2023년 2월

박사학위 논문

Therapeutic experiences for herpes zoster and risk factors for zoster-associated pain: A retrospective single-center observational study

조선대학교 대학원

의 학 과

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대상포진의 치료적 경험과 포진 관련 통증의 위험 인자:
단일기관 후향적 관찰 연구

2023년 2월 24일

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2022년 10월

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대상포진 (herpes zoster, HZ)은 잠재된 수두 대상포진 바이러스의 재활성화에 의해 발생하는 질환이다. 대상포진 후 신경통 (postherpetic neuralgia, PHN)은 HZ에 이어 2차적으로 발생하는 신경통증의 일종으로, HZ 후 3개월 이상 지속되는 통증으로 정의된다. 대상포진 관련 통증 (zoster-associated pain, ZAP)은 HZ로 인한 신경성 통증, 특히 6개월 이내의 급성 신경성 지속성 통증을 정의한다. PHN 또는 ZAP은 우리가 관심을 가져야 할 건강 문제로, 약물과 중재 요법의 불충분한 효과, 기분과 수면 장애, 불안, 우울증, 삶의 질 저하로 인해 사회경제적 문제를 일으킬 수 있다. 따라서 HZ 치료는 바이러스 자체 치료뿐만 아니라 HZ 관련 합병증의 예방과 치료도 고려되어야 한다. 이 후향적 연구는 전자 진료기록의 검토를 통해 HZ의 임상특성, 임상치료 경험, PHN 또는 ZAP의 유무, PHN 또는 ZAP 관련 위험인자를 분석하기 위해 수행되었다. 이 연구는 발진 발생 72시간 이내에 항바이러스제를 사용한 환자는 55.9% 이였고, 항바이러스제를 5일 이상 사용한 환자는 62.7%였다. 항바이러스제, 가바펜티노이드, 삼환계 항우울제 (tricyclic antidepressants, TCAs), 스테로이드와 중재법들의 치료적 적용은 퇴원 시 통증 강도, 즉 숫자통증척도 (numeric rating scale, NRS)를 유의하게 감소시키는 데 효과적이었다. 그러나 퇴원 후 6개월 동안 통증 이 조금이라도 있는 (NRS ≥1) 또는 중등도/중증 통증 (NRS ≥4)의 ZAP은 각각 17.9%, 7.6%의 환자에서 발생하였다. 체간 병변과 심한 통증을 수반한 환자, 5일 이상 항바이러스 치료와 항생제 치료가 필요한 환자들이 통증이 조금이라도 있는 (NRS ≥1) ZAP 발생률 상승에 기여하였다. 반면에, 증등도/중증 토증 (NRS ≥4)의 ZAP 발생률은 입원 시 통증이 심하고, 고령, 5일 이상 항바이러스 치료 및 TCAs 치료가 필요한 환자에서 높게 발생하는데 기여하는 것으로 확인되었고, 마약

성 진통제들의 사용은 반대로 증등도/중증 통증의 ZAP 발생률을 감소시키는데 기여하는 것으로 확인되었다. 그 외에도 HZ 치료방법의 선택을 위해, 의사들은 스테로이드를 HZ 후 합병증을 고려하여 선정하였고, 가바펜티노이드, TCAs, 진통제들은 입원 시 환자의 전신상태와 통증민감도를 고려하여 선택하는 것으로 확인되었다. 그러나 HZ의 약리학적 및 비약리학적 치료법의 PHN 또는 ZAP의 예방에 미치는 상승효과 또는 부가효과를 평가하기 위해 다양한 치료법들의 조합으로 얻어진 하위그룹에 추가 연구가 필요하다.

