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A study on the synergistic effects of neuromodulation and opioid-sparing analgesics in postherpetic neuralgia

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Abstract: Postherpetic neuralgia (PHN) is a common complication of herpes zoster, which seriously affects patients' quality of life. This study analysed the synergistic effect of neuromodulation and opioid dilution analgesics in the treatment of PHN. 120 patients with PHN from Affiliated Hospital of Southwest Medical University between December 2020 and December 2023 were categorized into PR and PO groups, both groups were treated with pulsed radiofrequency, PO group was added with Oxycodone hydrochloride. VAS scores, inflammatory factor indexes [tumour necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-2 (IL-2), interleukin-10 (IL-10)], immune indexes [percentage of $CD4^+$ T cells, $CD8^+$ T cells, $CD4^+$ /$CD8^+$] and clinical efficacy were mainly evaluated. Secondary indicators included sleep quality (PSQI) scores, anxiety self-assessment (SAS) scores, disease control time, adverse reactions and recurrence rates. Post-treatment, both groups' indicators were significantly improved. IL-2 and IL-10 levels, $CD4^+$ T cells percentage, $CD4^+$ /$CD8^+$ and clinical efficacy were higher in PO group than PR group. VAS score, TNF-α and IL-1β levels, $CD8^+$ T cells percentage, PSQI score, SAS score, disease control time, adverse reaction and recurrence rate were lower than PR group (P<0.05). The combination treatment efficacy of PHN is remarkable and is worth promoting its use in the clinic.

Keywords: Postherpetic neuralgia; neuromodulation; opioid dilution analgesics; immune indicators; inflammatory indicators

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INTRODUCTION

Postherpetic neuralgia (PHN) is an intractable chronic pain syndrome with persistent pain for >1 month after the healing of acute herpes zoster rash, which is caused by abnormal discharges of the nerves themselves, with long-lasting pain episodes and a long course of the disease (Tang *et al.*, 2023). In terms of clinical symptoms, PHN is mainly characterized by pain, which may appear before or along with the rash, with localized paroxysmal or persistent burning, stabbing, throbbing and cutting pains, etc. The degree of pain worsens with age and the symptoms are less pronounced in children and more severe in the elderly (Chen *et al.*, 2024). Patients are often accompanied by psychological, sleep and quality of life changes and may also experience anorexia, chronic fatigue and other discomforts, as well as affecting vision, resulting in facial paralysis and hearing impairment. PHN is highly susceptible to varying degrees of anxiety and depression, which in turn affects the quality of life of the patient (Zhou *et al.*, 2021).

The pathogenesis of PHN is complex. Varicella-zoster virus (VZV) causes chickenpox by initial infection and after healing, it lurks in the posterior root ganglia of the spinal cord or sensory ganglia of the brain. When the body's immunity declines due to advanced age, chronic diseases, HIV infection, surgery and the use of immunosuppressive drugs, the virus is activated to replicate and spreads along the sensory nerves to the innervating dermatomes, causing not only skin damage, but also attacking the sensory nerve tissues and triggering both peripheral sensitization and central sensitization (Y Li *et al.*, 2024). Peripheral sensitization is caused by the immune response and inflammation after tissue damage in the affected area, which prompts the release of histamine and other substances to stimulate and sensitize nociceptors and at the same time, the expression of nociceptors and voltage-gated ion channels in the peripheral injury-sensing neurons is altered, lowering the threshold of neuronal excitation. On top of this, damaged neurons may also produce abnormal spontaneous discharges due to the occurrence of structural changes such as fibrosis, which continues to generate pain signals even in the absence of ongoing tissue damage (Q Liu *et al.*, 2024). The type, nature and degree of pain in PHN are characterized by diversity and individual differences and sometimes changes in environmental temperature can cause pain episodes in patients with PHN, which can seriously affect their daily lives (Niemeyer *et al.*, 2024).

In terms of treatment, medication is an important tool. Calcium channel modulators such as pregabalin and

