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ORIGINAL RESEARCH

A Study on the Efficacy and Safety of Intravenous Lidocaine Infusion Combined with Pulsed Radiofrequency in Preventing Postherpetic Neuralgia: A Randomized, Double-Blind, Controlled Trial

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Objective: To investigate the efficacy and safety of intravenous infusion of lidocaine combined with pulsed radiofrequency in the prevention of postherpetic neuralgia.

Methods: A total of 110 patients with herpes zoster who met the criteria were finally included by calculating the sample size and randomly divided into two groups: intravenous pumping of lidocaine combined with pulsed radiofrequency treatment group (group P) and intravenous pumping of normal saline combined with pulsed radiofrequency treatment group (group C). The follow-up period of this study was 12 months. The VAS score, PSQI score, average dose of pregabalin (mg/d), IL-6 and Gal-3 levels in blood were used to evaluate the efficacy before operation and 1, 3, 6 and 12 months after operation. The adverse events occurred during the treatment in the two groups were recorded.

Results: The data showed that the VAS score, PSQI score, IL-6 and Gal-3 levels of the two groups after operation were significantly lower than the baseline values. Compared with group C, the incidence of PHN in group P decreased by 18.2%, the VAS score and PSQI score were significantly decreased at each time point after operation, the dose of pregabalin was significantly reduced at 3 months, 6 months and 12 months after operation, and the level of IL-6 was significantly decreased in group P ($P < 0.05$). No adverse reactions occurred in the two groups after treatment.

Conclusion: Intravenous injection of lidocaine combined with pulsed radiofrequency therapy is more effective in treating acute herpes zoster neuralgia. Compared with pulsed radiofrequency therapy alone, it can significantly reduce the incidence of postherpetic neuralgia and provide more prolonged pain relief, and also improve patients' sleep disorders.

Keywords: herpes zoster, lidocaine, pulsed radiofrequency, postherpetic neuralgia

Introduction

Herpes Zoster (HZ) is a common skin disease, it is caused by Varicella-zoster virus (VZV) infection of the Dorsal root ganglion (DRG) or gasserian ganglion of the trigeminal nerve. It has a lifetime incidence of up to 30%, especially in middle-aged and elderly people with weakened immunity. In the course of herpes zoster, the acute phase is usually defined as the first 30 days after the appearance of the rash. However, some patients will develop postherpetic neuralgia (PHN), a typical neuropathic pain, several months or even years after the acute stage. PHN significantly impairs the patient's sleep quality due to its persistent pain. Sleep disorders can also be a risk factor for the occurrence and development of PHN, and they interact with each other. Numerous studies have confirmed that up to 64% of patients report sleep disturbances during the acute stage of herpes zoster. When the pain progresses to PHN, sleep problems remain prominent and are one of the most affected aspects during PHN. Pain directly leads to difficulty in falling asleep,

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sleep interruption, and shortened sleep duration. Pittsburgh Sleep Quality Index (PSQI) is a self-assessment scale that covers seven aspects: sleep quality, sleep onset time, sleep duration, sleep efficiency, sleep disorders, use of hypnotic drugs, and daytime functional impairment. It can conduct a multi-dimensional assessment of the patient's sleep status and effectively quantify the impact of PHN on the patient's sleep. A review indicates that among patients with acute herpes zoster, approximately one quarter (25%) will experience the acute pain to transform into chronic PHN.[1] A study based on the US administrative claims database (for the years 2019–2021) indicates that the standardized annual incidence rate of PHN ranges from 35 to 38 cases per 100,000 person-years.[2] Studies have shown that if the pain associated with herpes zoster persists after 180 days of onset, the likelihood of pain relief becomes very low, at which point the condition is considered to be "definite" postherpetic neuralgia.[3,4] Early, therefore, actively explore and try all kinds of effective treatments for pain control is particularly important.

