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REVIEW

Efficacy and Safety of Pulsed Radiofrequency in Herpes Zoster Related Trigeminal Neuralgia: A Systematic Review and Meta-Analysis

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Purpose: Pulsed radiofrequency (PRF) is a neuromodulation technique for neuropathic pain. However, the effects of PRF on zoster-related trigeminal neuralgia (TN) remain unclear. The purpose of this meta-analysis is to investigate the efficacy and safety of PRF in the management of zoster-related TN.

Patients and Methods: We searched PubMed, Embase, Cochrane Library, Chinese Biomedical Database (CBM), Chinese National Knowledge Infrastructure (CNKI), and Wanfang for randomized controlled trials from their inception to August 2022. The primary clinical outcomes included pain intensity and adverse events. Secondary clinical outcomes included pain remission rate, trigeminal postherpetic neuralgia (TPHN) incidence, rescue analgesic dose, sleep quality, and quality of life (QoL).

Results: Eight studies with 788 participants were included for final analysis. PRF group exhibited lower pain scores (week 1: MD −2.10, 95% CI −3.28 to −0.93, *P*=0.0005; week 4: MD −1.56, 95% CI −2.60 to −0.51, P=0.003; week 12: MD −1.52, 95% CI −2.68 to −0.35, *P*=0.01), lower risk of TPHN incidence (RR 0.22, 95% CI 0.06 to 0.81, *P*=0.02) and better sleep quality (week 4: MD −2.52, 95% CI −3.28 to −1.77, P<0.01; week 12: MD −2.25, 95% CI −2.90 to −1.60, *P*<0.01) than control group. Besides, pain remission rate (RR 1.08, 95% CI 0.93 to 1.26, *P*=0.31) and adverse events (RR 0.95, 95% CI 0.71 to 1.27, *P*=0.74) were comparable in both groups.

Conclusion: PRF is an effective and safe treatment and it yields better effects in pain relief, improvement of sleep quality, and prevention of developing TPHN. Although PRF provides a comparable pain remission rate with the control, it is still a preferred and alternative treatment for relieving zoster-related facial pain.

Keywords: herpes zoster, trigeminal nerve, neuropathic pain, neuromodulation

Introduction

Herpes zoster (HZ) is a cutaneous disease secondary to HZ virus infection in spinal nerves and cranial nerves, characterized by vesicular rashes with burning, tingling or stabbing pain along the affected innervated area.[1,2] The reported annual morbidity of HZ ranges from 3.9 to 42/100,000 person-years and the incidence is even higher in elderly patients because of the decreased immunity.[3,4] As HZ virus invades gasserian ganglion (GG) or trigeminal nerve, the reactivation and replication of the virus would cause neuronal edema and necrosis of the infected ganglion and nerve, leading to zoster-related trigeminal neuralgia (TN),[5,6] which accounts for approximately 15%-20% HZ patients.[7] Nowadays it is also a challenging and intractable neuropathic pain, which is lack of completely effective treatment. In addition, previous studies indicated that zoster-related trigeminal pain was more refractory than herpetic neuralgia in areas from the cervical to lumbosacral level.[8,9] This chronic and severe facial pain caused by HZ infection has led to a great social burden and a poor patients' quality of life (QoL).[10] Therefore, pain physicians should explore an effective method to relieve the severe neuropathic pain and prevent the complication of trigeminal postherpetic neuralgia (TPHN).

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Consistent with zoster-related pain located in the trunk, the primary treatment of zoster-related TN is drug therapy. However, lots of patients did not respond to oral medication and some adverse events, such as nausea, vomiting and dizziness, were intolerable for elderly patients. Interventional treatment needs to consider when patients failed to conservative medication. Nevertheless, it is difficult for patients to benefit from neuro-destructive surgery as classical TN does.[11,12] Because these treatments were poorly effective, 73% of patients experienced more severe pain symptoms after surgery.[13]

Neuromodulation technique, such as nerve block (NB), gasserian ganglion stimulation (GGS), and pulsed radio-frequency (PRF), is an alternative treatment for zoster-related TN. Observational studies on NB of GG for zoster-related TN have shown that 50% pain reduction was achieved in 66.7% of patients at 3 months after local anesthetics and steroids injection.[14] Nevertheless, NB only provided a relatively shorter duration of pain relief and the use of steroids remains controversial due to its side effects.[4,14] GGS is a neuromodulation technique, which has been gradually applied in treating trigeminal neuropathy with a 44%–50% long-term pain remission rate according to previous studies.[11] Based on gate control theory,[15] GGS could inhibit or reduce the transmission of pain signals, and normalize or improve pain sensation in the process of stimulation. But the application of GGS was limited by the complications of permanent hypoesthesia, electrode dislocation, and a high overall cost. PRF is a minimally invasive treatment that delivers intermittent pulse current to target nerves and inhibits ectopic discharge, thus regulating neurological function and alleviating neuropathic pain. To date, several systematic reviews and meta-analysis have illustrated that PRF is a safe and effective measure for herpetic neuralgia from the cervical to lumbosacral areas.[16,17] However, the effects of PRF on zoster-related TN remain unclear. Although some studies reported PRF of GG could relieve facial pain, reduce the incidence and severity of TPHN and improve patients' QoL,[18–20] we could not draw a clear conclusion because possible confounding existed in most of the trials. Moreover, the only multicenter trial existed information bias and lacked a control group. The above reasons may result in low-level evidence.

Therefore, we aimed to conduct a systematic review and meta-analysis of randomized controlled trials (RCTs) to investigate the efficacy and safety of PRF in the management of zoster-related TN and provide clinical guidance about treatment options for these patients.

Materials and Methods

This review was performed in accordance with the Cochrane Handbook for Intervention Reviews and the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement.[21,22] The review's protocol was registered in PROSPERO (number CRD42022353618).

Literature Search

We selected relevant studies in English and Chinese languages from their inception to August 2022 by searching databases of PubMed, Embase, Cochrane Library, Chinese Biomedical Database (CBM), Chinese National Knowledge Infrastructure (CNKI), and Wanfang. The unpublished relevant studies were searched in Chinese Clinical Trial Registry and National Institutes of Health Register (ClinicalTrials.gov). The search terms and strategy are available in Supplement 1.

Selection Criteria

We included studies if they were RCTs done in patients with zoster-related TN and undesirable pain control (visual analog scale (VAS) or numeric rating scale (NRS)>3), compared PRF to another treatment strategy, and reported postoperative pain evaluation. We excluded observational and retrospective studies, studies without clear description of inclusion and exclusion criteria, and studies with unavailable data.

Data Extraction

Two authors (CHW, ZD) extracted literature independently by inspecting the titles, abstracts, and full texts of studies to assess whether the literature was included in this review or not. Data would be extracted as follows: (1) Basic information (author, publication year, sample size, duration of follow-up). (2) Characteristics of the subject included in the study (age, gender, mean course of disease). (3) Intervention and comparison (duration of treatment, parameters of

PRF and dosage of control group). (4) Primary clinical outcomes included VAS or NRS scores after PRF or control treatment and adverse events; secondary clinical outcomes included pain remission rate, TPHN incidence, rescue analgesic dose, sleep quality assessed by Pittsburgh sleep quality index (PSQI) and QoL assessed by 36-item Short-Form Health Survey (SF-36). Both authors would review the collected data and the disagreement between them would be resolved by another author (BGW).

