Background: Postherpetic neuralgia (PHN) occurs in 9% to 34% of herpes zoster (HZ) patients, and the incidence of PHN is positively correlated with age. A number of patients suffer from poor therapeutic effects or intolerable side effects and need to accept minimally invasive analgesia.

Objectives: This study aimed to investigate the effects of spinal cord stimulation (SCS) and pulsed radiofrequency (PRF) on the treatment of elderly patients with HZ-related pain persisting beyond the acute phase.

Study Design: A prospective, randomized-controlled trial.

Setting: Research was conducted at the National Pain Management and Research Center, China-Japan Friendship Hospital (Beijing, China).

Methods: We selected 63 patients aged over 50 years with zoster-related pain of 1 to 6 months onset. They were randomly divided into an SCS group and a PRF group. In the SCS group, the stimulus electrodes were placed in the affected spinal ganglion segment of the epidural space for 2 weeks. In the PRF group, the radiofrequency needle was percutaneously punctured in the affected dorsal root ganglion. The main outcome measures were the Numeric Rating Scale (NRS-11) score, response rate, and complete remission rate. The secondary endpoint was defined as the use of analgesics and calcium channel antagonists.

Results: The NRS-11 score in the SCS group decreased to 2.90 ± 1.83 (1 week post operation) and 4.37 ± 2.43 (24 weeks post operation), while that in the PRF group decreased to 3.13 ± 1.78 and 4.23 ± 2.64, respectively (compared with baseline, P < .001); there was no significant difference between the 2 groups (P > .05). The effective rate of pain management was in the range of 56.67% to 81.25%, and the complete pain relief rate ranged from 37% to 71%. The number of patients still using analgesics and calcium channel antagonists after operation were significantly less than those pre-operation (P < .001). Univariate and multivariate logistic regression analyses showed that the operation method, age, gender, and course of disease did not affect surgical efficacy.

Limitations: The main limitation of this study is that all the cases were from the same center.

Conclusion: It therefore can be concluded that SCS and PRF can effectively relieve PHN.

Key words: Spinal cord stimulation, pulsed radiofrequency, postherpetic neuralgia

Postherpetic neuralgia (PHN) refers to pain of more than 4 points (0-10 points) in the nerve innervation area after 90 days of herpes zoster (HZ) (1). Oxman et al (2-4) have shown that the range of incidence of HZ is 3.4% to 5.3%, and the incidence of HZ among people over 50 years old is remarkably increasing.
PHN occurs in 9% to 34% of patients with HZ, and the incidence of PHN is positively correlated with age (5,6). According to statistics, 3% to 22% of patients with HZ have PHN for 3 months, and 4% to 13% of patients have PHN for 6 months (7,8). PHN is a typical neuropathic pain persisting for months to years after resolution of the HZ. Calcium channel antagonist combined with analgesic is the most effective therapeutic approach for neuropathic pain (9). However, a number of patients still suffer from poor therapeutic effects or intolerable side effects and need to accept minimally invasive analgesia.

Spinal cord stimulation (SCS) and pulsed radiofrequency (PRF) are commonly used neuromodulation techniques in the treatment of patients with PHN, yet only a limited number of prospective randomized controlled studies on these 2 methods exist. In the present study, a prospective, randomized controlled study was undertaken to assess the efficacy of SCS and PRF in the treatment of zoster-related pain persisting beyond the acute phase in elderly patients.

**Methods**

**Inclusion criteria**

Inclusion criteria were as follows: age ≥ 50 years old, with HZ-related pain persisting for 30 to 180 days; the affected nerve was a spinal nerve (excluding cranial nerve); Numeric Rating Scale (NRS-11) score ≥ 4; patient utilizing antiviral drugs, neurotrophic drugs (methylcobalamin or neurotropin), and calcium channel antagonists (pregabalin or gabapentin). Exclusion criteria were as follows: history of allergy to local anesthetics; severe heart, lung, brain, liver, and kidney diseases; abnormal bleeding and coagulation; having mental disorders. This study was conducted in accordance with the Helsinki Declaration, and the study protocol was approved by an independent ethics committee of the China-Japan Friendship Hospital. All patients provided written informed consent for the operation as well. All patients underwent a detailed medical history and physical examination.

