Journal of Pain Research

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ORIGINAL RESEARCH

# The Efficacy of CT-Guided Pulsed Radiofrequency of the Dorsal Root Ganglion Combined with Methylene Blue Sympathetic Injection on Herpes-Zoster Neuralgia: A Retrospective Study

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**Objective:** This study aimed to investigate the efficacy of Computed Tomography (CT) Guided Pulsed Radiofrequency (PRF) of the Dorsal Root Ganglion (DRG) combined with Methylene Blue (MB) sympathetic injection in acute herpes zoster neuralgia.

**Background:** MB is a nitric oxide synthesis inhibitor that has been reported to exert analgesic and anti-inflammatory properties. In this study, MB was injected to the thoracic or lumbar sympathetic nerve to inhibit sympathetic nerve conduction or destroy nerve endings. This is the first report for thoracic or lumbar sympathetic nerve MB injection.

**Materials and Methods:** 64 patients in study were divided into two groups: PRF combined with sympathetic nerves MB injection group (group A; n = 32,); PRF group (group B; n = 32). The therapeutic effects of each group were compared using the Numeric Rating Scale (NRS) scores and the average doses of Pregabalin (mg/d) immediately after surgery (T1) and at one month (T2), three months (T3), six months (T4), nine months (T5), and twelve months (T6) post-operation. The incidence of postherpetic neuralgia (PHN) and complications in the two groups were observed and enrolled.

**Results:** No significant differences in general conditions between the two groups. Compared with the preoperative baseline scores (T0), the NRS at T1 to T6 were significantly decreased in both groups. NRS was lower at T1 to T6 in the group A compared with the same times points in group B ($P< 0.05$). The incidences of PHN in group A were significantly lower at T3 to T6 compared with group B. The daily doses of pregabalin was lower in the A group than B group at T1 to T5, and it was not significantly different at T6 between the two groups. Finally, no adverse complications were recorded in both groups.

**Conclusion:** CT-Guided PRF Combined with MB sympathetic Injection in the treatment of HZ neuralgia is safe and effective, reducing PHN.

**Keywords:** pulsed radiofrequency, methylene blue, sympathetic injection, herpes-zoster neuralgia

## Key Summary Points

Herpes zoster neuralgia has a significant impact on the lives of elderly people in clinical practice, and the formation of PHN further affects the quality of life in the future. However, the treatment effect of PHN is not satisfactory, and we pay more attention to early treatment plans to prevent the occurrence of PHN.

There are several researches on sympathetic nerve block in herpes zoster neuralgia, and mostly focus on epidural and stellate ganglion block. Our study mainly achieved sympathetic nerve block treatment in the thoracolumbar region under CT guidance, which has not been studied in clinical practice.

Received: 8 January 2025
Accepted: 30 June 2025
Published: 11 July 2025



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MB is a nitric oxide synthesis inhibitor that has been reported to exert analgesic and anti-inflammatory properties. In this study, MB was injected to the thoracic or lumbar sympathetic nerve to inhibit sympathetic nerve conduction or destroy nerve endings within a specific period. The aim was to reduce sympathetic-related symptoms in acute HZ.

In our study, CT-Guided Pulsed Radiofrequency Combined with Methylene Blue sympathetic Injection for Zoster-Associated Pain was found to be an effective and safe intervention for reducing the incidence of PHN.

## Introduction

Varicella-zoster virus (VZV) has been shown to cause chickenpox. Once the VZV infection has been resolved, the virus stays in the cranial sensory ganglia and spinal dorsal root ganglia (DRG). When cell-mediated immunity declines in some individuals, it can lead to the reactivation of the VZV in the ganglia. This reactivated virus then undergoes retrograde transport along cranial or peripheral nerves, resulting in the emergence of pain and rash symptoms.[1] In the United States, over 90% of adults have been infected with chickenpox, yet there is no reliable method for predicting infection that can potentially undergo reactivation.[2] Acute herpes may have severe symptoms among elderly and may cause PHN in aged individuals. Several have aimed to develop interventions for the treatment of HZ patients but there are no drugs to prevent PHN. The risk of developing PHN in patients with acute HZ neuralgia increased from 5% under the age of 60 to 10% between the ages of 60 and 69 years, and 19% over the age of 70.[3] Several investigations have reported that the incidence of PHN has increased by 9–34%.[4] In terms of pathogenesis, PHN is linked to the loss of DRG cells and axons in the affecting nerve root and peripheral nerve due to HZ.[5,6]

Various clinical approaches are used for the management of HZ, including pharmaceutical interventions, physiotherapy, acupuncture, nerve blocks, electric spinal cord stimulation, and pulsed radiofrequency (PRF).[7] PRF, extensively utilized in clinical settings, is a neuromodulation technique. It involves the application of alternating and repetitive pulsed currents via a radiofrequency instrument to modulate aberrant electrical signals surrounding affected nerves, thereby eliciting analgesic effects.[8,9] Because the temperature of the electrode head end is <42°C, it rarely causes nerve tissue damage. However, some patients do not benefit from this treatment and often require additional treatments. The application of sympathetic block in the treatment of HZ has not been explored previously. Many studies have focused on blocks of stellate ganglia and epidural block.[10–14] However, the use of Thoracic and Lumbar Sympathetic nerve block is yet to be reported. Therefore, we injected Methylene Blue (MB) into the sympathetic nerves to induce prolonged analgesic properties to the sympathetic trunk or ganglion, and then compared the effect and safety of combining with MB sympathetic injection in the treatment of acute herpes pain.

## Methods

### Study Design

This was a retrospective study and approval was obtained from the Ethics Committee of the Affiliated Hospital of Jiaxing University (LS2021-KY-398). All patients were informed about the risks and complications of the study before treatment, and signed the consent before participating in the study. In summary, 70 patients with herpes zoster neuralgia who were treated at the hospital, from October 2021 to May 2022, were enrolled. Five patients were excluded, and one patient was lost to follow-up. Finally, 64 remaining patients were divided into two groups based on the mode of operation: PRF combined with sympathetic nerves MB injection group (group A; n = 32); PRF group (group B; n = 32) (Figure 1).