Quality Assessment

Using the Cochrane risk of bias tool, two researchers (CHW, ZD) assessed the methodological quality and risk of bias of the included studies in the following aspects: selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias. The judgments of bias were reported as "low risk", "high risk", or "unclear risk" according to its methodological section.

Statistical Analysis

Review Manager statistical software (RevMan Version 5.4, Cochrane Collaboration, Oxford, England) was used to perform the meta-analysis. We used relative risk (RR) with 95% confidence interval (CI) to report dichotomous data, and used mean difference (MD) or standardized mean difference (SMD) with 95% CI to present continuous variables for quantitative analysis. Pain intensity, rescue analgesic dose, PSQI and SF-36 scores were regarded as continuous data, while pain remission rate, adverse events and TPHN incidence were classified as dichotomous data. The chi-square test and I^2 test were used to evaluate the heterogeneity of the included studies. Random effect models would be used when heterogeneity was present in the studies which meant the P value < 0.10 and $I^2 > 50\%$, else fixed-effect models would be applied to get the pooling effect of outcomes. When heterogeneity was obviously significant, a "leave-one-out" sensitivity analysis would be performed to investigate the source of heterogeneity. The level of significance was set at P value < 0.05.

Results

Study Selection

We initially identified 950 references by searching databases and 504 references of which were excluded because of duplicates. A total of 446 references were screened for titles and abstracts, and 29 references of which were evaluated as eligible after the first level of screening. The full texts of the preliminary eligible references were then retrieved, 21 references of which were excluded based on the inclusion and exclusion criteria. As a result, 8 remaining studies[23–30] were selected for our final analysis (Figure 1).

Study Characteristics

Our review included studies published between 2013 and 2022, with a total of 788 participants. All the participants were diagnosed with zoster-related TN and accepted PRF or other treatment with the results of postoperative pain evaluation. Three trials[23,29,30] included patients who had suffered zoster-related TN over 3 months. One trial[28] included patients with course of disease over 1 month, while the other trials[24–27] involved patients within 3 months. The mean age of the patients ranged from 48.3 to 67.2 years. Only one trial[23] did not report the exact duration of disease. The mean duration of disease in the other trials ranged from 5.8 days to 5.5 months. Prior to and after treatment, all of the included trials[23–30] reported a 10-point VAS to assess the pain intensity. Five trials[23–25,28,29] of which reported pain remission rate. Gu et al[23] defined pain remission as the postoperative VAS was less than 4, while the other trials[24,25,28,29] considered pain remission when patients achieved 50% pain reduction or more. Six trials[25–30] reported adverse events after treatment, two[25,26] of which reported TPHN incidence. Rescue analgesic dose, PSQI and SF-36 were reported in different trials,[25–27,29,30] respectively. Follow-up lasted for 2 days to 12 months in the included studies. The detailed characteristics of the studies is listed in Table 1.

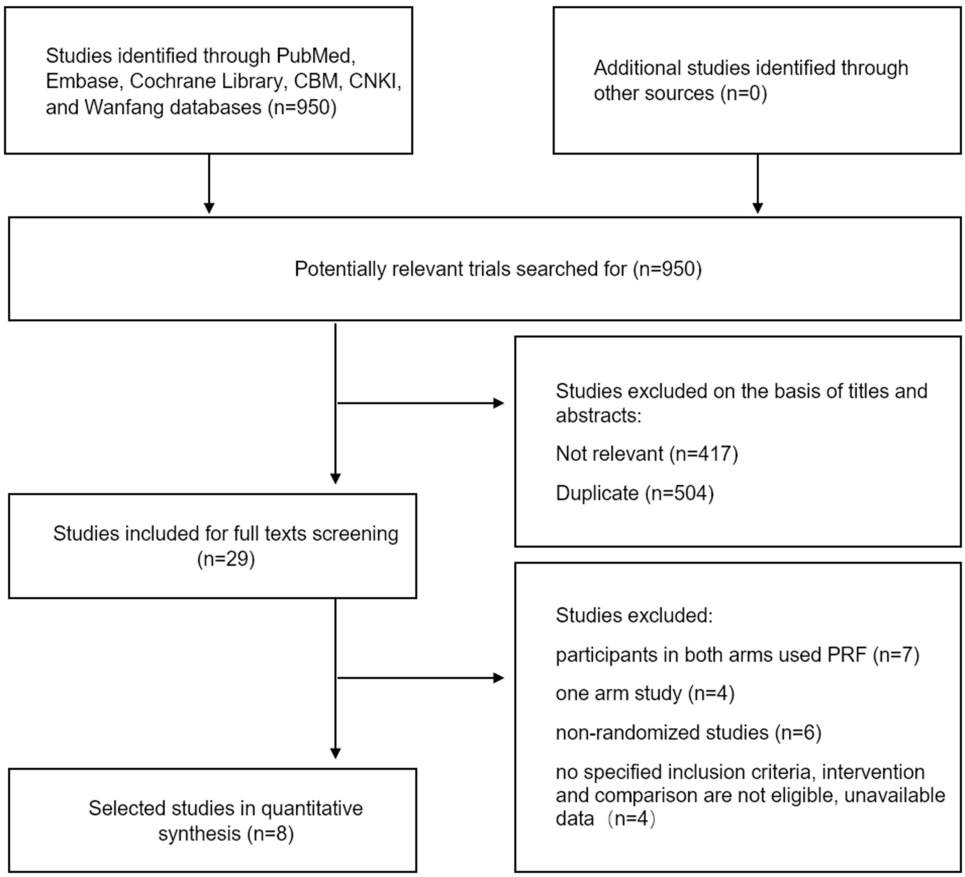

Figure 1 Flow diagram of study screening.

Risk of Bias Assessment

Seven trials[23,25–30] were assessed as "low risk" of sequence generation since the participants were grouped by digital random method. As a result of non-reporting of an appropriate random sequence generation method, and the lack of allocation concealment, one trial[24] was classified as "high risk". Six trials[23,25,26,28–30] were deemed "unclear risk" of allocation concealment due to a lack of information. Only one trial[27] was rated as "low risk" of this item because its allocation procedure depended on a computer-generated allocation sequence. Seven trials[23–26,28–30] exhibited performance bias because of the lack of information about blinding of personnel and outcome assessment. One trial[27] reported that personnel and participants were unaware of the groupings due to well-designed placebo devices and sham PRF group, and this trial was classified as "low risk" of performance bias. Detection bias was assessed as "unclear risk" in all the trails[23–30] because of a lack of information. Three patients in one trial[26] were lost to follow-up without any explanation, raising some concerns in attrition bias. The other trials[23–25,27–30] were deemed "low risk" because no incomplete outcome data were detected. None of the included trials exhibited selective reporting, but four[23,24,29,30] of them did not report conflicts of interest and funding sources, which raised some concerns as regards other bias. Since no more than 10 studies were included, publication bias would not be assessed. The detailed results are summarized in Figure 2.

