores following treatment: $^{\#}P < 0.05$ indicates Group A vs. Group B.)
Abbreviations: PSQI, Pittsburgh Sleep Quality Index; T_1, before treatment; T_5, one week after the second treatment; T_6, 4 weeks after the second treatment; T_7, 12 weeks after the second treatment.)

Table 7. *Comparison of PSQI scores between groups.*

Time Point	Group A (n = 31)	Group B (n = 29)	*P* value
T_1	19 (2)	19 (2)	0.28
T_5	13 (4)	13 (3)	0.52
T_6	9 (4)	10 (2)	0.20
T_7	7 (2)	8 (1)	< 0.01

Abbreviations: PSQI, Pittsburgh Sleep Quality Index; T_1, before treatment; T_5, one week after the second treatment; T_6, 4 weeks after the second treatment; T_7, 12 weeks after the second treatment.

following the intervention. These symptoms, however, were self-limiting and abated spontaneously by the second day after the second treatment. There were no statistical differences in the prevalence of such adverse effects between the 2 groups ($P > 0.05$; Supplementary Table S8).

Discussion

This study highlighted the considerable analgesic effectiveness of repetitive HL-PRF therapy for patients with ZAP, along with the associated significant improvements in emotional states, quality of life, and sleep quality. Notably, the employment of a higher-voltage setting conferred superior benefits to those of the standard high-voltage procedure. Multiple treatment sessions have been shown to exhibit more effective short-term pain relief than does a single-session approach. A previous study demonstrated that acute pain could evolve into chronic pain and ultimately become a bio-psycho-social condition (25). Consequently, individuals suffering from ZAP experience persistent and severe pain, which significantly impacts their emotional well-being, disrupts their sleep patterns, and diminishes their overall quality of life (7). PRF therapy, which utilizes a high-voltage electric field delivered through pulsed currents, has shown the capacity to modulate the affected nerves and alleviate pain (12). Despite the ongoing debate regarding the optimal parameters for clinical application, our findings contributed valuable insights toward the refinement of PRF treatment protocols. Specifically, our research underscored the therapeutic promise of employing repetitive higher-voltage PRF sessions to manage ZAP, suggesting a potential paradigm shift in treatment strategies for this challenging condition.

In the current study, no statistically significant intergroup differences were found in the baseline demographic characteristics of the patients, including age, gender, BMI, and affected side and segments, suggesting that the 2 groups were comparable. The demographic profile of our study population was consistent with previous reports (2,26). It is noteworthy that multiple findings have emphasized the advantages of early PRF treatment in alleviating pain and preventing the progression to PHN (13,27,28). In our study, patients in the subacute stage, who constituted the vast majority of patients, achieved favorable pain relief outcomes. This finding accentuated the critical need for swift diagnosis and prompt initiation of PRF treatment for optimal clinical efficacy.

Our findings suggested that PRF treatment, regardless of the voltage, was effective in reducing pain, as demonstrated by the significant decrease in VAS scores in both groups over time. However, the group subjected to higher voltage (Group A) showed a more pronounced improvement in pain reduction than did the lower-voltage group (Group B). This is consistent with previous literature that suggested a voltage-response relationship in PRF application, in which higher intensities of voltage field might result in more substantial neuromodulatory effects (29). Furthermore, previous research has shown that repetitive PRF treatments with high voltage and extended duration (consisting of 3 treatment sessions spaced three days apart) results in enhanced analgesic effects (16). This finding is in line with those of our study, in that the second treatment session provided more substantial pain relief than the first.

Advancements in voltage settings not only provide superior analgesia but also lead to pronounced improvements in quality of life and reductions in negative emotions. At the 12-week post-treatment mark, patients who received higher output voltages demonstrated more substantial improvements in their quality of life, particularly in the areas of general activities and sleep. This enhancement in life quality corresponded with the significant reduction in pain reported by this group. Notably, the improvement in scores of life quality lagged behind the reduction in VAS scores, suggesting that effective pain management might result in broader enhancements in overall life satisfaction and daily functioning (28). Such evidence emphasizes the critical role of optimal pain control in improving patient outcomes beyond the simple alleviation of physical discomfort. Further analysis using the PSQI revealed consistent findings, with the higher voltage group showing a noticeable, albeit delayed, improvement in sleep quality at the 12-week mark. Additionally, previous studies have indicated that emotional state impacts chronic pain significantly (30). Consequently, the treatment of ZAP should adopt a biopsychosocial approach, incorporating insights from psychological research that underscore the significance of psychological factors in both sustaining and intensifying chronic pain. To support this approach, psychological and behavioral interventions should be promoted, since they play a crucial role in helping patients come to terms with the impact of pain and in cultivating self-management strategies for chronic pain, specifically for conditions like ZAP (31).

