The largest terminal branch of the maxillary nerve is the infraorbital nerve, which innervates the skin and mucous membrane of the palpebra inferior, ala nasi, and upper lip. The classic clinical feature of neuralgia of the infraorbital nerve is severe stabbing pain in the infraorbital nerve distribution.
area such as the cheek, lateral nose, and so on (1). It is a rare cause of chronic facial pain which is quite difficult to treat.

Up to now, treatments for neuralgia of infraorbital nerve were seldom reported, therefore, there is no optimal treatment to cure the condition. As early as 1990, de Vries and Smelt (2) described the therapeutic effects of 12 patients with posttraumatic infraorbital neuralgia and recommended a neural blockade using local anesthetic as the first-line treatment choice. Traditionally, neurodestructive methods should be tried for patients with refractory neuralgia of the infraorbital nerve who have failed to achieve benefits from conservative treatment (3,4). However, injection of neurolytic agents to the nerves generates side effects of necrosis and tissue fibrosis and leads to formation of neuroma (5,6). The thermal effect of radiofrequency thermocoagulation (RFTC) leads to degeneration of the target nerve and blockage of the nerve conduction, causing complications such as sensory deprivation. Open surgery for infraorbital neuralgia comprises infraorbital nerve sectioning and avulsion (7,8). Nowadays, open surgery to block nerve conduction has rarely been employed owing to the massive trauma involved.

Pulsed radiofrequency (PRF) has been successfully applied in the treatment of some painful disorders for nearly 18 years. In this method, radiofrequency current is generated intermittently, and heat is released during an intermittent period, which causes minor tissue injury surrounding the needle puncture and prevents nerve degeneration (9,10). The apparent advantage of PRF is nondestructive which offers attractive clinical prospects. Nevertheless, the majority of authors argue that the efficacy of PRF is less than conventional RFTC (11-14). The effect of PRF on the Gasserian ganglion for trigeminal neuralgia (TN) has been assessed in many reports (12,13,15,16), but only 3 successful case reports have reported PRF being used on the trigeminal branch (10,17,18). Among those only one article described that PRF treatment relieved one intractable infraorbital neuralgia patient (17).

In this study, accurate puncture aimed at the infraorbital foramen (IOF) was conducted under computed tomography (CT) guidance and PRF treatment was given for patients who suffered neuralgia of the infraorbital nerve and failed conservative treatment comprised of drug and nerve block using steroid and local anesthetic. Large samples were observed to evaluate analgesic effectiveness and safety of PRF for infraorbital neuralgia and factors affecting efficacy were analyzed.

**Methods**

**Patients**

From January 2011 to November 2012, 36 consecutive patients with severe neuralgia of the infraorbital nerve who presented to the Pain Center at Beijing Tian-tan Hospital affiliated to the Capital Medical University were enrolled in this study. Research protocol was approved by the ethics committee of Beijing Tian-tan Hospital. All patients signed informed consent.

**Inclusion criteria**

Patients experienced paroxysmal or constant severe stabbing pain and neurological examination showed sensation hypersensitivity in the distribution area of the infraorbital nerve (1). Participants were older than 18 years of age. Preoperative numeric rating scales (NRS) (0 indicates no pain, 10 indicates the most severe, unbearable pain) was greater than 7, and reduced less than 50% after conservative treatment comprised of oral antiepileptic drugs and injection into the infraorbital nerve with steroid and local anesthetic (19). Each patient had a positive response to a diagnostic block using 2% lidocaine 1 mL prior to PRF treatment (2,19,20). Exclusion criteria: Patients with preoperative abnormal blood routine; abnormal coagulation and blood biochemistry test; abnormal electrocardiogram (ECG); infection at the puncture site; history of psychiatric disorders and narcotic drug abuse; intra- and extra-cranial lesions causing secondary neuralgia screened by head magnetic resonance imaging (MRI) or facial CT; facial herpes zoster and traumatic episodes in the infraorbital nerve area; history of invasive treatment which included RFTC, neurolytic procedure, cutting and avulsion surgery aimed at infraorbital nerve were excluded.

