



## Our treatment methods in herpes zoster and postherpetic neuralgia: Retrospective analysis

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### Abstract

**Aim:** The aim of this study is to investigate the effectiveness of our treatment methods applied in the pain management of patients with HZ, PHN and risk factors associated with the development of HZ and PHN .

**Materials and Methods:** The study was conducted in our hospital pain medicine clinic. The demographic data of the patients, in which phase of the disease they admitted, in which dermatomes the disease was occurred, what medical treatments they received and type of interventional treatments were applied between the dates of January 2019 and January 2023 were recorded. Also, pain reduction was evaluated as beneficial when there's a reduction in the pain level equal or more than 50%, and below as useless. The dosage scheme and types of drugs used were recorded. The follow-up interval was determined as 6 weeks after the intervention.

**Results:** While 131 (56.2%) of 233 patients were diagnosed with HZ, 102 patients (43.8%) were diagnosed as PHN. The median age was significantly higher in the PHN group ( $p < 0.001$ ). Thoracic region (60.9%) is the most frequently involved dermatome for HZ and PHN, followed by lumbar, trigeminal nerve ophthalmic branch and cervical region. The most commonly used agents are pregabalin, tramadol and gabapentin, respectively. Interventional treatments, on the other hand, were generally effective regardless of the phase.

**Conclusion:** It has been determined sympathetic blocks and epidural injections in acute and subacute periods are more effective, and peripheral nerve blocks are effective in both periods. While it was found to be effective the pulse radiofrequency in lumbar region, it was found to be effective in the chronic period while it was not effective in the facial dermatome in the acute period.

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### Introduction

Following recovery from *Varicella zoster* virus infection, viral particles progresses to the dorsal root ganglion (DRG) of the related dermatome and remains latent, when cellular immunity decreases, it reactivates and causes herpes zoster (HZ) infection [1]. In HZ, malaria and headache develop 2-3 days before the maculopapular rash begins. Prodromal symptoms characterized by burning, stinging and pain are observed. Subsequently; vesicles with clear contents appear unilaterally, usually involving a single dermatome. It heals within 2-3 weeks, leaving a scar behind. During this period, in addition to antiviral treatments, acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) are used for mild to moderate pain (NRS = 4-6). While NSAIDs are insufficient, opioids may be necessary

for severe pain. Tricyclic antidepressants (TADs), anti-convulsants and interventional treatment methods can be applied in patients with poor pain control [1].

Despite all treatment methods, the incidence of postherpetic neuralgia (PHN) after acute HZ is 20%. Acute period is defined from the beginning of the infection until 30 days, subacute between 30-90 days, lasting more than 90 days, burning and/or electric shock-like pain accompanied by dermatomal, allodynia and hyperalgesia are defined as PHN [2]. The most important risk factor is age; the rate of developing PHN over the age of 50 is approximately 80%. However, the risk increases in cases accompanied by immunosuppression, diabetes mellitus (DM) and systemic lupus (SLE), severe pain in the acute phase and involvement of the ophthalmic nerve. During this period, topical treatments- capsaicin 0.075% and lidocaine patch 5%, pregabalin, gabapentin and amitriptyline are used for pain control. Interventional treatments are recommended

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in resistant cases [3].

The aim of this study is to investigate the effectiveness of treatments applied in pain management and risk factors in the development of PHN in patients followed up with a diagnosis of PHN or HZ in our clinic.

## Materials and Methods

The study was conducted after obtaining the approval of the clinical research ethics committee with number and date E1-23- 3351-3351- 08/03/2023. Patients followed up in our hospital pain medicine clinic, between January 2019 and January 2023 with the code G53.0 (postzoster neuralgia) were listed by the statistics unit in the hospital database. Following, the patients' medical records were extracted. Demographic data of the patients and the phase of the disease in which they were admitted (the first 1 month is classified as the acute phase, 1-3 months as the subacute phase, and 3 months later as PHN) were recorded. Records were obtained regarding which dermatomes the patient was seen in, which medical treatments they received, and what kind of interventional treatments were applied. In addition, the patients' numerical rating scale (NRS) scores between 0 and 10 before and after medical treatment and procedure were recorded. It was evaluated as beneficial at 50% and above, and as useless at below 50% of the patients. Dosage schedule and types of drugs used were recorded. The follow-up interval was determined as 6 weeks after intervention.