Ⅰ. INTRODUCTION

Herpes zoster (HZ) is an age-dependent disease caused by the reactivation of the latent varicella-zoster virus (VZV) [1]. HZ can cause various clinical symptoms and complications, such as zoster-associated pain (ZAP), postherpetic neuralgia (PHN), meningitis, and vasculitis [2]. PHN is a type of neuropathic pain, which is persistent pain for more than 3 months after HZ healing [3]. However, implementing this definition to diagnose the disease entails a risk of delaying the treatment of PHN. In light of this, PHN was recently subclassified as follows: acute herpetic neuralgia if pain persists within 1 month of the onset of skin lesions, subacute herpetic neuralgia if pain persists for 1−3 months, and PHN if pain persists beyond 3 months [4]. ZAP is an acute neuropathic persistent pain that lasts for at least 6 months [5]. Therefore, PHN or ZAP is a health issue that requires attention since it can cause socio-economic problems due to insufficient effects of medications, mood and sleep disturbance, anxiety, depression, and decreased quality of life [6, 7].

HZ treatment should be considered not only for viral treatment but also for preventing and treating complications. Antivirals, analgesics, corticosteroids, gabapentinoids, tricyclic antidepressants (TCAs), and other therapeutic interventions have been administered to prevent and treat ZAP or PHN [2, 8]. Antiviral medication is critical for the treatment of HZ as well as the prevention of ZAP or PHN, and its use is recommended within 72 hours of skin rashes for an average of 5 days [9, 10]. However, in clinical conditions, some patients may visit a hospital after 72 hours due to delayed diagnosis. Others may suffer from chronic infection and pain despite receiving adequate antiviral treatment within the prescribed period. HZ treatments can be expected to generate additional or synergistic effects when combined with pharmacological and non-pharmaceutical treatments. However, the combination of these treatments has produced conflicting results regarding PHN or ZAP prevention [8].

Therefore, further studies are required to determine whether the time gap between

initiation of treatment and onset of rash influences the effectiveness of HZ treatment, whether antiviral treatment is required for more than 5 days for effective treatment, whether pharmacological and non-pharmacological treatments are effective for preventing ZAP and the risk factors for ZAP. Therefore, this retrospective study aimed to analyze the clinical characteristics of HZ, therapeutic experience with HZ treatments, the presence of ZAP, and the risk factors associated with ZAP, through a review of electronic medical records.

Ⅱ. MATERIALS and METHODS

1. Study Design and Ethical Statement

The Institutional Review Board (IRB) of Chosun University Hospital approved this retrospective study based on an electronic medical record review (CHOSUN 2021-07-026) on July 29, 2021. The IRB waived the need to obtain written informed consent from patients because the patients' identification information was anonymized before the analysis, this study posed only a minimal risk to the participants. This study was conducted in accordance with the Declaration of Helsinki of 1964 and its subsequent revisions.

2. Selection of Study Population

This study enrolled 885 patients with HZ who had been treated between November 1, 2010, and June 30, 2021 (Fig. 1). This study excluded patients who had missing numeric rating scale (NRS) data on administration (n = 211), were hospitalized 15 days after HZ (n = 50), were under 20 years (n = 42), and had an American Society of Anesthesiologists physical status (ASA-PS) classification of IV or V (n = 1). Finally, 581 patients' data were selected for statistical analysis.