The inclusion criteria were as follows: 1) patients clinically diagnosed with acute herpes zoster pain; 2) disease duration of ≤30 days; 3) patient's age ≥40 years; 4) numerical rating scale (NRS) scores ≥4 before the surgery; and 5) those who agreed to undergo computed tomography (CT)-guided PRF or MB injection after being informed of the risks of surgery. The exclusion criteria were: 1) individuals with cardiopulmonary insufficiency, poor blood sugar control, or other severe diseases; 2) those with puncture site infection; 3) those who were allergic to lidocaine, MB, and other related drugs; 4) those who refused to provide treatment information and clinical data for scientific research; and 5) those who received PRF or other minimally invasive treatments before.

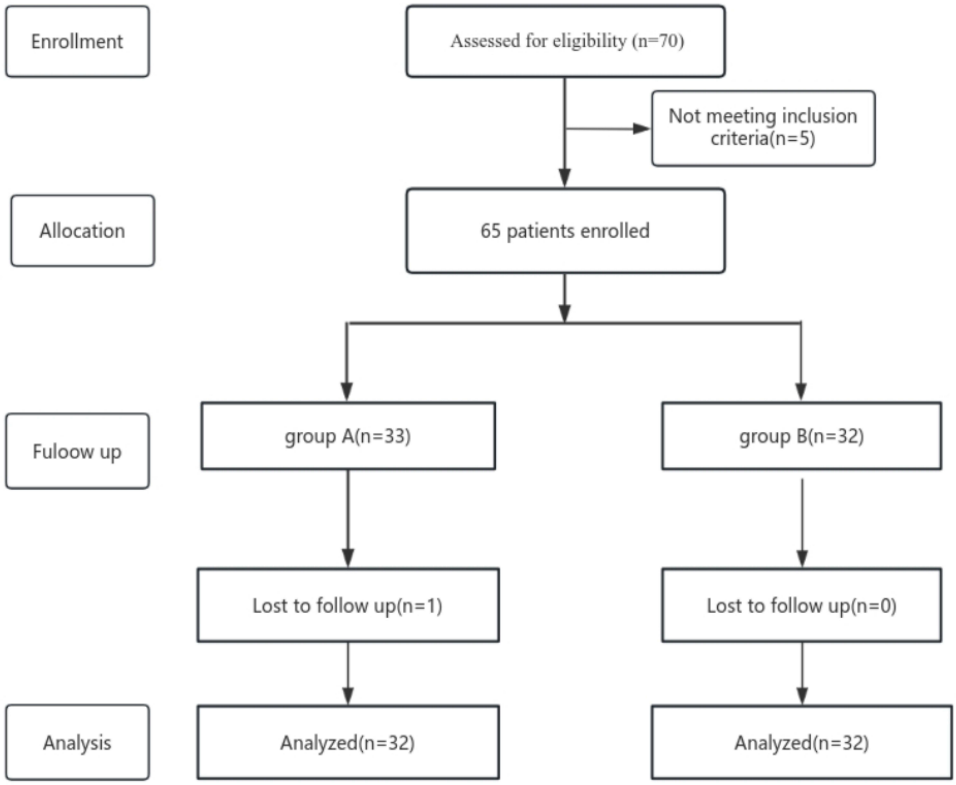


**Figure 1** Study flowchart of the 64 initial patients. Group A, PRF combined with sympathetic nerves MB injection group; Group B, PRF group.

## Surgical Procedures

All surgical operations in both groups were performed under the guidance of CT scan. Patients were positioned prone on the CT scan bed with pillows placed under the chest or axilla. Oxygen was administered continuously through a nasal cannula, and vital signs were monitored throughout the procedure. The targeted nerve location depended on the site of the skin lesion, with the most painful segment identified at the center and extending one segment above and below it (Figure 2A). Following routine disinfection, local anesthesia was induced using 0.5% lidocaine hydrochloride. Subsequently, the upper one-fourth of the intervertebral foramen served as the puncture target, guided by CT scan imaging. A trocar needle for PRF, sized 20 G, 100 mm long, with a working end length of 10 mm, was inserted along the indicated trajectory to a depth not exceeding the edge of epidural[8] (Figure 3A). Once the tip of the needle was in the target place, a radiofrequency instrument (Baylis Medical Inc., Montreal, QC, Canada) was employed to perform the following: (1) sensory test; voltage of <0.5 V and frequency of 50 HZ; the innervated area was observed for pain, swelling, numbness, or tingling sensations; (2) motor test: voltage of <0.5 V and frequency of 2 HZ; if tremors and pulsation were induced in the trunk muscle fibers, the puncture site was located near the target nerve. Once the puncture site was identified, the parameters for PRF were configured: temperature set at 42°C, duration at 300 seconds, pulse width at 20 milliseconds, and frequency at 2 Hz.[8] Upon completion of PRF stimulation, the electrode core was withdrawn without any observed aspiration of blood, gas, or fluid. Thereafter, 0.5 mL of a contrast solution was injected, and CT revealed no intravascular and cerebrospinal fluid injection (Figure 3B). Subsequently, 6mL of the treatment solution (15mg of 2% lidocaine hydrochloride, 500μg of methylcobalamin injection, 1mL compound betamethasone injection, and 1mL 30% iodohydrin; diluted to 6mL with 0.9% saline) was injected into each affected nerve 2mL for three ganglionic segments. The was CT scanning was conducted which revealed good contrast and drug diffusion, covering the pain-related neurospinal segments, and reconfirmed the absence of intravascular injection. The needle was removed and the puncture site was covered with an adjuvant in Group B. After 15 min of observation, no adverse reactions were observed. The patients were transferred to the ward. In group A, after the abovementioned treatment, the

