Randomized Trial

Efficacy of Pulsed Radiofrequency in the Treatment of Thoracic Postherpetic Neuralgia from the Angulus Costae: A Randomized, Double-Blinded, Controlled Trial

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Background: Postherpetic neuralgia (PHN) is often refractory to existing treatments. Pulsed radiofrequency (PRF) is known to be effective for treating neuropathic pain. In common, the targets of PRF treatment were the segmental dorsal root ganglion (DRG) neurons responsible for the pain. A potential complication that can occasionally occur with PRF treatment is damage to the adjacent tissue and organ. The effectiveness of the angulus costae as a puncture site for PRF has not been tested in thoracic PHN treatment.

Objective: The goal of this study was to investigate the therapeutic efficacy and safety of PRF for treating thoracic PHN through the puncture of the angulus costae.

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

Setting: Department of Anesthesiology, Xinhua Hospital, Shanghai Jiaotong University School of Medicine.

Methods: Ninety-six patients with thoracic (T2-11) PHN were equally randomized assigned into 2 groups. The electrode needle punctured through the angulus costae of each patient guided by x-ray; PRF at 42°C for 120 seconds was applied after inducing paresthesia involving the affected dermatome area. PRF was applied in the PRF group (n = 48) twice. It was also applied in the sham group (n = 48) twice without radiofrequency energy output. The treatment was done once a week for 3 weeks. Tramadol was used for flare pain when the visual analog scale (VAS) ≥ 3.

Outcomes Assessment: The therapeutic effect was evaluated by VAS, SF-36 health survey questionnaire, side effects (type, frequency, and onset time) before treatment, at days 3, 7, and 14, and at months one, 2, 3 and 6 after PRF. The average of tramadol (mg/d) administrated within the first month after treatment was also recorded.

Results: The postprocedure VAS scores in the PRF group were significantly lower than those in the sham group and lasted for 6 months after treatment ($P < 0.05$). The SF-36 score, such as physical functioning, physical role, bodily pain, general health perceptions, social function, emotional role, and mental health index were significantly improved until 6 months after treatment in the PRF group compared to the sham group ($P <$ 0.01-0.05). The average dosage of tramadol administered (mg/d) within the first month after treatment was also significantly reduced in the PRF group compared to the sham group ($P < 0.05$). There were no obvious signs of pneumothorax, bleeding, infection, or other severe side effects in either group ($P > 0.05$).

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

Conclusions: The strategy that the angulus costae be used as the PRF puncture point of an electrode needle and the final localization of the needle tip as determined by sensory testing is an effective and safe therapeutic alternative for thoracic PHN treatment. Benefits include that the procedure is minimally invasive, provides short-term pain relief, and improves quality of life.

Clinical Trial Registration: NO ISRCTN25588650.

Key words: Thoracic, postherpetic neuralgia, pulsed radiofrequency, angulus costae.

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Postherpetic neuralgia (PHN) results from injury to the nervous system caused by the varicella-zoster virus during shingles infection. It involves multiple mechanisms including neuroplasticity and sensitization of both peripheral and central neurons (1). Treatment strategies for PHN are complex and largely depend on the type and characteristics of pain experienced by the individual patient (2). PHN is often associated with severe pain and can seriously affect a patient's quality of life. This can adversely affect health services and society at large (3-5). Recently, some novel experimental therapies have achieved satisfactory clinical results treating PHN; however, α2- δ calcium modulator (pregabalin) can't completely relieve the pain (6). Herpes zoster vaccine in older adults has the risk of subsequent herpes zoster disease (7). Therefore, researchers are constantly exploring pain relief therapeutic options for patients with PHN and calling PHN a "never-ending challenge" (8).

Pulsed radiofrequency (PRF) is a novel therapeutic strategy that has recently been used by pain practitioners as a non- or minimally neurodestructive technique, where the short bursts of high-frequency current are applied to nervous tissue. Current is delivered in a pulse of 20 milliseconds followed by a silent period of 480 milliseconds to avoid radiofrequency heat lesions (9). Therefore, it can be repeatedly applied for long-term relief of pain. PRF is known to be effective in short- or long-term pain relief of cervical, lumbar, and postoperative pain and PHN (10-16).

The thoracic nerve (T1-12) is the most common region affected in PHN with an incidence of up to about 50% (17). The most common targets of PRF treatment are the segmental dorsal root ganglion (DRG) neurons responsible for the pain. A potential complication that can occasionally occur with PRF treatment is damage to the adjacent tissue and organ, since the DRG neurons from the neuroanatomical perspective have a deep anatomical location (18). Thus, clinical application of PRF in the treatment of PHN is limited. Future clinical studies aimed at defining an optimized PRF therapy regimen for each clinical application would also be a beneficial direction for future studies (16). Therefore, we designed a randomized, double-blinded, controlled clinical trial to explore the possibility of PRF application for thoracic PHN (T2 – T11). We used the angulus costae as the puncture point for the electrode needle. The final localization of the needle tip was determined by the sensation testing employed in the study, and the analgesic efficacy and safety profiles of PRF were monitored. The purpose of the study was to provide an easy methodology for PRF in the treatment of thoracic PHN.