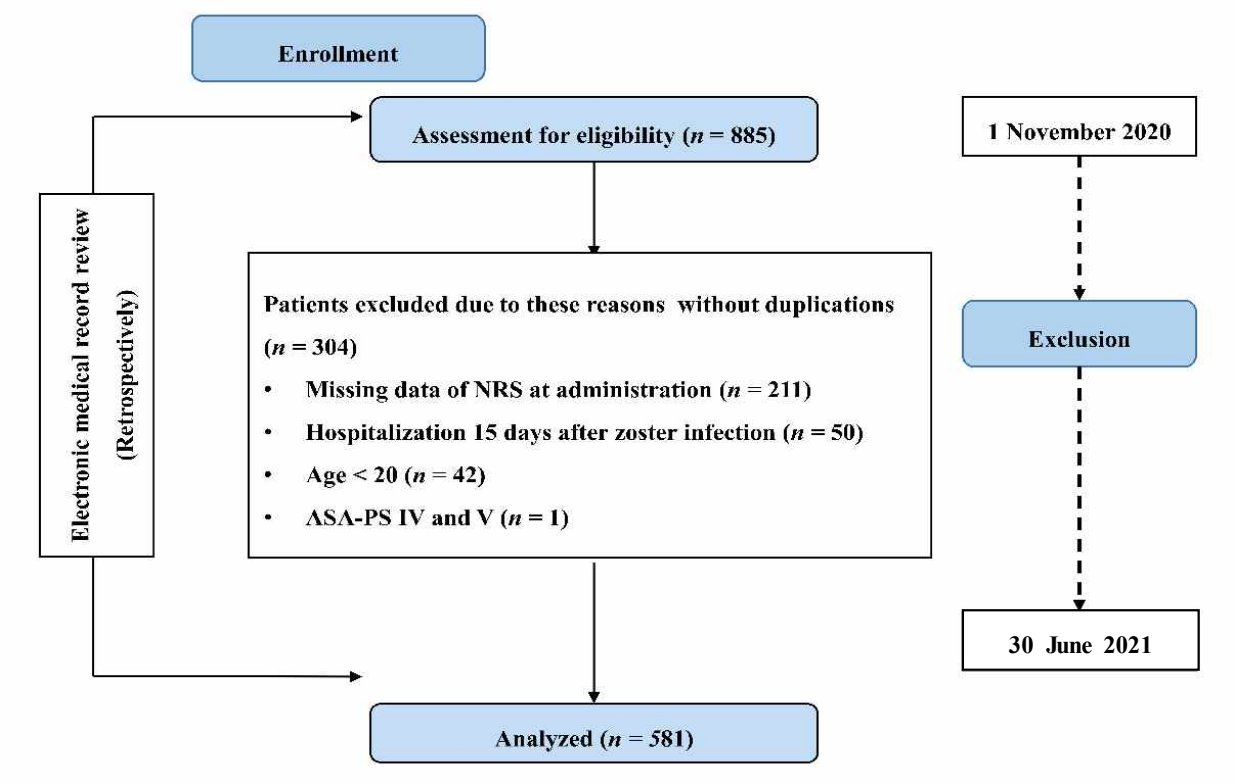

Fig. 1. Flowchart of the study. ASA-PS, American Society of Anesthesiologists - Physical Status; NRS: Numeric rating scale.

3. Outcomes

Sex, age, height, weight, body mass index (BMI), ASA-PS, the onset of skin lesions and pain development, dermatomal distribution, and length of stay (LOS) were assessed. The following categories were used to categorize the ages, BMIs, skin lesion onset, pain development, and dermatomal distributions. The participants were divided into four age groups: 20−39, 40−59, 60−79, and over 80 years. The BMIs were divided into three categories: ≤22.9, 23.0−24.9, and ≥25. The onset of skin lesions and pain development before administration were classified as ≤4 days and > 4 days. Dermatomal distributions were divided into four categories: head and neck, upper extremity, trunk, and lower extremity.

The NRS were recorded during the initial administration, at discharge, and 1, 3, and 6 months after discharge. The changes in NRS after treatments were calculated till

discharge. The NRS were classified as mild (NRS; 0−3), moderate (NRS; 4−6), and severe pain (NRS; 7−10). Furthermore, the presence of ZAP 6 months after discharge was determined via two NRS cutoffs, ≥1 and ≥4.

I collected the data on the following HZ drugs; antivirals, steroids, gabapentinoids, TCAs, analgesics, vitamins, antacids, antibiotics, and interventional treatments [intralesional injection (ILI), nerve blocks, low-level laser therapy (LLLT)]. Antiviral information included the prevalence of treatment, types, route of administration, combinations, initiating time after skin lesions and pain development, and the treatment duration. The initiating time of antivirals was categorized with cutoff value of 3 days, and the treatment duration of antivirals was categorized with cutoff value of 5 days. The steroid information included the prevalence of treatment and the route of administration. The gabapentinoids and TCAs information included the prevalence of treatment, types, and combinations for each medication. Analgesic information included the prevalence of treatment and types (nonopioid and opioid) and their combination. The prevalence of treatment was included in the information on other medications. The information on interventional treatments includes the prevalence of treatment, types, and their combinations.

4. Analysis

The primary endpoints were to examine HZ's clinical features and its clinical treatment experience. The secondary endpoints included the existence of ZAP with NRS ≥1 and NRS ≥4 during 6 months after discharge, respectively, and risk factors influencing the development of ZAP.

