Retrospective Study

Pulsed Radiofrequency to the Dorsal Root Ganglion in Acute Herpes Zoster and Postherpetic Neuralgia

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Background: Latent varicella zoster virus reactivates mainly in sensory ganglia such as the dorsal root ganglion (DRG) or trigeminal ganglion. The DRG contains many receptor channels and is an important region for pain signal transduction. Sustained abnormal electrical activity to the spinal cord via the DRG in acute herpes zoster can result in neuropathic conditions such as postherpetic neuralgia (PHN). Although the efficacy of pulsed radiofrequency (PRF) application to the DRG in various pain conditions has been previously reported, the application of PRF to the DRG in patients with herpes zoster has not yet been studied.

Objectives: The aim of the present study was to compare the clinical effects of PRF to the DRG in patients with herpes zoster to those of PRF to the DRG in patients with PHN.

Study Design: Retrospective comparative study.

Setting: University hospital pain center in Korea.

Methods: The medical records of 58 patients who underwent PRF to the DRG due to zoster related pain (herpes zoster or PHN) were retrospectively analyzed. Patients were divided into 2 groups according to the timing of PRF after zoster onset: an early PRF group (within 90 days) and a PHN PRF group (more than 90 days). The efficacy of PRF was assessed by a numeric rating scale (NRS) and by recording patient medication doses before PRF and at one week, 4 weeks, 8 weeks, and 12 weeks after PRF.

Results: Pain intensity was decreased after PRF in all participants. However, the degree of pain reduction was significantly higher in the early PRF group. Moreover, more patients discontinued their medication in the early PRF group, and the PRF success rate was also higher in the early PRF group.

Limitations: The relatively small sample size from a single center, short duration of review of medical records, and the retrospective nature of the study.

Conclusions: PRF to the DRG is a useful treatment for treatment-resistant cases of herpes zoster and PHN. Particularly in herpes zoster patients with intractable pain, application of PRF to the DRG should be considered for pain control and prevention of PHN.

Key words: Pulsed radiofrequency, dorsal root ganglion, herpes zoster, postherpetic neuralgia

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Herpes zoster is a viral infection resulting from the reactivation of the latent varicella zoster virus (VZV). The lifetime prevalence of herpes zoster is about 30% (1). Postherpetic neuralgia (PHN) is the most common complication of herpes zoster and has an estimated incidence of 12.5% of all patients with zoster aged > 50 years. The incidence of PHN also increases sharply with age (2).

Reactivation of the dormant VZV initiates in sensory ganglia such as the dorsal root ganglion (DRG) or trigeminal ganglion. As intraganglionic spreading of the virus occurs, newly synthesized viral particles are transported in both peripheral and central directions, causing neuronal damage (3-6).

If an appropriate degree of pain reduction is not established in the acute phase of herpes zoster, the risk of PHN development is increased (7,8). Although there is no definite consensus regarding the discriminative time point of PHN, pain that persists for more than 90 days after the onset of acute zoster rash is generally considered to be PHN (1,2,9).

To overcome sustained nociceptive input in the acute phase of herpes zoster, somatic blocks such as an epidural block can be applied. However, the efficacy of epidural blocks for the prevention of PHN is controversial (10,11). Moreover, the efficacy of other interventions in the PHN period also lacks sufficient supporting data (12,13). Conventional interventions with local anesthetics and steroids might be not sufficient to achieve long-term pain reduction in chronic neuropathic conditions such as PHN or in acute herpes zoster with severe neuronal damage.

Persistent intractable pain in patients with herpes zoster, despite the use of appropriate medical treatment and an aggressive nerve block (e.g., an epidural block), is a challenging condition for physicians.

Pulsed radiofrequency (PRF) is a variation of thermal radiofrequency in which pulsed energy waves are applied at temperatures no greater than 42°C and generating electromagnetic fields (14,15). This procedure has been shown to be safe, with minimal risk of thermal injury or neuronal damage. Moreover, no complications (e.g., thermal or nerve injuries) have been reported in the context of PRF (16,17). PRF is being increasingly used for conditions with intractable neuropathic pain such as trigeminal neuralgia (18,19), musculoskeletal pain conditions (20,21), and chronic cervical and lumbosacral pain that is resistant to conventional treatment (22-24).

Regarding herpes zoster-related pain, several studies have been published. One focused on PRF to the intercostal nerve (25), and the other focused on PRF to the peripheral branches of the trigeminal nerve (26).