**Operation**

Patients were made to lie supine on a CT scanning bed and were continuously monitored for vital parameters such as blood pressure, heart rate, ECG, and pulse oxygen saturation. The negative plate of Pain Management Generator (PMG – 230, Baylis Medical Inc., Montreal, Canada) was affixed to the upper back skin of the patients.

The puncture point was identified at the intersection between the connecting line drawn from the external canthus to the midpoint of the upper lip and the vertical line through the pupil on the affected side. After local infiltration anesthesia to the puncture point, the puncture needle was inserted at the point towards the IOF. The thin-layer CT scan (2 mm/layer, x-ray CT ma-
machine, model SOMATOM, SIEMENS Company, Munich, Germany) was performed to visualize the maxillary sinus. The puncture direction was adjusted according to the correlative position between the puncture needle and the IOF via CT imaging. Adjustment was repeated under thin-layer CT scanning until a 10 cm long insulated trocar with 5 mm bare needle tip for radiofrequency treatment (PMF-21-100-5, Baylis Company, Canada) was positioned in the IOF (Fig. 1).

The stylet was removed and a radiofrequency electrode (PMK-21-100, Baylis Company, Canada) was inserted to test impedance. Electrical stimulation with a sensory threshold value of 50 Hz was implemented to confirm the position. Prickling sensation in area innervated by the infraorbital nerve was induced by 0.1–0.2 volts covering the painful site. The depth and direction of the puncture needle were slightly adjusted corresponding to the feeling of the patient to ensure

![Fig. 1. Operative procedure. Localization for puncture. CT scan of maxillary sinus shows the needle was approaching the ipsilateral infraorbital foramen. CT scan of maxillary sinus shows the needle was entering the ipsilateral infraorbital foramen. 3-D reconstruction of spiral CT shows the needle entered the ipsilateral infraorbital foramen.](image-url)
accuracy of the puncture location.

The Pain Management Generator was set in automatic PRF mode, with parameters: 42°C, 2 Hz, 120 s. Treatment was given for a total of 2 cycles.

Data Collection
NRS, effective rate (effective rate = effective cases/total cases*100%), and additional carbamazepine dosage were recorded at postoperative day one, week one, week 2, month one, month 3, month 6, year one, and year 2. Facial physical exam was performed by a trained neurologist at weekly intervals until no neurological changes were found. Patients were divided into the effective group and the ineffective group based on postoperative one-month pain relief (NRS = 0) or more than 50% reduction of NRS and patients were satisfied with the effect. Preoperative clinical data consisting of age, gender, course of disease, left/right proportion, preoperative NRS and carbamazepine dosage, intraoperative parameters consisting of operation time, stimulus voltage given at 50 Hz for position, output voltage, and local tissue resistance were recorded.

Statistical Analysis
All statistical analyses were performed with SPSS 20.0 statistical software. Continuous variables with normal distribution are expressed as mean ± SD and Student’s t test was used for statistical analysis, chi-square test was used for categorical variables. Continuous variables without normal distribution are expressed as median (minimum–maximum) and rank-sum test was used. Because postoperative one-month NRS does not show normal distribution, Spearman correlation analysis was applied. A P-value of < 0.05 was considered statistically significant.

Results

Treatment Effects
All 36 patients suffering from severe infraorbital neuralgia successfully underwent IOF puncture under CT guidance. At one month after PRF treatment, there were 25 cases in the effective group. The other 11 patients in the ineffective group were shifted to RFTC treatment due to severe pain. A total of 36 patients completed 2 year follow-up, as shown in Fig. 2.

Preoperative NRS scores showed no significant difference between the 2 groups before treatment (P > 0.05). At postoperative day one, NRS scores in both groups were reduced. NRS decreased by 50% in the effective group and 25% in the ineffective group (P > 0.05). At one week, 2 weeks, and one month after treatment, the NRS in the effective group kept reducing, but the NRS in the ineffective group returned to preoperative level, and a significant difference was found between the 2 groups (P < 0.01). No significant difference was found between NRS in the 2 groups after RFTC treatment was introduced in the ineffective group (P > 0.05), as shown in Table 1.