Additionally, a retrospective study showed that pregabalin and oxycodone were the most commonly prescribed medications for patients suffering from ZAP (28). In our study, we observed a significant decrease in patients' use of pregabalin. These changes were especially pronounced in those who received higher-voltage therapy at the 4- and 12-week post-treatment marks. Such a decrease in medication usage might be clinically significant, considering the adverse side effects and potential for dependency associated with prolonged use of pain medications. Despite these findings, no significant differences in oxycodone consumption were noted, which might have been attributable to the limited effectiveness of PRF treatment for controlling breakthrough pain (BTP). BTP is characterized by intermittent, spontaneous episodes of short-lived and severe pain (32). Oxycodone, a critical rescue medication, has been consistently administered for managing such episodes of breakthrough pain (33). Future research should focus on uncovering the underlying mechanisms of BTP and on the development of more effective therapeutic approaches.

During this study, the absence of serious adverse events aligned with previous evidence, which portrayed PRF treatment as a safe modality for pain management (23). Nevertheless, it is important to recognize that some complications associated with PRF have been reported in literature, raising concerns about the procedure's safety profile (34). Previous research indicated that PRF application could cause acute injury to surrounding cells and nerve tissue, which might be reversible (35). This tissue damage might be linked to the activation of mitogen-activated protein kinases (MAPKs) in the spinal cord's dorsal horn, which can precipitate inflammatory pain responses, such as mechanical allodynia and cold hyperalgesia (23). In our study, we observed a transient increase in temporary pain in 6 patients after the PRF procedure. This temporary exacerbation might have been due to the nerve inflammation response triggered by PRF (23). However, it should be noted that this temporary pain did not lead to any long-term complications or increased medical expenses. This finding is corroborated by the absence of significant differences in treatment costs or the duration of hospital stays between the 2 patient groups. Therefore, PRF could be a safe, cost-effective approach for managing pain without adding extra financial burdens. At the same time, it is imperative for clinicians who administer PRF to proceed with caution, especially in preserving the integrity of healthy nerves, to prevent inadvertent damage.

This clinical trial sought to assess the effectiveness of administering PRF treatment at the maximum voltage tolerated by patients as a method of managing ZAP. The study was pioneering in its attempt to evaluate the therapeutic impact of administering 2 sessions of PRF treatment, potentially offering a fresh perspective on treatment protocols for ZAP. Nevertheless, there are several limitations to the study that should be considered. Firstly, the follow-up period was only 3 months, which did not allow for assessment of the long-term outcomes for patients. Longer follow-up periods should be necessary to understand the enduring effects of PRF on pain management and functional recovery. Secondly, the study did not include a control group that received only one session of PRF treatment. Consequently, it was difficult to distinguish the specific benefits of one treatment session versus 2. Including such a control group in future research

would clarify whether additional sessions provide incremental benefits. Thirdly, due to the small sample size, the study did not conduct subgroup analyses to examine the effects of PRF treatment across different stages of ZAP. Understanding how the treatment might affect patients at various stages of the condition would be essential for tailoring interventions to individual needs. Moreover, the study was conducted at a single center, which might have limited the generalizability of the results. Lastly, the study focused on spinal ZAP exclusively and did not include patients with zoster-associated pain facial who might have different treatment responses. Therefore, the results should be interpreted with caution, particularly emphasizing that they pertain to spinal ZAP specifically. Further prospective studies with larger sample sizes, longer follow-up durations, inclusion of various control groups, and detailed subgroup analyses would contribute to a better understanding of how PRF could be most effectively incorporated into pain management strategies for this condition. Such studies would be invaluable in refining treatment regimens and improving patient outcomes.

