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CLINICAL TRIAL REPORT

A Retrospective Observation of Gasserian Ganglion Pulsed Radiofrequency Therapy Combined with Low-Dose Morphine Injection in the Treatment of Ophthalmic Herpetic Neuralgia

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Purpose: This retrospective study was to investigate the efficacy of Gasserian ganglion pulsed radiofrequency therapy (PRF) combined with low-dose morphine injection in the treatment of refractory ophthalmic herpetic neuralgia.

Patients and methods: A total of 40 intractable ophthalmic herpetic neuralgia patients who received Gasserian ganglion PRF therapy in Pain Department of Nanjing Drum Tower Hospital were retrospectively analysed, with an average age of 70.2 ± 8.5 years and an average disease course of 30 (30, 60) days. According to different interventions, they were divided into two groups: Group A, 19 patients who received Gasserian ganglion PRF therapy combined with 0.2 mg morphine injection via puncture needle; Group B, 21 patients who received only Gasserian ganglion PRF therapy. Data related to the length of hospital stay and associated costs, numerical rating scale scores (NRS), intravenous morphine and oral oxycodone doses during hospitalization, Short form McGill pain questionnaire and Pittsburgh sleep quality index (PSI), and conditions of opioid use and postherpetic neuralgia after discharge were collected in the two groups. SPSS 25.0 was used to perform statistical analysis on data.

Results: The hospital stay, hospitalization costs, and oxycodone dosages for Group A were lower than those for Group B ($p = 0.02$, $p = 0.015$ and $p = 0.023$, respectively). The proportion of patients in group A still taking oral opioids 1 month after discharge and experiencing postherpetic neuralgia 6 months after the onset was lower than that in group B ($p = 0.004$ and $p = 0.049$). The NRS upon discharge, as well as the McGill and PSQI scores at the time of discharge and at 1, 3, 6 and 12 months post-discharge, were all significantly reduced compared to those measured upon admission in two groups ($p = 0.000$).

Conclusion: Gasserian ganglion PRF therapy combined with low-dose morphine injection offers an alternative option for managing intractable herpetic neuralgia and prevention of postherpetic neuralgia in ocular branches.

Clinical Trial Registration: ChiCTR2300073281.

Keywords: ophthalmic, herpetic neuralgia, pulsed radiofrequency, Gasserian ganglion, opioids

Introduction

Among patients with acute herpes zoster, trigeminal nerve involvement accounts for 8% to 28%, and ophthalmic branch involvement accounts for more than 80% of cases, especially in elderly men.[1] Unlike typical trigeminal neuralgia, herpetic zoster-associated facial pain is a medical problem and is often difficult to treat with oral tricyclic antidepressants, topical anaesthetics or capsaicin, intrathecal corticosteroids, local anaesthetics, and gabapentin, which have limited efficacy in postherpetic neuralgia.[2] Some patients with herpetic-associated trigeminal neuralgia are still dissatisfied with pain control after standardized drug treatment or cannot tolerate adverse drug reactions and require further nerve blocks and nerve regulation combined with analgesic drugs. Peripheral percutaneous electrical nerve stimulation has a certain application value in the treatment of herpetic neuralgia

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with trigeminal nerve involvement,[3–6] but due to its high cost and cumbersome operation, its wide application is limited to a certain extent. Trigeminal radiofrequency thermocoagulation is a minimally invasive, targeted treatment technique that produces a depolarizing response by rapidly changing the electric field of neuronal cell membranes and can be used for the treatment of acute and chronic postherpetic neuralgia. The effective rates in patients with 1 month and 3 months of disease duration were 64.7% and 62.4%, respectively.[7–9] For refractory herpes zoster neuralgia that does not respond to drug therapy, nerve block therapy, or peripheral nerve radiofrequency therapy, Gasserian ganglion pulsed radiofrequency therapy serves as an alternative option. A multicentre study confirmed that compared with radiofrequency therapy targeting the peripheral branches of the trigeminal nerve, radiofrequency therapy targeting the trigeminal Gasserian ganglion has a better curative effect and that the earlier the implementation, the better the outcome.[8] In the selection of radiofrequency parameters, Gasserian ganglion pulsed radiofrequency has higher safety and effectiveness than continuous radiofrequency.[9,10]