### Interventions

Epidural, peripheral nerve, intercostal, erector spinae (ESP), paravertebral, sphenopalatine ganglion and stellate ganglion blocks, etc. are applied to HZ patients in acute phase or subacute, depending on the dermatomal spread. During the procedures, dexamethasone and 0.25% bupivacaine mixture was used, varying amounts depending on the dermatome and type of block was performed. Interventions were performed by ultrasonography or fluoroscopy guidance and once a week, for 4 weeks. Lidocaine was preferred in stellate and sphenopalatine ganglion blocks. In patients those applied after 3 months, pulse radiofrequency (PRF) treatment was applied at 42 degrees for 4 minutes each, followed by injection of a mixture containing dexamethasone and local anesthetic. In our clinic, stellate ganglion block, ESP, and intercostal blocks are performed under ultrasonography guidance, while epidural blocks, DRG-PRF, and sphenopalatine ganglion block applications are performed under fluoroscopy guidance.

### Statistical analysis

Power analysis was performed with G-power version 3.9.4. based on the mean age values of the study titled "Clinical Efficacy of Pulsed Radiofrequency Combined with Intravenous Lidocaine Infusion in the Treatment of Subacute Herpes Zoster Neuralgia" by Zhang and Lee [4], it was found that a total of 54 patients, 27 in each group, should be included in the study for an effect size of 0.922, a margin of error of 0.05 and 95% power with t-test. Data were analyzed using the Statistical Package for Social Sciences, version 25.0 (SPSS Inc., Armonk, NY). The normal-

ity of the numerical data distribution was examined using the Shapiro-Wilk normality test. Continuous variables with normal distribution were presented as standard deviation, those without normal distribution were presented as median and interquartile range (IQR; 25th-75th percentile), and qualitative data were expressed as frequency and percentage. The categorical data were compared using the Chi-squares test, according to the frequency of expected counts, Fischer exact, Yate's Continuity correction test was applied. Numerical variables with parametric or nonparametric distribution between the groups were compared with independent samples t-tests or Mann-Whitney U tests. The confidence interval was 95% and the accepted margin of error was 5%. A value of  $P < 0.05$  was considered statistically significant.

## Results

While 131 (56.2%) of the 233 patients were diagnosed with acute-subacute stage HZ, 102 patients (43.8%) were PHN. The median age was significantly higher in the PHN group ( $p < 0.001$ ). There was no difference according to gender in both groups ( $p = 0.202$ ). The frequency of immunosuppressive diseases was also similar in the two groups ( $p = 0.213$ ). The median age of the patients, their distribution by gender, the presence of common systemic diseases and immunosuppressive diseases are given in Table 1.

Herpes zoster dermatome of the patients, disease period, and the number and distribution of medical agents used in the treatment are shown in Table 2. As expected, thoracic region (60.9%) is the most common region for HZ and PHN, followed by the lumbar, trigeminal nerve ophthalmic branch and cervical region. The most commonly used agents in medical treatment are pregabalin, tramadol and gabapentin, respectively. Almost half of the patients used two different agents, and only 2 patients used 3 different agents.

Interventional procedures that provide a significant reduction in pain and the percentage of success are shown in Table 3.

## Discussion

### Risk factors

As a result of our study, the median age of patients who developed HZ or PHN was found to be 69 (30-94) and while 97 of the patients did not have any accompanying systemic disease, 136 patients were found to have any accompanying systemic disease. While a positive correlation was found between the development of PHN and age, no significant difference was found between the presence of immunosuppressive disease and the development of PHN. In a meta-analysis including a total of 4417 patients, HIV and malignancy were identified as serious risk factors for the development of HZ, while a slightly increased risk was detected in autoimmune diseases such as DM, rheumatoid arthritis, renal disease and SLE [5]. In another meta-analysis, a positive correlation was found with female gender, autoimmune diseases, and systemic diseases such as DM, COPD, and asthma in terms of HZ development. In both studies, family history was found to be an additional risk factor [5,6]. In contrast to these results, Forbes et al. could not

**Table 1.** Demographic information of the patients, presence of systemic and immunosuppressive disease, and comparison between the acute-subacute period and the postherpetic neuralgia group (n=233).