SPSS Statistics for Windows, ver. 27.0 (IBM Corp., Armonk, NY, USA) was used for all statistical analyses. We used descriptive statistics for primary endpoints and the presence of ZAP. All data were presented as means (95% confidence intervals [CI]) or numbers (percentage) of patients (n [%]). We used binary logistic regression with the forward selection (conditional) method and the entry method for risk factors influencing the development of ZAP. Statistical significance was set at $p < 0.05$.

Ⅲ. RESULTS

1. Demographic and clinical features of the patients with HZ

Patients with HZ were hospitalized more frequently if they were women (57.7%), 60 years of age or older (57.7%), and head and neck (49.1%) or trunk was involved (33.6%) (Table 1). The mean lag time between the onset of the rash and first hospital visit was 4.3 days (95% CI, 4.1−4.6), and the mean lag time between the onset of pain and initial visit was 5.4 days (95% CI, 5.1−5.6) (Table 1). Approximately 60% of patients were admitted to the hospital within 4 days after the onset of rash or pain. (Table 1). They had been hospitalized for an average of 7.1 days (Table 1). No patients reported receiving immunosuppressive medications and had immunosuppressive disorders.

Table 1. Demographic Data (n = 581)

Gender (male/female)	246/ 335 (42.3/ 57.7)
Age (years)	60.8 (59.5−62.1)
20−39 years	66 (11.4)
40−59 years	180 (31)
60−79 years	280 (48.2)
≥ 80 years	55 (9.5)
Weight (kg)	62.4 (61.6−63.3)
Height (cm)	161 (160.2−161.7)
BMI	24 (23.8−24.3)
≤ 22.9	228 (39.2)
23.0−24.9	144 (24.8)
≥ 25	209 (36)
ASA-PS (I/II/III)	233/ 284/ 64 (40.1/ 48.9/ 11)
Time of skin lesions development (days)	4.3 (4.1−4.6)
≤ 4 days	345 (59.4)

> 4 days	236 (40.6)
Time of pain development (days)	5.4 (5.1 − 5.6)
≤ 4 days	345 (59.4)
> 4 days	236 (40.6)
Dermatomal distribution	285/ 44/ 195/ 57 (49.1/ 7.6/ 33.6/ 9.8)
Head and neck	285 (49.1)
Upper extremity	44 (7.6)
Trunk	195 (33.6)
Lower extremity	57 (9.8)
LOS (day)	7.1 (6.9 − 7.3)

All data are presented as means (95% confidence intervals [CI]), or numbers (percentage) of patients (n [%]). ASA-PS, American Society of Anesthesiologists physical status; BMI, body mass index; LOS, length of stay.

2. NRS in hospital and after discharge

NRS was 5.4 points on average during hospitalization time, and 85.2% of patients reported moderate-to-severe pain (Table 2). The NRS averaged 1.0 points after treatment, and 98.1% of patients reported mild pain. The average drop in the degree of decrease in NRS was 4.4, with 67.8% of patients showing a decrease of 4 points or more. The NRS averaged <1 point during 6 months after discharge.

Table 2. Numeric rating scale (NRS: 0−10) (n = 581)

At administration	5.4 (5.3−5.6)
Mild (NRS 0−3)	86 (14.8)
Moderate (NRS 4−6)	198 (34.1)
Severe (NRS 7−10)	297 (51.1)
At discharge	1 (0.9−1.1)
Mild (NRS 0−3)	570 (98.1)
Moderate (NRS 4−6)	5 (0.9)
Severe (NRS 7−10)	6 (1)

Degree of decreases in NRS after treatments	4.4 (4.3−4.6)
NRS 0−3 points	187 (32.2)
NRS 4−6 points	348 (59.9)
NRS 7−10 points	46 (7.9)
Average NRS after discharge	
1 month after discharge	0.6 (0.5−0.8)
3 months after discharge	0.1 (0−0.1)
6 months after discharge	0.1 (0−0.1)

All data are presented as means (95% confidence intervals [CI]), or numbers (percentage) of patients (n [%]).