Primary Outcome

Overall Pain Reduction

The pooled analysis of the 8 studies[23–30] assessed VAS at the end of follow-up was conducted and the results indicated that PRF was superior to other treatments in relieving zoster-related facial pain (MD −1.17, 95% CI −1.91 to −0.42,

Table 1 Characteristics of the Included Studies

Study	Inclusion Criteria	Sample Size (M/F)	Age (Mean ±SD)	Mean Course of Disease	Parameters	Outcomes	Baseline Scores (Mean ±SD)	Intervention	Follow-Up
Gu et al[23] 2015	1.V1 TPHN> 3 mons 2.VAS≥4	P:25/12 C:25/12	P:59.2 ±14.1 C:58.4 ±13.6	NR	P: sensory stimulation: 0.4–0.7V, 50Hz, 42°C; treatment parameters: 2Hz, 42°C, 120s for 1 time C: 2% lidocaine 0.3–0.5mL + 3.5mg compound betamethasone per 10 days, 3 times in total	1.VAS 2.pain remission rate	P: 8.2±1.3 C:8.3±1.5	P: GG PRF C: supraorbital nerve block	3 months
Liu et al[24] 2013	1.zoster-related TN <14 days 2.VAS≥7	28/32	67.2 ±17.6	5.8±2.6 days	P: sensory stimulation: 50Hz, 42°C; Treatment parameters: 2Hz, 20ms, 42°C, 120s for 2 times; 1% lidocaine 6mL per day, 10 times in total C: 1% lidocaine 6mL per day, 10 times in total	1.VAS 2.pain remission rate	P: 8.3±0.9 C:8.4±1.0	P: GG PRF+SGB C: SGB	2 days
Shi et al[25] 2020	1.V1 zoster-related TN <30 days 2.VAS≥4	P: 16/9 C: 11/14	P: 66.3 ±6.2 C: 65.4 ±9.4	P: 19.7 ±4.9 days C: 12.4 ±5.6 days	P: sensory stimulation: 0.3V, 50Hz, 42°C; treatment parameters: 2Hz, 42°C, 120s for 2 times C: 0.2% ropivacaine 0.5mL + 1.75mg compound betamethasone per 7 days, 2 times in total	1.VAS 2.pain remission rate 3. rescue drug dose 4.TPHN incidence 5.adverse events	P: 5.6±0.8 C: 5.6±1.0	P: supraorbital nerve PRF C: supraorbital nerve block	3 months
Sun et al[26] 2021	1.V1 zoster-related TN <10 days 2.VAS>5 3.did not accept invasive treatment before	P: 11/12 C: 9/11	P: 67.2 ±12.9 C: 66.8 ±13.1	P: 5.8±1.6 days C: 5.9±1.5 days	P: sensory stimulation: 0.5V, 50Hz, 42°C; treatment parameters: 2Hz, 20ms, 42°C, 300s for 1 time C: gabapentin 300mg PO, tid; tramadol 50–100mg PO, bid	1.VAS 3. PSQI 3.TPHN incidence 4.adverse events	P: 8.3±1.1 C: 8.0±1.0	P: supraorbital nerve PRF C: gabapentin and tramadol	3 months

(*Continued*)

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Table 1 (Continued).

Study	Inclusion Criteria	Sample Size (M/F)	Age (Mean ±SD)	Mean Course of Disease	Parameters	Outcomes	Baseline Scores (Mean ±SD)	Intervention	Follow-Up
Wan et al[27] 2019	1.HZ infection <90 days 2.age> 60 3.refactory to formal treatment 4.VAS≥5	P: 25/21 C: 27/20	P: 65.5 ±13.2 C: 65.9 ±13.6	P: 59.2 ±16.4 days C: 63.1 ±18.5 days	P: sensory stimulation: 50Hz, 42°C; treatment parameters: 2Hz, 20ms, 42°C, 40–90V, 900s for 1 time C: sham	1.VAS 2.SF-36 3.rescue drug dose 4.adverse events	P: 7.3±2.3 C: 7.3±2.4	P: GG PRF C: sham	6 months
Wang et al[28] 2019	1. zoster-related TN >1 mon 2.VAS>5	P: 9/9 C: 8/10	P: 53.6 ±7.7 C: 51.9 ±9.3	P: 2.7±2.1 months C: 3.0±1.1 months	P: sensory stimulation: 50Hz, 0.5–1.0mA, 42°C; treatment parameters: 2Hz, 42°C, 120s for 2 times; gabapentin 0.3g PO, tid C: 1% lidocaine 6mL + 7mg compound betamethasone per 5–7 days, 3 times in total; gabapentin 0.3g PO, tid	1.VAS 2.pain remission rate 3.adverse events	P: 6.6±1.2 C: 7.0±0.6	P: supraorbital/ maxillary/ mandibular nerve PRF+ gabapentin C: supraorbital/ maxillary/ mandibular nerve block+ gabapentin	12 months
Yuan et al[29] 2021	1.TPHN>3 mons 2.VAS≥5 3.age 18–70	P: 15/22 C: 17/20	P: 49.2 ±8.8 C: 48.3 ±9.1	P: 5.2±1.6 months C: 5.5±1.7 months	P: treatment parameters: 2Hz, 42°C, 120s for 2 times; gabapentin 0.3g PO, tid C: 1% lidocaine 6mL + 7mg compound betamethasone per 7 days, 4 times in total; gabapentin 0.3g PO, tid	1.VAS 2.pain remission rate 3. PSQI 4.adverse events	P: 6.8±1.5 C: 6.7±1.4	P: supraorbital/ maxillary/ mandibular nerve PRF+ gabapentin C: supraorbital/ maxillary/ mandibular nerve block+ gabapentin	3 months
Zhu et al[30] 2022	1.TPHN>3 mons 2.VAS>4	P: 95/84 C: 96/83	P: 53.1 ±3.8 C:52.7 ±3.2	P: 4.4±0.7 months C: 4.3±0.6 months	P: treatment parameters: 2Hz, 20ms, 45V, 42°C, 120s for 1 time; pregabalin 75mg PO, bid C: pregabalin 75mg PO, bid	1.VAS 2. SF-36 3.adverse events	P: 7.5±1.2 C: 7.7±1.3	P: GG PRF+ pregabalin C: pregabalin	1 month

Abbreviations: TN, trigeminal neuralgia; TPHN, trigeminal postherpetic neuralgia; P, PRF group; C, control group; NR, not report; VAS, visual analogue scale; SGB, stellate ganglion block; GG, gasserian ganglion; PRF, pulsed radiofrequency; PSQI, Pittsburgh sleep quality index.

