

Randomized Trial

High Voltage Pulsed Radiofrequency for the Treatment of Refractory Neuralgia of the Infraorbital Nerve: A Prospective Double-Blinded Randomized Controlled Study

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Background: A recent study showed that 50% of patients who suffered from refractory neuralgia of the infraorbital nerve obtained satisfactory efficacy after pulsed radiofrequency (PRF) treatment. A pilot study showed that increasing the output voltage of PRF significantly improved the efficacy for trigeminal neuralgia; however, whether increasing the output voltage of PRF can improve the treatment outcomes for neuralgia of the infraorbital nerve is unknown.

Objective: To evaluate the efficacy and safety of high voltage PRF treatment in comparison with standard voltage PRF for neuralgia of the infraorbital nerve.

Study Design: Prospective, single-center, double-blinded, randomized, controlled trial.

Setting: Beijing Tiantan Hospital, Capital Medical University.

Methods: A total of 60 patients with refractory neuralgia of the infraorbital nerve were randomly divided into the high voltage PRF group and the standard voltage PRF group to treat their infraorbital nerves. Neither the patients, pain physicians, nor the follow-up evaluators knew the patient group assignments. The primary outcome measure was the one-year response rate. The secondary outcome measures included the time to take effect after PRF, the one-month, 3-month, and 6-month response rates, the relapse rate, and adverse reactions.

Results: The intent-to-treat analysis showed that the one-month, 3-month, 6-month, and one-year response rates were all 90% in the high voltage group, which were significantly higher than the rates in the standard voltage group (67% [$P < 0.05$], 67% [$P < 0.05$], 63% [$P < 0.05$], and 60% [$P < 0.01$], respectively). Furthermore, 27% of the patients in the high-voltage group and 13% of the patients in the standard voltage group experienced minor transient (10 – 30 days) numbness in the innervation area after PRF; no other serious adverse reactions were observed in the 2 groups ($P > 0.05$).

Limitations: We did not investigate the dose-effect relationship between the output voltage and efficacy or the effect of a higher pulse dose on efficacy. This study was a single-center study, and multi-center, randomized, controlled studies are needed to obtain the highest level of empirical evidence. Additionally, the follow-up period lasted only one year in this study; thus, long-term efficacy needs to be further confirmed.

Conclusions: The results showed that high voltage PRF was effective and safe for patients with refractory neuralgia of the infraorbital nerve and could become a treatment option in patients who do not respond to conservative treatment.

Key words: Neuralgia, infraorbital nerve, pulsed radiofrequency, numeric rating scales, treatment

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The infraorbital nerve is the branch of the maxillary nerve (second branch of the trigeminal nerve). As the largest terminal branch of the trigeminal nerve, the infraorbital nerve passes through the infraorbital groove and the infraorbital canal, reaches the facial area via the infraorbital foramen, and then branches into several branches that spread to the lower eyelid, nose wing, and upper lip skin. Neuralgia of the infraorbital nerve, which is one refractory facial pain condition, refers to severe tingling of the innervation area of the infraorbital nerve.

In the past, old-fashioned surgeries, such as percutaneous infraorbital nerve ablation or open infraorbital neurectomy, were performed to block pain transmission in patients with neuralgia of the infraorbital nerve who did not respond to conservative treatments, such as medications and nerve blocks (1,2). However, nerve ablation inevitably results in anesthesia of the innervation area of the infraorbital nerve, causing patient discomfort with a significant impact on the quality of life. Despite its high short-term response rate, the pain relief does not last long, and patients must undergo a second treatment in case of relapse.

Recently, pulsed radiofrequency (PRF), which is a non-nerve ablation minimally invasive treatment technology, has been proven to be effective for many chronic pain conditions (3-7). We recently used standard voltage PRF to treat 36 patients with refractory neuralgia of the infraorbital nerve and showed that the 6-month, one-year, and 2-year response rates were 69%, 50%, and 50%, respectively; no serious adverse reactions were observed, but the efficacy was not satisfactory (8).

In 2015, a randomized controlled study showed that high voltage PRF of Gasserian ganglion significantly improved the treatment outcomes relative to standard voltage PRF in patients with trigeminal neuralgia (9). However, whether increasing the output voltage of PRF can improve the treatment outcomes of neuralgia of the infraorbital nerve is unknown. Thus, we conducted a prospective double-blinded randomized controlled study in 60 patients with refractory neuralgia of the infraorbital nerve to compare the efficacy and safety of standard voltage PRF versus high voltage PRF.