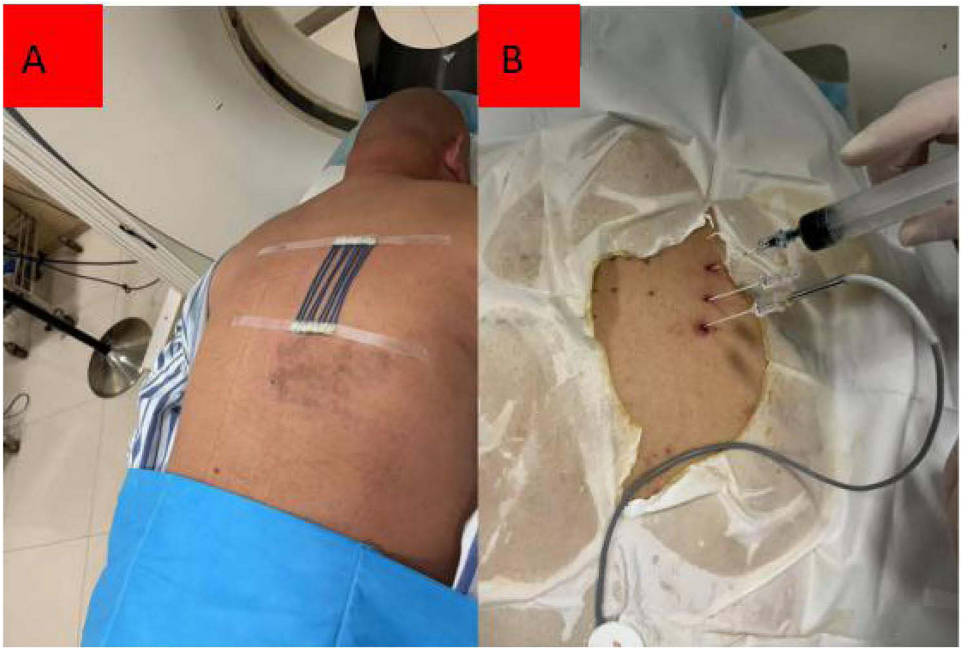


**Figure 2** Patients were positioned prone on the CT scan bed with pillows placed under the chest or axilla (**A**). The targeted nerve location depended on the site of the skin lesion, with the most painful segment identified at the center and extending one segment above and below it. In group A, after the PRF treatment, the position of one radiofrequency needle was adjusted and advanced to the vicinity of the sympathetic nerve of the same segment. Then a solution consisted of 2 mg of methylene blue, 1 mL of 30% iodohydrin, and 2 mL of 0.75% ropivacaine was injection (**B**).

position of a radiofrequency needle was adjusted and advanced to the vicinity of the sympathetic nerve of the same segment. Once the target position was reached, we administered 0.5 mL of contrast agent to ensure that there was no injection into the blood or spinal canal, and to confirm the absence of lung injury. Subsequently, a mixed solution comprising 5 mL of medication was injected. This solution consisted of 2 mg of methylene blue (2 mL, compliant with national drug standard H32024827, Jiangsu Jichuan Pharmaceutical Co., Ltd)., 1 mL of 30% iodohydrin, and 2 mL of 0.75% ropivacaine (imported drug registration number H20140763, AstraZeneca, Cambridge, UK) (Figure 2B). A CT scan was performed to verify the diffusion of the solution (see Figure 4). After removing the needle, the puncture site was covered with excipients. The patient was then transferred back to the ward with stable vital signs after a 15-minute observation period.

## Data Collection and Follow-Up

The following preoperative data were recorded: age, gender, pain duration, lateralization of pain, preoperative underlying disease, preoperative NRS, and preoperative pregabalin dose. A follow-up was conducted to evaluate NRS, pregabalin consumed and PHN incidence immediately after surgery (T1) and at 1 month (T2), 3 months (T3), 6 months (T4), 9 months (T5), and 12 months (T6) postoperatively.

The primary outcome was the NRS scores and the incidence of clinically significant PHN. The NRS scores were recorded from 0 to 10, with 0 indicating no pain and 10 indicating the most severe pain imaginable. Referring to previous studies, clinically significant PHN was defined as persistent pain according to NRS with an intensity ≥3.[9] Secondary outcomes were the average doses of pregabalin. In the analysis, the doses of oral drugs were converted to equivalent doses of pregabalin before treatment.

## Data Analysis

Data analysis was conducted by SPSS 25.0 (IBM, Chicago, USA). The Shapiro–Wilk test was performed to determine whether the measurements were normally distributed. Normally distributed data were expressed as mean ± standard deviation, whereas non-normally distributed data were expressed as median (quartiles). The Mann–Whitney *U*-test or independent *t*-test was