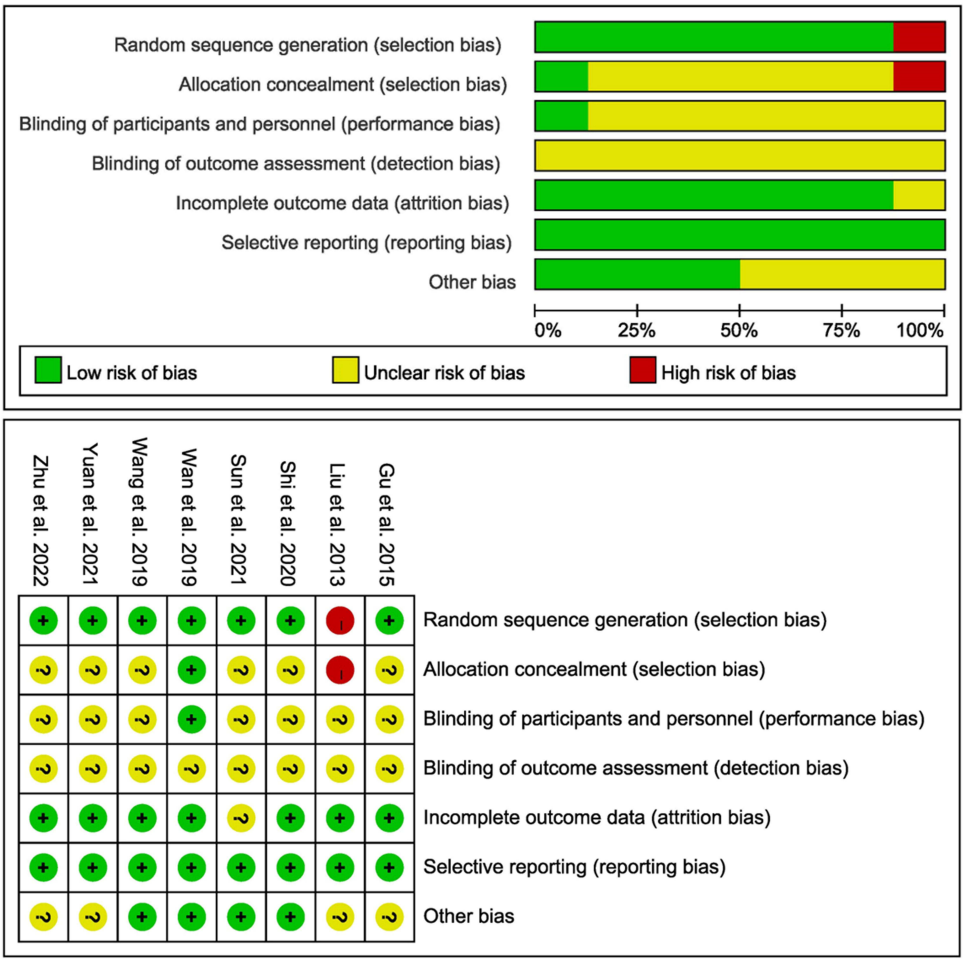


Figure 2 Risk of bias of the included studies.

P=0.002, I^2=99%, Figure 3). Because a high heterogeneity was detected, we carried out a sensitivity analysis with each study removed. The result yielded the pooled effect was robust and the source of heterogeneity did not be explored.

Pain Reduction at Different Time Points of Follow-Up

The subgroup analysis of 1–3 days[23,24,27,28] after intervention showed that both PRF and control group had a similar effect in relieving pain intensity (day 1–3: MD −1.91, 95% CI −4.10 to 0.28, P=0.09, I^2=99%, Figure 4). However,

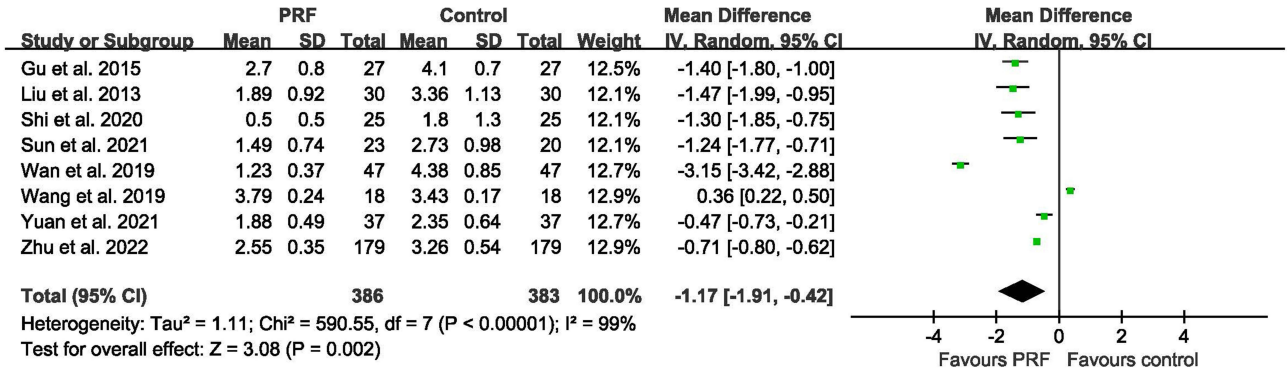


Figure 3 Comparison of PRF and control treatment: overall pain reduction at end of follow-up.