The European consensus-based (S2k) guidelines recommend that to prevent acute herpetic neuralgia from evolving into postherpetic neuralgia (PHN), analgesics should be used in the early stage of herpes zoster following a three-step analgesic regimen. For patients with moderate pain, weak opioids can be used in combination with nonopioids, and strong opioids can be used in combination with nonopioids in patients with severe pain.[11] However, high-dose systemic opioids are commonly associated with side effects such as nausea, vomiting, constipation, urinary retention, and psychiatric symptoms,[12] and some patients refuse to increase opioid doses because of fear of side effects. Barpujari et al[13] observed that μ-opioid receptors in peripheral sensory neurons play an important role in neuropathic pain, and that the loss of μ-opioid receptors aggravates the hyperalgesia caused by nerve injury and can weaken the analgesic effect of morphine. Additionally, in an animal model of inflammatory pain in rats, the topical application of opioids to injured sites reduced nerve fiber activity, reduced the occurrence of spontaneous pain, and reduced mechanical and chemical hyperalgesia.[14]

Although radiofrequency thermocoagulation is an ideal analgesic method for ophthalmic herpetic neuralgia, there are still a small number of patients with unrelieved pain, needing for prolonged oral administration of opioids or longer hospital stay, placing heavy psychological and mental burdens on patients. Further exploration of more effective and cost-effective minimally invasive interventional methods is needed. Therefore, we conducted a retrospective study to evaluate the therapeutic effectiveness of Gasserian ganglion pulse radiofrequency combined with local injections of low-dose morphine for intractable herpes zoster-related pain, as well as its safety profile, analgesic efficacy, and potential for opioid conservation.

Methods

General Information

This retrospective study was approved by the Ethics Committee of Nanjing Drum Tower Hospital (NO.2023–146-02), and informed consent was obtained from the subjects. Information on patients with herpetic neuralgia who were admitted to the pain department of Nanjing Drum Tower Hospital and underwent pulsed radiofrequency (PRF) treatment from June 2018 to December 2021 was collected from the electronic records system. Forty patients (18 males and 22 females) with an average age of 70.2 ± 8.5 years and an average disease course of 30 (30, 60) days were included. The inclusion criteria were as follows: age ≥18 years; disease duration ≤3 months; involvement of the ophthalmic branch of the trigeminal nerve; Treatments before admission such as pregabalin, gabapentin, and amitriptyline, opioids, peripheral nerve block or peripheral branch PRF resulted in poor pain control or intolerable side effects; and pain numerical rating scale (NRS) ≥5 points. The exclusion criteria were as follows: severe heart, liver, kidney and other organ dysfunction; pregnancy; and patients with intracranial infections and intracranial tumours.

Grouping

After admission, all patients were given standard drug treatment in accordance with the 2016 Chinese expert consensus on the diagnosis and treatment of postherpetic neuralgia. The first-line drugs pregabalin and amitriptyline or duloxetine were administered first, topical lidocaine patches were applied, and then tramadol sustained-release tablets were given orally; if the patient still reported significant pain, tramadol was replaced with oxycodone hydrochloride sustained-release tablets, and the patient was given intravenous morphine for relief when the pain was significant. Patients were assigned to the following two groups based on different minimally invasive intervention programmes: Group A, Gasserian ganglion PRF treatment plus 0.2 mg morphine

injection in the Gasserian ganglion; Group B, only Gasserian ganglion PRF therapy. After discharge, the patients continued to take tramadol (50mg to 100mg Bid) or oxycodone (10mg to 20mg Bid), and the dosage was adjusted based on the pain's intensity.

Operation Method

Gasserian Ganglion PRF Therapy

The patient was placed in the supine position, and puncture was performed 2.0 cm away from the corner of the mouth. After routine disinfection and draping, a radiofrequency puncture needle (21G, curved needle) was placed into the foramen ovale under computed tomography (CT) positioning, and high-frequency (50 Hz, 0.2 V) stimulation (Baylis, Canada) was performed. The position of the needle active tip (5mm) was adjusted to stimulate the ocular branch area (See Figure 1), and 300s of PRF treatment at 42~44°C was administered. Following the PRF, patients in Group A received an injection of 0.2mg morphine, diluted with normal saline to a volume of 0.2mL, through the puncture needle. Patients in Group B concluded the treatment.

Efficacy Evaluation Criteria

Pain NRS scores were collected on the day of admission and the day of discharge. Short form McGill pain questionnaire and Pittsburgh sleep quality index(PSQI) were collected on admission, at discharge, and 1 month, 3 months, 6 months and 12 months after discharge. The dosage of oxycodone sustained-release tablets and the dose of intravenous morphine during hospitalization and duration of opioids treatment following discharge were obtained from the medical record system. The incidence of pain persisting 6 months after the onset (postherpetic neuralgia) was recorded. As economic benefit indicators, the length of hospital stay and hospitalization expenses of patients were collected. The primary outcomes of this study were the reduction in NRS scores and McGill pain questionnaire and the dosage and duration of opioids administration. Secondary outcomes included PSQI, duration of hospital stay, associated costs, and the incidence of PHN.