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gabapentin, which can regulate neurotransmitter release and relieve pain, have good efficacy in neuropathic pain, can effectively relieve pain symptoms and are relatively well tolerated, with common adverse effects including dizziness, drowsiness and peripheral edema, which may affect the patient's daily life (Huerta *et al.*, 2023). Tricyclic antidepressants play an analgesic role by regulating the monoamine neurotransmitter system, in addition to analgesia, they have a certain antidepressant effect on patients accompanied by depression, with more adverse reactions, such as dry mouth, constipation, blurred vision, cardiac arrhythmia, etc., especially for the elderly, which may increase the risk of falls and other risks due to adverse reactions (Lin *et al.*, 2019). Lidocaine patch can be used to relieve local pain by blocking sodium ion channels and inhibiting nerve impulse conduction, it is a localized drug with fewer systemic adverse effects, it has a better relieving effect on localized pain, it is easy to use, it is only effective for the pain at the patch site and it has limited effect on patients with a wide range of pain (Bianchi *et al.*, 2021). Tramadol, opioid analgesics can act on the opioid receptors of the central nervous system to exert analgesic effects, but the analgesic effect is stronger and it has a better relieving effect on moderate to severe pain. Among them, the most common is oxycodone hydrochloride and some patients have experienced significant reduction in pain level and improvement in sleep quality after using oxycodone hydrochloride (Gónima Valero *et al.*, 2023). In addition, PHN can also be treated by minimally invasive interventions. Nerve block is the injection of local anesthetic or a mixture of medications around a nerve root, stem, plexus or node for analgesia, through which the transmission of pain signals can be effectively blocked and pain can be relieved quickly. Neuromodulation includes radiofrequency, peripheral nerve electrical stimulation and spinal cord electrical stimulation (Guo *et al.*, 2019). Pulsed radiofrequency is more commonly used, which mainly outputs in an intermittent high-voltage state, forming high voltage and low temperature around the nerves, affecting neurotransmitter release by changing the membrane potential of nerve cells and being able to continuously and reversibly inhibit the excitatory afferents of the C fibers, thus realizing the blocking effect on the relevant neural nociceptive conduction and achieving the purpose of relieving pain (Zhang *et al.*, 2022). For the treatment of PHN, a variety of combined therapeutic modalities are constantly being developed to improve analgesic effects and patient’s quality of life.

Therefore, this study evaluated the clinical efficacy and pain relief of pulsed radiofrequency combined with oxycodone hydrochloride in the treatment of patients with PHN. The study analysed the inflammatory markers and immune indices after treatment, clarified the efficacy of the combination therapy and assessed its impact on improving the quality of life of the patients, thus providing more therapeutic options for clinical practice.

MATERIALS AND METHODS

Study design and participants

This study is a systematic evaluation and integration aimed at comparatively analyzing the clinical effectiveness of pulsed radiofrequency combination with opioid analgesics in the treatment of patients with PHN and further evaluating its effects of inflammatory and immune indices. This is a retrospective study, 120 PHN patients from The Affiliated Hospital of Southwest Medical University were selected between December 2020 and December 2023 and were divided into two groups, PR group and PO group, according to the different interventions. The flow chart of the study design is shown in fig. 1.

Inclusion and exclusion criteria

Inclusion criteria

(1) The patient met the clinical diagnostic criteria for PHN (Gross *et al.*, 2020); (2) The patient's herpes was located on the chest or back; it had not been treated by traditional Chinese or Western medicine; (3) Age 18 to 80 years; (4) Neuralgia lasting more than 4 weeks; (5) The patient has good compliance and is willing to cooperate with the treatment plan developed in the study; (6) The patients had good overall mental status, were basically healthy and could truthfully express their complaints about their symptoms and answer relevant questions from healthcare professionals; (7) Those who can tolerate the drugs involved in this study; (8) The patients and their family members are informed and consented and signed an informative consent form.

Exclusion criteria

(1) Malignant tumor of any site or type; (2) Patients with combined hemorrhagic and coagulation disorders, or with severe liver or renal function defects, severe cardiovascular disease or other more serious diseases; (3) Combined chronic infectious diseases; (4) Combined cerebral, cardiac, hepatic and renal functional abnormalities; (5) Patients who have participated in clinical drug trials or clinical studies; (6) Patients with combined neurological and psychiatric diseases that make it difficult to communicate normally; (7) Requesting to stop treatment or automatic discharge for personal reasons; (8) Presence of systemic viral infection symptoms; (9) Those who are allergic to the drugs used in this study; (10) Other conditions that, in the opinion of the study physician, should not be included; (11) Other circumstances affecting the indicators of follow-up observation.

Ethical statement

The study was performed in compliance with the Declaration of Helsinki and hospital ethical guideline and was endorsed by the hospital ethical committees.

Interventions

Both groups of patients were treated with nerve pulse

radiofrequency. Nerve pulsed radiofrequency treatment method: CT-guided spinal nerve pulsed radiofrequency treatment was adopted. Patients were positioned in the prone positions and the CT-guided radiofrequency cannula needle (10cm) was punctured to the posterior edge of the intervertebral foramen of the target segment and the outer edge of the pedicle root and injected with 0.3-0.5 mL of iodinol to confirm that the position was correct. The pulse therapy instrument was R-2000B radiofrequency temperature-controlled thermocoagulator and the acting and non-acting electrodes of the instrument were pasted to the corresponding parts of the patient for testing. Skin pain or numbness appeared when stimulated by 50 Hz, <0.5 V voltage and there was no intercostal muscle fleshy twitching when stimulated by 2 Hz, >2 times the voltage. The position of the tip of the needle was clarified to be close to the dorsal root ganglion and then the radiofrequency mode was turned on (42°C, duration 240 s, frequency 2 Hz, pulse width 20 ms, voltage 45 V, interval 15 s) for pulsed radiofrequency treatment of the dorsal root ganglion and the treatment was carried out for 1 cycle.

