Efficacy of Pulsed Radiofrequency or Short-Term Spinal Cord Stimulation for Acute/Subacute Zoster-Related Pain: A Randomized, Double-Blinded, Controlled Trial

Background: Postherpetic neuralgia (PHN) is the final stage of varicella zoster infection and a severe refractory neuropathic pain. Hence preventing transition of herpes zoster-related pain to PHN is a very important therapeutic principle for patients at an early stage, especially for older patients. Both pulsed radiofrequency (PRF) and short-term spinal cord stimulation (stSCS) have been proven to be effective to relieve acute/subacute zoster-related pain. However, which treatment could achieve better analgesic effects remains unclear.

Objectives: This study aimed to investigate the therapeutic efficacy and safety of PRF and stSCS in patients with acute/subacute zoster-related pain.

Study Design: Prospective, randomized, double-blinded study.

Methods: Ninety-six patients with acute/subacute zoster-related pain were equally randomized into 2 groups: PRF group and stSCS group. Patients in the different groups were treated with high-voltage, long-duration PRF or stSCS. The therapeutic effects were evaluated using a Numeric Rating Scale (NRS-11) and the 36-Item Short Form Health Survey (SF-36) at different time points. The average dose of pregabalin (mg/d) administrated at different time points was also recorded.

Results: The posttreatment NRS-11 scores in the 2 groups were significantly lower compared with baseline ($P < 0.001$). The NRS-11 scores in the stSCS group were significantly lower than those in the PRF group at 30 and 180 days after treatments ($P < 0.05$). The SF-36 scores of general health, social function, role-emotional, mental health, bodily pain, physical function, physical role, and vitality could be significantly improved at each time point after treatments in the 2 groups. Some SF-36 scores could be significantly improved at some time points in the stSCS group compared with the PRF group. The rescue drug (pregabalin) dosages were lower in the stSCS group than those in the PRF group at days 90 and 180 after treatments. There was no bleeding at the puncture site, infection, postoperative paresthesia, nerve injury, or any other serious adverse effects in either group.

Limitations: Single-center study, relatively small number of patients.

Conclusions: PRF and stSCS are both effective and safe therapeutic alternatives for patients with acute/subacute zoster-related pain, however, stSCS could achieve more pain relief and improvement of life quality compared with PRF.

Key words: Pulsed radiofrequency, short-term spinal cord stimulation, zoster-related pain, Numeric Rating Scale, 36-Item Short Form Health Survey
Postherpetic neuralgia (PHN) can be defined as neuropathic pain (NP) persisting more than 3 months after nervous system injury caused by the varicella-zoster virus (1-3). PHN is the most severe syndrome resulting from herpes zoster (HZ) and is a refractory chronic pain syndrome with a complex cause and pathogenesis, which is unclear by far (4,5). Effective therapeutic treatment for PHN remains largely obscure, hence early treatment and preventing the transition of HZ to PHN are essential strategies, which is in line with international perception concerning chronic pain management (6,7).

Pulsed radiofrequency (PRF) is a modified technique that delivers short pulses of high-frequency current to nervous tissue (8). PRF is usually believed to modulate the pain pathology with non- or minimal neural damage (9,10). Many animal studies have demonstrated that PRF is safe and effective treatment to reduce the NP (11,12). In clinical studies, PRF has also been widely proved to be effective for refractory NP, such as PHN, cervical or lumbar radicular pain, failed back surgery syndrome, and various peripheral neuralgia conditions (13-15).

Spinal cord stimulation (SCS) was first used by Shealy et al. (16) at Case Western Reserve University for the treatment of intractable cancer pain in 1967. With more than 50 years of development and accumulation, SCS has been well considered as an effective treatment of pain relief for a wide variety of etiologies, especially for NP (17-19). Our previous studies have certified that both short-term SCS (stSCS) (20) and PRF (15,21) could relieve acute/subacute zoster-related pain and reduce the incidence of PHN. Thus the aim of this study was to verify which treatment could be more effective for acute/subacute zoster-related pain.