Pulsed Radiofrequency (PRF), as a new treatment method, can limit heat generation to below 42°C by applying pulsed current, with almost no risk of thermal or nerve damage. In clinical practice, PRF has been widely used in the treatment of many diseases of chronic pain, such as trigeminal neuralgia, chronic spinal pain and musculoskeletal pain, etc.[5] Compared with simple drug treatment, PRF can offer more lasting and comprehensive pain control. At present, at least 20 independent studies have explored the application of PRF in the treatment of herpes zoster-related pain. These studies cover various types such as prospective randomized controlled trials, retrospective analyses, case reports, as well as systematic reviews and meta-analyses. The number of patients involved has exceeded 2000. A PRF treatment study showed that the overall effective rates in patients during the acute phase, subacute phase and chronic phase were 88%, 72% and 52% respectively. Overall, PRF treatment has been reported as a minimally invasive interventional technique with relatively high safety. Multiple studies have clearly demonstrated that no significant complications or severe side effects were observed during the treatment process.[6] However, in clinical practice, it has been found that even with PRF treatment, some patients still retain the residual effect of central sensitization, eventually developing post-herpetic neuralgia.[7]

At present, there is no ideal clinical prevention method for PHN. In this context, the ectopic pacemaker hypothesis highlighted by Marshall Devor provides a new perspective to understand the pain development process of HZ and PHN. This hypothesis proposes that pain in both conditions is triggered by hyperexcited ectopic pacemaker sites at different locations in the primary sensory neurons that cause varicella zoster virus infection, and that this peripheral input is exacerbated by central sensitization induced and maintained by ectopic activity.[8] Based on this hypothesis, the application of membrane stabilizers may be more effective in blocking the persistence and progression of herpes zoster associated pain. Studies have shown[9] that some patients still develop PHN after using thermocoagulation to damage peripheral sensory nerves to treat herpes zoster associated neuralgia. This phenomenon also supports the possibility that central sensitization plays a role in the development of herpes zoster associated pain.

Lidocaine, as a sodium ion channel blocker, can prevent the intake of extracellular sodium ions into cells. When administered intravenously, lidocaine can pass through the blood-brain barrier and directly act on the spinal cord and upper brain centers. By blocking the voltage-gated sodium channels on the nociceptive neurons in the dorsal horn of the spinal cord, it can stabilize the membrane potential of the neurons and directly inhibit their sensitization state. The electromagnetic field generated by pulsed radiofrequency directly regulates the damaged nerves, interferes with the transmission of pain signals, thereby inhibiting the peripheral sensitization process, and works synergistically with lidocaine to relieve pain. Previously, studies have confirmed the positive role of lidocaine as a membrane stabilizer in effective pain relief.[10,11] There are also randomized controlled studies that show that the conventional treatment of herpes zoster combined with intravenous lidocaine can significantly reduce the intensity of pain and the frequency of pain outbreaks, proving that lidocaine can be used as an auxiliary means to enhance the effect of conventional treatment.[12] However, there are no relevant studies on the use of intravenous pump lidocaine combined with PRF in the treatment of acute herpes zoster neuralgia. Therefore, the aim of this study is to observe the clinical efficacy of intravenous pump lidocaine combined with PRF in the treatment of acute herpes zoster neuralgia, and to explore its preventive effect on the occurrence of PHN.

Methods

Study Design and Ethical Approval

Patients with acute herpes zoster neuralgia who were treated in the Affiliated Hospital of Jiaxing University from October 2022 to October 2023 were enrolled in this study. The study protocol received approval from the Institutional Review Board of the First Hospital of Jiaxing (Approval No.: 2022-LY-407; Date: September 23, 2022) and was prospectively registered with the Chinese Clinical Trial Registry (Registration ID: ChiCTR2200064664; URL: http://www.chictr.org.cn). All procedures adhered to the ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines. Informed consent for this study was obtained from all participants themselves. All participants provided written informed consent and were explicitly aware of the risks and potential complications of treatment before participation in the study.

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: 1) met the diagnostic criteria for herpes zoster with a disease duration of <30 days; 2) patients who failed to respond to medical treatment and had not received invasive treatment; 3) patients with herpetic neuralgia with involvement of cervical, thoracic or lumbar ganglia and gasserian ganglion of the trigeminal nerve; 4) Visual Analog Scale (VAS) > 3. Exclusion criteria were as follows: 1) patients with infection or tumor at the puncture site; 2) patients with severe cardiovascular and cerebrovascular diseases, liver and kidney dysfunction, bleeding and coagulation dysfunction; 3) diabetic patients with poor glycemic control; 4) long-term use of immunosuppressive agents or systemic failure; 5) suffering from mental diseases and unable to cooperate with the operation; 6) allergic to lidocaine or betamethasone sodium phosphate; And 7) patients with atrioventricular block of second degree or above.