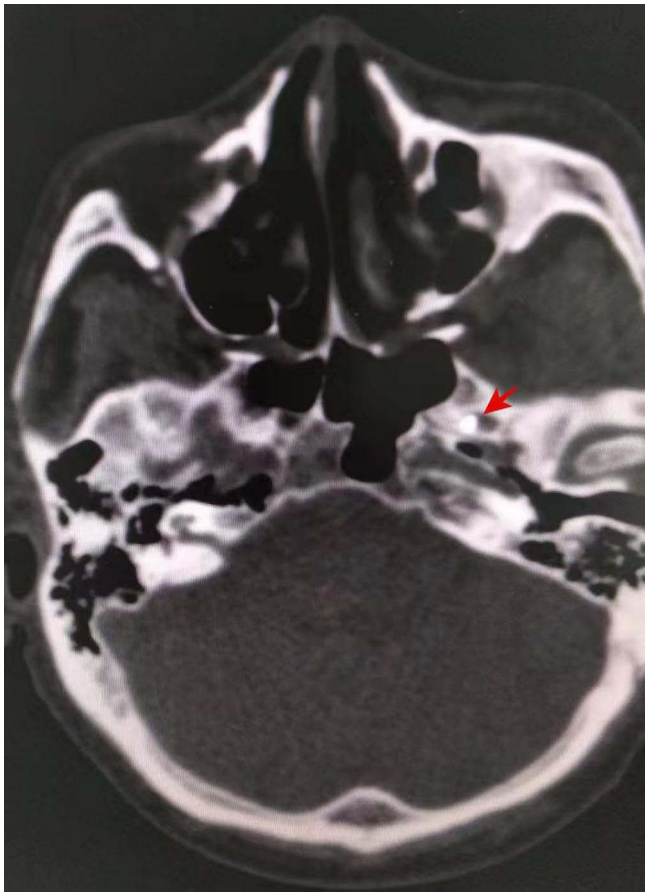

Figure 1 Intraoperative images of Gasserian ganglion PRF. This image demonstrates that the tip of the puncture needle (red arrow) is positioned within the foramen ovale.

Safety Evaluation Criteria

The incidences of intracranial haemorrhage, intracranial infection, other cranial nerve injuries, blindness, and respiratory depression within 72 hours after PRF treatment in each group were recorded.

Statistical Analysis

SPSS 25.0 software was used for the statistical analyses, and the distribution of all measurement data was assessed for normality using Shapiro–Wilk Test. Nonnormally distributed data were expressed as median (quartile) and compared between two groups by Mann–Whitney test. Normally distributed data were expressed as mean (standard deviation, SD) and compared with the independent sample *t* test. Categorical variables were presented as numbers (percentages) and were compared by Pearson Chi-Square test. Wilcoxon signed-rank test was used for intragroup comparisons. $p < 0.05$ was considered statistically significant.

Results

Comparison of General Patient Information

There were no significant differences in sex composition, disease duration, NRS scores, McGill scores and PSQI on admission among the two groups. The baseline data of each group are shown in Table 1.

Comparison of Pain, Quality of Life and Opioids Between Two Groups

The hospital stay, hospitalization costs, and oxycodone dosages for Group A patients were lower than those for Group B patients ($p = 0.02$, $p = 0.015$ and $p = 0.023$, respectively). See details in Table 2 and Figures 2–4. The proportion of patients in group A still

Table 1 Comparison of the General Information of the 2 Groups of Patients

	Group A	Group B	X^2 value/F value/Z value	P value
Male, s n/total N (%)	6/19(31.6%)	12/21(57.1%)	2.634[a]	0.105
Age (year), mean (SD)	70.0(8.4)	70.4(8.8)	0.037[b]	0.848
Duration (days), median (quartile)	30(30,60)	30(25,30)	−1.260[c]	0.208
NRS at admission, median (quartile)	665,70	6(5,7)	−0.791[c]	0.429
McGill at admission, mean (SD)	26.3(0.6)	26.9(0.4)	−0.679[c]	0.497
PSQI at admission, mean (SD)	14.8(0.7)	15.3(0.5)	−0.082[c]	0.935

Notes: [a]tested by Pearson Chi-Square test; [b]tested by independent sample *t* test; [c]tested by Mann–Whitney test.
Abbreviation: PSQI, Pittsburgh sleep quality index.