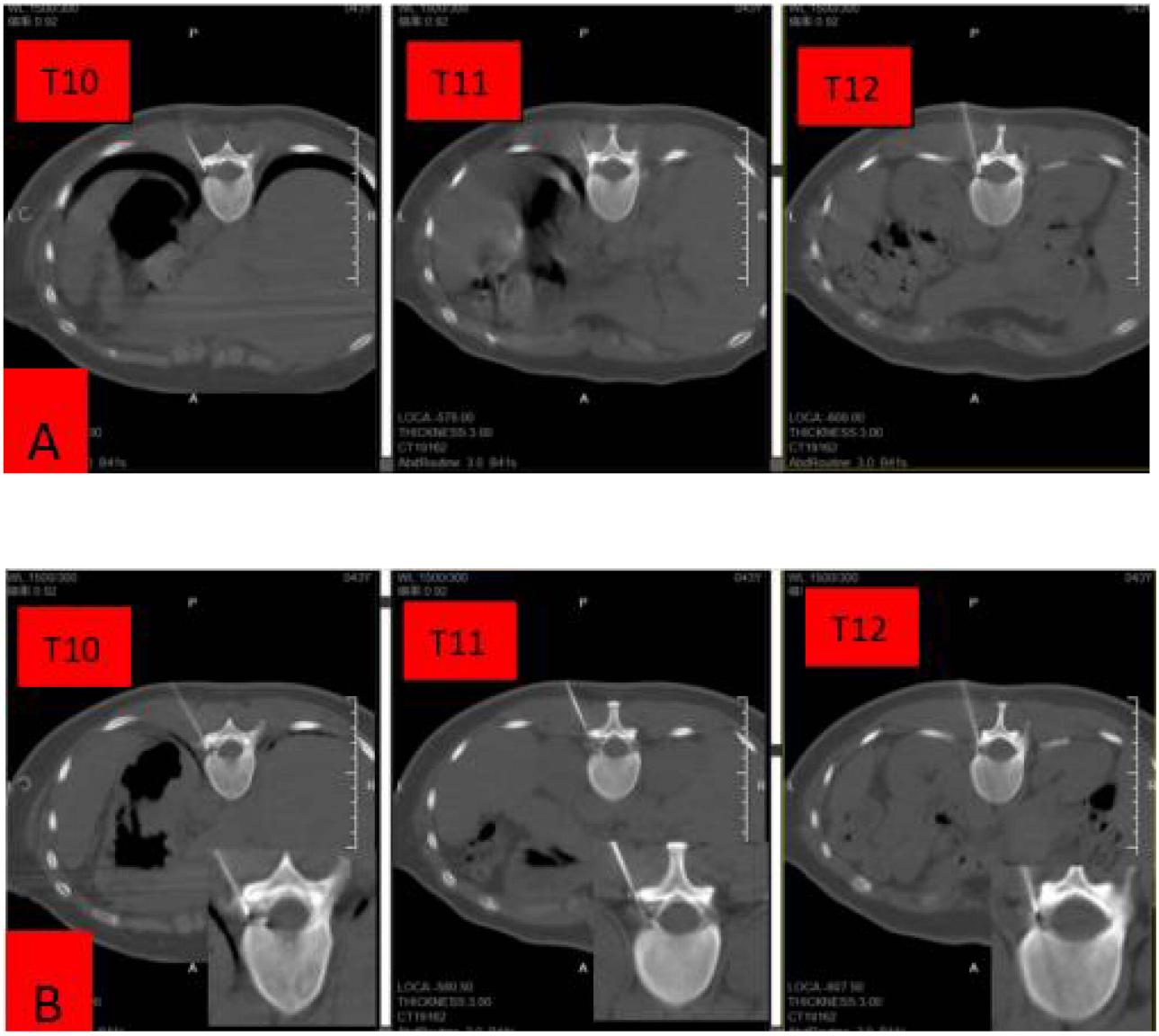


**Figure 3** (**A**) The upper one-fourth of the thoracic 10/11/12 (T10/T11/T12) intervertebral foramen was considered as the puncture target for the trocar needle for PRF. (**B**) After PRF, 0.5 mL of a contrast solution was injected, and CT revealed drugs display wrapped around the epidural space with no intravascular or cerebrospinal fluid injection.

performed for continuous variables. Categorical variables were analyzed by the $\chi 2$ test or Fisher's exact test. Pain intensity over time was determined using repeated measures analysis of variance. A P-value of <0.05 was considered statistically significant.

# Results

## Patient General Characteristics

The general characteristics of enrolled patients, including age, gender, pain duration, affected side, preoperative underlying disease, preoperative NRS and pregabalin doses before operation are shown in Table 1. Notably, there were no significant differences between the two groups (P > 0.05) (Table 1).

## Nrs

Before treatment, there were no significant differences in NRS scores between both groups (P < 0.01; Figure 5C). Following treatment, NRS scores decreased at each time point (T1-T5) (Figure 5A and B). However, when comparing the two groups, NRS scores were significantly lower in Group A compared to Group B at 1-, 3-, 6-, 9-, and 12-months post-treatment (Figure 5C and Table 2).

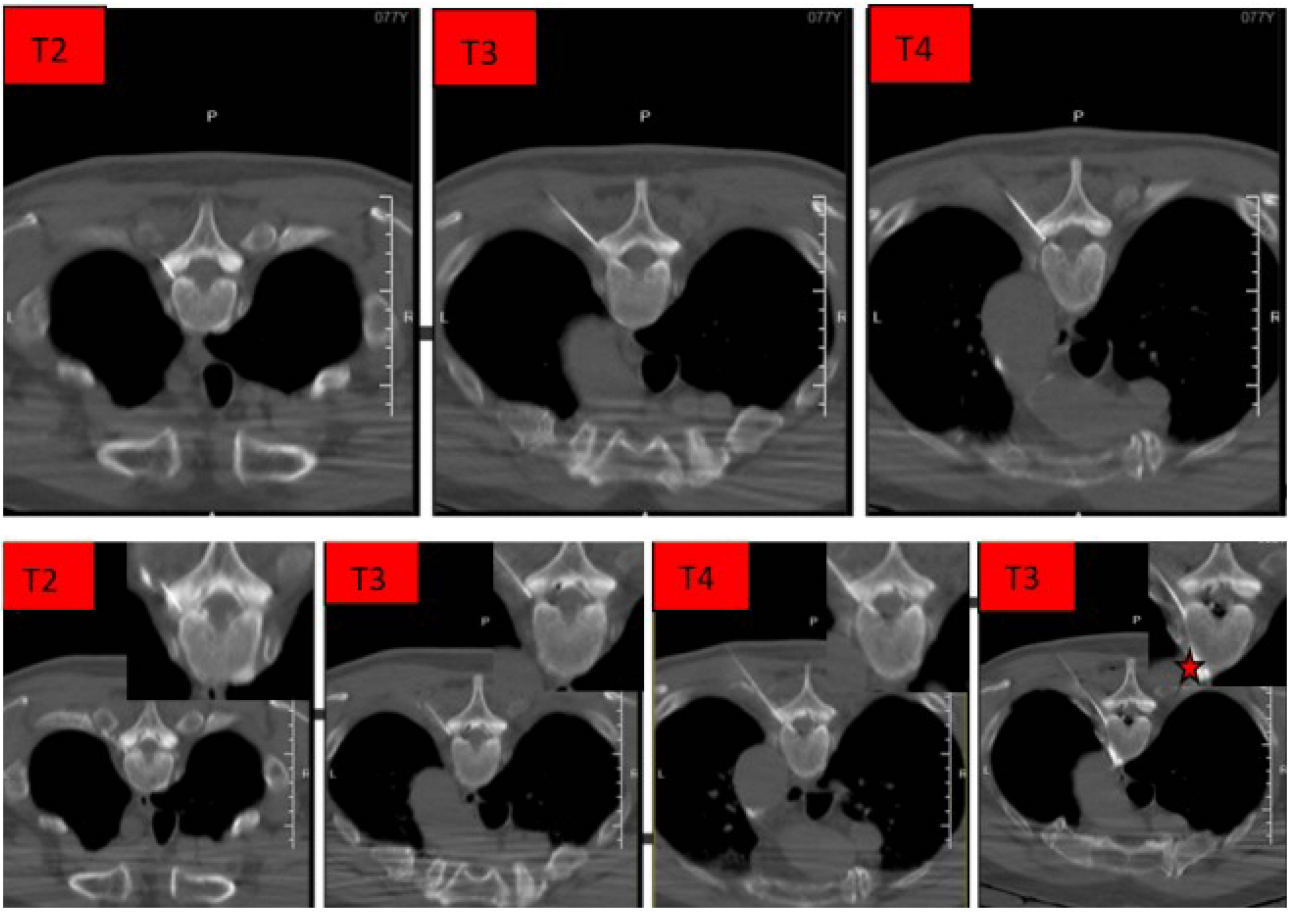


**Figure 4** After PRF and solution injection, we adjusted the position of one radiofrequency needle, advanced it to the vicinity of the sympathetic nerve of the same segment, and after reaching the target position (star on the T3), we gave 0.5mL contrast agent to confirm that without blood or spinal canal injection, also confirm without lung injury, and then 5mL of mixed solution containing 2mg MB 2mL, and CT observation to verify the diffusion of the solution again.