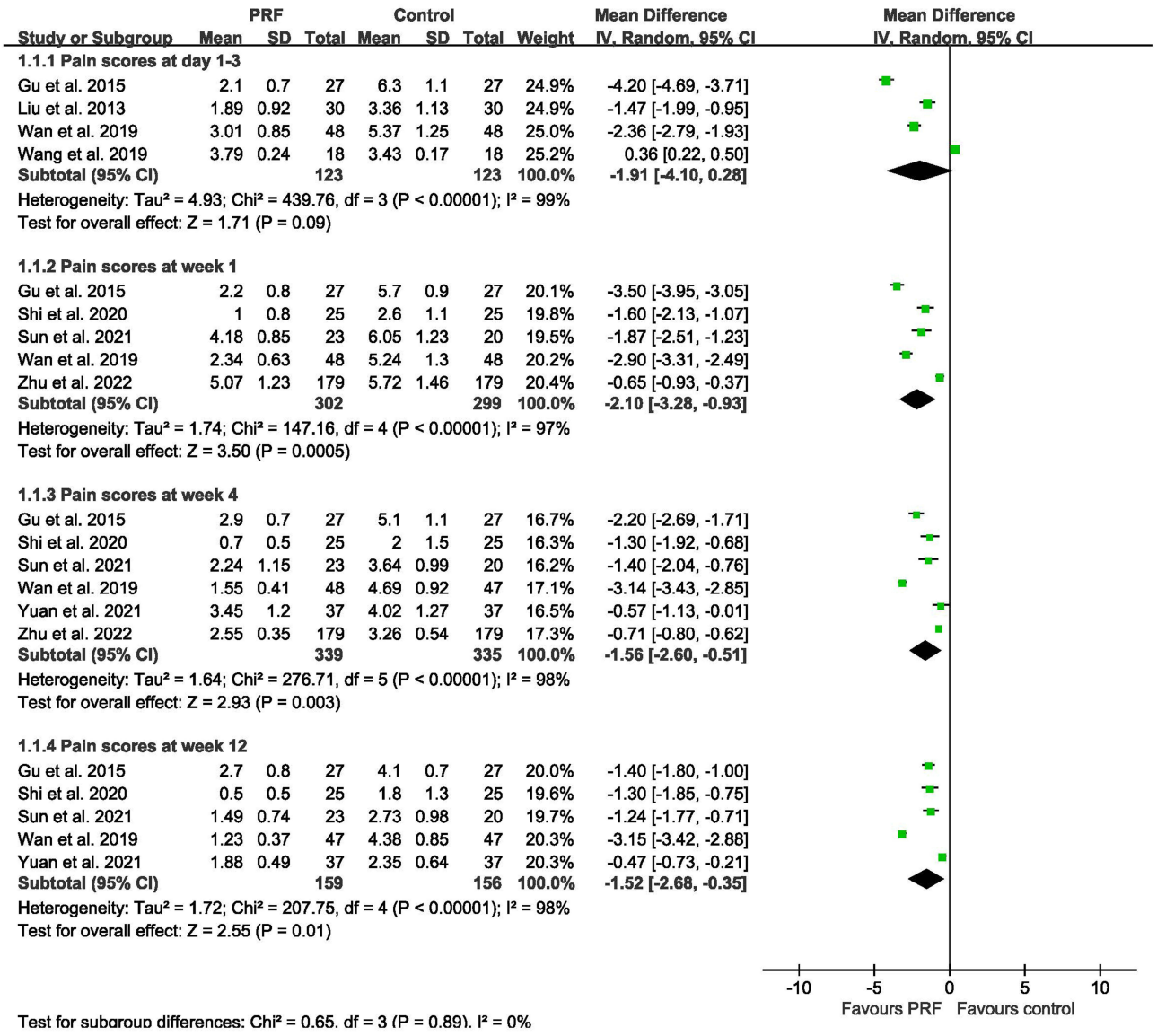


Figure 4 Comparison of PRF and control treatment: pain reduction at different time points of follow-up.

subgroup analysis of 1 week,[23,25–27,30] 4 weeks[23,25–27,29,30] and 12 weeks[23,25–27,29] indicated that PRF was more effective in pain reduction than other treatments (week 1: MD −2.10, 95% CI −3.28 to −0.93, P=0.0005, I^2=97%; week 4: MD −1.56, 95% CI −2.60 to −0.51, P=0.003, I^2=98%; week 12: MD −1.52, 95% CI −2.68 to −0.35, P=0.01, I^2=98%, Figure 4). Nevertheless, the subgroup analysis exhibited a high heterogeneity and a sensitivity analysis was performed. The overall effect in each group did not differ when either study was removed, which suggested the explanation of heterogeneity was not identified.

Pain Reduction in Different PRF Targets

PRF target on GG[23,24,27,30] yielded a better analgesic effect than other treatments (GG PRF: MD −1.68, 95% CI −3.01 to −0.35, P=0.01, I^2=99%, Figure 5). While PRF target on trigeminal nerve[25,26,28,29] showed a similar analgesic effect when compared with other treatments (trigeminal nerve PRF: MD −0.63, 95% CI −1.42 to 0.16, P=0.12, I^2=96%, Figure 5). Statistical heterogeneity was also detected and the source of which was unclear. When each study was excluded, the pooled effect remained stable.

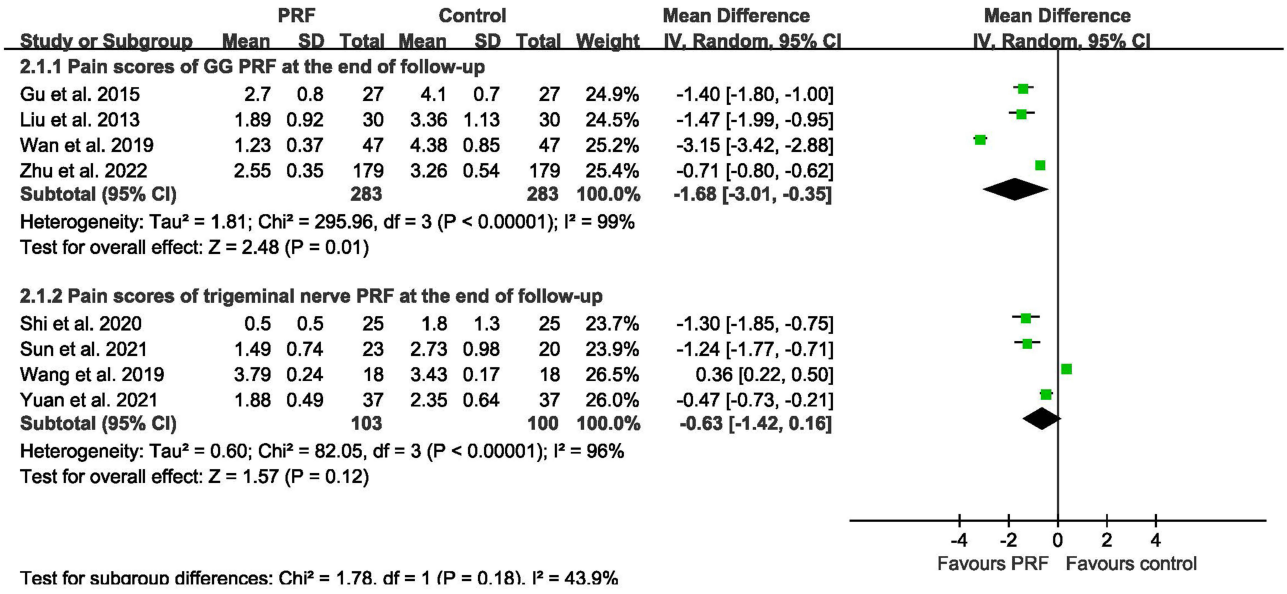


Figure 5 Comparison of PRF and control treatment: pain reduction in different PRF targets.

Pain Reduction in Different Courses of Disease

In terms of patients with course of disease <3 months, the result indicated that VAS scores were lower in PRF group than control group at 4 weeks[25–27] and 12 weeks[25–27] after intervention (week 4: MD −1.97, 95% CI −3.34 to −0.60, P=0.005, I^2=95%; week 12: MD −1.91, 95% CI −3.34 to −0.49, P=0.008, I^2=97%, Figure 6). Regarding patients with course of disease >3 months,[23,29,30] the result also favored PRF group with a better analgesic effect (week 4: MD −0.90, 95% CI −1.36 to −0.43, P=0.0002, I^2=82%, week 12: MD −0.92, 95% CI −1.83 to −0.01, P=0.05, I^2=93%, Figure 6). The heterogeneity was statistically significant in this subgroup analysis. Thus, we performed a sensitivity analysis and the result was not changed after each study was removed.