METHODS

Study Design

This was a prospective, single-center, double-blinded, randomized, controlled study comparing the

efficacy and safety of high voltage PRF with standard voltage PRF treatment in patients with refractory neuralgia of the infraorbital nerve (China Clinical Trial Registration: NO ChiCTR-ONRC-12002939).

Patients

We screened 71 patients with refractory neuralgia of the infraorbital nerve who visited the pain clinic of Beijing Tiantan Hospital, between December 2013 and May 2015 and enrolled 60 eligible patients into this study. The study protocol was approved by the Ethics Committee of Beijing Tiantan Hospital. The procedure, effects, and potential adverse reactions of PRF were explained to the patients. Each patient signed the informed consent form prior to the study.

The inclusion criteria were as follows: age \geq 18 years; paroxysmal or persistent severe tinkling in the facial innervation area of the infraorbital nerve and a neurological examination showing hypersensitivity (10), preoperative numerical rating scale (NRS) (0: no pain; 10: unbearable, most intense pain) $>$ 7, NRS reduction $<$ 50% after conservative treatment, such as oral anti-epileptic drugs and steroid infraorbital nerve block, and diagnostic block confirmation of neuralgia of the infraorbital nerve (11-13). The exclusion criteria were as follows: abnormal preoperative blood test or electrocardiogram (ECG); puncture site infection; neuralgia secondary to a lesion around the infraorbital foramen, such as an intracranial or extracranial tumor or maxillary sinusitis; mental illness; history of past narcotic drug abuse; received infraorbital nerve radiofrequency thermocoagulation (RFTC); or had undergone an invasive procedure, such as neurolytic solution injection, neurectomy, or avulsion.

The patients were assigned into the high voltage PRF group and the standard voltage PRF group using a computer-generated random number sheet, with 30 patients per group. Sealed opaque envelopes were used for allocation concealment.

Operation

The patient was positioned supine on the computed tomography (CT) examining table; the blood pressure, heart rate, electrocardiogram (ECG), and pulse oximetry were continuously monitored. The negative electrode plate of the PMG-230 pain treatment generator (Baylis Medical Inc., Montreal, Que, Canada) was attached to the patient's back.

The surface projection point of the ipsilateral infraorbital foramen (i.e., the point where the line between

the outer corner of the eye and the midpoint of the upper lip crosses the vertical line that passes the pupil) was punctured. After skin disinfection and local topical anesthesia administration at the puncture site, a needle was inserted upward, backward, and outward until it reached the bone surface near the infraorbital foramen. A thin slice (2 mm) CT scan (medical x-ray CT scanner,

model SOMATOM, SIEMENS, Munich, Germany) of the maxillary sinus was performed to determine the position of the puncture needle relative to the infraorbital foramen and to adjust the direction of the needle. The thin slice CT scan was repeated after needle adjustment until the insulated RF trocar needle (bare tip: 5 mm, length: 10 cm; PMF-21-100-5, Baylis Medical Inc.,