The DRG contains many receptor channels and is an essential location for nociceptive signaling. The proximal terminal ending of the nerve cell body of the DRG extends to the spinal cord dorsal horn (27). Sustained abnormal electrical activity to the spinal cord via the DRG in acute herpes zoster can result in neuropathic processes such as central sensitization and increases the risk of PHN development. Therefore, the DRG is a high priority target for treatment of zoster-related pain. The effects of PRF on the DRG in patients with PHN have been reported (28). However, the application of PRF to the DRG in patients with herpes zoster has not yet been described.

We retrospectively evaluated the clinical effects of PRF on the DRG in patients with herpes zoster and patients with PHN.

Methods

Participants

Medical records were retrieved for all patients who underwent PRF due to zoster-related pain (acute herpes zoster or PHN) between January 2010 and March 2016. For this retrospective analysis, we only included the medical records of patients in this group who underwent PRF on the DRG from the cervical to the lumbosacral level.

Patients who underwent PRF of the trigeminal nerve and patients who were lost to follow-up before 12 weeks after PRF were excluded from the present analysis.

Permission to conduct this study was obtained from the Institutional Ethics Committee of Daejeon St. Mary's Hospital, Republic of Korea (DC16RISI0067).

Procedure

The patients who visited our pain center with moderate to severe zoster-related pain generally underwent an epidural block to the involved level. PRF was conducted on the DRG of the involved level in cases for which conventional blocks achieved only temporary pain reduction. All PRF procedures were conducted by physicians experienced in pain management (ED Kim, DH Jo).

For the procedure, the patient was placed in a prone position on a translucent operation table. A fluoroscope was placed obliquely toward the ipsilateral side. A 22-gauge 10-cm electrode with a 10-mm active tip (Radionics Inc., Burlington, MA, USA) was inserted adjacent to the DRG with fluoroscopic guidance. The needle tip position was adjusted so that it was inferior to the pedicle in the anteroposterior view and positioned in the posterocranial portion of the intervertebral foramen in the lateral view of the fluoroscopic image (Fig. 1).

Sensory stimulation with 50 Hz of current was

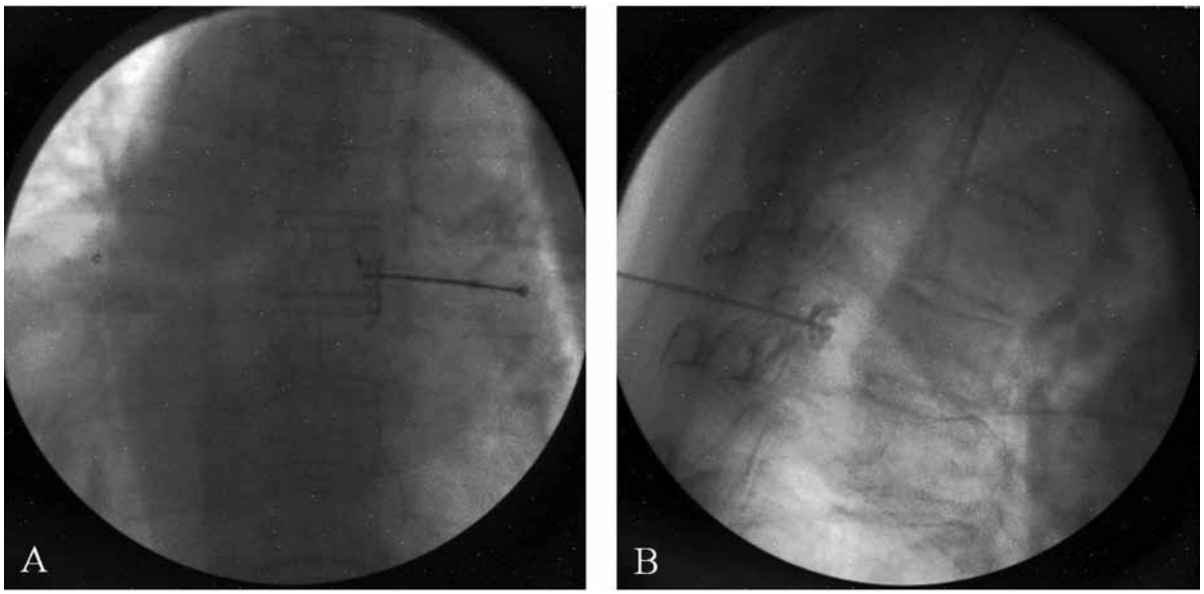


Fig. 1. *Fluoroscopic images of pulsed radiofrequency to the dorsal root ganglion. A: anteroposterior (AP) view. B: lateral view.*

applied to determine the correct needle electrode position. If a tingling sensation was perceived in the involved dermatome at less than 0.5 V, the needle electrode was considered to be in the appropriate position. After confirming the needle position, PRF was conducted for 360 seconds at 42°C with 20 milliseconds current, 2 Hz, 45 V. Impedance was maintained at less than 500 Ω throughout the procedure.