Table 2 Comparison Between the 2 Groups

	Group A	Group B	X^2 value/ Z value	*P* value
Associated with hospitalization				
Hospital stay (day), median (quartile)	5(3,8)	10(5.5,17)	**−2.310[a]**	**0.02**
NRS at discharge, median (quartile)	1(0,1)	1[1,2]	−1.481[a]	0.139
McGill at discharge, median (quartile)	7(6,8)	7(6,9)	−0.233[a]	0.816
PSQI at discharge, median (quartile)	6(5,7)	7(6,7.5)	−1.004[a]	0.315
Hospital costs (RMB), median (quartile)	9859(5368,14,335)	14,308(8626,18,876)	**−2.424[a]**	**0.015**
Morphine (mg), median (quartile)	5(0.2,15)	0(0,10)	−1.949[a]	0.051
Oxycodone (mg), median (quartile)	50(0,140)	180(60,395)	**−2.281[a]**	**0.023**
1 month post-operation				
McGill, median (quartile)	4(4,9)	7(4.5,11.5)	−1.839[a]	0.066
PSQI, median (quartile)	5(4,9)	7(5,10)	−1.628[a]	0.104
Oral opioids, n/total N, (%)	7/19, 36.8%	17/21, 81.0%	**8.087[b]**	**0.004**
3 months post-operation				
McGill, median (quartile)	3(3,8)	6(3,8)	−1.042[a]	0.297
PSQI, median (quartile)	6(3,8)	4(4,8)	−1.099[a]	0.272
Oral opioids, n/total N, (%)	5/19, 26.3%	11/21, 52.4%	2.824[b]	0.093

(*Continued*)

Table 2 (Continued).

	Group A	Group B	X^2 value/ Z value	*P* value
6 months post-operation				
McGill, median (quartile)	3(3,7)	5(3,6.5)	−1.006[a]	0.314
PSQI, median (quartile)	4(3,7)	5(4,7)	−0.987[a]	0.324
Oral opioids, n/total N, (%)	5/19, 26.3%	9/21, 42.9%	1.200[b]	0.273
12 months post-operation				
McGill, median (quartile)	3(2,6)	3(2,5)	−0.280[a]	0.780
PSQI, median (quartile)	3(3,6)	4(3,5)	−1.095[a]	0.274
Oral opioids, n/total N, (%)	5/19, 26.3%	7/21, 33.3%	0.234[b]	0.629
Incidence of PHN(6months after onset), n/total N, (%)	5/19, 26.3%	12/21, 57.1%	**3.879[b]**	**0.049**

Notes: [a]tested by Mann–Whitney test. [b]tested by Pearson Chi-Square test; The bold lines in the table indicate p < 0.05, which is statistically significant.
Abbreviation: PSQI, Pittsburgh sleep quality index.

taking oral opioids 1 month after discharge was lower than that in group B (p=0.004, Figure 5). The incidence of patients in group A who continued to experience postherpetic neuralgia 6 months after the onset was lower than that in group B (p = 0.049, Figure 6). There were no significant differences in McGill and PSQI scores between the two groups at discharge, and at 1, 3, 6 and 12 months post-operation. Additionally, there were no significant differences in the doses of rescue morphine administered during

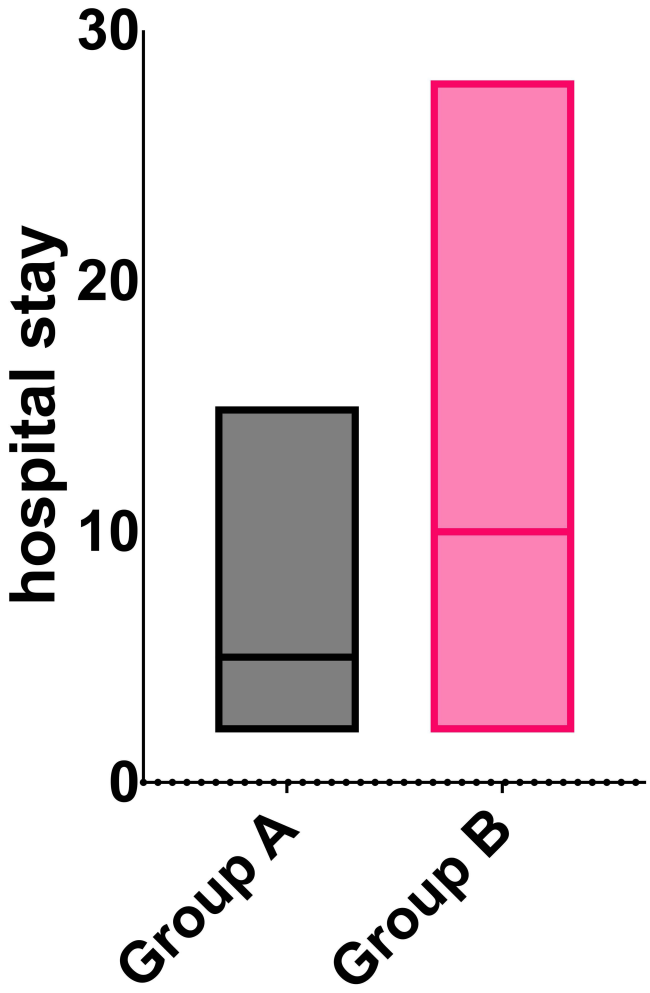

Figure 2 Compared to Group B, the hospital stay for Group A was significantly shorter. p = 0.02.