## PHN Incidence

Comparison results for the incidence of clinically significant PHN in group A at 1, 3,6 and 12 months after treatment compared with the group B are shown in Figure 6 ($P < 0.05$).

**Table 1** Presurgery General Conditions in Patients

| Variables | Group A (n=32) | Group B (n=32) | P-value |
|---|---|---|---|
| Age, years, mean±SD | 63.19±10.149 | 64.38±11.100 | 0.793 |
| Gender, n | | | |
| Male | 17 | 12 | 0.209 |
| Female | 15 | 20 | |
| Pain duration, mean±SD, days | 17.34±10.213 | 15.22±9.245 | 0.515 |
| Side, n | | | |
| Left | 18 | 15 | 0.453 |
| Right | 14 | 17 | |

(*Continued*)

**Table 1** (Continued).

| Variables | Group A (n=32) | Group B (n=32) | P-value |
|---|---|---|---|
| Underlying disease, n | | | |
| Hypertension(HTN), n | 9 | 6 | 0.309 |
| Diabetes mellitus(DM), n | 3 | 1 | |
| HTN&DM, n | 1 | 2 | |
| Hyperlipidemia, n | 2 | 2 | |
| None, n | 17 | 21 | |
| Pre-NRS, mean±SD | 5.78±0.420 | 5.69±0.471 | 0.400 |
| Pregabalin dose (mg/day) | 159.38±25.201 | 164.06±29.742 | 0.495 |

**Notes**: The demographic characteristics of the patients: gender, age, pain duration, affected side, preoperative underlying disease, preoperative NRS and pregabalin doses were found have no significant differences between the two groups ($P > 0.05$).

## Pregabalin Consumption

After treatments, the dosages of pregabalin significant declined in both groups at each point in time ($P < 0.01$; Figure 7A and B). Compared with group B, the dosages of pregabalin were significantly lower at 1, 3, 6 and 9 months after treatment in group A ($P<0.05$; Figure 7C and Table 3).

## Side Effects

Throughout the operation and follow-up period, neither group experienced adverse complications such as nerve injury, vascular puncture, lidocaine or MB toxicity, or complete spinal anesthesia. Similarly, no cases of hypotension, bradycardia, pleural puncture, or pneumothorax were recorded. No patients discontinued treatment due to adverse complications. Notably, in Group A, all patients exhibited blue urine post-surgery, lasting approximately 3–5 days. However, urine routine tests revealed no abnormalities, and patients reported no discomfort.

# Discussion

Pain specialists prioritize the management of acute HZ neuralgia due to its refractory nature and the severe pain associated with PHN. An observational cohort study of HZ revealed that a significant proportion of individuals with HZ eruptions on the arms and lower limbs experienced concurrent symptoms resembling CRPS as the pain progressed. Furthermore, the study found that patients exhibiting CRPS-like symptoms were at a higher risk of developing PHN.[5,10,15] Studies have also shown that early prophylactic measures for people at high risk of herpes zoster neuralgia may effectively prevent the development of PHN.[15] Virus reactivation and continuous replication in the dorsal root ganglia and downward conduction causes severe ganglionitis and neuritis, inducing deep sympathetic stimulation and vasoconstriction of intraneural arterioles, accompanied by decreased blood flow to the intraneural capillary beds, and ischemia of the nerve.[16] The sympathetic nervous system (SNS) is an important factor that regulates the occurrence of neuralgia. During the acute phase of HZ, inflammation causes sympathetic hyperactivity, which in turn reduces intramembranous blood flow, leading to tissue hypoxia and intramembranous oedema. Although under normal physiological conditions it has been found that sympathetic efferent nerves function separately from primary afferent neurons, tissue or nerve injury may promoting the coupling of the two systems. Therefore, activation of SNS may amplify the primary afferent neuron activity, thereby increase pain.[16] The above studies demonstrate that early intervention of sympathetic nerves during the acute phase of HZ reduces painful repetitive stimulation, thus preventing intraneural arterial vasospasm. In addition, it reduces central sensitivity, decreases ischemic nerve damage and suppresses the incidence of PHN.[7,17,18] It is for these reasons that we designed this meaningful study.