Methods

Study Participants

In accordance with the ethical Guidelines for Pain Research in Humans, the current study was designed as a prospective, randomized, controlled and double-blinded clinical trial from Feb. 2008 through May 2011. The study protocol was approved by the Human Ethics Committee of Shanghai Xinhua Hospital. This trial was registered with controlled-trials.com, number ISRCTN25588650. Consent was signed by patients before being recruited into the study. According to the anatomic characteristics of PHN, this study focused on PHN whose pain area was at T2-T11.

Inclusion Criteria

Eligible patients were between 60 and 90 years old and whose PHN history was longer than 6 months. Other inclusion criteria were those with PHN that had been refractory to formal treatment according to the International Association for the Study of Pain guidelines (such as antiepileptic medicine, antidepressants, opioids and physical treatments), and a visual analog scale (VAS) score > 3 on a scale of 0-10.

Exclusion Criteria

Exclusion criteria included intolerance to the study, uncooperative behavior, and the inability to finish the self-evaluation questionnaires (VAS, SF-36).

Randomization and Sequence Generation

Using a computer-generated random allocations sequence, 96 patients with thoracic (T2-11) PHN were randomized and assigned into 2 equal groups: a PRF group and a sham group. PRF was applied to the PRF group (n = 48) twice. In the sham group (n = 48), the method was followed as in the PRF group except that radiofrequency energy was not applied. The treatment was carried out once a week for 3 weeks among all patients. (Fig. 1 and Table 1)

Description of Interventions

In our pain clinic, the therapeutic region was first determined by the thoracic segment affected by herpes zoster, which is usually accompanied with specific neuropathic pain (NP). The lesion of one segment of dorsal root ganglion (DRG) leads to the alteration of the near-

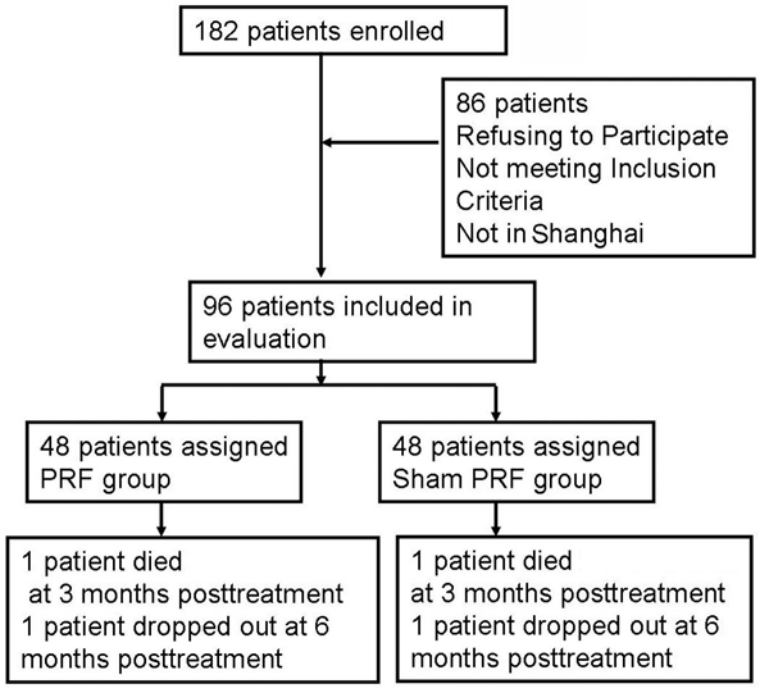

Fig. 1. *Study flowchart. All 96 randomized patients were included in the intention-to-treat analysis by use of repeated measures analysis of variance with mixed effects modelling that includes patients with incomplete follow-up data.*

by DRG (19), and is then expanded up and down one adjacent segment. For instance, for the T3 segment, the T2, T3, and T4 thoracic intercostal nerves were selected for PRF treatment (Fig. 2). The order of puncture was arranged from a higher level of the thoracic segment to the lower level thoracic segment.

Patients were placed prone on the treatment bed with a suitable pillow under the chest and the C-arm image intensifier above the back. The C-arm was in the anteroposterior position and in a pulsed mode to minimize the dose of radiation when the thoracic intercostal nerve puncture was started. The intercostal nerve level and angulus costae were confirmed with the C-arm. A 21-gauge, straight, sharp RF cannula with a 5-mm exposed tip was inserted vertically until the needle tip touched the lower edge of the rib, and was then connected to a radiofrequency heating element. The needle tip was moved slowly under the sensation testing mode (50 Hz, 0.3 - 0.5 V) from the lower edge of the rib upwards into the intercostal space. The moving distance was within 1.5 cm. During this time patients were asked about any abnormal sensations (mainly soreness, numbness, swelling, and sometimes a twitching-like or prickly sensation). In the absence of abnormal sensation reporting, the needle tip was further guided to the lower edge of the rib, puncturing 0.1-0.2 cm deeper into the tissue. This was repeated until the patient reported an abnormal sensation.