Conclusion

In summary, our findings suggested that utilizing higher voltage settings in the original high-voltage long-duration PRF treatment for spinal ZAP would result in better outcomes regarding pain alleviation, quality of life enhancement, reductions in negative emotional states, and decreased reliance on medication. Moreover, a regimen of multiple sessions may be more beneficial than the single-treatment approach, without incurring additional financial burdens or jeopardizing patient safety. Nevertheless, there is still a need for larger-scale, longer-term studies to corroborate these results and provide more robust evidence to inform clinical practice.

Author Contributions

Xixia Feng: conception or design of the work, data analysis and interpretation, drafting the article, critical revision of the article. Xueyin Zhao: literature research, data collection, data analysis and interpretation, drafting the article. Ruihao Zhou: literature research, data collection, data analysis and interpretation. Lu Chen: data collection, data analysis and interpretation. Guo Chen: conception or design of the work, supervision, interpretation, and critical revision of the article. Tao Zhu: conception or design of the work, supervision and interpretation, and critical revision of the article. Ling Ye: conception or design of the work, data analysis and interpretation, critical revision of the article, correspondence.

References

1. Rowbotham MC, Davies PS, Fields HL. Topical lidocaine gel relieves postherpetic neuralgia. *Ann Neurol* 1995; 37:246-253.
2. Yang F, Yu S, Fan B, et al. The epidemiology of herpes zoster and postherpetic neuralgia in China: Results from a cross-sectional study. *Pain Ther* 2019; 8:249-259.
3. Gruver C, GuthmillerKB. Postherpetic Neuralgia, StatPearls. *StatPearls Publishing*© 2023, StatPearls Publishing LLC., Treasure Island (FL) ineligible companies. Disclosure: Kevin Guthmiller declares no relevant financial relationships with ineligible companies., 2023.
4. Johnson RW, Rice AS. Clinical practice. Postherpetic neuralgia. *N Engl J Med* 2014; 371:1526-1533.
5. Dworkin RH, Portenoy RK. Proposed classification of herpes zoster pain. *Lancet* 1994; 343:1648.
6. Torcel-Pagnon L, Bricout H, Bertrand I, et al. Impact of underlying conditions on zoster-related pain and on quality of life following zoster. *J Gerontol A Biol Sci Med Sci* 2017; 72:1091-1097.
7. Patil A, Goldust M, Wollina U. Herpes zoster: A review of clinical manifestations and management. *Viruses* 2022; 14:192.
8. Ishikawa R, Iseki M, Koga R, Inada E. Investigation of the correlation between postherpetic itch and neuropathic pain over time. *Pain Res Manag* 2018; 2018:9305126.
9. Mbinta JF, Wang AX, Nguyen BP, et al. Herpes zoster vaccine effectiveness against herpes zoster and postherpetic neuralgia in New Zealand: A retrospective cohort study. *Lancet Reg Health West Pac* 2023; 31:100601.
10. Crosbie B, Lucey S, Tilson L, Domegan L, Kieran J. Acute herpes zoster and post herpetic neuralgia in primary care: A study of diagnosis, treatment and cost. *Eur J Clin Microbiol Infect Dis* 2018; 37:627-631.
11. Chang MC. Efficacy of pulsed radiofrequency stimulation in patients with peripheral neuropathic pain: A narrative review. *Pain Physician* 2018; 21:E225-E234.
12. Park D, Chang MC. The mechanism of action of pulsed radiofrequency in reducing pain: A narrative review. *J Yeungnam Med Sci* 2022; 39:200-205.
13. Kim K, Jo D, Kim E. Pulsed radiofrequency to the dorsal root ganglion in acute herpes zoster and postherpetic neuralgia. *Pain Physician* 2017; 20:E411-E418.
14. Lin S, Lin M, Dai Z, Wang F, Lin K, Liu R. Novel bipolar high-voltage pulsed radiofrequency targeting the cervical sympathetic chain for treating acute herpetic neuralgia. *Neuromodulation* 2023; 26:1808-1816.