Adverse Events

Six trials[25–30] with 131 participants mentioned adverse events as an outcome of research and none of the trials reported severe complications such as nerve injury, intracranial infection and so on. The observed adverse events included facial swelling, nausea, dizziness, drowsiness, fatigue, rash and bradycardia during surgery. There was no significant difference in adverse events between PRF and control group (RR 0.95, 95% CI 0.71 to 1.27, P=0.74, I^2=0%, Figure 7). The robust pooled effect was also obtained through a sensitivity analysis.

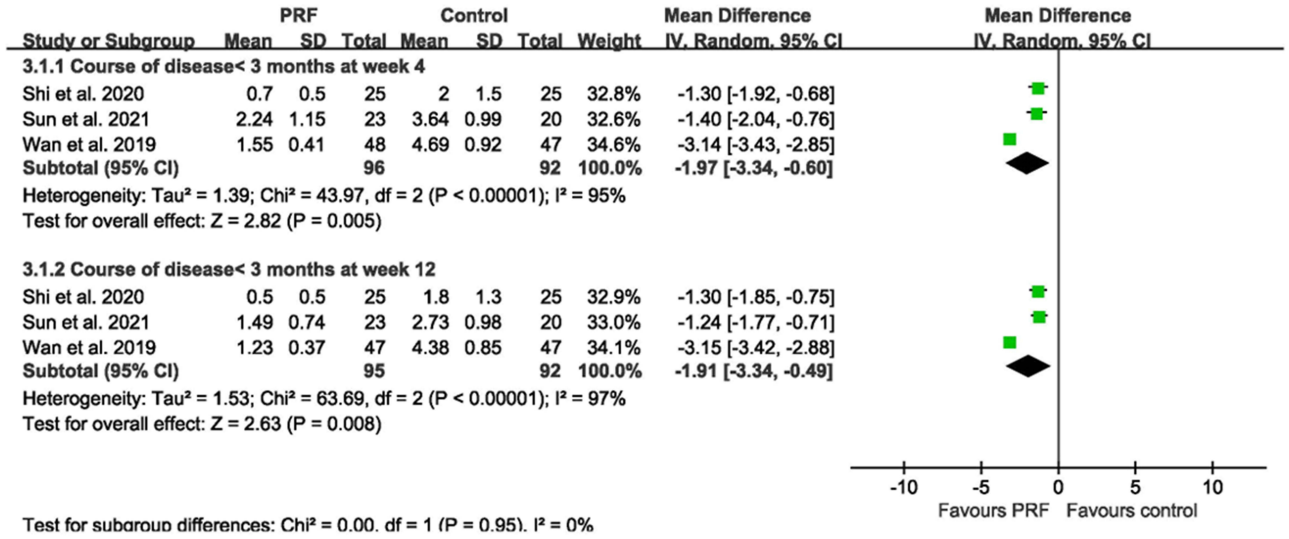
Secondary Outcome

Pain Remission Rate

Five trials[23–25,28,29] reported pain remission rates in different evaluation criteria. In this review, we defined pain remission as VAS scores decreasing over 50% at the end of follow-up. According to our criteria, four trials[24,25,28,29] were involved in the meta-analysis and the result indicated that there was no significant difference between PRF and control group (RR 1.08, 95% CI 0.93 to 1.26, P=0.31, I^2=0%, Figure 8). The sensitivity analysis also yielded a stable pooled effect.

TPHN Incidence

Shi et al[25] and Sun et al[26] reported TPHN incidence in their studies and the lower risk of TPHN incidence in PRF group indicated that PRF was superior to control group in preventing the development of TPHN (RR 0.22, 95% CI 0.06 to 0.81, P=0.02, I^2=0%, Figure 9). The sensitivity analysis was unable to perform because only two trials were included.



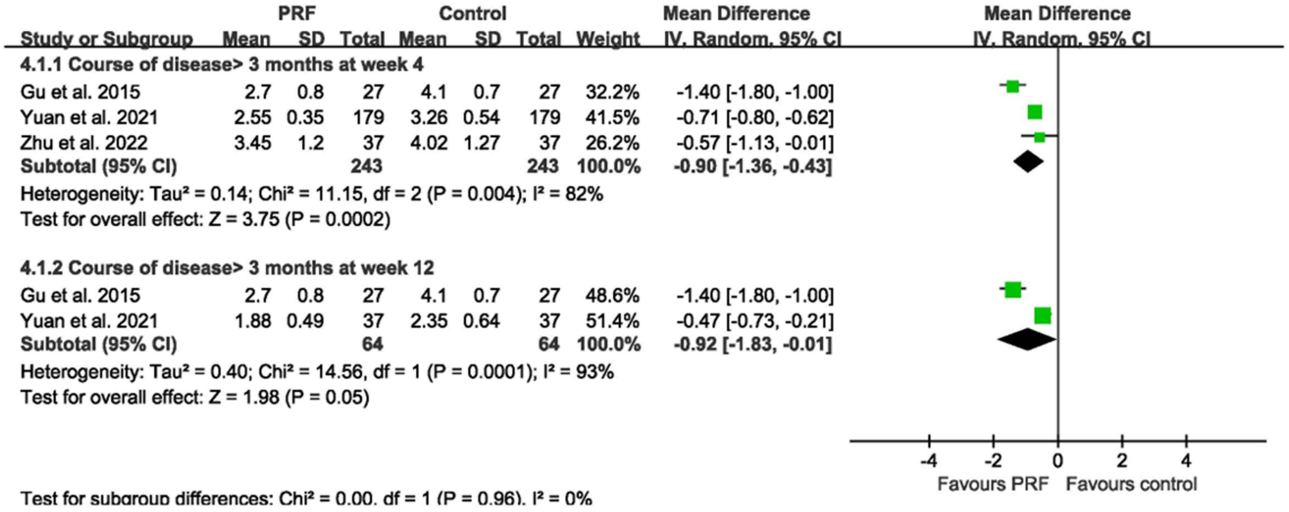


Figure 6 Comparison of PRF and control treatment: pain reduction in different courses of disease.

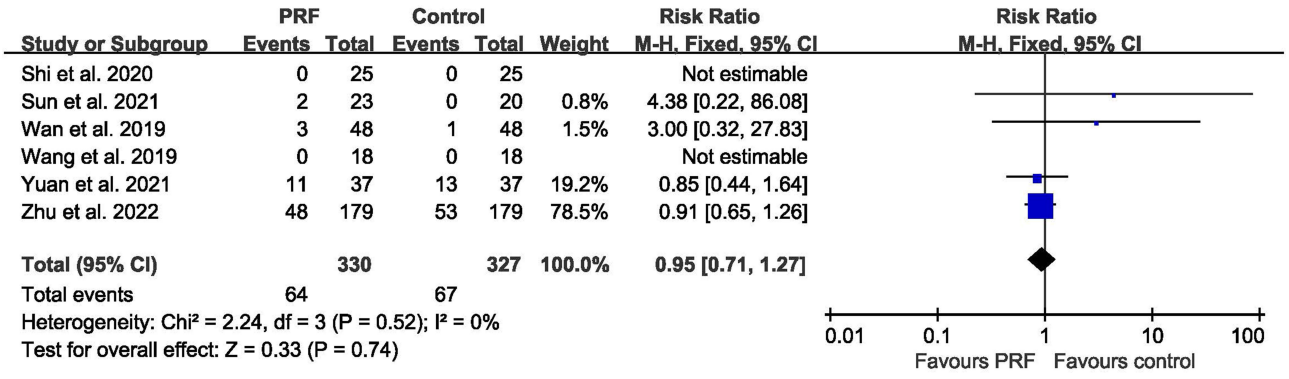


Figure 7 Comparison of PRF and control treatment: adverse events.