METHODS

Study Patients

The current study was designed as a prospective, randomized, controlled, clinical trial conducted from April 26, 2019 to September 25, 2019. The study protocol was approved by the human ethics committee of the First Affiliated Hospital of China Medical University (No: 2018-308) and registered at chictr.org.cn (No: ChiCTR1900022586). An informed consent form was signed after all patients read it carefully.

Inclusion Criteria

Patients were included according to the following criteria: (1) patients were aged older than 60 years and whose HZ history was less than 90 days; (2) HZ affected the spinal nerves (cervical/thoracic/lumbar nerve); (3) Numeric Rating Scale (NRS-11) score 4 or greater; and (4) patients had been refractory to conventional therapies according to the international association for the study of pain guidelines (22) (such as antiepileptic drugs, opioids, antidepressants, and other physical treatments).

Exclusion Criteria

Patients were excluded for the following reasons: (1) refusal to participate in this trial; (2) poor general situation, unable to be treated; (3) coagulation disorders or applied anticoagulant; and (4) intellectual inability to complete the self-evaluation questionnaires.

Randomization and Sequence Generation

After inclusion and exclusion criteria were examined, 96 patients were assigned randomly into 2 groups through a computer-generated random allocation sequence: the PRF group in which high-voltage, long-duration PRF on dorsal root ganglion (DRG) was applied (n = 48), and the stSCS group in which stSCS was applied (n = 48) (Fig. 1). Patients in the 2 groups received corresponding treatments and follow-ups at different time points as shown in Fig. 2.

Description of PRF

All patients were in the prone position and received 3 L/min of oxygen with continuously monitored life signs after reaching the operating room. The therapeutic target area was determined by our previous study (21). Two 18-gauge (G) radiofrequency needles (21-G for cervical HZ) were carefully inserted via computed tomography (CT) guidance until the needle tip reached the upper edge of the intervertebral foramen and were subsequently connected to a PRF element (Fig. 3). The needle tip was moved slowly under the sensation testing mode (50 Hz, 0.3–0.5 V) to reach the target DRGs. After the ideal DRGs were attained, high-voltage and long-duration PRF with the basic settings of 42°C, 2 Hz, 20 ms, and 900 seconds was performed. The initial electric voltage (40 V) was then gradually increased until the patients could not tolerate the abnormal sensations (21). The individual maximal voltages ranged from 70 to 100 V until PRF treatment was terminated. High-voltage and long-duration PRF treatment was applied to patients twice on days 0 and 9 in the PRF group.
**Description of stSCS**

All patients were in the prone position and received 3 L/min of oxygen with continuously monitored life signs after reaching the operating room. A modified Tuohy needle was inserted into the epidural space under the guidance of C-arm in frontal and lateral positions. Then a 1 x 8 multicontact stimulation electrode was inserted through the needle and positioned until the tip of electrode reached an appropriate anatomic position guided by C-arm to achieve the best stimulation according to the patient’s statement (Fig. 3). Each patient was successfully implanted with only one electrode and obtained appropriate stimulation defined as “comfortable paresthesia covering at least 50% of the painful area.” (23) After implantation of the electrode, patients would receive a short-term electrical stimulation for 10 days.

**Blinding**

The PRF or stSCS procedures were performed by the same doctor. All follow-ups were performed by another investigator who did not know which treatment was applied to the patient. The instrument was operated by a nurse and she did not participate in any other therapeutic and follow-up activities.

**Drug Administration**

Patients were administered pregabalin before and after treatments for pain control in accordance with the pain degrees. Other analgesics were avoided. The dosage was increased or decreased according to the alteration of the pain severity.

**Outcome Measures**

**NRS-11**

The NRS-11 scores were evaluated pretreatment and in the morning on days 10, 30, 90, and 180 after treatments.