Patients in the PO group were treated with the addition of Oxycodone hydrochloride. Oxycodone hydrochloride extended-release tablets (NDT: J20110014, BARD PHARMACEUTICALS LIMITED), orally, 10 mg/dose, 2 times/d, if the patient's pain is not well controlled, the dose needs to be increased appropriately, but the maximum dose should not be more than 60 mg/d (Jin *et al.*, 2021). The patient is required to maintain the treatment for 1 month.

Observational indicators

Primary indicators

Pain scores

Pain visual analog score (VAS) was used to assess the pain level of patients in both groups before and after treatment. It was counted as 0~10 score, 1~3 as mild pain, 4~7 as moderate pain and >7 ~ 10 as severe pain (Bielewicz *et al.*, 2022).

Inflammation indicators

Referring to the research method of Kanlioglu *et al* (Kanlioglu Kuman *et al.*, 2021), 3 mL of fasting venous blood was drawn from patients pre- and post- treatment, centrifuged and processed and then preserved in cold storage to be detected and the levels of tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-2 (IL-2) and interleukin-10 (IL-10) were measured using enzyme-linked immunosorbent assay.

Human TNF-α ELISA kit (Item No.: ml077385, Shanghai Enzyme-linked Biotechnology Co., Ltd.), Human IL-1β ELISA kit (Item No.: CB10347-Hu，Shanghai COIBO BIO Technology Co., Ltd.), Human IL-2 ELISA kit (Item No.: ml106410，Shanghai Enzyme-linked Biotechnology Co., Ltd.), Human IL-10 ELISA kit (Item No.: ml064299，Shanghai Enzyme-linked Biotechnology Co., Ltd.) were used to detect levels of TNF-α, IL-1β, IL-2 and IL-10 respectively.

Immunity indicators

Immune indicators were observed in both groups and the levels of immune indicators in peripheral blood samples were measured using enzyme-linked immunosorbent assay (Aljabr *et al.*, 2022). Human $CD4^+$ T cells ELISA kit (JKbio 14552, Shanghai Jingkang Bioengineering Co., Ltd.), Human $CD8^+$ T cells ELISA kit (JKbio 14553, Shanghai Jingkang Bioengineering Co., Ltd.) were used to detect the percentage of $CD4^+$ and $CD8^+$ T cells respectively.

Clinical treatment effect

Observe the clinical therapeutic effects of the two groups of patients. Apparent effect: patients' pain symptoms subside, sleep quality and daily life return to normal. Effective: patients' pain symptoms improved obviously, but still have paroxysmal pain, sleep quality and daily life improved obviously. Ineffective: The above criteria are not met and the pain is not reduced or even aggravated. Total effective rate = (obvious effect + effective) / total × 100%.

Secondary indicators

Sleep quality scores

Sleep quality was assessed using the Pittsburgh Sleep Quality Index scale (PSQI), with scores inversely related to quality of sleep (J Liu *et al.*, 2021).

Self-assessment scale of anxiety

The Self-Assessment Scale for Anxiety (SAS) was applied to assess the anxiety level of the patients in both groups, with a critical value of 50 scores, with higher scores indicating greater anxiety (Xu *et al.*, 2023).

Disease control time

The time of disease control, including the time of stopping blisters, scab, remove scabs and stop pain, was recorded in both groups.

Adverse reactions

The occurrence of adverse reactions, including nausea/vomiting, hot flashes/sweating and headache during treatment was recorded for both groups.

Recurrence rate

Record the recurrence rate at 6-month follow-up after the end of treatment.

Follow-up visits

This study was primarily scheduled for a 6-month post-treatment follow-up to assess the durability of the effect and to address any potential adverse reactions or problems.

Sample size calculation

Sample size was based on a power analysis performed with

G*Power 3.1.9.7 computer software to determine the sample size required to detect a statistically significant difference. The sample size was calculated based on the VAS score as the primary outcome. Considering an α level of 0.05 and 85% efficacy, we calculated that a sample size of 49 patients was required for each group. Considering the potential uncertainties, a sample size of 60 cases per group was chosen for this study and we believe that the sample size of this study is able to draw reliable conclusions.

Statistical methods

SPSS27.0 statistics software was applied for analysis of the data. Measurements that conform to normally distributed value are represented as ($\bar{x}$±s) and comparisons among groups adopts act independently pattern t examination and counting data is expressed as rate (%) using x^2 test. P<0.05 indicates a statistically significantly difference.

RESULTS

Basic information

In this study, 120 patients with PHN from The Affiliated Hospital of Southwest Medical University between December 2020 and December 2023 were randomized to PR group (n=60) and PO group (n=60) based on different interventions. The baseline demographic and baseline characteristics in both groups are presented in table 1 and these characteristics showed no remarkable discrepancy among the groups (P>0.05). Thus, the randomization process achieved the important goal of randomly assigning participants to the both groups, the both groups were comparable at the pre-treatment level and the confounding of demographic/clinical factors did not affect the analysis of results.