Table 1. *Baseline characteristics of the study participants*

Patient	PRF group n = 48 (completed 46)	Sham group n = 48 (completed 46)
Male/Female	25/23 (24/22)	22/26 (22/24)
Age (years)	73.04 ± 6.52 (73.14±6.64)	71.14± 7.2 (71.18±7.30)
Left/right(T4-12)	25/23 (24/22)	28/20 (26/20)
Weight(Kg)	68.38±7.58 (68.61±7.59)	70.93±8.09 (71.56±7.60)
Pain duration (months)	23.02±15.14 (23.28±15.41)	25.19±15.26 (25.59±19.49)
Living status (Single/Not Single)	18/30 (18/28)	14/34 (13/33)

Data are mean ± SD or numbers.

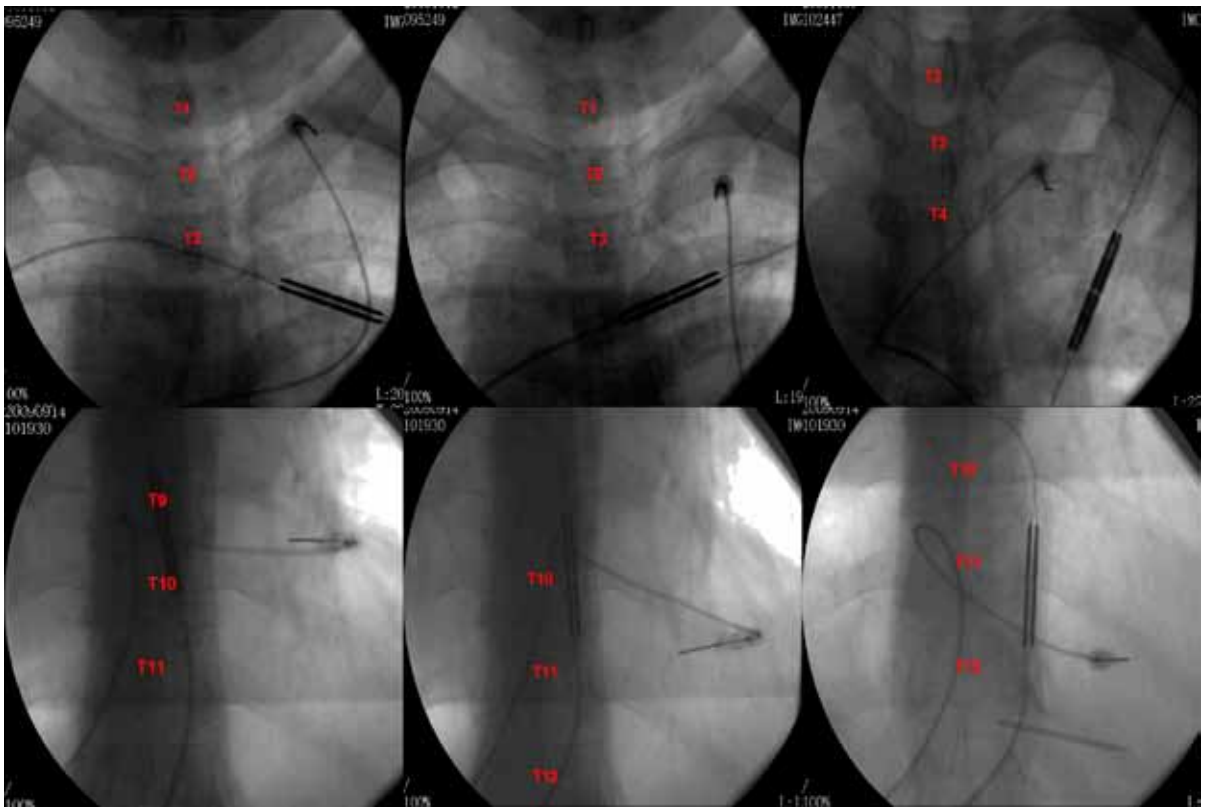

Fig. 2. *X-ray photo of PRF treatment. For PHN of the T3 segment, theT2, T3, and T4 thoracic intercostal nerves were selected for PRF treatment. For PHN of the T10 segment, the T9,T10 and T11 thoracic intercostal nerves were selected for PRF treatment.*

Generally the puncture depth that is considered safe and effective is less than 1.5 cm beneath the rib. The paresthesia thus induced should be over the region involving the pain, and ideally, the area of paresthesia should cross the midclavicular line, or to the approximate edge of the sternum. This usually is the ideal distance between the needle tip and intercostal nerve (within 0.1 mm), with the radiofrequency catheter vertical to the targeted intercostal nerve (Fig. 3). This position allows the electrode needle tip to be vertical to the intercostal nerve to provide the target with maximum exposure to the PRF heat.