**The 36-Item Short Form Health Survey Score Evaluation**

The 36-Item Short Form Health Survey (SF-36) scores including general health, social function, role-emotional, mental health, bodily pain, physical function, physical role, and vitality were evaluated pretreatment and in the morning on days 10, 30, 90, and 180 after treatments.

**Average Pregabalin Dosage**

Pregabalin was administered orally once every 12 hours for pain control. The average dosages of preg-
balin (mg/d) were collected pretreatment and on days 10, 30, 90, and 180 after treatments.

**Side Effects**
Any side effects, including bleeding at the puncture site, infection, postoperative paresthesia, nerve injury, and other adverse reactions, were recorded on day 10 after treatments.

**Statistical Analysis**

**Sample Size**
In our pilot study, the effective rate of the peripheral nerve modulation in the test group was 88%, and the effective rate in the positive control group was 45%, so the difference between the effective rates in the 2 groups was 43%. Based on this information, we then calculated that the estimated sample number was at least 22 in each group, which provided 80% power and a level of statistical significance of 0.05 (α = 0.05).

**Data Analyses**
Numeric variables are expressed as mean ± standard deviation values, and categorical variables are described using the number of frequencies and percentages. To assess whether group differences were compatible with pure chance, exploratory tests were performed. Therefore all reported P values are descriptive. Associations of age with categorical variables were assessed by the 2-sample Wilcoxon test. Association of categorical variables were tested using the Fisher exact test. Statistical analysis was performed using the Statistical Package for Social Sciences Version 19.0 (IBM Corporation, Armonk, NY). A P value < 0.05 was considered to be statistically significant.

**RESULTS**

**Patient Demographics**
A total of 127 patients were initially examined, and 31 patients had to be excluded because of the following: 15 patients did not meet inclusion criteria, 7 patients declined to participate, and 9 patients for other reasons. Two patients in the PRF group and 2 patients in the stSCS group were dropped out within 180 days; one patient in the stSCS group survived less than 180 days. Hence the data of these 5 patients were excluded from the analysis (Fig. 1). The demographic characteristics of the patients, including age, gender, body weight, disease duration, and HZ location (cervical/thoracic/lumbar HZ) before treatment were similar between the 2 groups (Table 1).

**NRS-11**
There was no significant difference in NRS-11 scores before treatment in the 2 groups. After treatments, NRS-11 scores significantly declined in both groups at each time point (P < 0.001; Fig. 4), however, NRS-11 scores significantly declined on days 30 and 180 after treatment in the stSCS group compared with the PRF group (P < 0.05; Fig. 4).

**SF-36**
There was no significant difference in baseline SF-36 scores in the 2 groups. There were significant
improvements in the index scores, including general health, social function, role-emotional, mental health, bodily pain, physical function, physical role, and vitality, at each time point after treatment in the 2 groups \( (P < 0.001; \text{Fig. 5}) \). The scores of general health, social function, mental health, bodily pain, physical role, and vitality could be significantly improved at some time points in the stSCS group compared with the PRF group \( (P < 0.05; \text{Fig. 5}) \).

**Rescue Drug Dosage**

After treatments, the dosages of pregabalin administered significantly declined in both groups at each time point \( (P < 0.001; \text{Fig. 6}) \). The dosages were significantly lower in the stSCS group than those in the PRF group on days 90 and 180 after treatments \( (P < 0.05; \text{Fig. 6}) \).

**Side Effects**

No patient withdrew from the trial owing to adverse reactions during treatments. After treatments, there was no bleeding or infection at the puncture site, postoperative paresthesia, nerve injury, or any other serious adverse effects.

**Discussion**

Both PRF and stSCS could effectively relieve pain and significantly reduce the average dosage of pregabalin in patients with acute/subacute zoster-related pain. The results also exhibited that the 2 treatments could improve quality of life according to the increases of SF-36 scores. StSCS provided better analgesia and improvement of life quality than PRF treatment. No significant difference was observed in adverse reactions between the 2 groups.