Primary results

VAS score

VAS score is an important index to assess the degree of pain. The results of the VAS scores of the both groups are displayed in table 2. Pre-treatment, no obvious discrepancy was found among the VAS scores of the both groups (P>0.05). Post-treatment, the scores in both groups were markedly reduced (P<0.05). The score of PO group was 2.78±0.38 markedly below the score in the PR group of 5.19±0.91 (P<0.05). It indicated that both treatments could relieve pain, with better relief in the PO group.

Inflammatory indicators

The results of the comparison of inflammatory indicators among the both groups are demonstrated in table 3. Pre-treatment, no remarkable discrepancy was found among the levels of inflammatory indicators in the both groups (P>0.05). Post-treatment, TNF-α and IL-1β were markedly reduced in both groups, with 6.31±1.16 ng/L and 3.79±1.11 ng/L in patients in the PO group being markedly below the levels of 10.01±1.80 ng/L and 6.40±1.19 ng/L in patients in the PR group, respectively (P<0.05). IL-2 and IL-10 were markedly elevated in both groups, 29.04±4.30 pg/L and 29.95±3.00 pg/L in patients of PO group were both markedly above 17.25±3.71 pg/L and 23.17±2.59 pg/L in PR group, respectively (P<0.05). It indicated that the inflammatory indicators levels in both groups improved remarkably post-treatment and the improvement was better in the patients of PO group.

Immune indicators

We analyzed and compared the results of the immune function indicators of the both groups as presented in table 4. Pre-treatment, the comparison results of the immune function indicators of the both groups were not statistical significant (P>0.05). Post-treatment, the $CD4^+$ T cells percentage and $CD4^+/CD8^+$ were markedly increased in both groups, with 48.93±3.91% and 1.71±0.41 in PO group being markedly above 42.89±4.01% and 1.44±0.44 in PR group, respectively (P<0.05). The percentage of $CD8^+$ T cells was markedly reduced in both groups, which was 22.71±2.96% in PO group was remarkably below 25.87±4.43 in PR group (P<0.05). This indicates that the immunotherapy in both groups improved markedly post-treatment and the improvement of the immune function in the PO group was more remarkable.

Clinical efficacy

We analysed the clinical efficacy of patients in both groups and the results are shown in table 5. The total clinical efficacy rate of patients in the PR group was 75.00% (45/60), while the total clinical efficacy rate of patients in the PO group was 90.00% (54/60). The difference in clinical efficacy between both groups was statistically significant (P<0.05). The results showed that the clinical efficacy of patients treated with combination therapy was better.

Secondary results

PSQI and SAS scores

The results of the comparisons of PSQI and SAS scores among the both groups are demonstrated in table 6. Pre-treatment, no remarkable discrepancy was found in the comparisons of PSQI and SAS scores among the both groups (P>0.05). Post-treatment, the PSQI scores and SAS scores of patients in both groups were decreased remarkably (P<0.05). The PSQI scores and SAS scores of patients in PO group were 7.43±0.84 and 27.88±5.39, respectively, which were obviously below the 9.96±1.23 and 44.46±8.83 scores of PR group (P<0.05). It illustrated that the improvement of sleep quality and anxiety level was better in patients of PO group after treatment.

Disease control time

The disease control time of the both groups of patients is presented in table 7. The time to stop blistering, scab, remove scabs and stop pain of patients in PO group were 4.25±1.22 d, 8.11±1.45 d, 11.21±1.55 d, 14.39±2.50 d were markedly below 5.28±1.70 d, 10.10±1.84 d, 13.88±1.39 d, 18.69±2.79 d in PR group (P<0.05). It indicated that the PO group had better control of their condition and faster recovery.