3. Incidence of ZAP

Patients with moderate-to-severe pain were 7.2% at 1 month, 0.7% at 3 months, and 0.7% at 6 months after discharge (Table 3). At 1, 3, and 6 months after HZ treatment, 17.9% of patients complained of pain above NRS 1. At 1, 3, and 6 months after HZ treatment, 7.6% of patients complained of moderate-to-severe pain (Table 3).

Table 3. Incidence of zoster-associated pain (ZAP) (n = 581)

NRS after discharge (0~3/4~6/7~10)	
At 1 month	539/ 29/ 13 (92.8/ 5/ 2.2)
At 3 months	577/ 4/ 0 (99.3/ 0.7/ 0)
At 6 months	577/ 1/ 3 (99.3/ 0.2/ 0.5)
Presence of ZAP during 6 months (No/Yes)	
Cutoff with NRS ≥1	477/ 104 (82.1/ 17.9)
Cutoff with moderate/severe pain	537/ 44 (92.4/ 7.6)

All data are presented as numbers (percentage) of patients (n [%]). NRS, numeric rating scale; ZAP, zoster-associated pain.

4. Treatments

Antiviral medications were administered to all patients, with 99.5% receiving them intravenously (Table 4). Acyclovir, famciclovir, valaciclovir and acyclovir were administered to 92.9% of patients. 27.5% of patients received either intravenous, oral, or topical antivirals. Among these, the combination of intravenous and topical antivirals was the most common. Of the patients, 55.9% were administered antiviral treatment within 72 hours after the onset of the rash. On average, antiviral drugs were administered for 6.7 days, with 62.7% of patients receiving them for more than 5 days.

Table 4. Antiviral treatment for herpes zoster (n = 581)

Antiviral Tx. (Yes)		581 (100)
Administration route		
	Oral agents (Yes)	48 (8.3)
	IV agents (Yes)	578 (99.5)
	Topical agents (Yes)	126 (21.7)
Types of antivirals		
	Acyclovir	540 (92.9)
	Famciclovir	2 (0.3)
	Valaciclovir	1 (0.2)
	Acyclovir and Famciclovir	23 (4)
	Acyclovir and Valaciclovir	15 (2.6)
Combination		
	Monotherapy	421 (72.5)
	Polytherapy	160 (27.5)
	Oral, IV agents	30 (5.2)
	IV, Topical agents	113 (19.4)
	Oral, IV, Topical agents	17 (2.9)
Tx. duration		6.7 (6.5−6.9)
	Tx. within 72 h of rash (Yes)	325 (55.9)
	Tx. over 5 days (Yes)	364 (62.7)

All data are presented as means (95% confidence intervals [CI]), or numbers (percentage) of patients (n [%]). IV, intravenous; Tx, treatment.

Steroids, gabapentinoids, and TCAs administered in 46.8%, 97.1%, and 74.2% of cases, respectively (Table 5). Analgesics were administered to 99% of patients, and opioids were administered to 92.1% (Table 5). Other drug treatments included vitamins (96.2%), antibiotics (18.8%), and antacids (87.4%) (Table 5).

Table 5. Other pharmacological treatments for herpes zoster (n = 581)

Steroid Tx. (No/Yes)		309 (53.2)/272 (46.8)
Administration route	Oral agents	11 (1.9)
	IV agents	261 (44.9)
Gabapentinoid Tx. (No/Yes)		17 (2.9)/564 (97.1)
Types	Gabapentin	542 (93.3)
	Pregabalin	21 (3.6)
	Gabapentin and Pregabalin	1 (0.2)
TCA Tx. (No/Yes)		150 (25.8)/431 (74.2)
Types	Amitriptyline	11 (1.9)
	Nortriptyline	419 (72.1)
	Amitriptyline and Nortriptyline	1 (0.2)
Analgesics Tx. (No/Yes)		6 (1)/575 (99)
	Nonopioid	12 (2.1)
	Opioid	535 (92.1)
	Nonopioid and opioid	28 (4.8)
Other Tx.		
	Vitamin (Yes)	559 (96.2)
	Antibiotics (Yes)	109 (18.8)
	Antacids (Yes)	508 (87.4)

All data are presented as numbers (percentage) of patients (n [%]). IV, intravenous; TCA, tricyclic antidepressant.; Tx, treatment.