Effective cases (effective rate) were 25 (69%), 25 (69%), 23 (64%), 18 (50%), and 18 (50%) at postoperative month one, month 3, month 6, year one, and year 2, respectively. Seven of 25 patients in the effective group recurred post-operative, 2 recurrent patients moved to RFTC treatment and pain resolved, the other 5 patients received another PRF treatment and the effect was satisfactory, as shown in Fig. 2.

Additional Drugs
Carbamazepine was stopped in 23 (92%) of 25 patients following PRF treatment in the effective group one month after operation, 2 (8%) took low-dose carbamazepine (50 – 100 mg/time, 1~3 times per day) to fully control the pain. High-dose carbamazepine was required for 11 patients in the ineffective group at one month after operation, and carbamazepine was stopped after they received RFTC treatment and pain resolved rapidly.

Adverse Effects
After PRF 9 patients (25%) (8 cases [32%] in the effective group, one case [9%] in the ineffective group) felt mild numbness. The post facial procedure physical exam showed mild hypoesthesia in the area innervated by the infraorbital nerve simultaneously. The incidence of mild numbness or hypoesthesia showed no significant difference between the 2 groups (P > 0.05). Numbness was mild, which was endurable to patients and disappeared in about one month after PRF treatment. However, obvious sensory deprivation occurred in the same area after shifting to RFTC treatment.

Factors Affecting Efficacy
Gender, age, course of disease, left/right proportion, preoperative carbamazepine dosage and NRS, intraoperative stimulus voltage for position, and operation time showed no significant difference between the 2 groups (P > 0.05), but output voltage and tissue resistance in the ineffective group were significantly lower than the effective group (P < 0.01), which is shown in...
Fig. 2. Flow chart and outcomes of the study. PRFT = pulsed radiofrequency treatment; NRS = numeric rating scales; RFTC = radiofrequency thermocoagulation.
Table 1. Comparison of postoperative NRS between the 2 groups.

<table>
<thead>
<tr>
<th>Time Points</th>
<th>Effective group</th>
<th>Ineffective group</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>NRS</td>
<td>No.</td>
<td>NRS</td>
</tr>
<tr>
<td>Preoperative</td>
<td>25</td>
<td>8 (7–10)</td>
<td>11</td>
</tr>
<tr>
<td>Day 1</td>
<td>25</td>
<td>4 (2–9)</td>
<td>11</td>
</tr>
<tr>
<td>Week 1</td>
<td>25</td>
<td>4 (0–10)</td>
<td>11</td>
</tr>
<tr>
<td>Week 2</td>
<td>25</td>
<td>3 (0–6)</td>
<td>11</td>
</tr>
<tr>
<td>Month 1</td>
<td>25</td>
<td>0 (0–4)</td>
<td>11</td>
</tr>
<tr>
<td>Month 3</td>
<td>25</td>
<td>0 (0–3)</td>
<td>11 (RFTC applied)</td>
</tr>
<tr>
<td>Month 6</td>
<td>23*</td>
<td>0 (0–3)</td>
<td>11</td>
</tr>
<tr>
<td>Year 1</td>
<td>18#</td>
<td>0 (0–3)</td>
<td>11</td>
</tr>
<tr>
<td>Year 2</td>
<td>18</td>
<td>0 (0–2)</td>
<td>11</td>
</tr>
</tbody>
</table>

Values are expressed as median (minimum–maximum).
NRS = numeric rating scales; RFTC = radiofrequency thermocoagulation.
* 2 patients removed due to recurrence.
# Other 5 removed due to recurrence.

Table 2. Comparison of preoperative clinical data and intraoperative parameters.