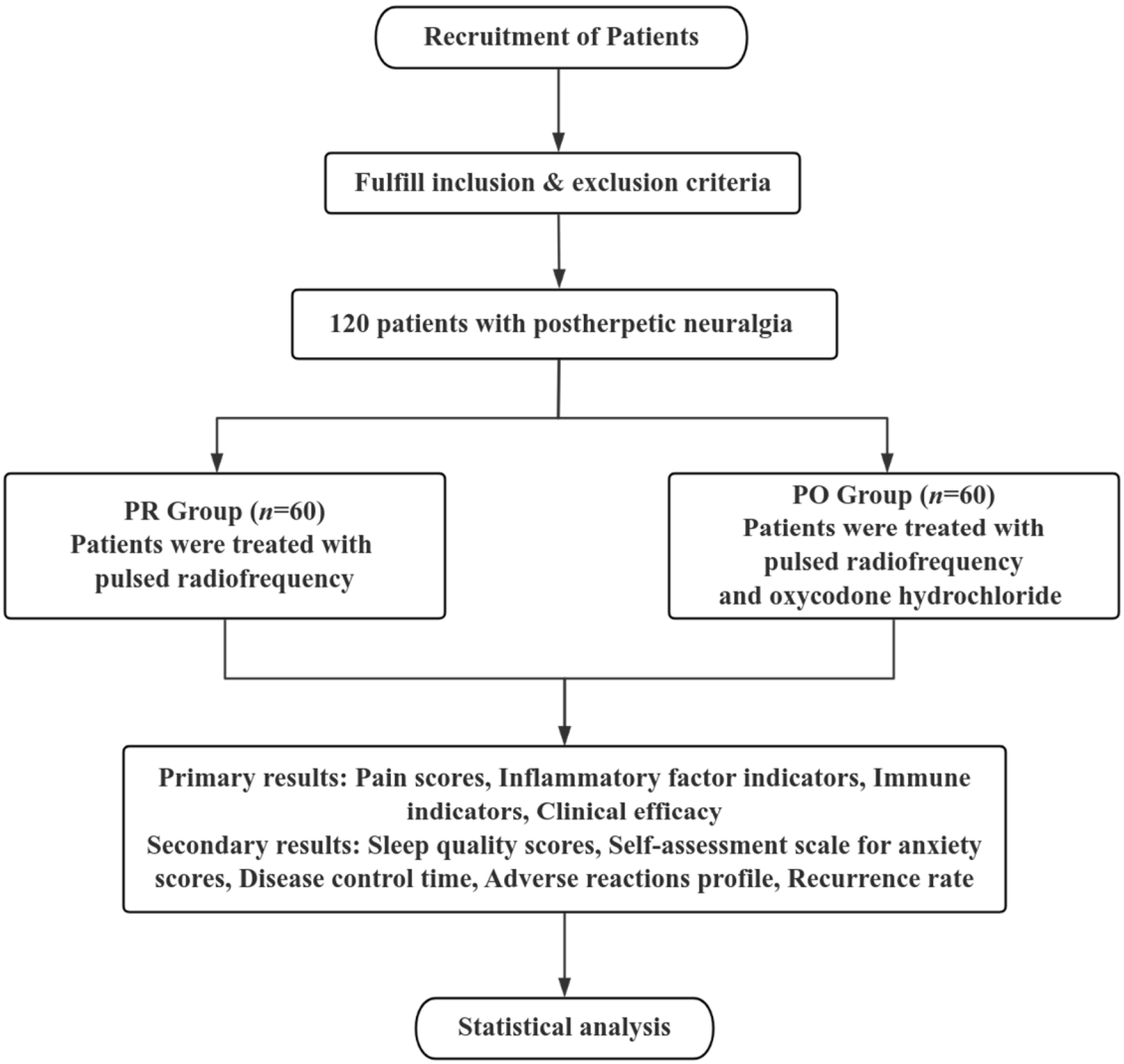

Fig. 1: Flow chart of the study design

Table 1: Patient demographics and baseline disease characteristics

Parameter	PR group (*n*=60)	PO group (*n*=60)	t/x^2	*P*
Age (year)	53.98±7.57	53.73±6.44	1.641	0.102
Duration of illness (months)	9.59±1.21	9.58±1.37	-0.075	0.940
Height (cm)	159.26±5.44	159.43±4.41	-1.432	0.153
Weight (kg)	65.75±6.71	66.17±5.83	-0.452	0.651
Body mass index (kg/m^2)	23.14±2.46	23.43±2.33	-1.249	0.213
Sex (male/female)	33/27	34/26	0.648	0.421
Smoking (yes/no)	20/40	22/38	0.057	0.811
Alcohol consumption (yes/no)	35/25	33/27	0.161	0.689
Hypertension (Yes/no)	13/47	14/46	0.103	0.749
Diabetes (Yes/no)	16/44	17/43	0.024	0.877
Temperature (℃)	36.26±0.28	36.32±0.29	1.350	0.178
Breathing (breaths/min)	17.51±2.14	17.22±2.01	0.306	0.760
Heart rate (beat/min)	74.55±7.10	74.68±5.90	-0.612	0.541
Systolic blood pressure (mmHg)	118.53±5.68	118.77±5.28	-0.334	0.738
Diastolic blood pressure (mmHg)	75.93±5.55	76.16±5.27	0.534	0.594

Table 2: VAS score ($\bar{x}$±s, score)

Time	PR group	PO group	*t*	*P*
Pre-treatment	7.54±0.98	7.48±0.95	-0.341	0.734
Post-treatment	5.19±0.91	2.78±0.38	-18.930	<0.001
t	-13.611	-35.581		
P	<0.001	<0.001		

Table 3: Comparison of inflammation indicators ($\bar{x}$±s)

Norm	Time	PR group	PO group	*t*	*P*
TNF-α (ng/L)	Pre-treatment	17.31±3.09	17.76±2.95	0.816	0.416
	Post-treatment	10.01±1.80*	6.31±1.16*	-13.384	<0.001
IL-1β (ng/L)	Pre-treatment	10.20±2.65	10.02±2.48	-0.384	0.702
	Post-treatment	6.40±1.19*	3.79±1.11*	-12.423	<0.001
IL-2 (pg/L)	Pre-treatment	12.27±3.42	12.31±2.99	0.068	0.946
	Post-treatment	17.25±3.71*	29.04±4.30*	16.080	<0.001
IL-10 (pg/L)	Pre-treatment	13.49±3.15	13.63±2.43	0.273	0.786
	Post-treatment	23.17±2.59*	29.95±3.00*	13.251	<0.001

Note: "*" represents marked discrepancy compared with pre-treatment, $P<0.05$.