The intralesional injection was administered to 17.4% of patients, nerve blocks to 67.1%, and LLLT to 92.8% (Table 6). These interventional treatments were administered in combination with two or more medications rather than alone, and these multi-interventional treatments were administered to 78.1% of patients (Table 6).

Table 6. Treatments for herpes zoster (n = 581)

Interventional Tx. (No/yes)		38 (6.5)/543 (93.5)
Types	ILI (Yes)	101 (17.4)
	Nerve block (Yes)	390 (67.1)
	LLLT (Yes)	539 (92.8)
Combinations		
	Monotherapy	90 (15.5)
	Polytherapy	453 (78.1)
	NBs, LLLT	353 (60.8)
	ILI, LLLT	66 (11.4)
	ILI, NBs, LLLT	34 (5.9)

All data are presented as numbers (percentage) of patients (n [%]). ILI, Intralesional injection; LLLT, low−level laser therapy; NB, nerve block; Tx, treatment.

5. Risk factors associated with ZAP

5.1. ZAP with NRS ≥ 1 during 6 months after discharge

Truck lesions were a 1.8 times stronger predictor of a ZAP incidence than head and neck lesions were ($p = 0.008$) in the binary logistic regression with a forward selection (Conditional) method (Table 7). Severe pain during administration indicated increased ZAP incidence 1.8 times that indicated by mild pain ($p = 0.008$). The requirement of antivirals for more than 5 days and antibiotics indicated increased ZAP incidence 1.7 times ($p = 0.029$) and 1.7 times ($p = 0.038$) more than did the requirement of antivirals 5 days or less and non-antibiotics, respectively.

Binary logistical regression using the entry method (Table 7) identified trunk lesions (ref. lesion on head and neck, p = 0.005), administering antivirals for more than 5 days (ref. 5 days or less, p = 0.041), and combination treatment with ILIs, nerve blocks, and LLLT (ref. no interventional treatment, p = 0.030) as risk factors for ZAP. While receiving antivirals for more than 5 days for trunk lesions indicated an increasing ZAP incidence, a combination treatment with ILIs, nerve blocks, and LLLT indicated a decrease in ZAP occurrence. Despite the lack of statistical significance, the pharmacological and non-pharmacological treatments exhibited contradictory correlations with ZAP incidence (Table 7). Treatment with antivirals, gabapentinoids, analgesics, and interventions had a positive effect in lowering the ZAP incidence; however, treatment with steroids, TCAs, vitamins, antibiotics, and antacids had a negative effect tendency in reducing ZAP occurrence.

Table 7. Logistic regression for the development of ZAP with NRS ≥ 1 (n = 581)

	B	S.E.	OR	95% CI	P value
Variable Selection Methods: Forward Selection (Conditional)					
Lesion on trunk (ref. lesion on HN)	0.598	0.225	1.819	1.17−2.828	0.008*
Severe pain at administration (ref. mild pain)	0.598	0.226	1.818	1.167−2.833	0.008*
Antiviral Tx. > 5 days (ref. ≤ 5 days)	0.525	0.241	1.691	1.054−2.711	0.029*
Antibiotic Tx. (ref. no Tx.)	0.547	0.263	1.728	1.032−2.895	0.038*
Variable Selection Methods: Enter					
Age 40−59 (ref. 20−39 years)	0.629	0.512	1.876	0.688−5.113	0.219
Age 60−79 (ref. 20−39 years)	0.855	0.511	2.352	0.864−6.399	0.094
Age ≥ 80 (ref. 20−39 years)	0.466	0.647	1.594	0.449−5.659	0.471
Sex: Female (ref. male)	-0.017	0.236	0.983	0.619−1.562	0.944