Randomization and Blinding

A total of 112 patients were enrolled and randomly assigned to 2 groups by computer-generated random allocation sequence: intravenous infusion of lidocaine combined with pulsed radiofrequency group (group P, n=55); Normal saline infusion combined with pulsed radiofrequency treatment group (group C, n=55). The two groups of patients received corresponding treatment and follow-up at different time points. These procedures were performed by the same investigator, and all follow-up visits were performed by another investigator. Seal the envelope method was adopted to realize allocation concealment, set blind for grouping patient information, responsible for the follow-up and data collected by the researchers and patients do not know randomization. The instrument was operated by a nurse who was not involved in the study.

Procedures

All patients received the same treatment regimen prior to surgery: oral pain medication (pregabalin 150mg/day) and topical acyclovir ointment. All are performed by our pain in patients with the same high qualification doctor operation. Intravenous infusion of lidocaine hydrochloride combined with pulsed radiofrequency (group P): 2% lidocaine hydrochloride was diluted every 200mg to 200mL to make a 0.1% solution, and the infusion rate was 0.1mg/(kg·h) (for example, taking a patient of 60kg as an example, the infusion rate was 6 mg/h). After the infusion, 200mL was pumped again with the same scheme. Operation steps are as follows: stable patients were placed in treatment bed, and routine monitoring vital signs. The patient was placed in the prone position with a thin pillow under the chest or abdomen. Thin-slice CT scan (slice thickness of 2mm) was used to select the puncture point, and the routine disinfection towel was used after marking. Rf pulses were applied to the dorsal root ganglia of the spinal cord, 3 segments at a time, by expanding 1 segment at the top and bottom, centered on the segment where the patient had the most pain. Local anesthetic infiltration was first performed using 1.0% lidocaine hydrochloride, and the radiofrequency trocar (20G, 150mm in length, 10mm in movable end) was slowly advanced under CT guidance. Finally, the needle tip is located in the upper quadrant of the foramina, and root pain can occur before the puncture point reaches the chest wall. The radiofrequency therapeutic instrument (Baylis Medical Inc., Montreal, QC, Canada) was connected to conduct sensory test. The parameters were set as follows: voltage was 0.1–0.5 V, frequency was 50 Hz, and discomfort such as acid, swelling, numbness or tingling in

the original pain area could be caused by radiofrequency. Low frequency current was used in the exercise test, and the parameters were set as follows: the voltage was 0.1–0.5V, and the frequency was set as 2 Hz. If the muscle fibrillation and pulsation in the area of the diseased nerve root were reproduced, the puncture needle was located near the target. We then adjusted the instrument parameters to set temperature, time, pulse width, and frequency to 42°C, 300 s, 20 ms, and 2 Hz. At the end of the pulsed radiofrequency, the electrode core was removed and the absence of blood, gas, or fluid in the puncture needle was confirmed. The patients in group C were given normal saline intravenous pump injection after admission. After that, pulsed radiofrequency surgery was performed, and the pulsed radiofrequency treatment method was the same as that of group P. Rescue method: if the patient still experiences significant pain after treatment, a CT or B-ultrasound-guided paravertebral nerve block procedure can be performed: A puncture is made at the corresponding spinal segment of the patient's pain area. After confirming that there is no blood, gas or fluid when the puncture needle is withdrawn, 100mg of 2% lidocaine hydrochloride and 1mg of mecobalamin injection are injected. 5mL of the treatment solution is injected into each segment, completing the block. The number of repeated blocks should not exceed 3 times. For patients whose pain has not been significantly relieved and has persisted for more than 3 months (with a VAS score > 3), treatment with tramadol hydrochloride sustained-release tablets (100 mg/d) is administered, with a maximum total dose of 200mg q12h. Additionally, intermittent paravertebral nerve block is used.

Data Collection and Follow-Up

Primary outcome: the incidence of PHN. According to the IASP (International Society of Pain) standard, PHN was defined as persistent pain for ≥3 months after the appearance of rash.[3] Secondary outcome measures: The VAS score and Pittsburgh Sleep Quality Index (PSQI) score were recorded before operation (T0), 1 month after operation (T1), 3 months after operation (T2), 6 months after operation (T3), 12 months after operation (T4), and the oral dose of pregabalin capsule was recorded. Blood samples were collected before treatment and 14 days (±3 days) after surgery to detect the serum levels of Gal-3 and IL-6. In addition, the salvage treatment was recorded, including the number of postoperative paravertebral block and the use of tramadol hydrochloride sustained-release tablets. Adverse reactions such as blood pressure reduction, heart rate slowdown, and postoperative infection were observed throughout the study period.