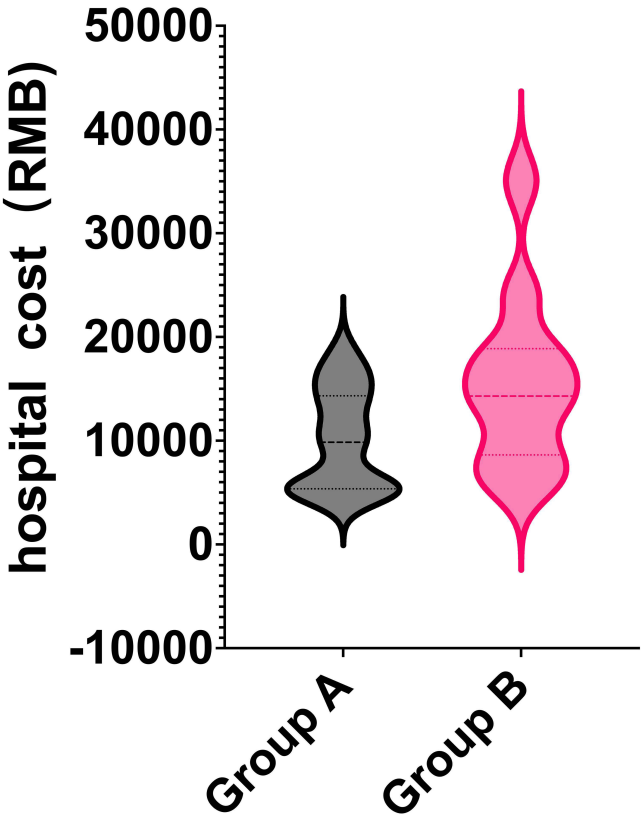

Figure 3 Comparison of hospital costs between two groups. The hospital costs for Group A were lower than that for Group B. $p = 0.015$.

hospitalization, or in the proportion of patients taking opioids at 3, 6 and 12 months post-operation, between the two groups (for details, see Table 2).

Comparison of Pain and Quality of Life Within Groups

Wilcoxon Signed Ranks Test showed that the NRS upon discharge, as well as the McGill and PSQI scores at the time of discharge and at 1, 3, 6 and 12 months post-discharge, were all significantly reduced compared to those measured upon admission in both patient groups ($p = 0.000$). See details in Table 3 and Figures 7–9.

Safety Analysis

There was no intracranial haemorrhage, intracranial infection, other cranial nerve injury, blindness, or respiratory depression within 72 hours postoperatively in each group.

Discussion

In this study, a retrospective study was conducted on Gasserian ganglion PRF therapy for 40 patients with ophthalmic herpetic neuralgia (duration < 3 months). The results indicated that Gasserian ganglion PRF therapy combined with local low-dose morphine injection could reduce the dosage of oral opioids during hospitalization, curtail the duration of opioid use, and lower the incidence of post-operative neuralgia for patients with ophthalmic herpetic neuralgia. Additionally, this approach offered a favorable cost–benefit effect, enabling a reduction in both the duration of hospital stays and associated costs. Meanwhile, there were no complications, such as intracranial haemorrhage, intracranial infection, other cranial nerve injuries, or blindness, indicating that Gasserian ganglion PRF therapy combined with local low-dose morphine injection was safe. This innovative approach offers an alternative option for managing herpes zoster neuralgia in ocular branches and prevention of postherpetic neuralgia.