15. Jia Y, Chen Z, Ren H, Luo F. The effectiveness and safety of 42°C pulsed radiofrequency combined with 60°C continuous radiofrequency for refractory infraorbital neuralgia: A prospective study. *Pain Physician* 2019; 22:E171-E179.
16. Zhang E, Fei Y, Xu L, Huang B, Yao M. Effect of repeated high-voltage long-duration pulsed radiofrequency on herpetic neuralgia. *Pain Physician* 2022; 25:E1047-E1055.
17. Dworkin RH, O'Connor AB, Kent J, et al. Interventional management of neuropathic pain: NeuPSIG recommendations. *Pain* 2013; 154: 2249-2261.
18. Cleeland CS, Ryan KM. Pain assessment: Global use of the Brief Pain Inventory. *Ann Acad Med Singap* 1994; 23:129-138.
19. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: The GAD-7. *Arch Intern Med* 2006; 166:1092-1097.
20. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: The PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. *JAMA* 1999; 282:1737-1744.
21. Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practice and research. *Psychiatry Res* 1989; 28:193-213.
22. Arakawa K, Kaku R, Kurita M, Matsuko Y, Morimatsu H. Prolonged-duration pulsed radiofrequency is associated with increased neuronal damage without further antiallodynic effects in neuropathic pain model rats. *J Pain Res* 2018; 11:2645-2651.
23. Lin FY, Huang KF, Chen JC, Lai MF, Ma KH, Yeh CC. The clinical application of pulsed radiofrequency induces inflammatory pain via MAPKs activation: A novel hint for pulsed radiofrequency treatment. *Int J Mol Sci* 2021; 22:11865.
24. Dong X, Zhu X, Xiao J. Effect of different pulsed radiofrequency voltage patterns on postherpetic neuralgia therapy. *J Changzhi Med Coll* 2021; 35:140-144.
25. Williams HR, Pandit JJ. Red hair and pain sensitivity: Insights into genomics of pain? Anesthesiology and *Perioperative Science* 2023; 1:15.
26. van Oorschot D, Vroling H, Bunge E, Diaz-Decaro J, Curran D, Yawn B. A systematic literature review of herpes zoster incidence worldwide. *Hum Vaccin Immunother* 2021; 17:1714-1732.
27. Saguil A, Kane S, Mercado M, Lauters R. Herpes zoster and postherpetic neuralgia: Prevention and management. *Am Fam Physician* 2017; 96:656-663.
28. Chen L, Li J, Liu H, Yang P, Zuo Y, Ye L. Interventions for zoster-associated pain: A retrospective study based on the clinical database. *Front Neurol* 2022; 13:1056171.
29. Teixeira A, Sluijter ME. Intradiscal high-voltage, long-duration pulsed radiofrequency for discogenic pain: A preliminary report. *Pain Med* 2006; 7:424-428.
30. Kerns RD, Sellinger J, Goodin BR. Psychological treatment of chronic pain. *Annu Rev Clin Psychol* 2011; 7:411-434.
31. Turk DC, Swanson KS, Tunks ER. Psychological approaches in the treatment of chronic pain patients--when pills, scalpels, and needles are not enough. *Can J Psychiatry* 2008; 53:213-223.
32. Greenfield K, Holley S, Schoth DE, et al. A protocol for a systematic review and meta-analysis to identify measures of breakthrough pain and evaluate their psychometric properties. *BMJ Open* 2020; 10:e035541.
33. Davies A, Zeppetella G, Andersen S, et al. Multi-centre European study of breakthrough cancer pain: Pain characteristics and patient perceptions of current and potential management strategies. *Eur J Pain* 2011; 15:756-763.
34. Facchini G, Spinnato P, Guglielmi G, Albisinni U, Bazzochi A. A comprehensive review of pulsed radiofrequency in the treatment of pain associated with different spinal conditions. *Br J Radiol* 2017; 90:20150406.
35. Cahana A, Vutskits L, Muller D. Acute differential multi-centre European study of breakthrough cancer pain: Pain characteristics and patient perceptions of current and potential management strategies. *Eur J Pain* 2011; 15:756-763.
36. Cahana A, Vutskits L, Muller D. Acute differential modulation of synaptic transmission and cell survival during exposure to pulsed and continuous radiofrequency energy. *J Pain* 2003; 4:197-202.