We decided not to carry out a motor nerve function test, nor note the depth determination by the C-arm because of the anatomical characteristics of the intercostal nerve and the no-heat-lesion feature of the PRF. The electrode needle was fixed by the index finger and thumb at the determined puncture point of the skin to maintain the depth and position of the needle tip. The mode of the PRF instrument was turned into the working mode subsequently to initiate treatment. The PRF was done using the Pain Management Generator (PM-230, Baylis Medical Company, Montreal, Canada). The PRF settings were 42°C, 120 seconds/twice for the same level.

Blinding (Masking)

The PRF procedures were performed by the same investigator (Dr. Ma Ke) and all follow-ups were performed by another investigator (Dr Fan Yinghui, Jin Yi and Huang Xuehua). The doctors participating in the PRF treatment or follow-up activities were unaware of the groupings or the mode of the PRF used for each patient. The instrument was operated by a nurse (Mei Ling) of our pain management center. The standard PRF program was applied to the PRF group, with the same procedure applied to the sham group without an energy output. The nurse did not participate in any other

therapeutic and follow-up activities, or trial discussions.

Drug administration

The patients were administered tramadol after their PRF treatment for pain control according to the severity of the pain. The other premedication treatments, such as tricyclic antidepressants (amitriptyline) and gabapentin, continued as maintenance therapy; the dosage was increased or reduced according to the alteration of the PHN pain severity.

Outcome Measures

VAS

VAS scores were evaluated before treatment and in the morning (8:00 – 10:00) on days 3, 7, and 14, and months one, 2 and 6 after treatment.

Average dosage of rescue medication (mg/d)

Tramadol 50-200 mg twice a day orally was used as rescue medication for pain control at VAS ≥ 3 and when the frequency of acute pain flares was more than 3 times per day. The average dosages of tramadol (mg/d) were collected on days one, 3, 7, 14, and 28 after the treatment in each group. To prevent gastric side effects, metoclopramide was used at the dose of 5mg/ three times a day for 3 to 7 days.

SF-36 score evaluation

SF-36 score including physical functioning, physical role, bodily pain, general health perceptions, vitality, social function, emotional role and mental health index were evaluated before the treatment and on months one, 2, 3, and 6 after treatment.

Side effects

Any side effects, including bleeding at the adjustment site, infection, and increased pain, were recorded for each group on days one, 3, 7, 14, and 28 after treatment. (Fig. 4)

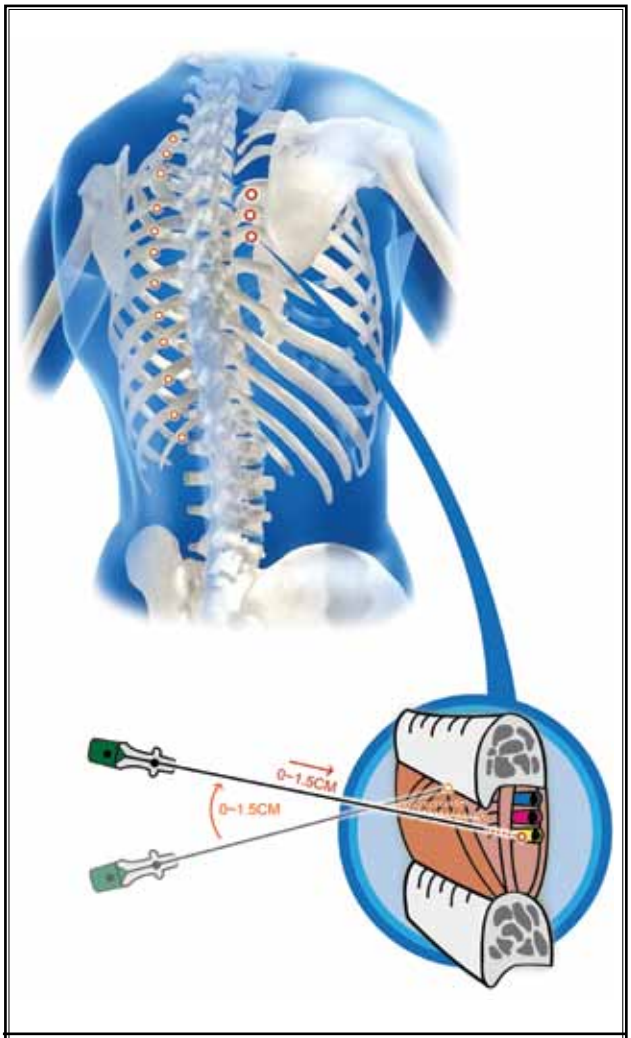

Fig. 3. *Schematic diagram of PRF in the treatment of thoracic PHN through puncture of the angulus costae.*

Statistical analysis

Sample Size

According to our pilot study, the effective rate of the peripheral nerve adjustment in the test group was 70%, and the effective rate in the positive control group was 20%, so the difference between the effective rates in the 2 groups was 50%. We then calculated that the estimated sample number was at least 23 in each group, which provided 80% power and a level of statistical significance of 0.05 (α = 0.05). Quantitative data were presented as mean and standard deviation.