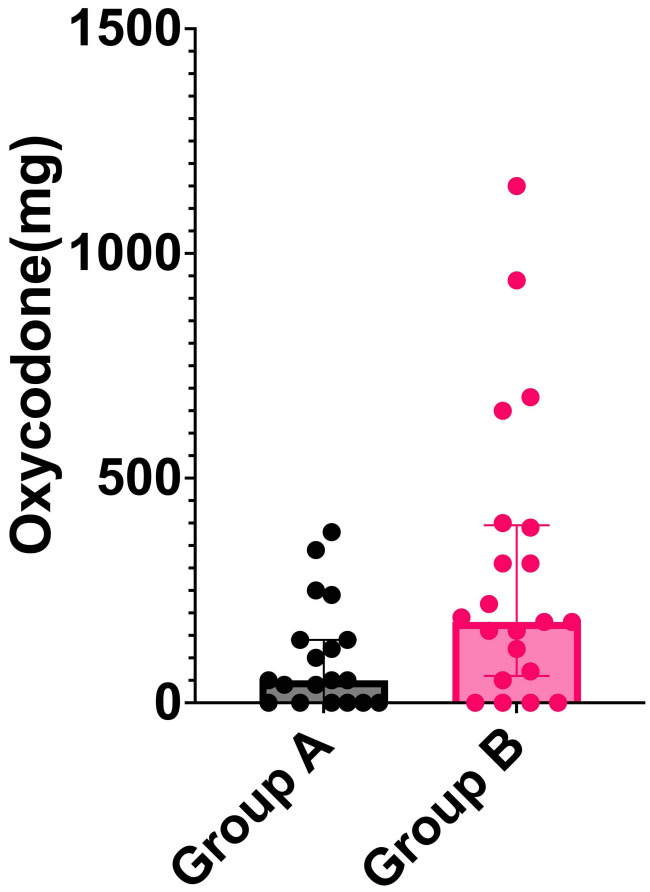

Figure 4 Comparison of oxycodone during hospitalization between two groups. The dosage of oxycodone of Group A was significant less. $p = 0.023$.

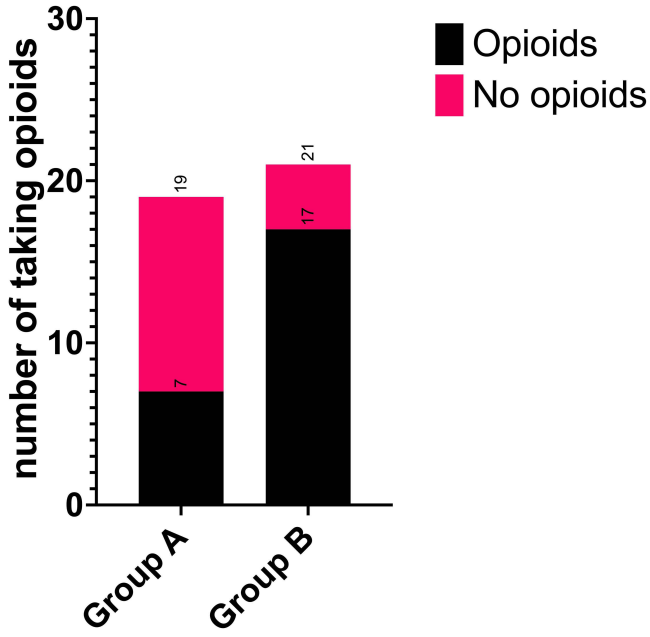

Figure 5 Comparison of opioids use 1 month post-operation between two groups. The proportion of patients in group A still taking oral opioids one month after discharge was lower than that in group B ($p = 0.004$).

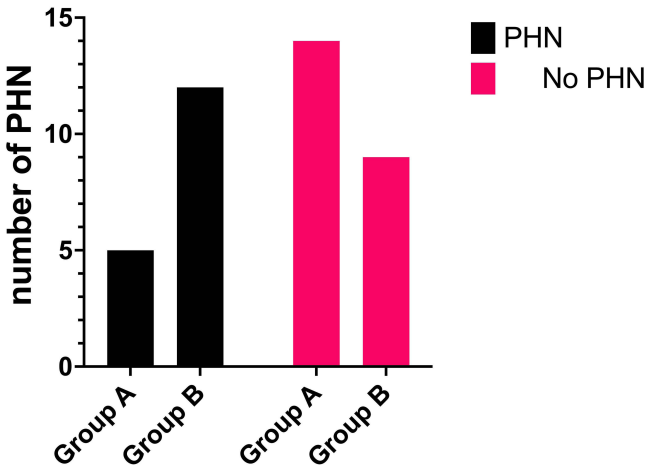

Figure 6 Comparison of incidence of PHN between two groups. The incidence of patients in group A who continued to experience postherpetic neuralgia six months after the onset was lower than that in group B (p = 0.049).