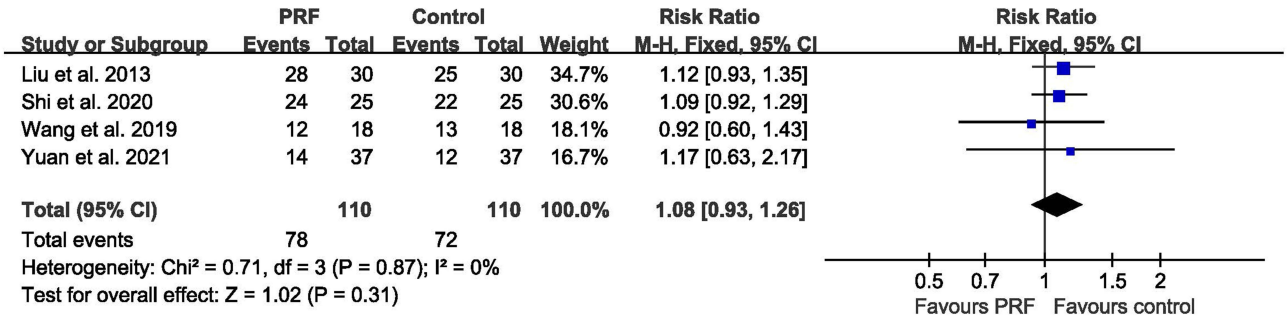


Figure 8 Comparison of PRF and control treatment: pain remission rate.

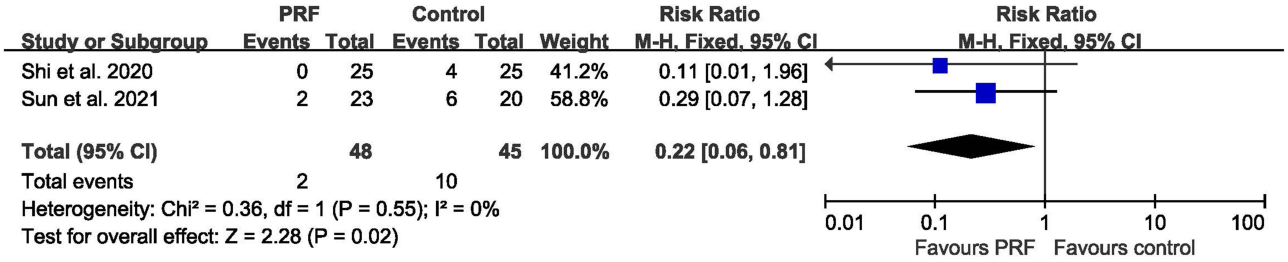


Figure 9 Comparison of PRF and control treatment: TPHN incidence.

Sleep Quality

Sun et al[26] and Yuan et al[29] examined sleep quality by using PSQI and the pooled effect showed that PRF group had a better sleep quality when compared with control group at 4 weeks and 12 weeks after intervention (week 4: MD −2.52, 95% CI −3.28 to −1.77, $P<0.01$, $I^2=0\%$; week 12: MD −2.25, 95% CI −2.90 to −1.60, $P<0.01$, $I^2=0\%$, Figure 10). The sensitivity analysis was unable to perform because only two trials were included.

Sf-36

Wan et al[27] and Zhu et al[30] reported SF-36 changes from 1 week to 6 months and 1 week to 4 weeks after intervention respectively. All domains of SF-36 in the two trials indicated that PRF could improve QoL in patients with zoster-related TN when compared with control group (all $P<0.01$).

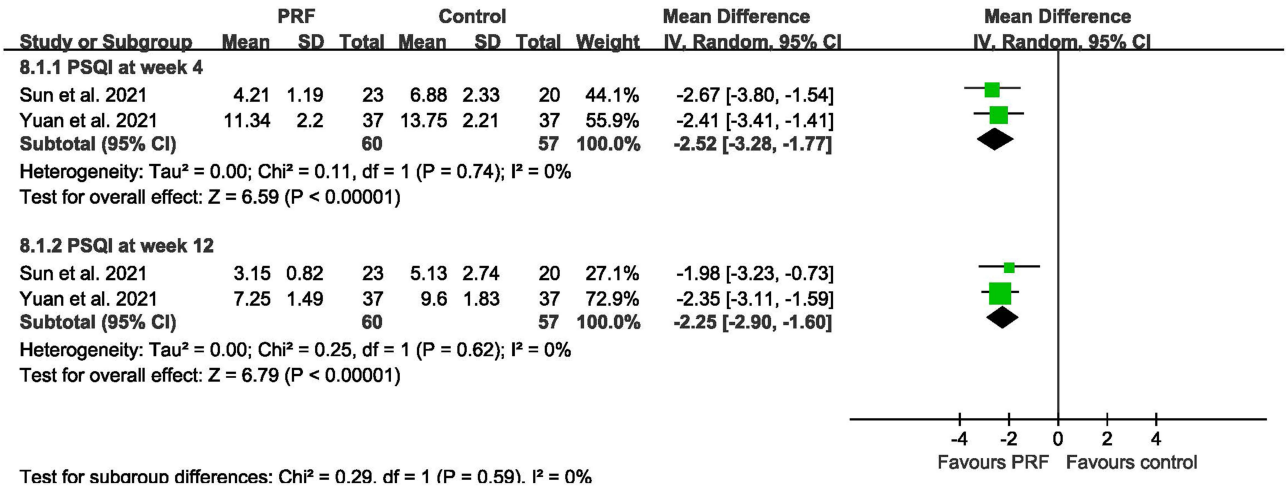


Figure 10 Comparison of PRF and control treatment: sleep quality.

Rescue Analgesic Dose

Yuan et al[29] and Wan et al[27] reported the use of rescue analgesics after intervention. Wan et al[27] used pregabalin as a rescue analgesic drug but did not mention a specific regimen. Yuan et al[29] reported three cases using rescue analgesics in PRF group and ten cases in control group, while the type, dose and frequency of analgesic drugs were not mentioned. Owing to the above unknown data, it was not pooled in this meta-analysis.

Discussion

Main Findings

There are three main findings in our meta-analysis. First, PRF significantly alleviated zoster-related facial pain when compared with control group, but the remission rate was similar in both groups. Second, PRF seemed to have the strength of preventing the development of TPHN. Third, no severe adverse events were observed and the reported complications were comparable in either group.