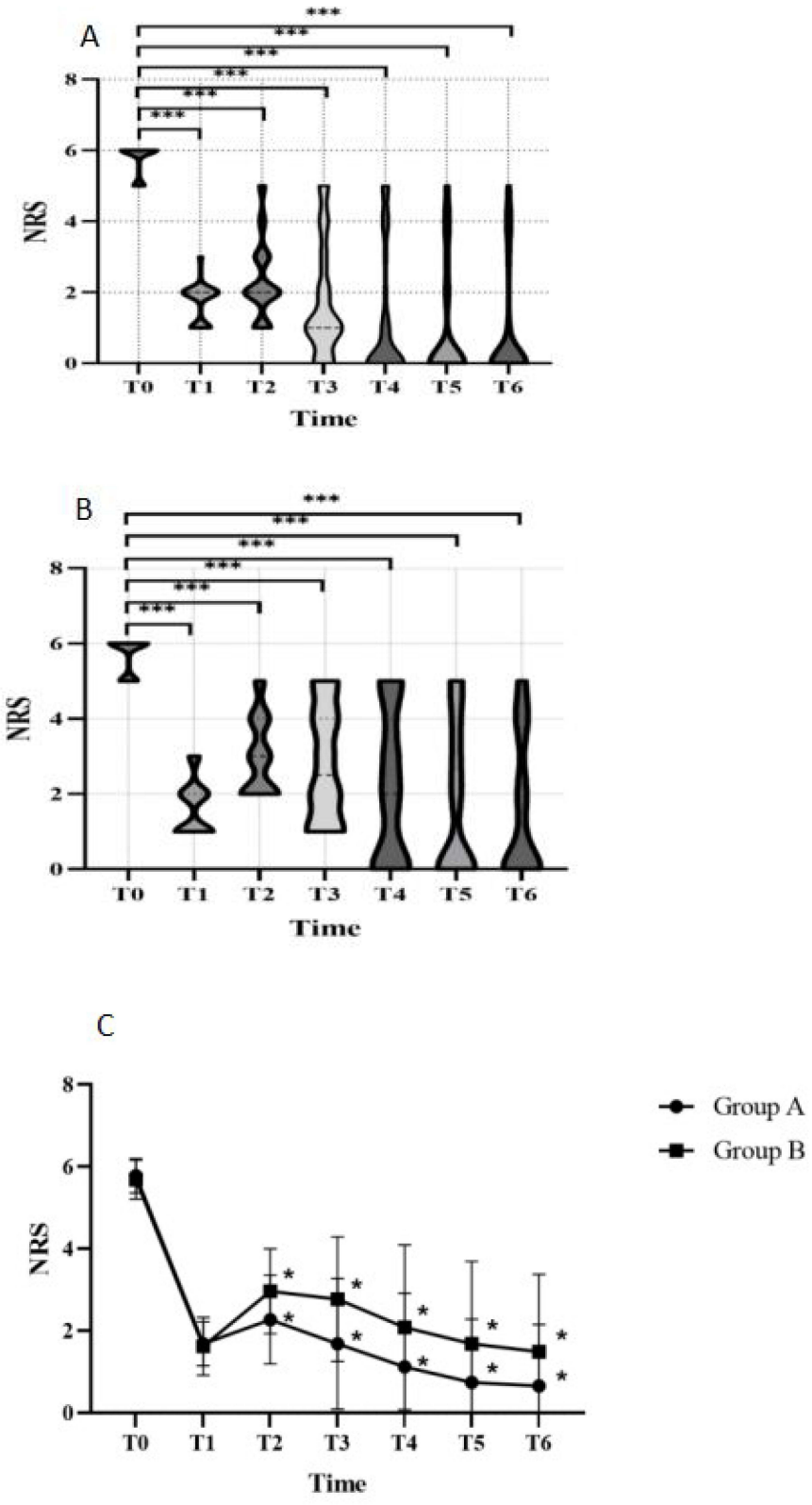


**Figure 5** Comparison of NRS scores in Group A (**A**) and group B (**B**) at various time points before and after treatment. ***P < 0.01. Comparison of NRS score before and after surgery in two groups (**C**). Comparison of postoperative NRS scores between A and B groups. Data are expressed as mean ± SD. *Compared with Group B, P < 0.05. Group A: pulsed radiofrequency combined with cut the sympathetic nerves group; Group B: pulsed radiofrequency group. T0: at baseline; T1: post-treatment; T2: 1 months after treatment; T3: 3 months after treatment; T4: 6 months after treatment; T5: 9 months after treatment; T6: 12 months after treatment.

**Table 2** Comparison of NRS Score Before and After Surgery in Two Groups [Sores, M ($Q_1$, $Q_3$)]

| Group | N | $T_0$ | $T_1$ | $T_2$ | $T_3$ | $T_4$ | $T_5$ | $T_6$ |
|---|---|---|---|---|---|---|---|---|
| A | 32 | 6 (6, 6) | 2 (1, 2) | 2 (2, 3) | 1 (1, 2.75) | 0 (0, 1.75) | 0 (0, 0) | 0 (0, 0) |
| B | 32 | 6 (5, 6) | 1.5 (1, 2) | 3 (2, 4) | 2.5 (1, 4) | 2 (0, 4) | 0 (0, 3.75) | 0 (0, 3.75) |
| *Z*-value | | −0.842 | −691 | −2.658 | −2.918 | −2.089 | −2.112 | −2.248 |
| *P*-value | | 0.400 | 0.490 | 0.008 | 0.004 | 0.037 | 0.035 | 0.025 |

**Notes**: Group A: pulsed radiofrequency combined with cut the sympathetic nerves group; Group B: pulsed radiofrequency group. T0: at baseline; T1: post-treatment; T2: 1 months after treatment; T3: 3 months after treatment; T4: 6 months after treatment; T5: 9 months after treatment; T6: 12 months after treatment.

Sympathetic nerve symptoms associated with HZ were reported early in the 20th century.[10–12,14,19] The stellate ganglion block has been extensively studied,[13,20–26] yet the efficacy of sympathetic block alone remains insufficient.[27] Previous research has demonstrated that prolonged sympathetic nerve block leads to improved outcomes in HZ treatment. However, due to the presence of Horner's sign, long-term stellate ganglion blockade is not feasible. Therefore, we employ chemical denervation of the sympathetic nerves below the level of Thoracic 4 (T4) to alleviate acute pain in HZ affecting the upper limb, thoracic, or lumbar regions. MB is selected for its prolonged analgesic effect, facilitating a durable block of the thoracolumbar sympathetic nerves. This approach aims to mitigate repetitive pain episodes and prevent vasospasm of intraneural arterioles. Therefore, they may reduce central sensitization, decrease ischemic nerve injury, and prevent the development of PHN. This is consistent with our results. In addition, we found a statistically significant difference in NRS and dose of medication taken after 1 month in group A combined with PRF-based MB sympathetic injection compared to group B (Figure 5C); and this difference persisted up to 12 months postoperatively. Further analysis revealed that the incidence of PHN was significantly lower in group A compared to group B at 1, 3, 6, 9 and 12 months postoperatively (Figure 6). This suggests that addition of sympathetic intervention to pulsed radiofrequency can effectively relieve pain, reduce the use of medications, and improve the quality of life of patients with HZ.

The activity of efferent sympathetic nerves and primary afferent neurons are separate under the normal physiological conditions. The excitation of the sympathetic and primary afferent nerves does not affect each other, and there is no information communication between them.[28] In the presence of nerve injury, tissue trauma, or inflammation, chemical