<table>
<thead>
<tr>
<th></th>
<th>Effective group (( n = 25 ))</th>
<th>Ineffective group (( n = 11 ))</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/Female</td>
<td>11/14</td>
<td>5/6</td>
<td>0.936</td>
</tr>
<tr>
<td>Age (years)</td>
<td>63 ± 13</td>
<td>61 ± 11</td>
<td>0.703</td>
</tr>
<tr>
<td>Duration of disease (years)</td>
<td>5.7 ± 3.7</td>
<td>3.8 ± 2.8</td>
<td>0.142</td>
</tr>
<tr>
<td>Left/Right-sided</td>
<td>10/15</td>
<td>5/6</td>
<td>0.760</td>
</tr>
<tr>
<td>Preoperative Carbamazepine dose (mg/d)</td>
<td>660 ± 315</td>
<td>527 ± 317</td>
<td>0.253</td>
</tr>
<tr>
<td>Preoperative NRS*</td>
<td>8 (7–10)</td>
<td>8 (7–10)</td>
<td>0.597</td>
</tr>
<tr>
<td>50Hz Sensory stimulation voltage (V)</td>
<td>0.1 ± 0.0</td>
<td>0.1 ± 0.0</td>
<td>0.433</td>
</tr>
<tr>
<td>Output voltage (v)</td>
<td>61 ± 10</td>
<td>52 ± 9</td>
<td>0.009</td>
</tr>
<tr>
<td>Tissue resistance (Ω)</td>
<td>451 ± 84</td>
<td>350 ± 67</td>
<td>0.005</td>
</tr>
<tr>
<td>Duration of operation (min)</td>
<td>31 ± 11</td>
<td>31 ± 10</td>
<td>0.982</td>
</tr>
</tbody>
</table>

* Denotes values are expressed as median (minimum–maximum), otherwise as mean ± standard deviation.

Table 2. Intraoperative output voltage was significantly negatively correlated at postoperative one-month NRS \((r = -0.332, P = 0.048)\), the scatter plot of correlation analysis is shown in Fig. 3.

**Discussion**

The results of this study showed that the one-month, 3-month, 6-month, one-year, and 2-year effective rate of PRF treatment for patients with refractory infraorbital neuralgia was 69%, 69%, 64%, 50%, and 50%, respectively, which is encouraging. Carbamazepine was withdrawn in 92% of patients receiving effective PRF treatment, and low-dose carbamazepine was needed to fully control pain in the remained 8% one month after operation. Results indicated that PRF is an alternative treatment for patients with infraorbital neuralgia following ineffective conservative treatment, which removes the necessity of destructive therapy such as RFTC treatment in many patients.

The NRS of patients in the effective group showed a declining tendency. An almost 50% reduction of the NRS was observed at day one as well as week one after treatment, and an approximately 62.5% reduction was recorded at week 2. Further the best effect was achieved at month one. After PRF treatment, an extended recovery period was required to gradually reach the best efficacy, which paralleled previous studies (21,22). At present, the mechanism of efficacy of PRF treatment for neuropathic pain remains ambiguous, and probably involves downgraded microglial activation (23), increased met-enkephalin levels (24), and so on. PRF gradually improves the symptoms of
neuropathic pain through a series of neuromodulation effects (25), rather than quickly blocking pain conduction. Mild tissue damage incurred by the procedure and short-term pathologic changes of the target tissue, such as edema of endoneurium produced by the electric field effect itself (21,26-28), need a period of time to recover, which might result in a delayed effect. In clinical practice, symptomatic treatment should be given pending action of PRF and alternative treatment should not be considered in haste.

Clinically, the diagnosis of neuralgia of the infraorbital nerve is identified and confirmed by the characteristics of pain in patients and the diagnostic nerve block using local anesthetics during a pain attack. Although all patients in the study had a positive response to a diagnostic block which is a prerequisite to radiofrequency treatment, only part of our patients obtained satisfactory efficacy after PRF treatment. Destructive therapy causing long-term blockage of nerve conduction could be theoretically effective. However, in contrast with the mechanism of destructive therapy, the needle tip temperature is not more than 42°C in PRF treatment, and the pain-relieving mechanism possibly involves neuromodulation of nervous tissue caused by the electric field effect (29,30), rather than blockage of nerve conduction. Therefore, diagnostic block can only confirm the diagnosis but cannot predict the effect of non-lesion PRF.