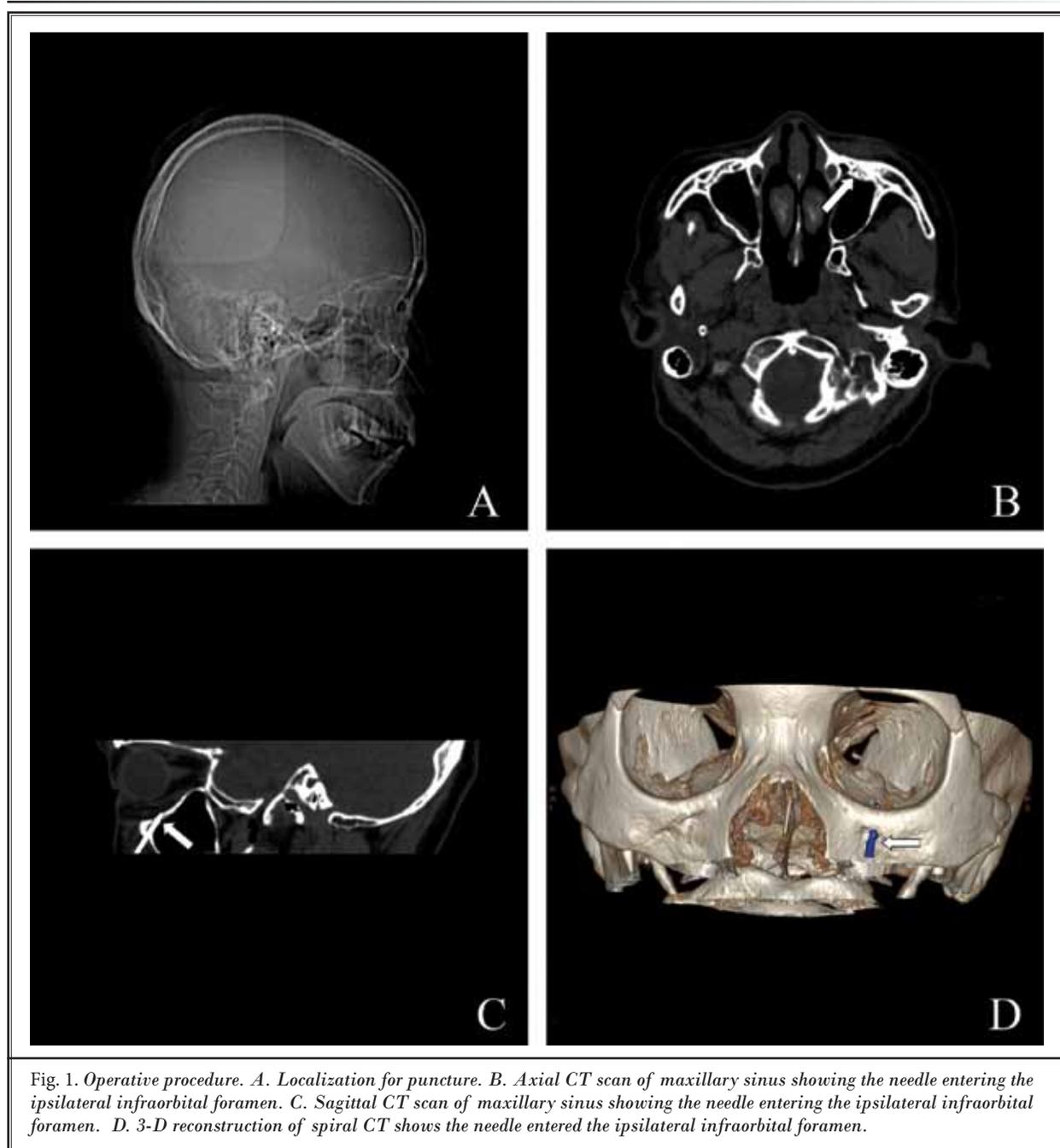


Fig. 1. Operative procedure. A. Localization for puncture. B. Axial CT scan of maxillary sinus showing the needle entering the ipsilateral infraorbital foramen. C. Sagittal CT scan of maxillary sinus showing the needle entering the ipsilateral infraorbital foramen. D. 3-D reconstruction of spiral CT shows the needle entered the ipsilateral infraorbital foramen.

Montreal, Que, Canada) reached the infraorbital foramen (8) (Fig. 1). The plunge was pulled back to ensure that there was no blood or air.

The needle core was removed, and the RF electrode (PMK-21-100, Baylis Medical Inc., Montreal, Que, Canada) was inserted to test the resistance. Next, electrical stimulation positioning was performed with the 50 Hz sensory threshold; here, 0.1 to 0.2 V should excite tingling in the innervation area of the infraorbital nerve. The depth and direction of the needle were slightly adjusted based on patient sensation to ensure the selection of the correct puncture site. The puncture procedure was performed by an experienced interventional pain physician.

Upon the completion of the puncture, an envelope was opened. According to the random number, a designated staff member set up the parameters of the PRF apparatus for either the standard voltage or high voltage PRF treatment. For the standard voltage group, the automatic PRF mode was used (standard parameters: 42°, 2 Hz, 120 s, 2 times). For the high voltage group, the manual PRF mode was used (maximum temperature: 42°; the UP knob was turned to increase the output voltage until the maximum voltage [bearable without causing pain in conscious patients] was reached; 120 s, 2 times) (9). At one month after treatment, patients who did not respond to the PRF received RFTC; the same puncture procedure was performed, and the RFTC mode was used (60°, 75 s; 65°, 75 s; 70°, 75 s; 75°, 75 s; and 80°, 75 s) (8).