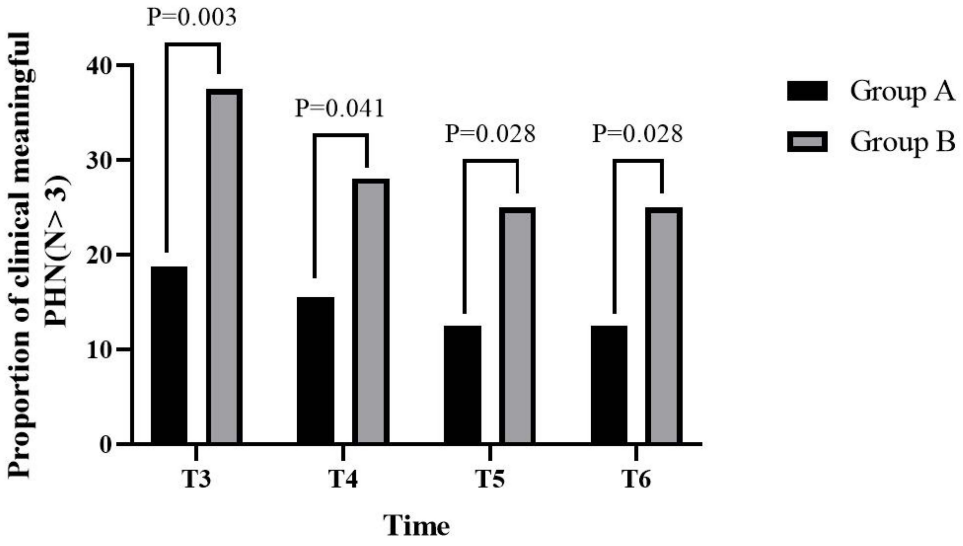


**Figure 6** Comparison of the proportion of clinical meaningful PHN in two groups after treatment. Vertical axis (The proportion of clinical meaningful PHN)=The people of clinical meaningful PHN (NRS>3)/Total number of persons group A (or B)100%. Compared with group B, $P < 0.05$. Group A: pulsed radiofrequency combined with cut the sympathetic nerves group; Group B: pulsed radiofrequency group. T3: 3 months after treatment; T4: 6 months after treatment; T5: 9 months after treatment; T6: 12 months after treatment.


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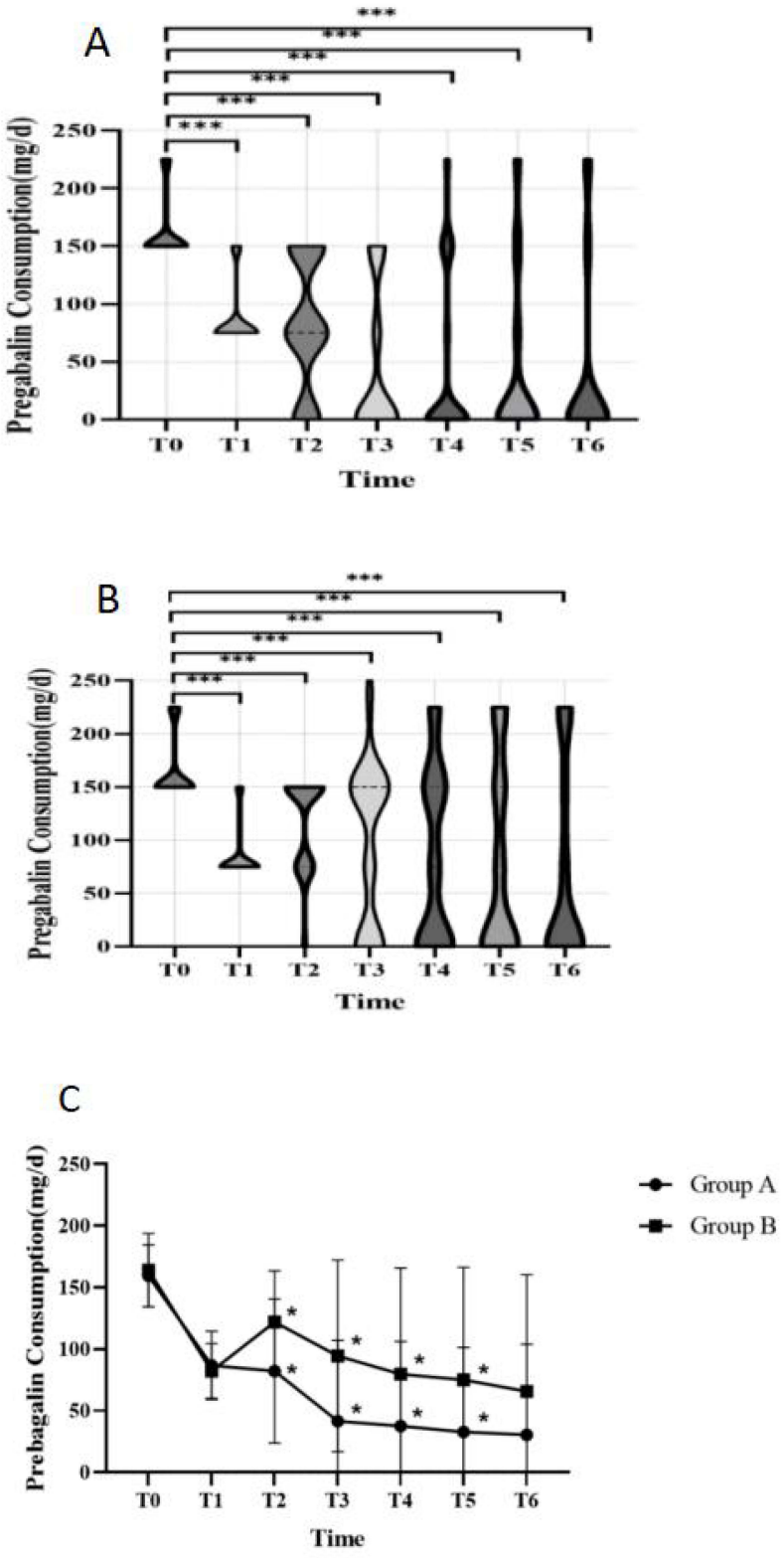


**Figure 7** Comparison of pregabalin consumption in Group A (**A**) and Group B (**B**) at various time points before and after treatment. ***P < 0.01.Group A: pulsed radiofrequency combined with cut the sympathetic nerves group; Group B: pulsed radiofrequency group. Comparison of Pregabalin Consumption before and after surgery in two groups (**C**). *Compared with group B, P < 0.05. Group A: pulsed radiofrequency combined with cut the sympathetic nerves group; Group B: pulsed radiofrequency group. T0: at baseline; T1: post-treatment; T2: 1 months after treatment; T3: 3 months after treatment; T4: 6 months after treatment; T5: 9 months after treatment; T6: 12 months after treatment.