Ophthalmic herpes zoster, involving the trigeminal nerve, accounts for 10% to 25% of all shingles patients,[15] and intractable facial pain caused by herpes virus infection is difficult to treat. The mechanism of trigeminal herpetic neuralgia is still unclear; it may be related to central sensitization, peripheral sensitization, and inflammatory lesions of the trigeminal Gasserian ganglion and Schwann cells.[16,17] Some patients with trigeminal herpetic neuralgia are dissatisfied with pain control despite standard drug treatment and require further minimally invasive interventional therapy.[16] At present, the commonly used neuromodulation techniques include electrical stimulation of the peripheral trigeminal nerve, Gasserian ganglion PRF therapy and peripheral trigeminal nerve PRF ablation. Electrical stimulation of the peripheral trigeminal nerve is relatively expensive, has limited effects and is associated with poor patient experiences during treatment, limiting its application. Trigeminal nerve PRF ablation can produce reversible mild axonal damage and

Table 3 Comparison of Pain and Quality of Life Within Groups

	Group A			Group B		
	Mean (quartile)	**Z value**	***p* value**	**Mean (quartile)**	**Z value**	***p* value**
NRS						
On admission	5(5,7)			6(5,7)		
At discharge	1(0,1)	−3.848[a]	0.000	1(1,2)	−4.044[a]	0.000
McGill						
On admission	26(24,28)			27(26,28)		
At discharge	7(6,8)	−3.861[b]	0.000	7(6,9)	−4.028[b]	0.000
1 month post-operation	4(4,9)	−3.830[b]	0.000	7(4.5,11.5)	−4.021[b]	0.000
3 months post-operation	3(3,8)	−3.828[b]	0.000	6(3,8)	−4.021[b]	0.000
6 months post-operation	3(3,7)	−3.828[b]	0.000	5(3,6.5)	−4.035[b]	0.000
12 months post-operation	3(2,6)	−3.831[b]	0.000	3(2,5)	−4.028[b]	0.000
PSQI						
On admission	16(12,17)		0.000	15(14,16.5)		
At discharge	6(5,7)	−3.830[c]	0.000	7(6,7.5)	−4.043[c]	0.000
1 month post-operation	5(4,9)	−3.821[c]	0.000	7(5,10)	−4.021[c]	0.000
3 months post-operation	4(4,8)	−3.833[c]	0.000	6(4,8)	−4.020[c]	0.000
6 months post-operation	4(3,7)	−3.830[c]	0.000	5(4,7)	−4.024[c]	0.000
12 months post-operation	3(3,6)	−3.830[c]	0.000	4(3,5)	−4.024[c]	0.000

Notes: Wilcoxon Signed Ranks Test, [a]compared with NRS on admission; [b]compared with McGill on admission; [c]compared with PSQI on admission.

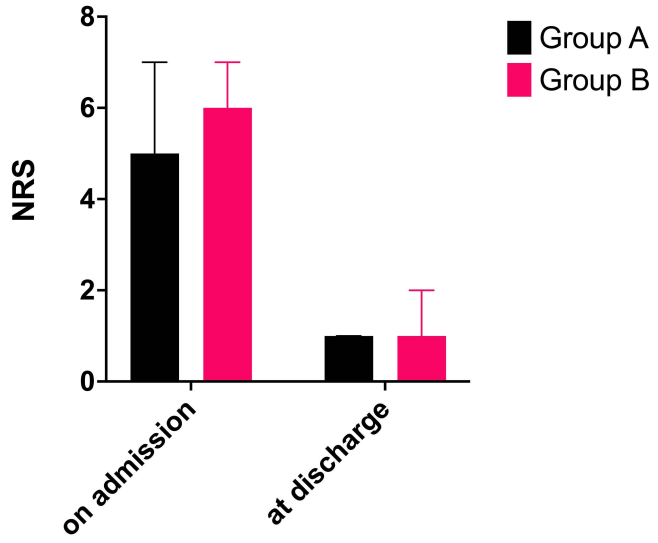

Figure 7 Intra-group Comparison of NRS in two groups. NRS upon discharge was significantly reduced compared to that measured upon admission in both patient groups (p = 0.000).

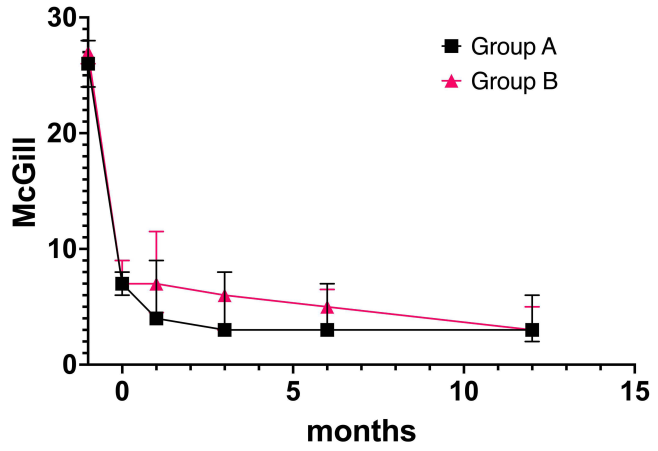

Figure 8 Intra-group Comparison of McGill questionnaire. McGill scores at the time of discharge and at 1, 3, 6 and 12 months post-discharge, were significantly reduced compared to those measured upon admission in both patient groups (p = 0.000).