Efficacy Analysis

In terms of pain intensity, there was a statistically significant VAS decrease by PRF for zoster-related TN when compared with NB or pharmacotherapy. The subgroup analysis at different time points of follow-up yielded a non-significant difference in VAS scores between PRF and control at 1–3 days after intervention, while PRF yielded a better pain reduction at 1, 4, and 12 weeks after intervention. The results suggested that the analgesic effect of PRF seemed to develop slowly and needed more time to achieve its optimum. Meanwhile, this finding is consistent with other literature, which illustrated that the neuromodulation effect of PRF occurred gradually and reached its maximal at 3 months after intervention.[8] This phenomenon could be explained by the possible mechanisms of PRF. It is believed that zoster-related neuropathic pain develops because HZ virus-induced persistent inflammation and neuronal damage alter the function of neurons and cause ectopic spontaneous discharges, leading to peripheral and central sensitization.[31–34] However, for established changes in the peripheral and central nervous systems, PRF depends on the regulation at the microscopic or subcellular levels,[35] such as regulation of plasticity of synapses,[36] inhibition of ectopic spontaneous discharge and enhancement of noradrenergic and serotonergic descending inhibitory pathways,[37] to reverse sensitization and the process is relatively longer. In contrast, NB could provide prompt analgesic effect, as well as vasodilation, microcirculation improvement and prevention of TPHN development. Nevertheless, the application of steroids remains controversial due to its contradictions and side effects, although some studies reported it could reduce inflammatory reactions and neuronal edema.[8] Besides, some concerns existed because of a small sample size and a lack of control group in the above studies. Given the clinical effects of pain reduction and side effects of drugs, PRF is a preferred treatment. Concerning the remission rate, PRF and control group yielded a comparable outcome, which indicated that PRF and NB with or without gabapentin could provide an over 50% pain reduction, but for the pain intensity after treatment, PRF was superior to NB.

With regard to pain reduction of different PRF targets, the results showed PRF target on GG was superior to control group in pain relief, while PRF target on trigeminal nerve showed an identical analgesic effect when compared with control group, which confirmed PRF target on GG provided better clinical effects from another side. This finding is also consistent with the previous study that investigated GG PRF and trigeminal nerve PRF for the treatment of TPHN.[8] It draws the same conclusion that GG PRF was more effective in pain management and improvement of QoL with an efficiency rate of 86.7% compared with 68.9% of trigeminal nerve PRF. It is believed that HZ virus reactivates and replicates in the latent dorsal root ganglia (DRG), leading to partial inflammatory reaction, neuronal edema and even necrosis in the affected ganglia.[34] GG contains sensory afferent neuron body, similar to DRG, and it is equally essential in the process of signal transmission from the peripheral trigeminal nerves to the central nervous system.[38] Compared with PRF of trigeminal nerve, PRF target on GG is closer to the impaired neurons, so as to exert a better neuromodulation effect, which might be the explanation for our findings.

Regarding pain reduction in patients with different course of disease, most relevant studies reported that the shorter the time from pain onset to PRF, the better the pain reduction would appear,[39,40] especially in patients who received PRF

within 3 months after herpes onset. However, most of the patients in previous studies were involved with zoster-related thoracic neuralgia. For patients with zoster-related TN, the effects of PRF of course of disease < 3 months and > 3 months have not been identified. The subgroup analysis of pain reduction in patients with different courses of disease revealed that the neuromodulation effect of PRF was valid in patients with either course of disease < 3 months or course of disease > 3 months.

TPHN incidence is also required to be investigated because this condition is persistent and unresolvable, and it needs more medical attention. Some studies indicated that PRF, NB, glucocorticoids, antiviral drugs and HZ vaccine were effective measures of PHN prevention, but these protective measures, except for HZ vaccine, were lack of strong evidence.[41,42] Our meta-analysis of TPHN incidence indicated that based on a better pain reduction, PRF was superior to NB and medication in preventing TPHN.

Safety Analysis

It is well known that elderly patients aged over 60 are the most susceptible population of HZ infection with a 60%–75% incidence of developing PHN,[43] and this condition is more intractable especially when HZ virus invades trigeminal ganglion. Elderly patients should cause us more attention because their renal function decreases with aging, and the decreased pharmacokinetic and pharmacodynamic changes would lead to more drug-related adverse reactions.[44,45] PRF, as a minimally invasive neuromodulation technique, is different from NB or medication and it does not need to consider contraindications to drugs for elderly patients with multiple comorbidities. In our meta-analysis, no severe complications were observed and the reported adverse events were comparable in both PRF and control group. It is important to note that four cases (1.21%) of bradycardia in the included study were reported during foramen ovale puncture.[27] Besides, Jia et al also reported three cases (3.53%) of transient bradycardia during PRF procedure.[19] However, the bradycardia was almost transient and it could be resolved without any treatment. Therefore, PRF is a relatively safe and acceptable method for most elderly patients with zoster-related TN.

Implications of Further Studies

Existing studies have confirmed PRF as an effective treatment for zoster-related neuralgia in the trunk. Similarly, our meta-analysis provides evidence of the efficacy and safety of PRF for zoster-related neuralgia in the orofacial region. More attention should be focused on the comparison of different modes or parameters of PRF (voltage, duration) in zoster-related neuralgia. In addition, the included studies did not involve a comparison of GGS or trigeminal nerve stimulation with PRF. The reason might be attributed to financial burden or some considerations of electrode dislocation induced inadequate analgesia. However, spinal cord stimulation is the more preferred neuromodulation technique than PRF in patients with zoster-related neuralgia in the trunk.[16] Thus, RCTs should be designed to further investigate the efficacy and safety of GGS or trigeminal nerve stimulation versus PRF in zoster-related TN in the future.

Strengths and Limitations

There are several strengths in our meta-analysis. First, to our knowledge, it is the first study conducting quantitative synthesis of efficacy and safety of PRF in zoster-related TN, while other meta-analysis mainly focused on zoster-related neuralgia in the trunk. Second, we performed a subgroup analysis of patients at different time points of follow-up, with different courses of disease and different PRF targets. These various clinical effects of PRF were described in detail in our review. Third, this review was performed based on the Cochrane standards and system error could be reduced by the assessment of two independent authors.

However, our meta-analysis also has some limitations. First, most of the primary outcomes exhibited a considerable heterogeneity and the source of which may attribute to the different PRF settings, PRF target, NB formula and combination treatment in PRF group or the control, which caused some inconsistency in this meta-analysis. Second, blinding designs were not reported in most of the included studies, which led to a decline in methodological quality. Third, most of the included studies followed up within 3 months, long-term effects could not be identified.

Conclusion

PRF is an effective and safe neuromodulation technique and it yields better effects in pain relief, improvement of sleep quality and prevention of developing TPHN in patients with zoster-related TN. Although PRF provides a comparable pain remission rate with the control, it is still a preferred and alternative treatment for relieving zoster-related facial pain.

Consent for Publication

The authors confirm that all the contents in this review can be published.

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