	All patients (n=233)	HZ (n=131)	PHN (n=102)	P
Age (median; min-max)	69.0 (30.0-94.0)	67.0 (30.0-85.0)	72.0 (34.0-94.0)	<b>&lt;0.001*</b>
Gender (n/%)				
Female	132 (56.7)	79 (60.3)	53 (52.0)	0.202
Male	101 (43.3)	52 (39.7)	49 (48.0)	
Systemic disease (n/%)				
None	97 (41.6)	61 (46.6)	36 (35.3)	
HT	53 (22.7)	26 (19.8)	27 (26.5)	
DM	46 (19.7)	24 (18.3)	22 (21.6)	
Malignancy	28 (12.0)	18 (13.7)	9 (8.8)	
CAD	25 (10.7)	14 (10.7)	11 (10.8)	
COPD/Asthma	13 (5.6)	5 (3.8)	8 (7.8)	
CRF	8 (3.4)	3 (2.3)	5 (4.9)	
Others	42 (18.0)	21 (16.0)	21 (20.6)	
Immunosuppressive disease (DM, Malignancy, transplantation, splenectomy, etc.) (n/%)	99 (42.5)	51 (38.9)	48 (47.1)	0.213

HZ: Herpes zoster, PHN: Postherpetic neuralgia, HT: Hypertension, DM: Diabetes mellitus, CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, CRF: chronic renal failure, \* Mann-Whitney U test.

find a connection between cancer and the development of HZ and found that female gender was controversial and that SLE, DM, and serious immunosuppressive conditions increased the risk [7]. The findings of our study are similar to all three studies in terms of age and systemic disease. While advancing age was identified as a risk factor in our study, it was determined that it was not an additional risk factor, unlike immunosuppressive conditions. Family history was not questioned in our study.

When examined in terms of dermatomal distribution, thoracic dermatomes are most frequently involved as a single dermatome [8]. It is stated that thoracic dermatome involvement is 53%, cranial nerve involvement is 20%, trigeminal nerve is 15%, and cervical dermatomes are involved in 4-20%, while lumbosacral is involved in 11% of patients has been detected [9]. In our results, thoracic involvement was observed most frequently in 60.9% of the patients (n=142). Lumbosacral was determined as 15.8% (n=37), trigeminal as 10.8% (n=25), and cervical as 18%. Among cranial nerve involvement, trigeminal and facial nerve involvement is frequently seen, and the virus remains latent in the gasser and geniculate ganglia. In trigeminal ganglion involvement, V1 involvement is the most common, while V2-V3 involvement is rare [10]. Herpes zoster ophthalmicus constitutes 10-25% of HZ cases [11]. We observed trigeminal involvement in 10.8% of the patients, and among these, isolated V1 was the most common (8.2%), and V1+V2 was the second most common. In the literature, the frequency of multidermatomal involvement has been frequently observed in the cervical region. Especially in the cervical and trigeminal ganglia, the short ganglion-skin distance, the richness of the head and neck in cervical dermatomes, and the complexity of the cervical ganglion are various reasons [12]. We frequently observed tigem-

inal and cervical dermatomes in patients with multidermatomal involvement, and rarely observed thoracolumbar involvement.

While the incidence of HZ is 1.2-3.4/1000 patients annually, this rate rises to 3.9-11.8% in the elderly, 5-20% of these patients develop PHN over time [13]. In this study, no information was found regarding the rate at which HZ patients developed PHN, but it was determined that 43.8% (n=102) of the patients presented during the PHN period and 56.2% (n=131) during the acute-subacute period.

#### Medical treatment

Among the gabapentinoids, pregabalin was the most frequently used agent in our patients, regardless of the HZ or PHN period, and gabapentin was the second most frequently used. While TADs were never used, serotonin and norepinephrine reuptake inhibitors (SNRIs) were used in 1 patient. In the past, TADs were used as systemic agents in the treatment of PHN, but the advanced age of the patient and anticholinergic side effects limited their use over time and gabapentinoids took their place. Among this group of agents, gabapentin is preferred due to its acute analgesic effect by inhibiting the release of Substance-P and its relatively low cost [14]. However, Perez et al. found no difference between pregabalin and gabapentin in terms of cost [15]. Gabapentinoids are preferred because they have lower side effect profiles and require less monitoring than anticonvulsant agents such as carbamazepine and valproic acid. The advantage of pregabalin is that it has a more predictable and linear pharmacokinetics. While NSAIDs are generally ineffective in acute pain during HZ period, opioid agents tramadol and oxycodone are recommended. It is also recommended to use the agents used in the treatment of PHN in the acute period [16]. In the acute pe-