Data Collection and Follow-up

Before the operation, general information, such as age, gender, duration of illness, left/right ratio, preoperative NRS, and carbamazepine dosage, was collected. During the operation, information such as the stimulation voltage during 50 Hz test positioning, output voltage, local tissue resistance, and operation time was collected. The response criteria included NRS = 0 or a NRS reduction > 50% after the operation and patient satisfaction with the treatment outcomes. The trained neurology evaluators were unaware of the group assignments. The time to take effect, the NRS at the different time points, the carbamazepine dosage, and the adverse reactions after the operation were evaluated. Postoperative day one, week one, week 2, and month one were evaluated at clinic visits; postoperative month 3, month 6, and year one were followed up by phone. The response rate (effective [n]/N × 100%) was calculated at the different time points.

Statistical Analysis

The SPSS software (Oblimin, SPSS version 21.0; IBM, Armonk, NY IBM) was used for the statistical analysis. Normally distributed measurement data were expressed as $x \pm SD$ and analyzed with the 2-sample t-test. Count data were analyzed with the Chi-square test. Non-normally distributed measurement data were expressed as the median (minimum ~ maximum) and analyzed with the 2 independent sample rank sum test. The response rate was compared with the intent-to-treat analysis. A $P < 0.05$ was considered statistically significant.

RESULTS

General Information of the 2 Groups

The intraoperative output voltage was significantly higher in the high voltage group than in the standard voltage group ($P < 0.01$). No significant difference was observed in the preoperative or intraoperative clinical information between the 2 groups ($P > 0.05$) (Table 1).

Treatment Effects (see Fig. 2 for progression of study participants)

In the standard voltage group, the response rate was 67% (20/30) at one month after the operation; in this group, 18 patients discontinued carbamazepine, and 2 controlled pain with low-dose carbamazepine (50 – 100 mg, 1 – 3 times a day). Moreover, of these 20 patients, one patient (5%) experienced slightly worse pain 2 to 3 days after the operation, which gradually improved with the higher dose of carbamazepine and non-steroidal anti-inflammatory drugs. For the remaining 19 patients (95%), pain gradually improved after the operation. The mean time to take effect was 7 (1 – 30) days. At one month after treatment, 10 patients (33%) did not respond to the PRF and received RFTC. Two patients (10%) who initially responded to the PRF had recurrent pain 5 and 11 months after the operation (NRS > 7, ineffective treatment with oral carbamazepine) and received RFTC. All patients who underwent the RFTC had NRS = 0 and discontinued carbamazepine after the operation (Table 2). Two patients were lost to phone follow-up one year after the operation. The intent-to-treat analysis showed that the response rates at one month, 3 months, 6 months, and one year after the operation were 67%, 67%, 63%, and 60%, respectively (Table 2).

In the high voltage group, the response rate was 90% (27/30) one month after the operation; in this group, 20 patients discontinued carbamazepine, and

Table 1. Comparison of the baseline patient characteristics and intraoperative data between the 2 groups.

	Standard voltage group	High voltage group	P value
Patient No.	30	30	
Age (year)	65 ± 14	61 ± 12	0.288
Male (%)	14 (46.6)	11 (36.6)	0.194
Disease duration (year)	2.9 ± 3.1	3.5 ± 3.2	0.639
Left/Right-sided	13/17	9/21	0.284
Dosage of preoperative carbamazepine (mg/day)	704 ± 278	717 ± 442	0.902
Preoperative NRS	8 (7 - 9)	8 (7 - 9)	0.546
PRF output voltage (v)	50 ± 10	96 ± 9	0.000
Tissue resistance (Ω)	428 ± 89	392 ± 96	0.202
50 Hz stimulating voltage (v)	0.1 (0.1 to 0.2)	0.1 (0.1 to 0.2)	0.276
Surgery duration (min)	35 ± 8	33 ± 5	0.131

Values are expressed as the means ± standard deviation unless otherwise stated, * median (minimum ~ maximum). NRS, numeric rating scales; PRF, pulsed radiofrequency.