Statistical Analysis

Sample Size

The sample size was calculated based on the incidence of PHN at 3 months after surgery. In our pilot study, the incidence of clinically significant PHN was 7% in group P and 33% in group C. From this information, we calculated a minimum sample size of 45 per group (α=0.05, β=0.1). The estimated rate of loss to follow-up was set at 15%, and the minimum sample size in each group was calculated to be 53.

Data Analysis

SPSS 26.0 (IBM, Chicago, USA) software was used for statistical analysis. The Shapiro–Wilk test was performed to determine if the measurements were normally distributed. Data with normal distribution were expressed as mean ± standard deviation, and data with skewed distribution were expressed as median (quartile). The Mann–Whitney *U*-test or independent sample *t* test was used for continuous variables, categorical variables were expressed as percentages, and the chi-square test or Fisher's exact test was used for categorical variables. $P<0.05$ was considered statistically significant.

Results

Characteristics of the Patients

A total of 112 patients were enrolled in this study, and 1 patient in each group P and C was lost to follow-up. A total of 110 patients were enrolled, including 55 patients in group P and 55 patients in group C. All patients completed the operation and statistical analysis was performed. Between the two groups of gender, age, course of the disease, sick side, herpes zoster involving parts, preoperative VAS score and PSQI score such as general data, no significant statistical difference ($p > 0.05$; Table 1). No significant differences were observed in the basic diseases and history of malignant tumors between the two groups of patients ($p > 0.05$; Table 2).

Table 1 Comparison of Baseline Data Between the Two Groups

Variable	Group P (n=55)	Group C (n=55)	*P* value
Gender (case, male/female)	(21/34)	(31/24)	0.085
Age (years, $\bar{x} \pm s$)	63.9±12.8	64.6±12.9	0.795
Course of the disease (days, Q1-Q3)	20(14,30)	15(10,30)	0.064
Affected side (case, left/right)	(29/26)	(30/25)	0.848
Involved parts (case, %)			
Head and face area	13(23.6)	14(25.5)	0.648
Trunk area	34(61.8)	35(63.6)	
Limb parts	8(14.5)	6(10.9)	
Preoperative VAS score (Q1-Q3)	6(6,7)	6(6,7)	0.274
Preoperative PSQI score (Q1- Q3)	14(14,16)	14(13,15)	0.134

Table 2 Comparison of Patient's Medical History Characteristics

Concomitant Diseases (Cases, %)	Group P (n=55)	Group C (n=55)	*P* value
Malignant tumor	5(9.1)	4(7.3)	0.728
Hypertension	17(30.9)	29(52.7)	0.099
Diabetes	10(18.2)	7(12.7)	
No	28(50.9)	21(38.2)	

Occurrences of PHN

In group P, 6 patients developed PHN, with an effective rate of 89.1%. Sixteen patients in group C developed PHN, and the effective rate was 70.9%. Compared with group C, the effective rate of group P was significantly higher ($p=0.03 < 0.05$; Figure 1).

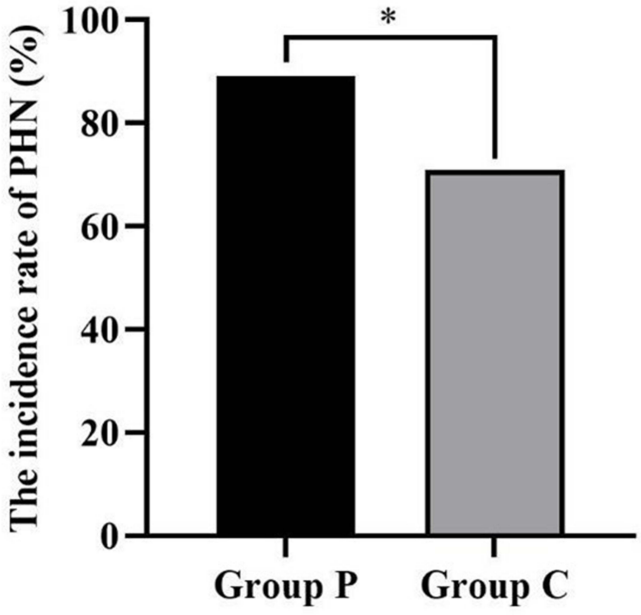

Figure 1 Comparison of the incidence of PHN between the two groups after surgery.
Note: *The incidence of PHN in group P was significantly lower than that in group C, $P<0.05$.