**Table 3** Comparison of Pregabalin Consumption Before and After Surgery in Two Groups [mg/d, M ($Q_1$, $Q_3$)]

| Group | N | $T_0$ | T1 | T2 | T3 | T4 | T5 | T6 |
|---|---|---|---|---|---|---|---|---|
| A | 32 | 150 (150, 150) | 75 (75, 75) | 75 (18.75, 150) | 0 (0, 131.25) | 0 (0, 56.25) | 0 (0, 0) | 0 (0, 0) |
| B | 32 | 150 (150, 150) | 75 (75, 75) | 75 (18.75, 150) | 0 (0, 131.25) | 0 (0, 56.25) | 0 (0, 0) | 0 (0, 0) |
| *Z*-value | | 0.683 | −0.750 | −2.859 | −2.620 | −2.218 | −2.115 | −1.881 |
| *P*-value | | 0.495 | 0.453 | 0.004 | 0.009 | 0.027 | 0.034 | 0.060 |

**Notes**: Group A: pulsed radiofrequency combined with cut the sympathetic nerves group; Group B: pulsed radiofrequency group. T0: at baseline; T1: post-treatment; T2: 1 months after treatment; T3: 3 months after treatment; T4: 6 months after treatment; T5: 9 months after treatment; T6: 12 months after treatment.

and anatomical coupling may occur between sympathetic postganglionic and primary sensory neurons. This collaboration between the two nerve types plays a role in pain mediation. Various uncertain mechanisms underlie this phenomenon, including the abnormal activation of α-adrenergic receptors due to chemical coupling between primary afferent neurons and sympathetic ganglia following nerve injury. Perl and Sato et al found that nerve damage leads to activation of α-adrenergic receptors and triggers the release of norepinephrine from sympathetic postganglionic C-fibre nociceptors in the injured nerves, leading to increased sensitivity of these nerves to α-adrenergic receptors.[29–32] Administration of α1-adrenergic antagonists (eg phentolamine) has been shown to relieve sympathetically induced pain. Another mechanism involves anatomical coupling. After sciatic nerve injury, numerous sprouting axons form a basket-like structure around large-diameter sensory neurons in the DRG. Sympathetic stimulation repetitively activates these axons. A third potential mechanism is an indirect coupling effect mediated through neurovascular conduction. Winnie and Hartwell hypothesized that an acute inflammatory response triggers robust sympathetic impulses, resulting in decreased neuronal blood flow and neuronal ischemia subsequent to nerve injury. In our study combine with long-effecting MB sympathetic nerve injection, trying to increase the control area of the vascular dilation, temporary inhibition sympathetic nerve hyperplasia and conduction pain, reducing nerve conduction complex changes during the acute phase of HZ, but the status of sympathetic block cannot replace the pulse radiofrequency because his treatment is more inclined to symptomatic treatment.[33–35]

MB is a low molecular weight, partially fat-soluble dye that has been used in several clinical scenarios.[36,37] Evidence demonstrates that MB can treat malaria, methemoglobinemia, osteoarthritis-related pain, cardiac bypass surgery and traumatic brain injury.[38–45] Local injections of MB can also improve the symptoms of painful disorders due to its ability to inhibit nerve conduction or disrupt nerve endings.[46,47] Recent studies have reported that both single MB injections and continuous infusion of MB via the thoracic paraspinal spine significantly relieved pain and improved quality of life in patients with PHN without causing severe adverse effects.[42,43] The damage produced by MB on nerves is reversible, with the damage recovering in about 20 days without damage to the neuronal structure. Therefore, MB can be injected around nerves for the relief of neuropathic pain, especially intractable neuropathic pain.[48] The mechanism by which MB relieves pain is currently unknown. A study by Evangelos suggested that MB promoted neuroprotection by staining unmyelinated sensory nerve fibers, reducing cysteine activation, and maintaining the mitochondrial membrane potential.[49] The study by Guo et al showed that the analgesic effect of MB was mediated by the enhanced glucose metabolism, increased pyruvate oxidation, altered acid-base balance and membrane potential inside and outside the nerve endings, as well as inhibition of nerve impulse conduction.[50] Furthermore, MB as an inhibitor of Nitric Oxide Synthase (NOS) and soluble Guanylate cyclase (sGC), can effectively block these pathways to exert antinociceptive effects.[51–53]

Moreover, MB possess anti-inflammatory properties as reported in various disease models.[42,54–56] In addition, it has been demonstrated that MB attenuates mitochondrial dysfunction-induced oxidative stress.[57–59] In our research, 20mg MB were injected into sympathetic nerve to control HZ pain in Group A, and the decrease in NRS and drugs were not different between the two groups. In addition, there was no additional side effect in both groups.[43] These confirmed that MB can reflect the analgesic effect in sympathetic nerve injection in HZ.

Selecting the appropriate target segment for sympathetic MB injection is crucial. In cases where long-term stellate ganglion blocking is not feasible due to the presence of Horner's sign (eyelid drooping), we selected MB injection

targeting the sympathetic nerves below the T4 level to alleviate acute pain associated with HZ affecting the upper limb, thoracic, or lumbar regions (see Figure 4). Previously, we utilized the sympathetic nerve radiofrequency technique for conditions such as hand hyperhidrosis or Raynaud's Disease, as well as lumbar sympathectomy for treating cold hypersensitivity in the feet. In this research, we administered T4 sympathetic MB injection for upper limb herpes and L2/L3 sympathetic MB injection for lower limb herpes. For other types of thoracic HZ, sympathetic nerve injection is normally applied in the middle herpes damage area (Figure 4).

## Conclusion

CT-Guided Pulsed Radiofrequency Combined with Methylene Blue sympathetic Injection for Zoster-Associated Pain was found to be an effective and safe intervention for reducing the incidence of PHN.

## Ethical Approval

The Medical Ethics Committee of the Affiliated Hospital of jiaxing University approved this study (LS2021-KY-398). All participants agreed to the study procedures and permitted the sharing of their imaging data (including pre- and post-treatment images) for future studies and publications. This study was conducted in accordance with the Declaration of Helsinki. Signed informed consent was obtained from all patients.

## Acknowledgments

Jie Chen and Jiajia Deng are co-first authors for this study. The authors thank the subjects of this study for their participation.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Funding

This work was supported by funding from Zhejiang Medical Association Clinical Medical Research Special Fund (2022ZYC-Z35),Jiaxing Provinces and Cities Jointly Cultivate Discipline –General Surgery (Minimally Invasive) (2023-PYXK-001, Key Discipline Established by Zhejiang Province and Jiaxing City Jointly – Pain Medicine (2019-ss-ttyx), Key Discipline of Anesthesiology of Jiaxing City (2019-zc-06) and Jiaxing Key Laboratory of Neurology and Pain Medicine. The journal's Rapid Service Fee was funded by the authors.

## Disclosure

The authors report no conflicts of interest in this work.

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