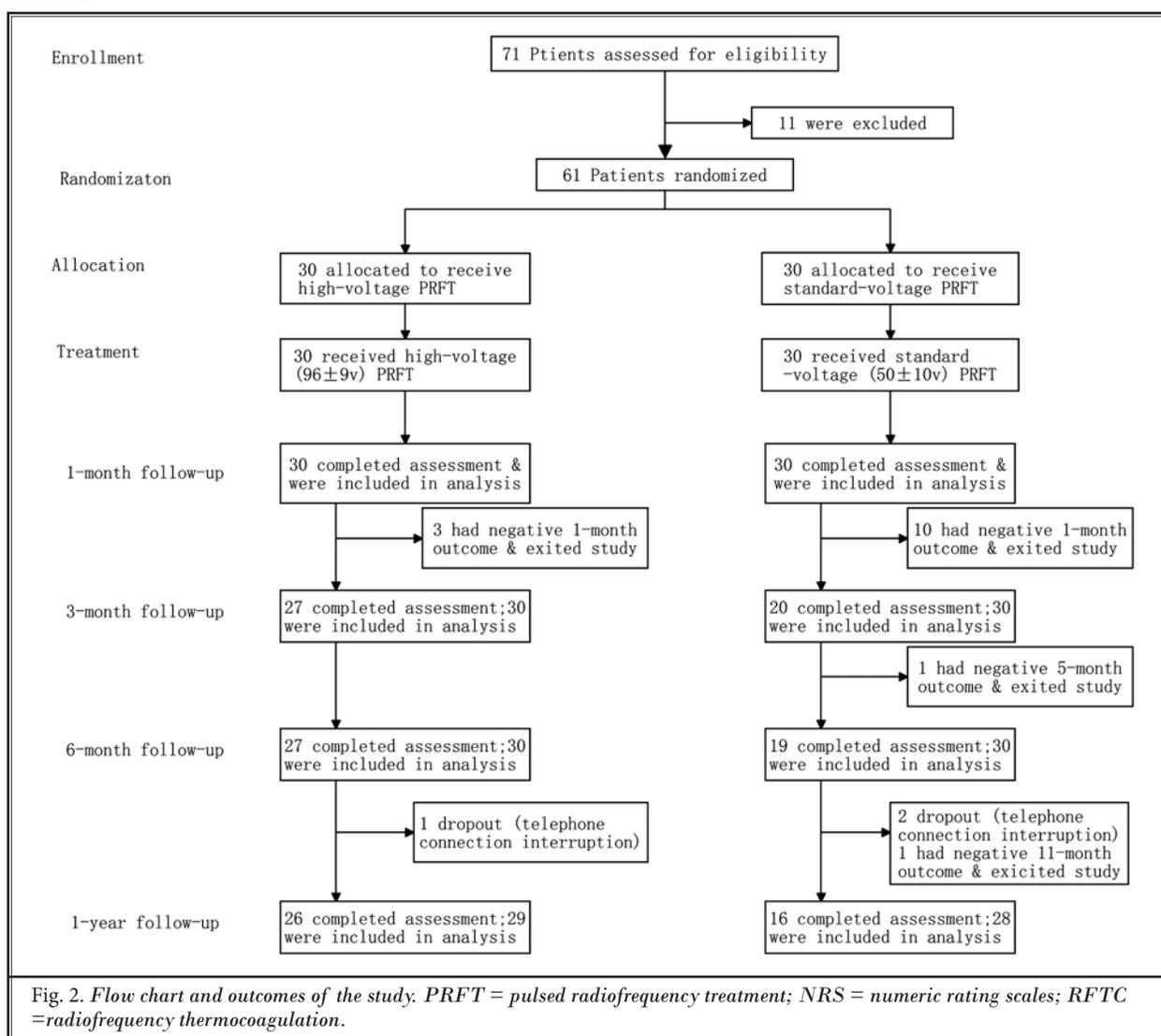


Table 2. Comparison of the postoperative response rates between the 2 groups (intent-to-treat analysis).

Time points	Standard-voltage group (n = 30)			High-voltage group (n = 30)			P value
	NRS = 0	NRS decrease > 50%	Response rate	NRS = 0	NRS decrease > 50%	Response rate	
1 month post-operation	18	2	67%	20	7	90%	0.028
3 months post-operation	18	2	67%	25	2	90%	0.028
6 months post-operation	15	4	63% (1 patient underwent RFTC after recurrence)	24	3	90%	0.015
1 year post-operation	13 (2 patients were lost to phone follow-up)	5	60% (Another patient underwent RFTC after recurrence)	20 (1 patient was lost to phone follow-up)	7	90%	0.007

NRS = numeric rating scales; RFTC = radiofrequency thermocoagulation.