Intent-to-Treat-Analysis

Endpoints were analyzed by intention to treat, including all data available from all 96 randomized patients. We used a linear mixed model with a Toeplitz covariance structure (smallest Akaike information criterion) for analysis of repeated measures structure to undertake an analysis of the primary and secondary endpoints of the full analysis set, which contained unbalanced data. A *P* value < 0.05 was considered statisti-

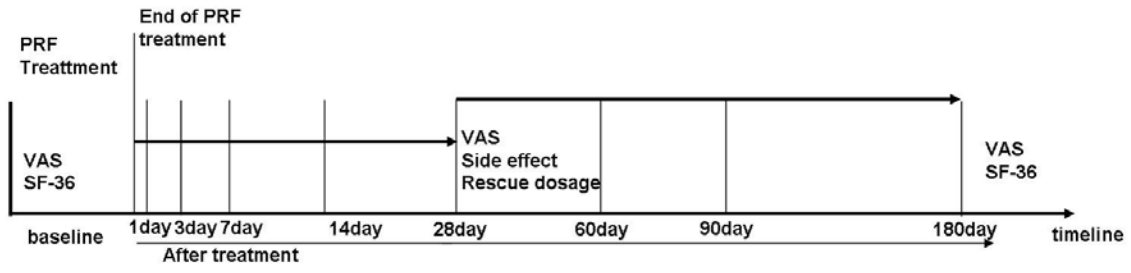

Fig. 4. *Timeline of study.*

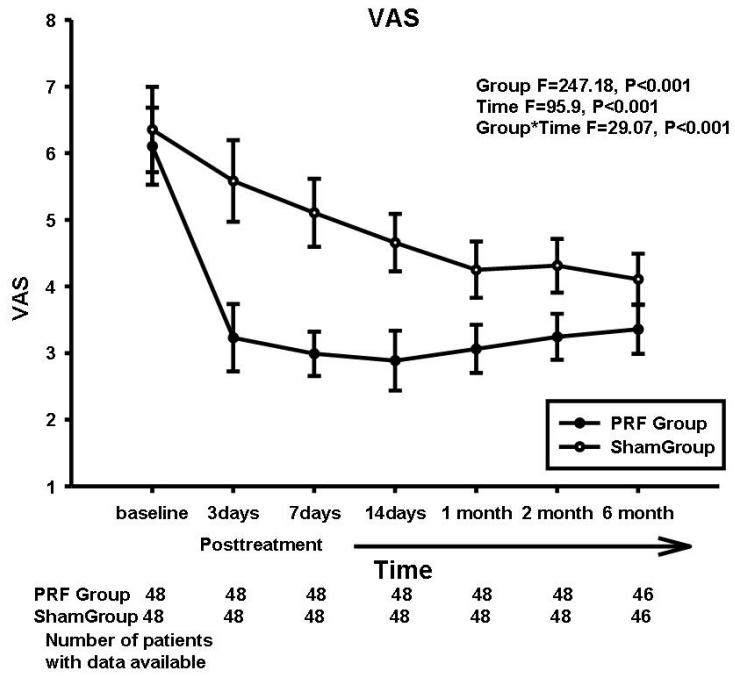

Fig. 5. *The changes in VAS of the 2 groups before and after PRF treatment.*
Figures shows VAS changes with lower scores indicating improvement. In all panels, the treatment P *value refers to the average treatment effect difference during all follow-up time point. The treatment vs time* P *value relates to a time-related change of this difference. A significant treatment by time interaction indicates that the treatment effect difference is not stable throughout the follow-up. The VAS was improved early and then stabilized during the follow-up time in the 2 groups.*

cally significant. The analysis was performed using SAS PROC Mixed, V9.13 software (SAS Institute, Cary, NC).

Results

Patient demography

The patients' demographic characteristics were similar and had no obvious effect on the outcome (Table 1).

VAS

The VAS decreased by 0.211 points (-0.23 – -0.18; t value-15.72, $P < 0.0001$) more in the PRF group than in the sham group after treatment. There was a significant interaction between treatment and follow-up time (F = 29.07, $P < 0.001$); this interaction suggests that the treatment effect over one month was not uniform across follow-up because of an early improvement in the PRF group A (Fig 5).

Rescue drug dosage (mg/d)

The rescue drug (tramadol) dosage administration per day was lower in the PRF group than those in the sham group after treatment. The decrease was 56.38 points (42.26 – 69.93; t value 7.09, P < 0.001) in the PRF group compared to the control (sham) group. There was a significant interaction between treatment and follow-up time (F = 4.65, *P* < 0.001) (Fig. 6).