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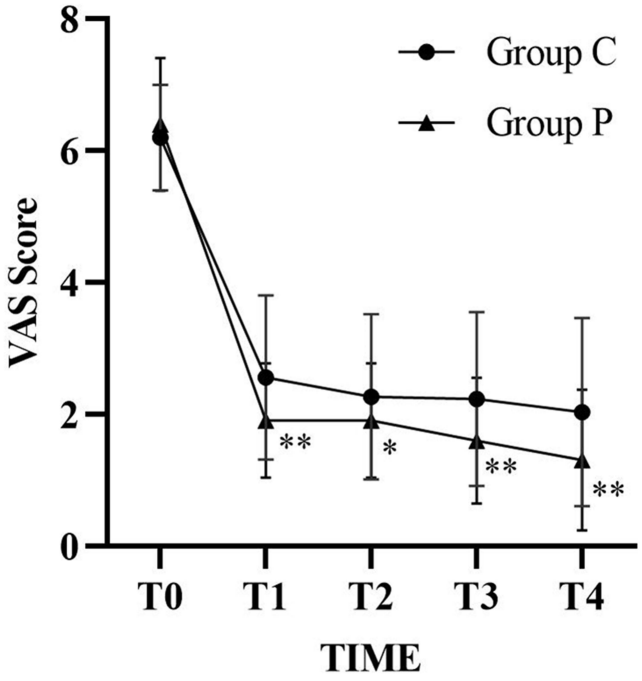

Figure 2 Comparison of VAS scores between the two groups before and after treatment.
Note: *Compared with group C, the VAS score of group P was significantly decreased, *P*<0.05; **Compared with group C, VAS score in group P was significantly decreased, *P*<0.01.

VAS Score

After treatment, the VAS scores of the two groups were significantly decreased ($P < 0.001$). Compared with group C, the VAS scores of patients in group P were significantly decreased at 1, 3, 6 and 12 months after treatment ($P < 0.05$; Figure 2).

PSQI Score

After treatment, PSQI scores were significantly decreased in both groups ($P < 0.001$). Compared with group C, the PSQI scores of patients in group P were significantly decreased at 1, 3, 6 and 12 months after treatment ($P < 0.05$; Figure 3).

Pregabalin Dosage

After treatment, the dose of pregabalin in the two groups was significantly reduced ($P < 0.05$). Compared with group C, P group of patients in March, June, 12 months after treatment of pregabalin dose were significantly lower ($P < 0.05$; Table 3).

Serum IL-6 and Gal-3 Levels

Before treatment, there was no significant difference in plasma IL-6 and Gal-3 between the two groups. After treatment, the plasma IL-6 and Gal-3 indexes of the two groups were significantly decreased ($P < 0.05$). Compared with group C, the level of IL-6 in group P was significantly decreased after treatment ($P < 0.05$). However, there was no significant difference in plasma Gal-3 levels between the two groups after treatment (Table 4).

Implementation of Postoperative Remediation

A total of 9 patients underwent paravertebral nerve block once at 2 weeks after operation, and 2 patients underwent paravertebral nerve block twice at 1 week and 2 weeks after operation. All patients with PHN were treated with tramadol hydrochloride sustained-release tablets for pain relief.