Supplementary Table S1. *Indicators pertaining to life quality in the Brief Pain Inventory (BPI).*

Circle the one number that describes how, in the last 24 hours, shingles pain has interfered with your:
(Does not interfere) 0 1 2 3 4 5 6 7 8 9 10 (completely interferes)
1. General activity
2. Mood
3. Walking ability
4. Normal work (includes both work outside the home and housework)
5. Relations with other people
6. Sleep
7. Enjoyment of life

Supplementary Table S2. *Generalized Anxiety Disorder (GAD-7) scale.*

Over the last 2 weeks, how often have you been bothered by the following problems?				
	Not at all	**Several days**	**More than half the days**	**Nearly every day**
1. Feeling nervous, anxious, or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3

Supplementary Table S3. *Patient Health Questionnaire-9 (PHQ-9) Scale.*

Over the last 2 weeks, how often have you been bothered by any of the following problems?				
	Not at all	**Several days**	**More than half the days**	**Nearly every day**
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite—being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

Supplementary Table S4. *Pittsburgh Sleep Quality Index (PSQI) scale.*

Instructions:
The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month.
Please answer all questions.

1. During the past month, when have you usually gone to bed at night?
   USUAL BEDTIME _____
2. During the past month, how long (in minutes) has it usually taken you to fall asleep each night?
   NUMBER OF MINUTES _____
3. During the past month, when have you usually gotten up in the morning?
   USUAL TIME OF GETTING UP _____
4. During the past month, how many hours of actual sleep did you get at night?
   (This may be different from the number of hours you spend in bed.)
   HOURS OF SLEEP PER NIGHT _____
5. During the past month, how often have you had trouble sleeping because you...

	Not during the past month	Less than once a week	Once or twice a week	Three or more times a week
a. Cannot get to sleep within 30 minutes				
b. Wake up in the middle of the night or early morning				
c. Have to get up to use the bathroom				
d. Cannot breathe comfortably				
e. Cough or snore loudly				
f. Feel too cold				
g. Feel too hot				
h. Had bad dreams				
i. Have pain				

   j. Other reason(s); please describe _____

6. During the past month, how would you rate your sleep quality overall?
   a. Very good b. Fairly good c. Fairly bad d. Very bad
7. During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep?
   a. Not during the past month b. Less than once a week
   c. Once or twice a week d. Three or more times a week
8. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?
   a. Not during the past month b. Less than once a week
   c. Once or twice a week d. Three or more times a week
9. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?
   a. No problem at all b. Only a very slight problem
   c. Somewhat of a problem d. A very big problem

Supplementary Table S5. *Comparison of pregabalin consumption between groups*.

Time Point	Group A (n = 31)	Group B (n = 29)	*P* value
T_1	300 (150)	300 (150)	0.656
T_5	225 (75)	225 (150)	0.752
T_6	150 (75)	225 (75)	0.041
T_7	150 (0)	225 (75)	0.020

(Abbreviations: T_1, before treatment; T_5, one week after the second treatment; T_6, 4 weeks after the second treatment; T_7, 12 weeks after the second treatment.)

Supplementary Table S6. *Comparison of oxycodone tablets between groups*.

	Group A (n = 31)	Group B (n = 29)	*P* value
T_1			
Use	31 (100%)	29 (100%)	N/A
Non-use	0 (0.00%)	0 (0.00%)	
T_5			
Use	19 (61.29%)	20 (68.97%)	0.60
Non-use	12 (38.71%)	9 (31.03%)	
T_6			
Use	10 (32.26%)	12 (41.38%)	0.59
Non-use	21 (67.74%)	17 (58.62%)	
T_7			
Use	3 (9.68%)	6 (20.69%)	0.29
Non-use	28 (90.32%)	23 (79.31%)	

Abbreviations: T_1, before treatment; T_5, one week after the second treatment; T_6, 4 weeks after the second treatment; T_7, 12 weeks after the second treatment; N/A, not applicable.

Supplementary Table S7. *Comparison of hospitalization costs and length of stay between groups*.

	Group A (n = 31)	Group B (n = 29)	*P* value
Hospitalization costs, mean ± SDs	14817.12 ± 1702.41	14450.36 ± 1374.36	0.36
Length of stay, median (IQRs)	11 (2)	10 (3)	0.23

Abbreviations: IQRs, interquartile ranges.

Supplementary Table S8. *Comparison of incidences of adverse reactions between groups*.

Adverse Reactions	Group A (n = 31)	Group B (n = 29)	*P* value
Occurred	4 (12.90%)	2 (6.90%)	0.73
Did not occur	27 (87.10%)	27 (93.10%)	