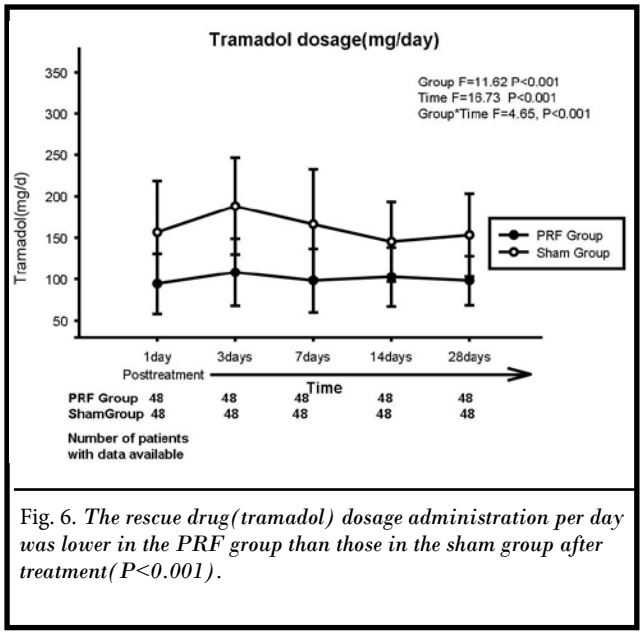

Fig. 6. *The rescue drug(tramadol) dosage administration per day was lower in the PRF group than those in the sham group after treatment(P<0.001).*

SF-36 Score

The index scores in general health, social function, emotional role, mental health index, bodily pain, physical function, and physical role showed significant improvement in the PRF group after treatment. Those improvements were significant after the treatment when compared to the sham group (*P* < 0.05 ~ 0.01).

There was no significant treatment and follow-up time interaction for vitality after the treatment in the 2 groups (F = 1.05, *P* = 0.38). The difference of vitality was 0.001 points (-0.03 - 0.03; t value: 0.06, *P* = 0.95 > 0.01) between the PRF group and the sham group (Table 2, Fig. 7).

Side Effects

There was no pneumothorax, infection, nerve injury, postoperative paresthesia, exacerbation of pain, or any other serious adverse effect after PRF. Needle injury of the intercostal artery was observed in one patient in the sham group during the third round of PRF treatment, but the wound rapidly recovered without any adverse effect during the follow-up period. Bradycardia was found in one patient from the PRF group during the second round of PRF. This patient's heart rate fell to 45 beats per minute, and returned to 60 to 70 beats per minute when the PRF was stopped; the position of the needle tip was adjusted slightly and the PRF procedure proceeded. The first and third round of PRF went smoothly and was successfully performed in the same patient. No complaint was recorded during the follow-up period.

Discussion

An electrode needle punctured through the angulus costae for delivery of PRF not only effectively relieved pain, but also significantly reduced the average dosage of rescue drug in the PRF group. Our results also demonstrated that the treatment significantly improved the SF-36 score, such as physical functioning, physical role,

Table 2. *SF-Score results*.

SF-36 score index	Difference	T value	*P* value*
General health perceptions	0.34 points (0.28 - 0.39)	11.66	< 0.0001
Social function	0.27 points (0.18-0.36)	5.99	< 0.0001
Emotional role	0.21 points (0.12-0.29;)	4.81	< 0.0001
Mental health index	0.33 points (0.27-0.39)	11.29	< 0.0001
Bodily pain index	0.32 points (0.23-0.42)	6.7	< 0.0001
Physical function	0.04 points (0.02-0.06)	2.97	< 0.01
Physical role	0.11 points (0.03-0.19)	2.75	< 0.01
Vitality	0.001 points(-0.03-0.03)	0.06	>0.05

* between the PRF group and the sham group.