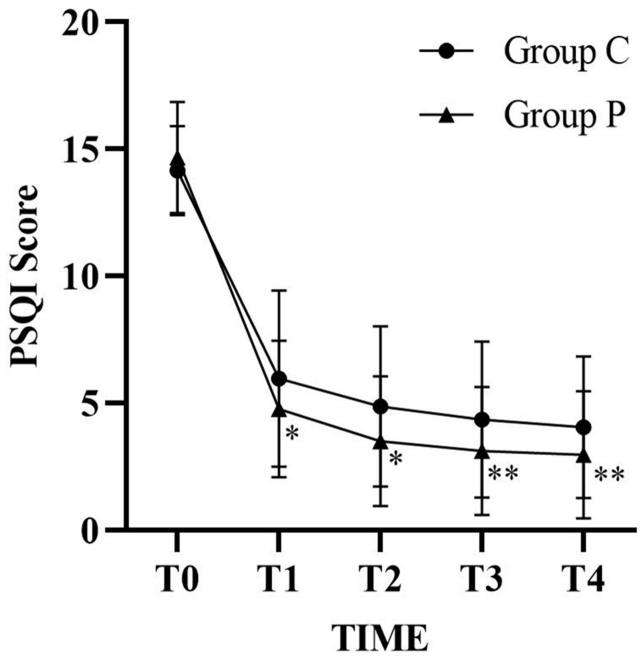

Figure 3 Comparison of PSQI scores between the two groups before and after treatment.
Note: *Compared with the C group, the PSQI score of the P group was significantly decreased, *P*<0.05; **Compared with group C, PSQI score in group P was significantly decreased, *P*<0.01.

Adverse Reactions

One adverse reaction occurred in group P: A thin female patient developed hypotension 1 hour after intravenous infusion of lidocaine hydrochloride (the lowest was 81/49 mmHg, the patient's usual blood pressure was 120–140/70-90 mmHg). The patient complained of no obvious discomfort and continued to observe after reducing the infusion rate by 20%. A repeat blood pressure measurement 1 hour later returned to normal (119/72mmHg), and the patient had no apparent

Table 3 Oral Pregabalin Doses (mg/Day) Before and After Treatment in Both Groups

Grouping	Pre-Operation			1m After the Operation			3m After the Operation			6m After the Operation			12m After the Operation		
	0	75	150	0	75	150	0	75	150	0	75	150	0	75	150
Group P (n)	0	0	55	39	10	6	47	3	5	48	1	6	49	0	6
Group C (n)	0	0	55	31	10	14	37	4	14	39	1	15	40	0	15
P value	1.00			0.069			0.021*			0.033*			0.030*		

Note: *Compared with group C, the oral dose of pregabalin in group P was significantly reduced, *P*<0.05.

Table 4 Comparison of Blood Indexes Between the Two Groups Before and After Treatment

Blood Indicators		Group P (n=55)	Group C (n=55)	*P* value
IL-6	Pre-operation	11.36±5.49	10.86±3.04	0.572
	After surgery	7.89±3.01	9.14±3.13	0.035*
Gal-3	Pre-operation	1.17±0.51	1.11±0.51	0.535
	After surgery	1.05±0.62	1.04±0.43	0.974

Note: *Compared with the C group, the levels of blood indexes in the P group were significantly lower, *P*<0.05.

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discomfort thereafter. After treatment, no bleeding or infection at the puncture site, pneumothorax, spinal cord injury, hematoma, or any other serious adverse effects were observed in either group.

Discussion

Herpes zoster is a self-limited disease caused by reactivation of VZV. In most cases, as the rash subside, the pain and other symptoms will also reduce or disappear, but there are still a part of patients will develop PHN. These patients have persistent pain, and in severe cases, they need to take analgesics for life. Herpes zoster pain is a pathological form of neuropathic pain with all the main clinical features of neuropathic pain, including paresthesia (numbness, itching, etc)., constant pain, and allodynia (pain caused by touch). In contrast to inflammatory pain, which worsens during activity, neuralgia is mostly manifested at night and during leisure. Many studies have reported that acute herpes zoster neuralgia and PHN have a great impact on the daily activities, work, sleep and mood of patients. Moreover, PHN is more difficult to treat, and the effect of current treatment methods on PHN is not exact.[12–14] Therefore, it is very important to treat herpes zoster neuralgia before it develops into PHN.