**Surgical Instruments**

Surgical instruments used included the SCS kit: stimulus electrode and electric pulse generator (1*8 compact 3778-75; Medtronic, Minneapolis, MN); PRF instrument: COSMAN G4 (Cosman Medical, Burlington, MA); and radiofrequency needle (Stericlin, Emmendingen, Germany).
**Sample Size and Statistical Analysis**

According to a previous study, the effective rate of PRF was 42%, and the effective rate of SCS was 64%. We then calculated that the estimated sample number was at least 28 in each group, which provided 75% power and a level of statistical significance of .05 (α = .05). SPSS Version 18.0 (IBM Corporation, Armonk, NY) was used for statistical analysis. In addition, the Student t test was used for comparing normally distributed data between the groups. Data were presented as mean ± standard deviation (SD). The log-rank sum test was used for comparing data with skewed distribution. The chi-square test was used to compare count data. All statistical analyses were conducted based on the intention-to-treat (ITT) principle. Patients who received treatment and completed the first follow-up were included in the statistical analysis. A $P$ value < .05 was considered statistically significant.

**RESULTS**

**Patients’ Basic Clinical Data**

From January 2018 to January 2019, 167 patients with HZ-related pain were recruited from the National Pain Management and Research Center at the China-Japan Friendship Hospital (Beijing, China). In this study, 104 patients were excluded: 23 patients aged under 50 years old, 27 patients who had fewer than 30 days of blistering or more than 180 days, 18 patients who had serious cardiovascular or cerebrovascular diseases, and 2 patients who had local infection. Moreover, 34 patients refused to accept operation, while 63 patients met the inclusion criteria. None of the patients had been previously vaccinated with the HZ vaccine. Eligible patients were randomly divided into the SCS group ($n = 31$) and the PRF group ($n = 32$). One case was lost in the SCS group, and 2 cases in the PRF group underwent RF thermocoagulation (RFT) one month later. The flowchart detailing the follow-up procedure is displayed in Fig. 1.

The results showed that 63 patients were aged 50 to 90 years old, with an average age of 65.33 ± 9.02 years. There were 22 patients with hypertension, 18 patients with diabetes, 9 patients with immune system diseases, 8 patients with malignant tumors, and 9 patients with a long-term history of glucocorticoid. The commonly involved nerves were thoracic nerve in 39 cases, cervical nerve in 16 cases, and lumbosacral nerve in 8 cases. The average duration of zoster-related pain was 2.82 ± 1.79 months. All patients preoperatively used analgesics

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**Fig. 1. Flow chart of follow-up procedure.**

Abbreviations: PRF, pulsed radiofrequency; SCS, spinal cord stimulation
Table 1. The patients’ basic clinical data.

<table>
<thead>
<tr>
<th></th>
<th>SCS group (n = 31)</th>
<th>PRF group (n = 32)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (men/women)</td>
<td>13/18</td>
<td>18/14</td>
<td>.745</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>66.53 ± 10.81</td>
<td>65.33 ± 9.10</td>
<td>.626</td>
</tr>
<tr>
<td>Complication</td>
<td></td>
<td></td>
<td>.548</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>13 (41.9)</td>
<td>5 (15.6)</td>
<td></td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>7 (22.6)</td>
<td>15 (48.4)</td>
<td></td>
</tr>
<tr>
<td>Immune diseases (%)</td>
<td>7 (22.6)</td>
<td>2 (6.3)</td>
<td></td>
</tr>
<tr>
<td>Malignant tumors (%)</td>
<td>4 (12.9)</td>
<td>4 (12.5)</td>
<td></td>
</tr>
<tr>
<td>Glucocorticoid history (%)</td>
<td>5 (16.1)</td>
<td>4 (12.5)</td>
<td>.937</td>
</tr>
</tbody>
</table>

Involved nerve

<table>
<thead>
<tr>
<th></th>
<th>SCS group (n = 31)</th>
<th>PRF group (n = 32)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical nerve (%)</td>
<td>3 (9.7)</td>
<td>13 (40.6)</td>
<td></td>
</tr>
<tr>
<td>Thoracic nerve (%)</td>
<td>25 (80.6)</td>
<td>14 (43.8)</td>
<td></td>
</tr>
<tr>
<td>Lumbosacral nerve (%)</td>
<td>3 (9.7)</td>
<td>5 (15.6)</td>
<td></td>
</tr>
<tr>
<td>Course of disease (month)</td>
<td>3.27 ± 1.80</td>
<td>2.31 ± 1.54</td>
<td>.073</td>
</tr>
<tr>
<td>NRS-11 score pre-operation</td>
<td>8.13 ± 1.07</td>
<td>7.73 ± 1.31</td>
<td>.236</td>
</tr>
</tbody>
</table>