Data Collection

The following data were collected from medical records and analyzed: age; gender; targeted DRG level; days from zoster onset to PRF; type(s) of epidural blocks before PRF; numerical rating scale (NRS) before PRF; NRS at one week, 4 weeks, 8 weeks, and 12 weeks after PRF; and doses of anticonvulsants and analgesics before PRF and at one week, 4 weeks, 8 weeks, and 12 weeks after PRF.

Outcome Measure

We divided the patients who underwent PRF on the DRG for zoster-related pain into 2 groups. The first group included patients who underwent PRF within 90 days after zoster onset (early PRF group). The second group included patients who underwent PRF more than 90 days after zoster onset (PHN PRF group).

The analgesic efficacy of PRF on the DRG was assessed by NRS and patient consumption of anticonvulsants and analgesics. To facilitate analysis, participant doses of anticonvulsants and analgesics were converted to pregabalin-equivalent doses (29,30) and oral morphine-equivalent doses (31), respectively.

The NRS and doses of anticonvulsants and analgesics of the early PRF group were compared to those of the PHN PRF group at the following time points: before PRF and one week, 4 weeks, 8 weeks, and 12 weeks after PRF. The numbers of patients who discontinued medication due to sufficient pain reduction were also compared between the 2 groups.

We also compared the success rate of PRF between the groups. Success was defined as a ≥ 50% decrease in the 12-week NRS compared with the pre-PRF NRS.

Statistical Analysis

Data are presented as mean ± standard deviation (SD) for continuous variables.

Data normality was evaluated using the Kolmogorov-Smirnov test. The Mann-Whitney U test or the independent t test was used to compare the outcomes between the 2 groups for continuous variables, whereas the Chi square test or Fisher's exact test was used for categorical variables. Repeated measures analysis of variance was used to assess changes of pain intensity and medication doses over time. All data were

analyzed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA), and *P*-values < 0.05 were considered statistically significant.

Results

A total of 83 patients underwent PRF due to zoster-related pain. Thirteen patients underwent PRF to the peripheral branches of the trigeminal nerve, and 10 patients were lost to follow-up before 12 weeks after PRF on the DRG, even in the absence of satisfactory pain reduction. Moreover, 2 patients had insufficient medical records. After exclusion of these patients, the medical records of 58 patients were analyzed. Among these, 29 underwent DRG PRF within 90 days of zoster onset (early PRF group), and another 29 patients underwent the procedure more than 90 days after zoster onset, in the PHN period (PHN PRF group) (Fig. 2).

Before undergoing PRF on the DRG, all participants underwent a transforaminal epidural block. Twenty-four patients underwent additional continuous epidural catheterization.

No demographic data analyzed, including age, gender, involved dermatome, history of underlying disease, and types of analgesics, showed a significant difference between the 2 groups. The pre-PRF NRS of the early PRF group and the PHN PRF group were 6.035 ± 0.944 and 5.897 ± 0939, respectively; these scores were not significantly different (*P* = 0.579) (Table 1).

The NRS of both groups decreased significantly over time. However, the NRS of the early PHN group were significantly lower than those of the PHN PRF group at all time points after the procedure (Fig. 3).

The doses of anticonvulsants and analgesics did not change significantly over time (Fig. 4A and B). The prescribed doses of anticonvulsants in the PHN PRF group were higher than those in the early PRF group at one week and 4 weeks after the procedure and the prescribed doses of analgesics in the PHN PRF group were higher than those in the early PRF group at all time points, with the exception of 12 weeks after the procedure. However, more patients discontinued their anticonvulsants in the early PRF group than in the PHN PRF group, starting at 8 weeks post-PRF. More patients also discontinued their analgesics in the early PRF group