However, there is still no unified conclusion on the occurrence mechanism of PHN, and most of them accept that the occurrence of PHN is mediated by both peripheral and central mechanisms.[15–17] Another hypothesis regarding the formation mechanism of PHN has received much attention in recent years, namely the “ectopic pacing hypothesis”. The ectopic pacemaker theory suggests that electrical hyperexcitability of primary afferent neurons after axonal injury and demyelination is an important basis for neuropathic pain.[18] Ho Kim S et al cut the spinal nerves of L5 and 6 at the distal end of the corresponding dorsal root ganglia, causing spontaneous pain as well as rapid attacks of mechanical allodynia and hyperalgesia. In this neuralgia model, it was found that the injured afferent neurons showed a large amount of sustained ectopic firing and also showed ectopic hyperexcitability in response to the applied stimulus.[19] Moreover, a large number of studies have proved the consistency of this hypothesis by verifying the simultaneous occurrence of allodynia induced by ectopic discharge and tactile nociception, the disappearance of allodynia after blocking ectopic potential, the elimination of allodynia by preventing the generation of ectopic potential, and the exclusion of experimental bias caused by pain-related heredity of research subjects in various basic experiments.[20] The exact reason for the occurrence of this ectopic potential in this hypothesis is not known, but ion channels appear to play an important role, including sodium, potassium, calcium channels, and particularly noteworthy sodium channels. Voltage-gated sodium channels are composed of an α subunit and a β subunit. Currently, 9 subtypes (Nav1.1-Nav1.9) have been identified, among which Nav1.3, Nav1.7, Nav1.8 and Nav1.9 have been confirmed to be related to neuropathic pain.[21] The Emer M. Garry established a rodent model of chronic VZV infection. The study found that the expression of Nav1.3 and Nav1.8 in sodium channels in the DRG of VZV infected rats was significantly increased. It is revealed that ectopic potential induced by over-expression and activation of sodium channel plays an important role in the formation of PHN.[22] We outline the basic process of its occurrence: VZV reactivation triggers membrane remodeling of afferent nerves and even adjacent nerves, in which pain-related sodium channels are largely over-expressed and over-activated, causing hyperexcited neurons to show enhanced membrane resonance, rhythmicity, and ectopic spikes. The resulting excess secretion constitutes the primary neuropathic pain signal and triggers and maintains central sensitization.[23] Therefore, the intervention of sodium channels is the main goal of treatment, and the present study was designed as a clinical exploratory trial on the basis of this hypothesis.

At present, a large number of studies have confirmed the effectiveness of PRF in treating various chronic pain disorders. It has been verified through a considerable number of clinical studies (involving over 2000 patients) that it can significantly relieve pain, reduce drug dependence, effectively lower the risk of post-herpetic neuralgia, and has rare serious adverse reactions. However, the exact mechanism of its neurological changes remains controversial. In the early stage of basic research, PRF has been questioned because no significant histological changes were found in the dorsal horn of rats.[24] However, many microscopic studies have shown that PRF can induce a variety of changes and affect many biological pathways involved in the regulation of chronic neuropathic pain, including neuroinflammatory response, regulating protein expression, ion channels, neurotransmitters, and glial cells. Some of these effects proved to be potentially reversible in animal models, which may have contributed to the persistent pain and development of PHN in some patients despite treatment in the clinic.[25] In order to compensate for the poor efficacy of PRF in some patients,

a number of clinical trials have been actively explored. Based on PRF treatment, other treatments including paravertebral nerve block and dorsal root ganglion ozone injection therapy have been combined. These methods have increased effectiveness compared with the use of pulsed radiofrequency alone, but they still have their limitations.[26–28] There is still a long way to go for the pain management of herpetic neuralgia. In the previous discussion of the possible mechanisms of PHN, we highlighted that the ectopic pacing hypothesis may play an important role, which is currently lacking in clinical studies. Based on this hypothesis, the use of membrane stabilizers can inhibit neuronal excitability to eliminate allodynia and avoid central sensitization. PRF precisely acts on the affected dorsal root ganglia, blocking the transmission of pain signals from the periphery to the spinal cord. The effects of both the overall treatment and the local treatment work together. Therefore, in this study, we tried to use sodium channel blocker - lidocaine intravenous pump injection combined with PRF to observe its efficacy and safety.