Abbreviations: NRS, Numeric Rating Scale; PRF, pulsed radiofrequency; SCS, spinal cord stimulation

Table 2. NRS-11 score pre- and post operation.

<table>
<thead>
<tr>
<th></th>
<th>SCS group (n = 31)</th>
<th>PRF group (n = 32)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-operation</td>
<td>8.13 ± 1.07</td>
<td>7.73 ± 1.31</td>
<td>.236</td>
</tr>
<tr>
<td>1 wk post operation</td>
<td>2.90 ± 1.83*</td>
<td>3.13 ± 1.78*</td>
<td>.672</td>
</tr>
<tr>
<td>4 wks post operation</td>
<td>4.07 ± 2.18*</td>
<td>4.47 ± 2.22*</td>
<td>.483</td>
</tr>
<tr>
<td>12 wks post operation</td>
<td>4.20 ± 2.27*</td>
<td>4.43 ± 2.37*</td>
<td>.728</td>
</tr>
<tr>
<td>24 wks post operation</td>
<td>4.37 ± 2.43*</td>
<td>4.23 ± 2.64*</td>
<td>.183</td>
</tr>
</tbody>
</table>

*compared with pre-operation P < .001

Abbreviations: SCS, spinal cord stimulation

Discussion

The mechanism of action of SCS is still speculative. By stimulating the dorsal horn of the spinal cord, the signal transduction of neuro-

(nonsteroidal anti-inflammatory drugs or opioids) and calcium channel antagonists (gabapentin or pregabalin). Two patients in the PRF group stopped calcium channel antagonists before operation because of adverse reactions. There was no statistical difference in the patients’ basic clinical data between the 2 groups, as shown in Table 1.

There was no significant difference in NRS-11 scores between the 2 groups pre-operation. The pain scores at 1, 4, 12, and 24 weeks post operation were significantly lower than those pre-operation (P < .001), while there was no significant difference between the 2 groups (P > .05) (Table 2, Fig. 2). The effective rate of pain treatment was in the range of 56.67% to 81.25%, and the complete relief rate of pain ranged from 37% to 71% (Fig. 3).

The number of patients who used analgesics and calcium channel antagonists in the 2 groups dramatically decreased from 4 to 24 weeks post operation (P < .001), while there was no significant difference between the 2 groups (P > .05) (Fig. 4). Univariate logistic regression analysis showed that gender, age, course of disease, and operation method had no influence on surgical efficacy. After adjusting for multiple factors, no significant difference was noted (Table 3).

Images of SCS and PRF of the dorsal root ganglion (DRG) during operation are shown in Fig. 5. For operative complications, there were 2 cases of pneumothorax in the PRF group, whereas no complication in the SCS group was observed.
pathic pain can be reduced; thus the occurrence of neuroplasticity changes can be decreased and central sensitization is accordingly suppressed (11). The peripheral mechanism is to reduce the release of harmful neurotransmitters from peripheral nerves and inhibit peripheral nerve sensitization. In addition, the occurrence of PHN is related to the dehydration of DRG and Wallerian degeneration. The electrical stimulation promotes nerve cell regeneration and stimulates Schwann cells to express neurotrophic factors. Electric field can also electrolyze microtissue proteins, release vasoactive substances, cause vasodilation through axon reflex and segmental reflex, and improve local blood flow around the nerve, which is of great significance for nerve repair (12). Electric field can cause ion movement, regulate the distribution of intracellular and extracellular ions, reduce the influx of calcium ions, stabilize the intracellular environment, block neuronal apoptosis, and play a protective role as well (13).