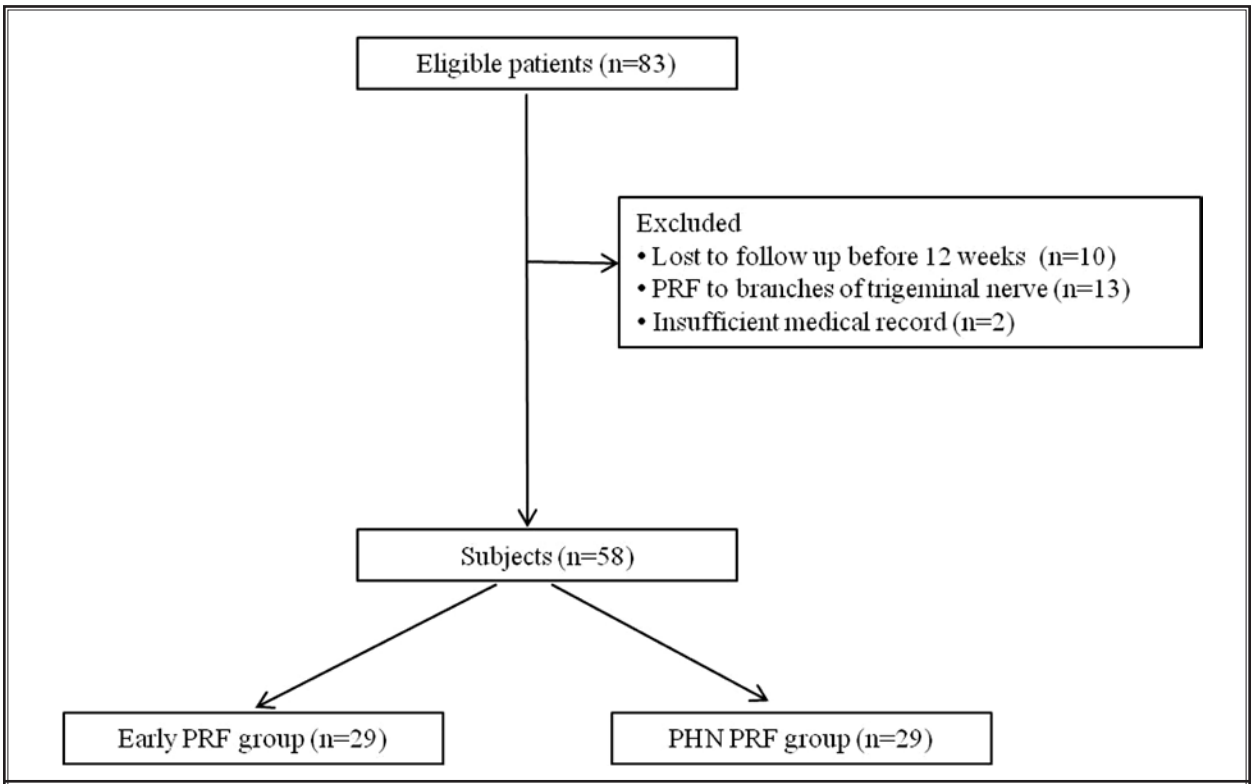
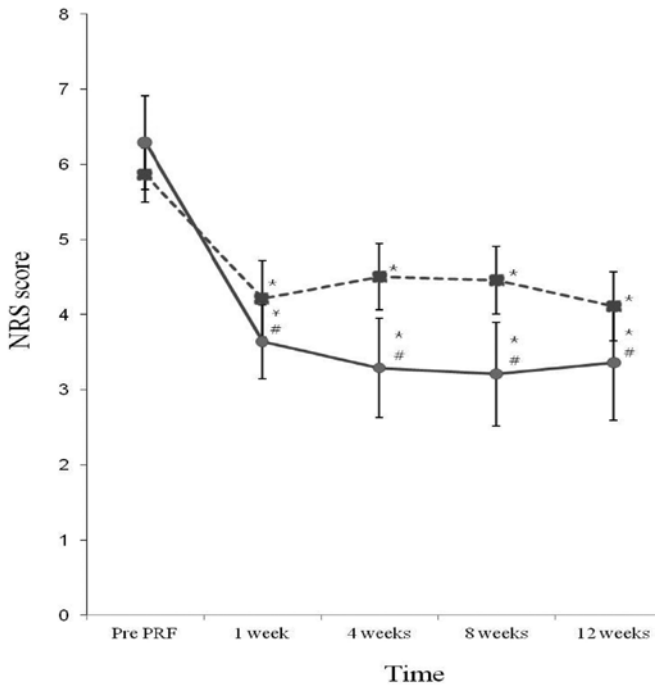


Fig. 2. *Flow diagram of the study participants.*

Table 1. *Patient demographic data*.