Lidocaine was first synthesized in 1921. It was initially used as a local anesthetic and antiarrhythmic drug, but its analgesic, anti-inflammatory and anti-hyperalgesic properties were soon discovered. A large number of studies have confirmed the feasibility of intravenous infusion of lidocaine for the treatment of various acute and chronic neuropathic pain from various aspects.[29–31] In vitro studies have shown that lidocaine preferentially binds to the inactive Voltage-Gated Sodium Channel (VGSC), preventing its re-conversion to the usable state, thereby inhibiting the excitability of cells. This is especially true when the VGSC is highly stimulated (corresponding to VGSC-dependent neuropathic pain episodes). In addition, lidocaine could attenuate the activation of inflammatory factors in activated macrophages and inhibit the neuroinflammatory response. It can also indirectly inhibit the excitability of afferent nerve cells by blocking potassium ion channels to inhibit outward potassium current and induce partial depolarization to promote the inactivation of sodium channels.[32–34] In animal experiments, D.K. AM et al showed that surgical incision could change the central sensitization of capsaicin-induced nociceptive neurons in rat brainstem and found that surgical incision could induce a series of neuronal spikes and increase their excitability, reflecting the central sensitization of most tested neurons. However, these spikes and central sensitization were significantly reduced after pretreatment with local infiltration of 2% lidocaine at the incision site.[35] Maria Luisa Sotgiu's experiment in rats also proved that intravenous infusion of lidocaine had a longer lasting and more effective inhibitory effect on dorsal horn neurons than peripheral neurons, and the size and duration of the inhibitory effect were comparable to those of acute rhizotomy.[36] In clinical practice, intravenous infusion of lidocaine has also been used in the treatment of perioperative analgesia, anti-hyperalgesia, chronic neuropathic pain, and so on. In terms of research on zoster associated pain, at present, we only searched two studies of Yue et al using intravenous lidocaine infusion in the treatment of PHN in 2017 and Wanyun Zhang using pulsed radiofrequency combined with intravenous lidocaine infusion in the treatment of patients with subacute herpes zoster related neuralgia (duration range from 30 to 90 days) in 2022.[10,37] In both studies, intravenous lidocaine had relatively good results. This study also confirmed the feasibility and safety of intravenous lidocaine infusion in the treatment of neuralgia associated with herpes zoster.

In this study, compared with the control group C, the incidence of PHN in group P was reduced by 18.2%. IL-6 and Gal-3 are commonly used as objective indicators for studying herpes zoster neuralgia.[38,39] Clinically, the levels of Gal-3 and IL-6, especially IL-6, can be detected through simple peripheral venous blood sampling. The levels of IL-6 and Gal-3 in both groups were lower than those before treatment. Compared with control group C, the IL-6 level in group P was significantly lower, which objectively reflects the superiority of lidocaine intravenous pump injection combined with PRF. The reason for no significant difference in the levels of Gal-3 between the two groups might be that the sample size of this study was insufficient, and secondly, it might be due to the problem of the detection reagents, causing deviation. However, there were still 6 patients with PHN in the P group. We followed up them for up to 12 months and found that the pain of these 6 patients was relieved after treatment, but the VAS score was still greater than 3. The other two cases were located in the trunk. In this study, the majority of patients with pain located in the trunk (62.7%), and the patients with head and face involvement were less than those in the trunk (24.5%), which is consistent with the epidemiology of herpes zoster itself, but the data showed that only a small number of patients with herpes zoster in the head and face had more PHN. Previous studies have also shown that the treatment and pain management of herpetic neuralgia in the trigeminal region are more challenging than in other sites.[40,41] This may be due to the complex structure of the trigeminal nerve and insufficient PRF energy to cover the area of herpes zoster infection. Li H and Wan C et al improved the effect

of PRF by increasing PRF voltage parameters and RF duration.[42,43] The two patients with PHN in the trunk were 73 years old and 80 years old, respectively. It is worth noting that the 73-year-old patient had insomnia for more than 10 years before herpes zoster. There is no doubt that long-term insomnia can reduce the patient's immunity, which may be the cause of the patient's development of PHN. We also noted in this study that most patients over 65 years old also had sleep quality problems before they developed herpes zoster, and it is well known that the occurrence of PHN is positively correlated with age.[44,45] In the past, we seem to pay little attention to the sleep quality problems of patients themselves. In addition to improving the poor sleep quality caused by pain, can reducing the sleep problems caused by other reasons also help to reduce PHN? This may require and merit our further investigation.

Limitations

Our study has some limitations that should be addressed. First, the patients enrolled were from a single pain management center, and future studies should involve multiple centers. Second, the mechanisms of central sensitization need to be verified in combination with functional imaging such as functional magnetic resonance imaging.

Conclusions

Intravenous infusion of lidocaine combined with pulsed radiofrequency therapy is an effective method for preventing post-herpetic neuralgia. This approach reduces the incidence of PHN, effectively alleviates the pain of patients with acute herpes zoster, reduces the dosage of medication, and improves the sleep disorders of patients.

Data Sharing Statement

Anonymized results data will be shared upon reasonable request to the corresponding author. These requests will be considered and processed within 6 months from the date of publication of the article. If the request is reasonable, the research plan can also be provided.

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Disclosure

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