Table 4: Immunity indicators ($\bar{x}$±s)

Norm	Time	PR group	PO group	*t*	*P*
$CD4^+$ T cells (%)	Pre-treatment	36.85±2.99	36.77±2.86	-0.150	0.881
	Post-treatment	42.89±4.01*	48.93±3.91*	8.353	<0.001
$CD8^+$ T cells (%)	Pre-treatment	29.82±4.09	29.73±3.49	-0.130	0.897
	Post-treatment	25.87±4.43*	22.71±2.96*	-4.594	<0.001
$CD4^+/CD8^+$	Pre-treatment	1.21±0.30	1.24±0.27	0.576	0.566
	Post-treatment	1.44±0.44*	1.71±0.41*	3.477	<0.001

Note: "*" represents marked discrepancy compared with pre-treatment, $P<0.05$.

Table 5: Clinical efficacy analysis

Group	Obvious effect (*n*)	Effective (*n*)	Ineffective (*n*)	Total effective rate (*n*, %)
PR group	21	24	15	45 (75.00)
PO group	24	30	6	54 (90.00)
x^2		7.792		
P		<0.05		

Table 6: PSQI and SAS scores ($\bar{x}$±s, score)

Norm	Time	PR group	PO group	*t*	*P*
PSQI	Pre-treatment	15.26±1.55	14.98±1.60	-0.974	0.332
	Post-treatment	9.96±1.23*	7.43±0.84*	-13.157	<0.001
SAS	Pre-treatment	63.76±8.93	63.94±8.02	0.116	0.908
	Post-treatment	44.46±8.83*	27.88±5.39*	-12.313	<0.001

Note: "*" represents marked discrepancy compared with pre-treatment, $P<0.05$.

Table 7: Disease control time ($\bar{x}$±s, d)

	Stop blistering	Scab	Remove scabs	Stop pain
PR group	5.28±1.70	10.10±1.84	13.88±1.39	18.69±2.79
PO group	4.25±1.22	8.11±1.45	11.21±1.55	14.39±2.50
t	-3.813	-6.580	-9.934	-8.891
P	<0.001	<0.001	<0.001	<0.001

Table 8: Incidence of adverse reactions (*n*, %)

	PR group	PO group	x^2	*P*
Nausea/vomiting	2 (3.33)	0 (0.00)	3.046	0.081
Hot flashes/sweating	1 (1.67)	1 (1.67)	0.000	1.000
Headache	1 (1.67)	0 (0.00)	2.020	0.155
Drowsiness	2 (3.33)	1 (1.67)	0.205	0.651
Itchy skin	2 (3.33)	1 (1.67)	0.205	0.651
Urinary tract infection	1 (1.67)	1 (1.67)	0.000	1.000
Joint pain	1 (1.67)	0 (0.00)	2.020	0.155
Total incidence	10 (16.67)	4 (6.67)	4.735	<0.05