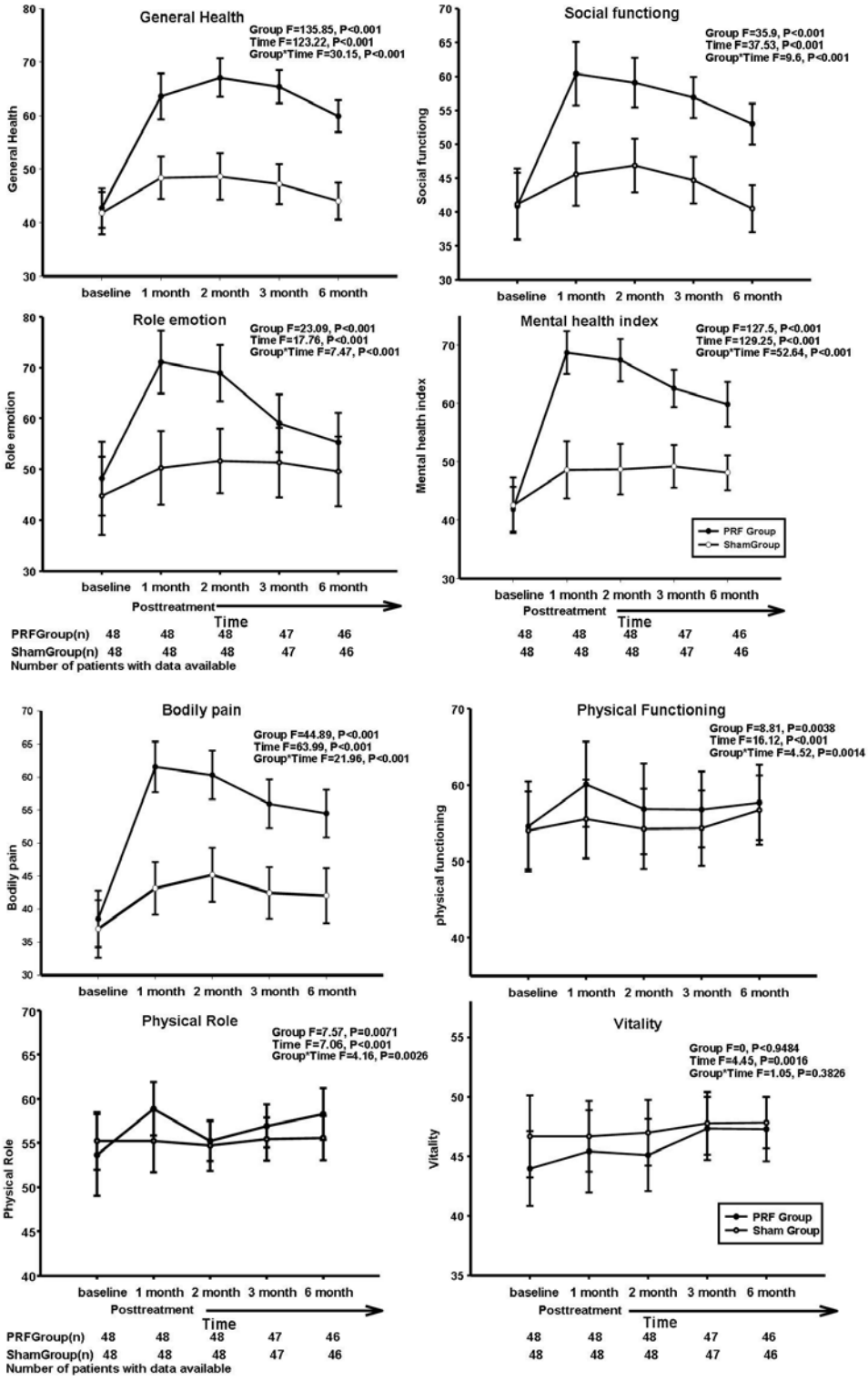

Fig. 7. *SF-36 part 1and SF-36 part 2 The changes in SF-36 in 2 groups. In all panels, higher scores indicate improvement. In panels, the treatment P value refers to the average treatment effect difference during follow-up time point. The treatment vs time p value relates to a time-related change of this difference. A significant treatment by time interaction indicates that the treatment effect difference is not constant throughout follow-up.*

bodily pain, general health perceptions, social function, emotional role, and mental health index, which reflect the overall quality of life. This therapeutic strategy of PRF in the treatment of PHN through puncture of the angulus costae was simple, convenient, and accompanied by unremarkable complications.

The reason peripheral intercostal nerves were chosen as the target of treatment is that peripheral nerve sensitization is very important to central nerve sensitization in NP (20). PHN impairs all sensory fiber groups - C, Aδ and A-β fibers - causing sharp pain, burning pain, allodynia and/or hypersensitivity. All these in turn lead to central sensitization (21). Peripheral nerve electricity modulation can reduce allodynia for a long time (22). Tactile brush stimulation in the peripheral allodynia area has been shown to reduce the area where pain occurs by more than 30% and last for several days (23).

Numerous clinical trials and animal experiments have confirmed the advantages of PRF on NP treatment over other available clinical methods (13,24-26). Compared to traditional RF which achieves analgesia through heat lesions, thermal lesion has been shown as not being an essential mechanism of neuroamodulation in PRF (27). Although the precise mechanism is elusive, most studies suggest that the analgesia achieved by PRF is through the pulse electric current and the biological effects induced thereby, including the effects on the DRG, c-fos gene expression regulation in the cornu dorsale medullae spinalis, and nerve fiber edema (28). PRF can reversibly block the nerve impulse propagation of the small unmyelinated nerve fibers (29-30). Microstructure research has indicated that PRF causes axonal changes more obviously in C fibers than the Aα or Aβ fibers, which is largely manifest within the mitochondria and micro cytoskeleton edema, leading to the abnormality of ATP metabolism and the function of the ion channel and pump, and thereby blocks the pain transfer in relevant nerves (27,31-34). No injury is observed on the outer membrane of the axons (32). In addition, a neuroanatomic study suggests that the abnormal neuron conduction properties and synaptic activity in the hippocampi induced by PRF can be quickly restored, which is unique and different from conventional RF (29,35). Therefore, the acute effects of PRF are more reversible and less destructive in nature than the classic conventional RF mode (35). The analgesic action of PRF also involves the enhancement of noradrenergic and serotonergic descending pain inhibitory pathways (36). The long-term analgesia of PRF is also closely connected with the gene expression alteration of neurons (37).