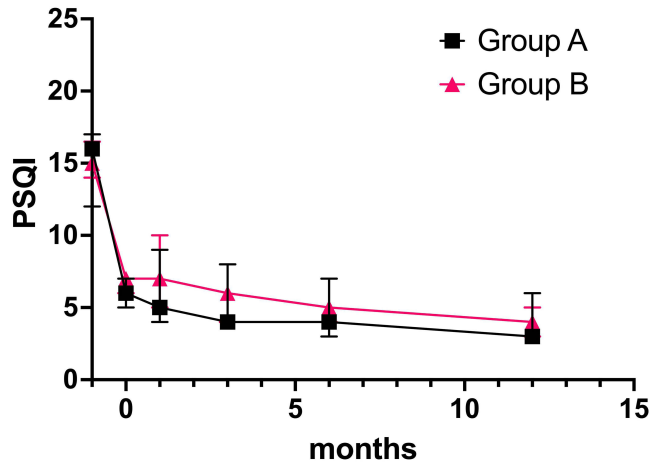

Figure 9 Intra-group Comparison of PSQI. PSQI scores at the time of discharge and at 1, 3, 6 and 12 months post-discharge, were all significantly reduced compared to those measured upon admission in both patient groups (p=0.000).

a small amount of mitochondrial oedema, which may have a transient nerve signal blocking effect and can reduce pain and improve quality of life.[18] However, a significant number of patients still experience pain following trigeminal peripheral nerve radiofrequency treatment. Jia et al studied the effect of trigeminal PRF treatment for ophthalmic herpetic neuralgia and proposed that the treatment site of the trigeminal nerve had a significant effect on the results, and Gasserian ganglion PRF therapy was more effective than peripheral branch PRF ablation.[8] In our study, two groups of patients with intractable herpetic pain in the ocular branch, who had previously undergone drug, peripheral nerve block, and even radiofrequency treatment, showed significant improvements in pain and sleep quality following treatment with Gasserian ganglion PRF. This suggests that Gasserian ganglion PRF offers effective pain relief for intractable herpetic neuralgia. Previous studies have shown that dorsal root ganglia PRF ablation at 42°C in rats does not induce changes in neural architecture except for transient endothelial oedema and collagen deposition.[19] In our study, no serious complications, such as intracranial haemorrhage, intracranial infection, other cranial nerve injuries, corneal infection, blindness and respiratory depression, occurred in each group of patients, indicating that with skilled operation, even if the affected area is the ocular branch, Gasserian ganglion PRF is safe.

In accordance with the WHO pain relief ladder, opioids may be prescribed for herpes-related pain, effectively reducing acute herpes zoster pain and preventing postherpetic neuralgia. However, due to the unacceptable side effects of opioids, particularly during the initial administration, their use is often discontinued throughout the treatment.[20,21] Therefore, the local targeted activation of μ-opioid receptors may be a new approach to relieve acute and chronic pain.[13] In this study, patients in Group A were given PRF therapy of the Gasserian ganglion and 0.2 mg of morphine was locally injected beside the Gasserian ganglion. This novel method reduced both the duration of hospital stays and associated costs for patients and lowered the cost of caregiving and financial burden. Although there was no significant difference in the proportion of patients taking opioids 6 months and even longer after operation between the two groups in this study, the approach of combining Gasserian ganglion PRF with low-dose morphine injection had reduced the use of opioids during hospitalization, shortened the duration of postoperative opioid use, and decreased the incidence of postherpetic neuralgia.

Limitations

This is a retrospective study with a small sample size; therefore, the research findings might exhibit bias. A large sample size and randomized controlled study are needed to further explore the combination of Gasserian ganglion PRF with low-dose morphine injection regimen for ophthalmic herpetic neuralgia.

Conclusion

In summary, under the operation of skilled personnel, Gasserian ganglion PRF therapy combined with low-dose morphine injection may reduce the length of hospital stay and hospitalization expenses, reduce the dosage of oral opioids, and shorten the duration of opioid use for patients with ophthalmic herpetic neuralgia with no obvious serious complications. This novel approach offers an alternative option for managing herpes zoster neuralgia and preventing postherpetic neuralgia in ocular branches.

Data Sharing Statement

De-identified data are available upon reasonable request from the corresponding author.

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Disclosure

The authors declare that they have no conflicts of interest.

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