In the present study, a prospective randomized controlled trial was conducted to confirm that the pain score was significantly reduced one week after SCS treatment, with an effective rate of 80.65%. The pain score slightly increased after 4 weeks, which was related to the discontinuation of analgesics and calcium channel antagonists in a number of patients. The analgesic effect lasted for 24 weeks. Three other retrospective studies also proved that VAS scores at post-SCS, 2 weeks, and 1, 3, 6, 9, and 12 months were significantly decreased compared with the baseline score after short-term SCS treatment (14-16).

The DRG is an important target area for the treatment of PHN. Furthermore, PRF with DRG can often be used for PHN treatment (17,18). PRF can form a high voltage environment near nerve tissue by pulsed current, influencing ion channel function and adenosine 5-triphosphate (ATP) metabolism of sensory nerve. PRF can inhibit excitatory afferent of sympathetic nerve C fibers, block pain conduction, and does not cause nerve damage.

Kim et al (19) revealed that DRG PRF was more effective than continuous epidural block in treating zoster-related pain after the acute phase of zoster. From a retrospective comparative study by Kim et al (20), the degree of pain reduction was significantly higher in the early PRF group and more patients discontinued their medication in the early PRF group. It was also reported in the literature that satisfactory analgesia was achieved by PRF during 12 weeks in both the DRG and intercostal nerve (21,22).
Considering that the target of PHN is the DRG, PRF was directly applied to the DRG in this study. It was further confirmed that the best time to treat PHN is from 30 to 180 days post onset of HZ. It should be noted that when C8-T2 is involved, the intervertebral foramen of lateral x-ray images cannot be clearly displayed due to scapular shielding. There may be some deviations in the accuracy of DRG PRF, while SCS can still precisely locate and has certain advantages. The disadvantage of SCS is its high price.

Univariate and multivariate logistic regression analyses showed that gender, age, course of disease, and operation method had no influence on the surgical efficacy. Results indicated that patients over 50 years of age with moderate or severe pain should be treated with SCS or PRF therapy within 30 to 180 days of onset.

The main limitation of this study is that all 63 cases were from the same center, and there were a relatively small number of patients. A multicenter study with a larger sample needs to be carried out in the future. This prospective randomized controlled study confirmed for the first time that SCS and PRF can significantly alleviate PHN. The 6-month effective rate

Table 3. Univariate and multivariate logistic regression analyses of gender, age, course of disease, operation method, and surgical outcome.

<table>
<thead>
<tr>
<th></th>
<th>Univariate regression</th>
<th></th>
<th></th>
<th></th>
<th>Multivariate regression</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B value</td>
<td>Standard error</td>
<td>P value</td>
<td>95% CI</td>
<td>B value</td>
<td>Standard error</td>
<td>P value</td>
<td>95% CI</td>
</tr>
<tr>
<td>Gender</td>
<td>0.396</td>
<td>0.479</td>
<td>.412</td>
<td>-.563-.1355</td>
<td>0.402</td>
<td>0.489</td>
<td>.415</td>
<td>-.578-.1382</td>
</tr>
<tr>
<td>Age</td>
<td>0.012</td>
<td>0.027</td>
<td>.466</td>
<td>-.041-.066</td>
<td>0.014</td>
<td>0.027</td>
<td>.617</td>
<td>-.041-.068</td>
</tr>
<tr>
<td>Operation method</td>
<td>-0.633</td>
<td>0.470</td>
<td>.183</td>
<td>-1.375-.0308</td>
<td>-0.812</td>
<td>0.579</td>
<td>.167</td>
<td>-1.973-.150</td>
</tr>
<tr>
<td>Course of disease</td>
<td>-0.025</td>
<td>-0.139</td>
<td>.860</td>
<td>-0.304-.254</td>
<td>-0.016</td>
<td>0.141</td>
<td>.909</td>
<td>-0.299-.267</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval

Fig. 4. Patients’ use of analgesics and calcium channel antagonists.
*compared with pre-operation P < .001
Abbreviations: CCB, calcium channel antagonists; PRF, pulsed radiofrequency; SCS, spinal cord stimulation
was in the range of 60% to 70%, and the complete remission rate was within 43% to 47%. Therefore, for patients with HZ-related pain persisting beyond the acute phase, especially those with high-risk factors such as diabetes, hypertension, cancer, kidney disease, and glucocorticoid history (23), SCS or PRF treatment should be given to help reduce the incidence of sequelae neuralgia.

Acknowledgments
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References