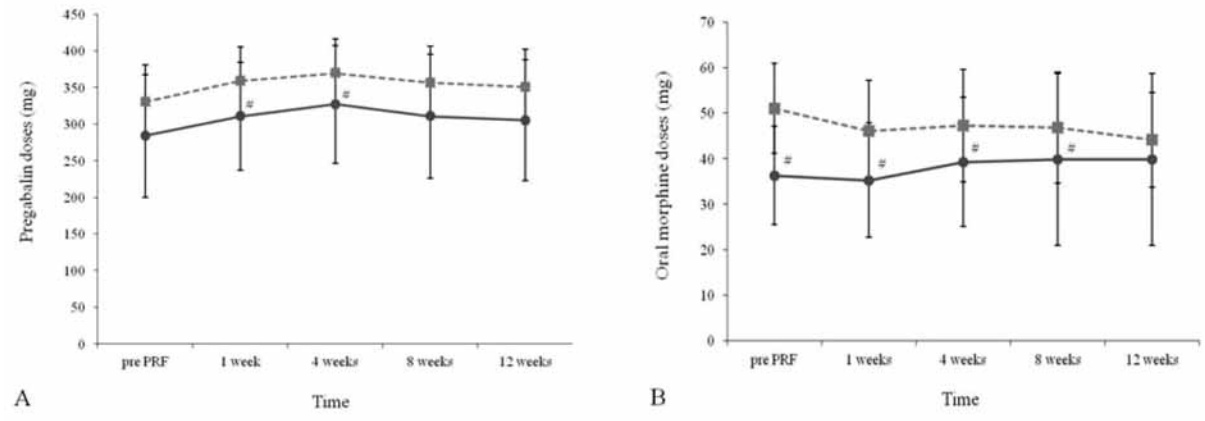
	Early PRF group	PHN PRF group	*P*-value
Age, years, mean ± SD	63.517 ± 8.428	67.620 ± 10.611	0.109
Gender, n, male/female	12/17	17/12	0.294
Involved dermatome, n			
Cervical, n	4	0	0.168
Thoracic, n	22	26	
Lumbosacral, n	3	3	
Underlying disease, n			
Hypertension (HTN), n	7	6	0.709
Diabetes mellitus (DM), n	7	6	
HTN & DM, n	4	2	
None, n	11	15	
NRS before PRF, mean ± SD	6.035 ± 0.944	5.897 ± 0939	0.579
Epidural catheterization before PRF, n	9	15	0.182
Analgesics at pre-PRF, n			
Tramadol/acetaminophen combination tablet only, n	17	14	0.171
Tramadol only, n	4	0	
Tramadol/acetaminophen combination tablet with opioid, n	5	9	
Tramadol with opioid, n	1	2	
Opioid only, n	2	4	

PRF: pulsed radiofrequency
PHN: postherpetic neuralgia



Both groups showed significant changes in the NRS over time. However, the NRS exhibited significantly greater reduction in the early PRF group compared with the PHN PRF group. Dotted line with square box and solid line with circle box indicate NRS changes in PHN PRF group and early PRF group, respectively.
NRS: numerical rating scale
PRF: pulsed radiofrequency
PHN: postherpetic neuralgia
*: $P < 0.05$ compared to the pre-PRF score.
#: $P < 0.05$ compared to the PHN PRF group.

Fig. 3. *Changes in NRS after PRF.*



A: dose changes of anticonvulsants
B: dose changes of analgesics
Dotted line with square box and solid line with circle box indicate dose changes of medications in PHN PRF group and early PRF group, respectively.
Doses of anticonvulsants and analgesics are expressed as pregabalin-equivalent doses and oral morphine-equivalent doses, respectively.
Doses of both medications were generally higher in the PHN PRF group; no significant changes in doses occurred over time in either group.
PRF: pulsed radiofrequency
PHN: postherpetic neuralgia
#: $P < 0.05$ compared to the PHN PRF group.