7 patients had controlled pain with low-dose carbamazepine (50 – 100 mg, 1 – 3 times a day). Of these 27 patients, 2 patients (7.4%) experienced worse pain on day 2 after the operation, which lasted 2 and 4 days and improved after symptomatic treatment with carbamazepine and non-steroidal anti-inflammatory drugs. For the remaining 25 patients (92.6%), pain gradually improved after the operation. The mean time to take effect was 4 (1 – 21) days, with no significant difference compared to the standard voltage group ($P > 0.05$). Moreover, 3 patients (10%) did not respond to PRF and received RFTC, and their pain was completely relieved. One patient with satisfactory treatment outcomes by month 6 after the operation was lost to phone follow-up by one year after the operation. The intent-to-treat analysis showed that the response rates were 90% at one month, 3 months, 6 months, and one year after the operation in the high voltage group, which were significantly higher than the rates in the standard voltage group (months one, 3, and 6, $P < 0.05$; year one, $P < 0.01$). No relapse was observed during the one-year follow-up (Table 2).

Adverse Reactions

Four patients (13%) in the standard voltage group and 8 patients (27%) in the high voltage group experienced mild numbness in the innervation area of the infraorbital nerve after the operation. The neurological examination showed mild tolerable loss of pain and thermal and tactile sensations in the innervation area of the infraorbital nerve on the operative side. The numbness gradually subsided within 10 to 30 days. Patients

who underwent RFTC experienced marked sensory loss and severe numbness in the innervation area of the infraorbital nerve on the operative side.

DISCUSSION

This study showed that the postoperative one-year response rate was 90% in the high voltage PRF group, which was significantly higher than the rate in the standard voltage PRF group (60%). Moreover, among the patients in the high voltage group who responded to the high voltage PRF, 74% had complete pain relief and thus discontinued anti-epileptic carbamazepine and did not experience recurrent pain during the one-year follow-up. These results were consistent with the findings of our previous study, in which the high voltage PRF of Gasserian ganglion was more effective than the standard voltage PRF for trigeminal neuralgia (9). This well-designed randomized controlled study demonstrated that properly increasing the electric field effect improved the efficacy of PRF for neuralgia of the infraorbital nerve. These results were promising and indicated that high voltage PRF could become a treatment option for patients who did not respond to conservative treatment and were scheduled to undergo ablation. We believe that the high voltage PRF technology will greatly reduce the number of patients who undergo ablation.

In 2006, Teixeira and Sluifjter (14) first administered a high voltage PRF (60 v) to the lumbar disc to treat lumbar disc-related pain and achieved satisfactory results. When PRF was used to treat the trigeminal neuralgia or neuralgia of the infraorbital nerve, the intraopera-

tive output voltage was negatively correlated with the postoperative NRS (8,15). In this study, no significant difference was observed in the preoperative and intraoperative clinical data between the 2 groups other than the intraoperative output voltage. The electric field intensity equals the voltage square divided by the resistance. Because no difference was observed in the resistance between the 2 groups, the patients in the high voltage group received greater electric field effects in the therapeutic area of the infraorbital nerve during the operation. The results confirmed that the level of the electric field effect was related to the PRF efficacy. In both groups, the intraoperative temperature was 42°, further demonstrating that the results were due to an electric field effect rather than the temperature effect of the PRF, which played a role in pain treatment.

Consistent with previous reports (8,9,15,16), this study showed that a recovery period was required in both groups of patients (high voltage group and standard voltage group). No significant between-group difference was observed in the time to take effect. Significant individual variability was observed in the length of the postoperative recovery period: Some patients experienced immediate pain relief after the operation, whereas other patients did not experience pain relief until one month after the operation. Some patients even experienced temporary worsening of the pain in the early postoperative stage. We posit that PRF may cause a series of plastic changes in the pain transmission pathways in patients with a longer time to take effect, resulting in slow neuromodulation for the treatment of neuropathic pain. A small number of patients experienced temporary worsening of pain after the operation, which might be related to the direct puncture injury. Hence, individual variability in the pain response after PRF should be taken into consideration when administering symptomatic treatment, such as anti-epileptic drugs, non-steroidal anti-inflammatory drugs, and neurotrophic drugs, as directed by the pain physician. Patients and physicians should wait for at least one month to achieve optimal results and must not switch to other treatments too soon. Of course, this hypothesis cannot explain why some patients experience pain relief immediately after the PRF. Therefore, the PRF may play a role in both slow neuromodulation and immediate pain block.