In this research, the pain was completely alleviated in patients shifting from ineffective PRF treatment to RFTC treatment. Efficacy of PRF is obviously less than RFTC, which merits further experimental and clinical research to explore the method to improve the effect of PRF. The result is similar to recently published research about the therapeutic efficacy of PRF treatment. Although all of the researchers now believe that the effect of conventional RFTC is superior to PRF (11-14), the nondestructive advantage of PRF and the decreased selection of neurolytic treatment to some degree are still promising (15,16). At one year follow-up, 7 cases

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Fig. 3. Scatter plot of correlation between PRF output voltage and NRS at one month after PRF treatment.
(28%) underwent a recurrence in the effective group in our research, which matches with the recurrence rate following PRF treatment on the Gasserian ganglion previously reported by us (13), suggesting some methods could be further probed to prolong the pain-relief duration and reduce the recurrence rate.

Accurate placement of the radiofrequency electrode in percutaneous radiofrequency treatment is the key to successful therapy. At present, it has been reported that puncture of the IOF where the infraorbital nerve passes through was guided by ultrasound and fluoroscopy (17). However, the position of IOF has anatomic variations (31). CT may be superior to other imaging techniques in representing precise bone structures and significantly increase accuracy of the puncture compared to traditional fluoroscopy (32-34). Our research used the three-dimensional reconstruction technique in spiral CT to guide the process of the IOF puncture and the puncture success rate reached 100%.

Preoperative conditions and distance between the intraoperative puncture needle and the target nerve, which probably affected the efficacy, were not significantly different between the 2 groups. The same PRF parameters were set in all patients, and it has been found that diverse efficacy is associated with intraoperative output voltage and tissue resistance, which is consistent to our retrospective report about PRF’s impact on the Gasserian ganglion for TN (15). Intraoperative output voltage in the effective group was higher than the ineffective group, and postoperative NRS was negatively correlated with intraoperative output voltage, suggesting the electric field effect in PRF influences the curative effect on pain. The local tissue resistance determined by the local anatomic structure was significantly higher in the effective group than the ineffective group. The electric resistance was fixed, so the intraoperative output of radiofrequency therapeutic device could be properly increased in order to improve efficacy in later research.

No significant adverse effects have been reported in PRF treatment of the Gasserian ganglion for TN (12,13,15,16,35), but mild, recoverable numbness was observed in 25% of patients receiving PRF treatment of the infraorbital nerve in our research, suggesting peripheral nerve tissue is more prone to minor injuries caused by PRF treatment than the Gasserian ganglion. Fortunately, low incidence, mild degree, and short-term recovery of numbness indicate PRF treatment of the peripheral branches of the trigeminal nerve is relatively safe.

The pain was reduced via the PRF electric fields’ effect on the dorsal root ganglion (36,37), the Gasserian ganglion (12,13,15,16,35), or on peripheral branches such as the greater occipital nerve (22,38,39) and the intercostal nerve (40). Cohen et al (41) argued that the efficacy of the dorsal root ganglion treated by PRF is better than that of the intercostal nerve to relieve postoperative chest pain. At present, the optimal position of PRF treatment remains equivocal, which guarantees further randomized, double-blind trials.

**Limitations**

Limitations of this study were that this was a case series report that was conducted in a single center and only looked at the 2-year effect of PRF for infraorbital neuralgia. Therefore, observation of long-term effect, efficacy of PRF treatment for other peripheral neuralgia, and improving the efficacy of PRF treatment remains to be further studied and multicenter randomized-controlled studies need to be initiated. Furthermore, quantitative sensory testing should be used to confirm if the PRF procedure was not destructive.

**Conclusions**

PRF treatment guided by CT for refractory infraorbital neuralgia is effective and safe, which possibly could become the first-choice intervention treatment in the future. Further augmentation of output voltage of PRF might be an option to improve efficacy.

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**Conflict of interest**

The authors declare they have no relevant conflicts of interest.
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