After HZ infection, the latent virus activates and damages primary sensory neurons \( (24) \). Chronic inflammatory cell infiltration, cell dehydration, increased apoptosis, and other pathological changes may occur in the damaged sensory neurons, which produce ectopic discharges and play an important role in the genesis of NP \( (25,26) \). The DRG is an oval inflation of the dorsal root, which contains primary neurons of sensory afferents. Our previous research \( (21) \) and others \( (27) \) have suggested that PRF on DRGs can relieve symptoms of PHN, hence DRGs were chosen as the target of PRF treatment in this study.

There are numerous animal experiments and clinical research that demonstrated that PRF can achieve better pain relief on NP compared with other therapeutic methods \( (28,29) \). Although the detailed mechanisms are unclear by far, studies mainly exhibit that the analgesia of PRF is through the pulse electric current and the biological effects, including the effects on neurons, glial cells, and nerve fibers \( (30) \). PRF is a modified technology from conventional radiofrequency; the modulation of PRF on the nervous system might be one of the attributes for its analgesic effect with non- or minimal neural damage. Hence patients in the PRF group obtained significant pain relief and experienced significant improvement of life quality after treatment \( (P < 0.001) \).

SCS technology has developed greatly after its invention in part by the increasing prevalence of chronic NP. SCS generates electric fields that change the electrical potential across membranes near the electrode between metal contacts residing in the epidural space \( (31) \). Numerous clinical case series and prospective studies have shown that SCS is beneficial in patients with many different kinds of NP \( (32,33) \). In the current study,
Fig. 5. Significantly improved mean SF-36 scores after treatment; *P < 0.001 indicates pretreatment vs. posttreatment. #P < 0.05 indicates PRF group vs. stSCS group.
patients enrolled were at acute or subacute stages after HZ infection and obtained good pain relief after stSCS treatment ($P < 0.001$). These patients avoided pain from converting to PHN and implanting permanent SCS. This therapeutic strategy reflects that early treatment can achieve a remarkable effect.

In our previous study, patients obtained good pain relief after stSCS treatment in which mean durations were $9.33 \pm 2.77$ days, and there were no serious side effects during the entire follow-up period (20). Hence patients in the stSCS group had been applied a short-term electrical stimulation for 10 days. The Ma et al (33) study demonstrated that more than one PRF treatment for PHN could achieve better analgesic effect. Consistent with duration of stSCS treatment, 2 PRF treatments were administered early and late during treatment in the PRF group. Compared with the PRF group, patients in the stSCS group achieved better analgesic effect and more improvement of life quality ($P < 0.05$). This may be because of the following reasons: (1) acute/subacute zoster-related pain is NP, which is caused by peripheral nervous system dysfunction but mainly maintained by central nervous system sensitization. The target of the PRF were DRGs, which are a part of the peripheral nerve system, nevertheless the therapy target of the stSCS were dorsal horn neurons, which are senior sensory neurons compared with DRGs. We considered that more senior therapeutic targets may be a reason for better analgesic effect. (2) Patients in the stSCS group obtained 10 days of continuous neuromodulation on dorsal horn neurons within the electric field, but patients in the PRF group only obtained 30 minutes of neuromodulation during 2 treatments. Although the 2 treatments differed from each other in the mechanism of neural regulation, we believe that longer term neuromodulation may be another reason for better analgesic effect.

However, several limitations in this study should be addressed in future research. First, patients enrolled were from only one pain management center and the number of patients was relatively small. Second, the patients were followed up only for 180 days. Future study should be a research across multiple centers with a longer follow-up. Nevertheless, it was still demonstrated that stSCS was a more effective pain relief method than PRF.

**Conclusions**

PRF or stSCS could both effectively relieve pain for patients with acute/subacute HZ. Nevertheless, stSCS could provide better pain relief with less analgesics and improved quality of life than PRF treatment.

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**References**