**Table 2.** Herpes zoster localization of patients, disease period and medical agents used in treatment (n=233).

	N/%	HZ (n=131)	PHN (n=102)
<b>Localization</b>			
Thoracic	142 (60.9)	71 (54.2)	71 (69.6)
Lumbar	32 (13.7)	17 (13.0)	15 (14.7)
Trigeminal-V1	19 (8.2)	15 (11.5)	4 (3.9)
Cervical	18 (7.7)	12 (9.2)	6 (5.9)
Sacral	5 (2.1)	4 (3.1)	1 (1.0)
Trigeminal V1 and V2	4 (1.7)	2 (1.5)	2 (2.0)
Thoracolumbar	4 (1.7)	4 (3.1)	-
Scalp	4 (1.7)	1 (0.8)	3 (2.9)
V2	2 (0.9)	-	-
Scalp, face and thoracal	1 (0.4)	1 (0.8)	-
Cervical thoracal	1 (0.4)	1 (0.8)	-
Cervical , trigeminal V1	1 (0.4)	1 (0.8)	-
<b>Phase</b>			
Acute		78 (59.5)	-
Subacute		53 (40.5)	-
<b>Drug</b>			
None	22 (9.4)	12 (9.2)	10 (9.8)
Pregabalin	162 (69.5)	95 (72.5)	67 (65.7)
Gabapentin	36 (15.4)	18 (13.7)	18 (17.6)
Tramadol	101 (43.3)	59 (45.0)	42 (41.2)
Duloxetine	2 (0.8)	2 (1.5)	-
Oxycodone	3 (1.3)	1(0.8)	2 (2.0)
Capsaicin (0.075%)	6 (2.6)	3 (2.3)	3 (2.9)
Capsaicin (8%)	1 (0.4)	-	1 (0.9)
<b>Number of agents used (topical and systemic)</b>			
1	92 (39.5)		51 (50.0)
2	103 (44.2)		38 (37.3)
3	2 (0.8)		1 (1.0)

HZ: Herpes zoster, PHN: postherpetic neuralgia, V1: ophtalmic branch of the trigeminal nerve, V2: maksiller branch of the trigeminal nerve.

riod, depending on the level of pain, paracetamol, NSAIDs or tramadol are recommended for mild to moderate pain, morphine and oxycodone for moderate to severe pain, and if no benefit is achieved, TADs and gabapentinoids are recommended as adjuvants [17]. Again, in the management of PHN, in the presence of mild pain, topical capsaicin is recommended. While lidocaine and lidocaine patches are recommended as first-line treatment, if the patient does not benefit, gabapentinoids can be added to the treatment as second-line treatment. If these do not provide benefit, opioids can be used. In the 3rd stage, interventional treatments can be evaluated [17].

The use of topical agents is recommended in mild PHN. In a meta-analysis including 12 studies in this group, it was stated that lidocaine patch was superior to low-high concentration capsaicin and other topical agents (diclofenac, aspirin, etc.) [18]. In addition, 8% capsaicin and lidocaine patch were significantly superior to oral agents. There are also results showing that it is more effective and the cost of topical capsaicin and lidocaine is the same [19]. We have rarely used 0.075% capsaicin, which is the form of capsaicin available in Turkey, and 8% capsaicin, which is not available in Turkey, as a topical agent in our patients.

As a result of the study, it was observed that topical lidocaine was almost never used, so no results could be found for this. In this sense, our results are incompatible with the literature. When viewed from the perspective of this literature, it brings with it a recommendation to increase the habit of using topical agents.

#### *Interventional treatment*

In cases where medical and topical agents are insufficient, paravertebral blocks and epidural injections are recommended for the treatment of HZ-related pain. In the management of PHN, it was stated in the 2016 review that PRF application was of low effectiveness, and it took its place as the second-line treatment in 2019 [20,21]. In a study examining 131 patients, it was determined that nerve blocks were more effective in the early phase of the disease, in the HZ period, and that PRF treatment was more effective in the subacute and PHN phase rather than the acute phase [22]. In our study, PRF treatment was applied mostly in the PHN phase (12/2), but in both periods, the procedures caused a 50% or more reduction in pain in patients.