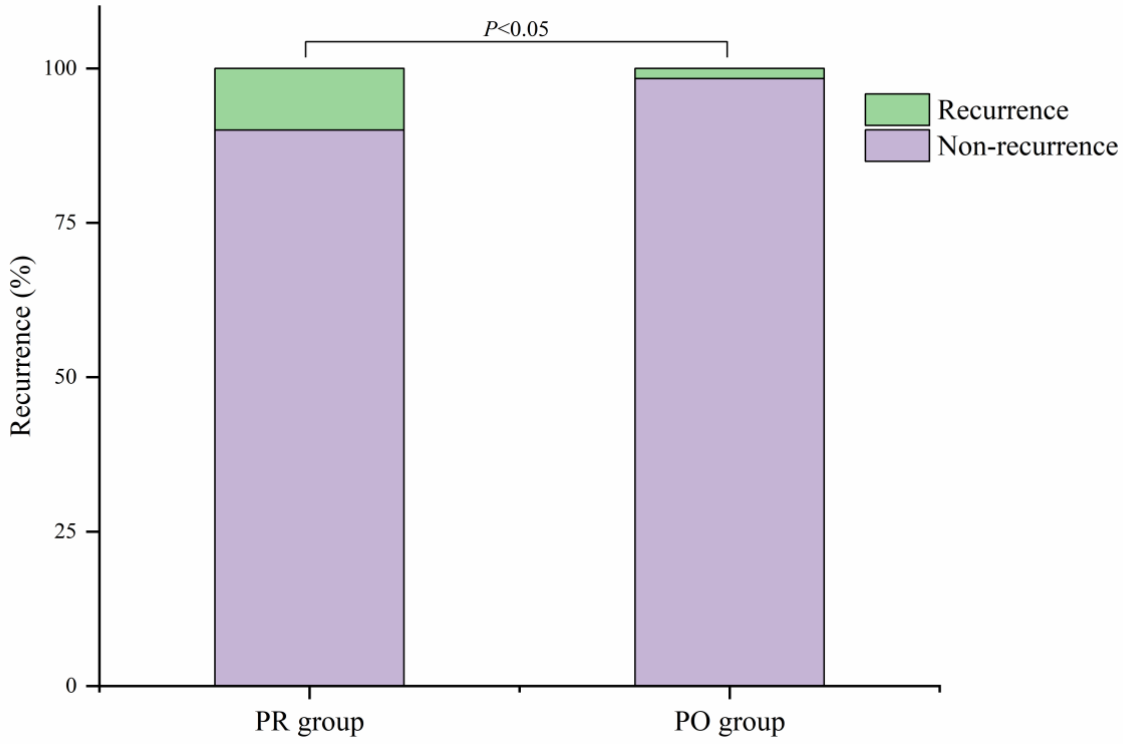

Fig. 2: Recurrence rate (%)

Adverse reactions

We followed up the patients to observe the adverse reactions. Adverse reactions of varying degrees such as nausea/vomiting during treatment in both groups are presented in table 8. The total incidence of adverse reactions in patients in the PR group was 16.67% (10/60) and in the PO group was 6.67% (4/60), with a remarkable discrepancy in the total adverse reaction incidence among the both groups (P<0.05). It illustrated that the combined treatment effectively reduced the adverse reactions of patients in PO group.

Recurrence rate

We recorded the recurrence of patients in both groups during the follow-up period, as demonstrated in fig. 2. The recurrence rate of patients in PR group was 10.00% (6/60) and 1.67% (1/60) in PO group and the recurrence rate of PO group was below that of PR group (P<0.05). It indicates that the combined treatment method used in this study can effectively reduce the recurrence rate of patients post-treatment.

DISCUSSION

PHN is the most common and troublesome complication of herpes zoster and is usually defined as a condition in which pain persists for more than 1 month after the herpes zoster rash has healed. Prompt treatment of herpes zoster can lead to recovery of skin symptoms in the herpes region, but some patients continue to have pain even after the

disappearance of skin symptoms and patients with recalcitrant PHN have a longer duration of pain, which leads to a lower quality of life (Schmader and Dworkin, 2018). The impact of PHN on patients is all-encompassing. Long-term pain suffering seriously interferes with the patient's daily life; sleep quality is drastically reduced due to pain and daily activities, such as dressing, washing and walking, may also be limited due to pain, resulting in a lower ability of patients to take care of themselves. Psychologically, patients are prone to negative emotions such as anxiety and depression, resistance to social activities and a significant reduction in social interactions, which seriously affects mental health and quality of life (Kapustin *et al.*, 2020). At present, the pathologic mechanism of PHN is not fully defined, but it is generally believed to be associated with a variety of factors. Non-disease factors such as age, gender, size of herpes episodes, pain at the beginning of the eruption, herpes at specific sites and surgery, immune dysfunction, etc., are all risk factors for the development of PHN. In terms of physiological mechanisms, edema and inflammation of the peripheral nerve trunk, increased activity of peripheral sensory afferent fibers, generation of ectopic impulses and consequently central synaptic regeneration and central sensitization, all of these affect the PHN (Koshy *et al.*, 2018).

Pharmacotherapy is the treatment of choice for PHN and often requires a combination of drugs to achieve a better therapeutic effect. Analgesic drugs are an important part of PHN treatment, among which oxycodone hydrochloride has more clinical applications. Oxycodone hydrochloride, as a member of the opioid class, has shown significant value in the treatment of PHN. According to the Three-Step Treatment Plan for Postherpetic Neuralgia (2021), oxycodone hydrochloride can be added as a short-term opioid when first-line medications are ineffective or in patients with moderate-to-severe pain (Hua *et al.*, 2023; Sutou *et al.*, 2021). In terms of mechanism of action, oxycodone hydrochloride binds to μ-opioid receptors in the central nervous system, effectively inhibiting nociceptive signaling in the neural pathway, thus exerting significant analgesic effects (Eldalal *et al.*, 2020). Clinical research data have amply demonstrated that opioid analgesics are effective in relieving burning pain, pinprick pain and nociceptive hypersensitivity in PHN (Gudin *et al.*, 2019). In addition, pulsed radiofrequency is emerging as a neuromodulation technique in the treatment of PHN. In clinical practice, pulsed radiofrequency treatment is usually performed under the precise guidance of imaging equipment and physicians are able to accurately puncture the radiofrequency needle near the diseased nerve to ensure the accuracy and safety of the treatment. Numerous studies have shown that some patients receive treatment with significant relief of pain symptoms and less impact on nerve function, greatly reducing the risk of complications such as hyperalgesia and dyskinesia (Wu *et al.*, 2020). Therefore, this study focuses on the combined treatment of PHN patients with pulsed radiofrequency and oxycodone hydrochloride, observing the pain relief effect, inflammatory indexes and immune indexes after treatment and analyzing the efficacy and safety of the combined use of the two treatments with a view to providing more reference for the clinic.