Fig. 4. *Changes in doses of prescribed medications after PRF.*

Table 2. *Numbers of patients who were able to discontinue the prescribed medication.*

	Anticonvulsants			Analgesics		
	Early PRF group (n = 29)	PHN PRF group (n = 29)	*P*-value	Early PRF group (n = 29)	PHN PRF group (n = 29)	*P*-value
Pre-PRF, n (%)	3 (10.3)	0 (0)	0.237	7 (24.1)	4 (13.7)	0.504
1 week, n (%)	3 (10.3)	0 (0)	0.237	10 (34.4)	2 (6.8)	0.010*
4 weeks, n (%)	4 (13.7)	0 (0)	0.112	13 (44.8)	2 (6.8)	0.002*
8 weeks, n (%)	11 (37.9)	1 (3.4)	0.002*	17 (58.6)	5 (17.2)	0.001*
12 weeks, n (%)	15 (51.7)	1 (3.4)	< 0.0001#	21 (72.4)	5 (17.2)	< 0.0001#

PRF: pulsed radiofrequency . PHN: postherpetic neuralgia. *: $P < 0.05$. #: $P < 0.0001$.

Table 3. *Success rates of PRF.*

	Early PRF group (n = 29)	PHN PRF group (n = 29)	*P*-value
Success of PRF, n (%)	24 (82.7)	5 (17.2)	< 0.0001#

PRF: pulsed radiofrequency. PHN: postherpetic neuralgia. #: $P < 0.0001$

at all time points after PRF than in the PHN PRG group (Table 2).

The success rate of PRF was significantly higher in the early PRF group than in the PHN PRF group (82.7% vs 17.0%, $P < 0.0001$) (Table 3).

Discussion

In the present retrospective analysis, the NRS of both groups were significantly decreased over time. However, greater pain reduction was achieved in the early PRF group compared with the PHN PRF group at all time points after PRF.

In patients with herpes zoster, application of PRF to the DRG can reduce signal transduction to the central nervous system by modulating nociceptive fibers. As a result, further neuropathic processes can be blocked before serious neuropathic conditions develop.

Although the PHN PRF group showed a significant decrease in NRS over time, the PRF success rate was

much lower in this group. Many cases of PHN exhibit structural reorganization at the level of the spinal cord dorsal horn (32,33). PRF on the DRG would be expected to be less effective in such conditions, which could explain the superior clinical outcomes in the early PRF group in this study.

A natural healing process of acute herpes zoster might be another explanation for the superior clinical outcomes of the early PRF group in our study. However, patients in the early PRF group showed poor responses to commonly used medical treatments including antiviral agents, anticonvulsants, and analgesics. Moreover, patients in this group showed only temporary responses to epidural blocks and even to continuous epidural catheterization for several weeks. The pre-PRF NRS of the early PRF group was 6.035 ± 0.944 after these conventional treatments. Thus, we believe it to be unlikely that the participants in the early PRF group experienced natural regression of pain.

PRF application to the DRG causes minimal tissue damage at the ultrastructural level (34), and cellular stress appears to be induced only in small A δ and C fibers (35). Recent studies have shown that PRF upregulates c-fos expression (36,37) and increases synaptic changes in transmission (38). These mechanisms may induce neuroplastic changes that could contribute to the long-term therapeutic effects of PRF.

In the present study, the prescribed doses did not change significantly over time for the patients who continued to take medication. However, the NRS consistently decreased over time. The decreased need for medication dose escalation also supports the long-term analgesic effect of PRF on the DRG. Since the early PRF group exhibited a significantly higher rate of medication discontinuation, the analgesic effect of PRF appears to be more profound in patients with herpes zoster.

Moreover, in our clinical experience, many participants reported that they self-decreased their medication doses. The present study was a retrospective analysis dependent on chart review; therefore, there may have been discrepancies between the actual doses taken and the prescribed doses recorded in the medical charts. This is a limitation of our study.

Other limitations of our study are its relatively small sample size and short duration of review of medical records. Further long-term observations will be needed to determine the effect duration of PRF on the DRG. However, to the best of our knowledge, PRF on the DRG is not generally performed in the acute phase of herpes zoster. Our analysis is the first study of PRF on the DRG in patients with herpes zoster.

Conclusion

In conclusion, PRF application to the DRG resulted in significant pain reduction in patients with herpes zoster and PHN that is resistant to conservative treatment. Moreover, the degree of pain reduction was significantly greater in patients with herpes zoster than in patients with PHN. We propose that application of PRF to the DRG should be considered for pain control and prevention of PHN in cases of herpes zoster that are resistant to conventional medication and blocks. For validation of our results in larger populations, further prospective trials with larger sample sizes and appropriate control groups will be needed to overcome the limitations of the small sample size and retrospective nature of the present study.

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