Sympathetic nervous system blockade (SNS) is recom-

**Table 3.** Type and distribution of interventional procedures that provide significant reduction in pain.

	HZ N=28	Success rate (beneficial / unbeneficial and %)	PHN N=55	Success rate (beneficial / unbeneficial and %)
Intervention	44		101	
Cervical-esi	1	1/1 (100)	5	3/5 (60)
Tesi	3	1/1 (100)	11	5/6 (80)
Lesi	1	1/1 (100)	5	3/5 (60)
Cesi	1	1/1 (100)	0	0
Stellat	9	9/9 (100)	22	11/22 (50)
Cervical DRG PRF	0		1	0/1 (0)
Intercostal Block	4	4/4 (100)	6	5/6 (83.3)
Intercostal PRF	2	2	6	6/6 (100)
Esp	6	4/2 (66%)	15	13/15 (86)
Paravertebral Block	0		8	8/8 (100)
SPG Block	4	4/4 (100)	4	4/4 (100)
SPG PRF	1	0/1 (0)	3	3/3 (100)
Gon,Lon,Son,Ion	3	3/3 (100)	4	4/4 (100)
Pudendal Block	1	1/1 (100)	0	0
Iv Lidocaine	7	5/7(71%)	8	8/8 (100)
Lumbar DRG PRF	1	1 /1 (100)	2 (2/2)	2/2 (100)
Thoracic Sympathetic Block	0	-	1	0/1 (0)

HZ: Herpes zoster, PHN: Postherpetic neuralgia, Cervical ESI: Cervical interlaminar epidural injection, Tesi: Thoracic interlaminar epidural injection, LESI: Lumbar interlaminar epidural injection, Cesi: Caudal epidural steroid injection, DRG: Dorsal root ganglion, PRF: Pulsed radiofrequency, ESP: Erector spina plane block, SPG: Sphenopalatine ganglion, GON: Greater occipital nerve, LON: Lesser occipital nerve ION: infraorbital nerve.

mended during the HZ period due to the hypothesis that HZ activates the sympathetic nervous system by causing viral inflammation in the DRG. It has been reported that blockade during this period suppresses irreversible damage. Some practitioners perform one blockade per week for 5 weeks. Stellate ganglion blockade is a type of SNS blockade and is recommended in the treatment of HZ originating from the head and face involving the trigeminal nerve, and it has been reported that blocks performed in the early stages will cause more than a 50% decrease in pain in patients for 6 to 12 months [23]. Epidural injections are recommended in the acute period because they provide indirect SNS blockade. In our practice, we apply stellate ganglion blockade for 4 weeks with 1 week intervals in both acute and chronic periods. Although more interventions were performed in the PHN period, the success rate of stellate ganglion blockade applied in the HZ period is significantly higher. Again, the success of epidural injections applied during the PHN period was found to be lower. This is compatible with the literature in this respect. Erector spina block, which is an area block that has increased in popularity in recent years, is frequently applied in PHN patients. In a study comparing the effectiveness of intercostal block and ESP in PHN, it was determined that the two interventions were not superior to each other in short-term pain control, but ESP was more effective than intercostal block in long-term pain control [24]. In the application of this study, the most frequently applied block in both the HZ and PHN phases is the ESP block, and it has been found to be effective in both periods, especially in the PHN phase. Compared to paravertebral block, there are also reports that both ESP and paravertebral blocks are effective in the HZ and PHN periods, but ESP is safer [25]. In our practice, paravertebral block was applied mostly in the PHN period and was found to be

effective.

Intravenous lidocaine has been reported to be effective in short-term pain control at a dose of 3 mg/kg in a number of chronic pain syndromes, including PHN, without any side effects. It has also been found to reduce mechanical allodynia and hyperalgesia for up to 6 hours at a dose of 5mg/kg. It was determined that the systemic analgesic dose decreased and the effect of PHN treatment increased in patients who received iv lidocaine infusion at a dose of 4mg/kg every day, including sixty PHN patients [26]. In this study, the number of interventions performed during the PHN period was generally higher, which can be explained by the fact that pain control during the PHN period is more difficult. Intervention in the acute period reduces the risk of PHN development [22]. However, in our study, there is no data on how often patients followed in the acute period develop PHN.

As a result, it was determined that sympathetic blocks and epidural injections applied in the acute and subacute periods were more effective, while peripheral nerve blocks were effective in both periods. Pulse radiofrequency was applied to very few patient groups in our study. In PRF applied patients, it was found to be effective in the lumbar region in both HZ and PHN, while it had no effect in the facial area in the acute period, but was found to be effective in the chronic period.

#### *Conflict of interest statement*

The authors declare that they have no conflict of interest.

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*Ethical approval*

Approval was received from the Clinical Research Ethics Committee of Health Sciences University, Ankara City Hospital No. 1 (decision no: E1-23- 3351-3351, date: 08/03/2023).

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