Delivery of PRF through puncture in the the angulus costae of thoracic ribs provides several advantages. From the neuroanatomical point of view, the radiofrequency emission from the angulus costae can modulate the whole axis of intercostal nerves, including the dermal, lateral, and anterior nerve branches. The paresthesia induced by PRF usually can cover the related dermatome region including the paravertebral and prothorax regions. This modulation of PRF on the whole axis of the intercostal nerve might be one of the attributes for its long-term analgesic effect. Meanwhile, we consider that the electrode puncturing route and procedure of ensuring the needle tip is vertical to the targeted nerve to be essential to achieving the maximum effect. The maximum current is produced from the needle tip under pulse mode, and forms an oval electric field. Therefore, the vertical relationship between the needle tip and the targeted nerve is critical and a prerequisite for PRF therapy (9,31,38). On the other hand, in conventional DRG-targeting PRF, it is rather difficult to keep the verticality between the electrode and the nerve, and hence may not be as effective.

From the perspective of safety to the underlying vasculature, the puncture of the angulus costae is one of the safest procedures. At the angulus costae, the neurovascular arrangement from up to down is the intercostal vein, then the artery, and lastly the intercostal nerve. In the other words, the vasculature is buried in the costal groove, and the nerve is located at the lower edge of the rib. Therefore, the puncture route we adopted is short, from the thin subcutaneous tissue to the targeted nerves where there are no major organs or blood vessels. During the procedure, the needle tip movement for sensory testing gets close to the intercostal nerves, and then to the blood vessels (arteries and veins). Under the sensory testing mode (50 Hz, 0.3 - 05V), the distance between the tip and targeted nerve can be well appreciated. The blood vessel, thus, does not get damaged unless an anatomical variation is present. Moreover, the C-arm operation is easy to operate. It only needs to determine and fix the anteroposterior position between the targeted rib and the needle, with no need to monitor the puncture depth laterally. There are anatomic variations of the intercostal nerves in each segment in terms of the depth beneath the skin; this usually causes a hurdle to practitioners, but this can be overcome and eliminated by the sensation testing described earlier during the PRF operation. When the paresthesia area covers the area with, it indicates that the tip is in the right spot and that the PRF emission

will target the nerve well. In combination with sensation testing to determine the tip depth, this method is simple and safe, with no obvious severe side effect.We concluded that in the patient who presented with bradycardia and had no previous history of bradycardia or coronary heart disease, the transient bradycardia might have been due to NP neural remodeling and dysfunction of the sympathetic nerve (20).

Regarding the patient's body position, we found that the prone position was the most acceptable for most patients; there was no need to adjust this position during the treatment. Each treatment was completed within 20 – 30 minutes, and all patients underwent the procedure comfortably.

A study using PRF for the treatment of thoracic postoperative pain suggested that targeting the DRG can provide greater long-term pain relief than targeting the intercostal nerve (18). However, DRG targeting carries with it the potential risk of pneumothorax. In addition, it has been reported that there is a risk of damage to the the artery of Adamkiewicz (ARM) when puncturing through the intervertebral foramen, and paraplegia can be caused by transforaminal injection (39). Besides, it is difficult to maintain the vertical position between the needle tip and the DRG neuron. Therefore, the procedure of PRF puncture from the angulus costae is easier and has a lower potential risk compared to the thoracic puncture methodology targeting the DRG. Since the comparison between targeting the intercostal nerve and the DRG is not the objective of the current study, and from the perspective of ethics and risk-benefit consideration, DRG control was not included. The proposed PRF procedure in our study provided an alternative to treat thoracic PHN.

There are some limitations in our current study design which are expected to be improved in further trials. First of all,our study was a single center study, and the number of patients was relatively small. Secondly, the 3 nerves level of PRF treatment was plotted and conducted according to the characteristics and the mechanism of NP, without comparing it to a single nerve level of PRF treatment. Nevertheless, it was still demonstrated as an ideal neural regulation and effective pain relief method. Thirdly, the patients were reluctant to receive cutaneous nerve function testing of the A α, A β, C nerve fibers. Only the VAS, average dosage of rescue drug, and SF-36 data (which reflect the severity of the symptoms) were recorded for the therapeutic result analysis. Therefore, the alteration or improvement of PHN affecting nerve function data was lacking in the study.

Conclusion

The puncture point for the PRF electrode needle at the angulus costae, combined with sensory testing for needle tip localization, appears to provide effective PRF treatment of thoracic PHN by providing short-term pain relief and improvement in the quality of life. This study demonstrated that the PRF method described herein is an effective and safe therapeutic alternative for the treatment of thoracic PHN.

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