The findings of this study revealed that post-treatment, the indicators of the both groups of patients were statistical significance versus the pre- treatment period. The VAS scores of patients in the PO group were markedly below the PR group (P<0.05), indicating that the combined treatment was effective in reducing the pain level of the patients. In the study of PHN, TNF-α and IL-1β belong to pro-inflammatory cytokines. When the body is infected with herpes zoster, the virus activates the immune response, leading to a large release of TNF-α and IL-1β. High levels of pro-inflammatory cytokines can damage the myelin sheath of nerve fibers, causing abnormal nerve conduction, as well as stimulate nerve endings, lowering the pain threshold and exacerbating pain perception. IL-2 plays a key role in immune regulation, it promotes the proliferation and activation of T-lymphocytes and enhances the body's immune function. IL-10 is an important anti-inflammatory cytokine that inhibits the synthesis and release of pro-inflammatory cytokines such as TNF-α and IL-1β and reduces the damage of inflammatory reactions to nerve tissues (Tripathy *et al.*, 2021). The findings demonstrated that TNF-α and IL-1β in patients of PO group were markedly below the PR group and IL-2 and IL-10 were markedly above the PR group (P<0.05). It indicates that the improvement of inflammatory indicators was better in PO group patients post-treatment. $CD4^+$ T cells and $CD8^+$T cells are key cells in the human immune system and the $CD4^+/CD8$= ratio is an important indicator reflecting the state of immune regulation in the body, which is clinically valuable for monitoring the development of the disease and determining the prognosis (Obeagu and Chukwu, 2024). The findings revealed that the percentage of $CD4^+$ T cells and $CD4^+/CD8^+$ were remarkably above the PR group in patients in the PO group and the $CD8^+$ T cells percentage in patients in the PO group were remarkably below the PR group (P<0.05). It indicated that the immune function of PO group patients improved more remarkably in the post-treatment period. The clinical efficacy of PO group patients was superior to PR group, indicating that the combination of neuromodulation and opioid dilution painkillers had remarkable efficacy in treating PHN, which could effectively reduce the inflammatory response and regulate the immune indicators. Similar findings were reported by Li *et al*. in a study of Xiao Chaihu Tang plus reduction in the treatment of acute herpes zoster (T Li *et al.*, 2024).

Patients with PHN are highly susceptible to anxiety because they suffer from chronic pain, their sleep is often severely disturbed and they are psychologically burdened

(Dym *et al.*, 2020). Therefore, in this study, the sleep quality of patients was assessed by PSQI and the anxiety level of patients was quantified by SAS score analysis. The findings revealed that the PSQI scores and SAS scores of patients in the PO group were remarkably below the PR group (P<0.05), suggesting that patients in the PO group demonstrated a better improvement in sleep quality and anxiety level post-treatment. Li *et al*. reported similar findings in a study of pulsed radiofrequency combined with nerve block therapy in patients with recalcitrant PHN (B Li *et al.*, 2024). In addition, the time to stop blistering, the scab, the scab removal and the stop pain were remarkably below that of the PR group in patients in the PO group and the adverse reaction and recurrence rates were also remarkably below the PR group (P<0.05). The results showed that the combination of the two treatments for PHN has good efficacy, can effectively improve sleep quality and anxiety level, reduce the time of disease control and reduce the adverse reactions and recurrence rate, which is worthy of further popularization and application in the clinic.

This study has certain limitations. The sample size is relatively small and fails to cover the different conditions of all PHN patients, which may lead to biased results and affect the extrapolation and reliability of the conclusions. There are differences in the patients' own underlying conditions, which may affect the generalizability of the study results. In addition, the relatively short follow-up period did not allow for adequate assessment of the long-term effects and safety of the treatment. Therefore, improvements should be made in this area in future studies to more fully assess the efficacy and safety of the combination of neuromodulation and opioid-dilution analgesics in the treatment of patients with PHN.

CONCLUSION

In this study, we analyzed the clinical efficacy of the combination of neuromodulation and opioid dilution analgesics in the treatment of patients with PHN, in order to provide a new therapeutic pathway for the treatment of this type of disease. The results showed that after the combined treatment, the patients inflammatory indexes and immune indexes and other indexes were improved and the incidence of complications and adverse reactions was reduced as well, which provides a scientific basis for the clinical treatment of related diseases. However, this study has a small sample size and a short follow-up period and failed to observe the long-term effectiveness of this method of treatment. Multi-centre, large-sample, high-quality clinical studies can be continued for verification in the later stage.

Ethical approval

This study was approved by the Ethics Committee of the The Affiliated Hospital of Southwest Medical University. The ethical approval number is 2019 (183).

Data availability statement

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Author contribution

Yu He: Developed and planned the study, performed experiments and interpreted results. Edited and refined the manuscript with a focus on critical intellectual contributions.

Jun Li: Participated in collecting, assessing and interpreting the date. Made significant contributions to date interpretation and manuscript preparation.

Yu He, Wei He: Provided substantial intellectual input during the drafting and revision of the manuscript.

Conflicts of interest

The authors declare that they have no financial conflicts of interest.

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