In this study, all patients underwent CT-guided puncture to ensure the correct puncture site and to prevent damage to the surrounding normal tissue. We set the maximum temperature of the PRF to 42°. During

treatment, no local anesthesia was given to block the infraorbital nerve, and the physician gradually increased the output voltage to reach the maximum voltage that the patient could tolerate without pain, thereby preventing potential target nerve injury associated with a higher output voltage and ensuring patient safety. Consistent with previous reports in which a small number of patients experienced minor, transient, reversible numbness in the innervation area of the infraorbital nerve after standard voltage PRF (8), in this study, 13% of the patients in the standard voltage group and a slightly higher percentage (27%) of the patients in the high voltage group experienced numbness, but the difference did not reach statistical significance. Animal studies showed that the nerve tissue might present transient, reversible, minor pathological changes after PRF of the normal sciatic nerve, such as nerve endometrial edema (17-19), which might have caused mild numbness in the innervation area of the infraorbital nerve after PRF in some patients in this study. Fortunately, all cases of numbness were mild and reversed in a short period. In contrast, patients who received RFTC after ineffective PRF treatment experienced severe, long-lasting sensory loss (with a significant impact on the quality of life) in the innervation area of the infraorbital nerve due to thermal effect-related protein denaturation, which is one of the restricting factors for the clinical application of ablation.

In this study, all patients who did not respond to PRF for neuralgia of the infraorbital nerve (10% in the high voltage group and 33% in the standard voltage group) underwent RFTC and experienced complete pain relief. Currently, it is believed that the response rate of pain relief is lower for non-ablative PRF than for conventional RFTC; however, in this study, high voltage PRF after parameter adjustment achieved a response rate of 90% in patients with refractory neuralgia of infraorbital nerve, thereby sparing these patients ablative treatment. Moreover, no major adverse reactions were observed in this study, and patients who did not respond to PRF could still receive ablative treatment. Therefore, we recommend high voltage PRF before ablative treatment in patients who do not respond to conservative treatment.

The efficacy of ablative treatment may not last for life. Even after neurectomy of the infraorbital nerve, the patient may relapse 12 to 15 months (average) after the initial operation and 9 to 12 months (average) after the second operation, indicating a shorter remission period after repeat neurectomy (20). This

study showed that 10% of the patients in the standard voltage PRF group had recurrent pain within one year after the operation, whereas no relapse was observed in the high voltage PRF group during the same period. Nevertheless, a longer follow-up period is needed to confirm whether high voltage PRF reduces the relapse rate. Moreover, randomized controlled clinical studies should be conducted in the future to compare the effectiveness, relapse rate, and safety of high voltage PRF and conventional RFTC to confirm the non-inferiority of high voltage PRF for clinical application.

Other researchers initially proposed the following PRF parameters: pulse frequency: 2 Hz; output voltage: 45 V; pulse width: 20 ms; temperature: 42°; and treatment time: 2 minutes. Currently, pain physicians are focusing on improving PRF parameters to improve its analgesic effects. At present, researchers are still in disagreement concerning whether PRF for 6 minutes or 8 minutes is more effective than the standard treatment time (2 minutes) in an animal model of neuropathic pain (21,22). This study showed that high voltage PRF was more effective than standard voltage PRF; however, we did not investigate the dose-effect relationship between the output voltage and efficacy or the effect of a higher pulse dose (by changing parameters such as the pulse frequency, pulse width, or treatment time) on efficacy. This study was a single-center study, and multi-

center, randomized, controlled studies are needed to obtain the highest level of empirical evidence. Additionally, the follow-up period lasted only one year in this study; thus, long-term efficacy needs to be further confirmed. More research is needed to investigate the efficacy of high voltage PRF for the treatment of other types of peripheral neuropathic pain or chronic pain. Furthermore, the physics, mechanism of action, and biological effects of high voltage PRF need to be investigated to clarify the scientific basis for high voltage PRF, which is a promising technology for clinical application. Detailed ex vivo and in vivo studies are needed to evaluate high voltage-related pathological and physiological changes in nerve tissue. Finally, electrophysiological techniques must be used to evaluate the safety of high voltage PRF for nerve tissue prior to clinical application.

CONCLUSION

For patients with refractory neuralgia of the infraorbital nerve who do not respond to conservative treatment, high voltage PRF is an effective, minimally invasive treatment option with no major adverse reactions. With a deeper understanding of non-ablative PRF and the continuous search for methods to improve the efficacy, PRF is a promising technology for clinical application.

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