ASA-PS II (ref. ASA-PS I)	-0.058	0.284	0.943	0.54−1.647	0.838
ASA-PS III (ref. ASA-PS I)	0.321	0.417	1.378	0.609−3.121	0.442
BMI: 23.0−24.9 (ref. ≤ 23)	0.275	0.282	1.317	0.758−2.288	0.329
BMI: ≥ 25 (ref. ≤ 23)	-0.265	0.280	0.767	0.443−1.329	0.345
Lesion on UE (ref. lesion on HN)	0.245	0.482	1.277	0.497−3.283	0.611
Lesion on trunk (ref. lesion on HN)	0.769	0.276	2.157	1.256−3.702	0.005*
Lesion on LE (ref. lesion on HN)	0.116	0.452	1.123	0.463−2.725	0.798
Time SLD ≥ 5 days (ref. < 5 days)	0.032	0.384	1.032	0.486−2.192	0.934
Time PD ≥ 5 days (ref. < 5 days)	0.130	0.301	1.138	0.631−2.053	0.667
Moderate pain_ADMI (ref. mild pain)	0.231	0.419	1.260	0.555−2.863	0.581
Severe pain_ADMI (ref. mild pain)	0.761	0.394	2.140	0.989−4.63	0.053
Antivirals Tx. (ref. no Tx.)	-0.676	1.379	0.509	0.034−7.589	0.624
Antivirals Tx. > 5 days (ref. ≤ 5 days)	0.523	0.257	1.688	1.02−2.792	0.041*
Antivirals Tx. after 3 days of rash onset (ref. ≤ 3 days)	0.013	0.348	1.013	0.512−2.005	0.970
Steroids Tx. (ref. no Tx.)	0.395	0.267	1.485	0.88−2.507	0.139
Gabapentinoids Tx. (ref. no Tx.)	-0.181	0.742	0.834	0.195−3.57	0.807
TCAs Tx. (ref. no Tx.)	0.280	0.303	1.323	0.731−2.397	0.355
Nonopioids Tx. (ref. no analgesics)	-1.914	1.669	0.148	0.006−3.883	0.251
Opioids Tx. (ref. no analgesics)	-1.706	1.327	0.182	0.013−2.448	0.199
Nonopioids and opioids Tx. (ref. no analgesics)	-1.250	1.397	0.287	0.019−4.431	0.371

Vitamins Tx. (ref. no Tx.)	1.153	0.890	3.169	0.554−18.118	0.195
Antacids Tx. (ref. no Tx.)	0.556	0.457	1.744	0.713−4.268	0.223
Antibiotics Tx. (ref. no Tx.)	0.405	0.294	1.500	0.842−2.671	0.169
ILI, NBs, or LLLT (ref. no interventions)	-0.699	0.514	0.497	0.182−1.36	0.174
NBs and LLLT (ref. no interventions)	-0.825	0.457	0.438	0.179−1.073	0.071
ILI and LLLT (ref. no interventions)	-0.573	0.543	0.564	0.195−1.635	0.291
ILI, NBs, and LLLT (ref. no interventions)	-1.567	0.723	0.209	0.051−0.861	0.030*

ADMI, at administration; ASA-PS, American Society of Anesthesiologists physical status; B, unstandardized beta; BMI, body mass index; CI, confidence intervals; HN, head and neck; ILI, Intralesional injection; LE, lower extremity; LLLT, low level laser therapy; LOS, length of stays; NB, nerve block; NRS, numeric rating scale; OR, odds ratio; PD, pain duration; S.E., standard error; SLD, skin lesion duration; Tx, treatment; UE, upper extremity; ZAP, zoster-associated pain.

5.2. ZAP with moderate/severe pain (NRS ≥ 4) during 6 months after discharge

Ages between 60 and 79 years were identified as a factor indicating an increased ZAP incidence 2.5 times that associated with ages between 20 and 39 years ($p = 0.008$) in the binary logistic regression with the forward selection (Conditional) method (Table 8). Severe pain during administration indicated an increased ZAP incidence 2.4 times that associated with mild pain ($p = 0.015$). The requirement of antivirals for more than 5 days and TCAs indicated 3.2 times ($p = 0.007$) and 4.0 times ($p = 0.013$) higher ZAP incidences than did the requirement of antivirals for 5 days or less and non-TCAs, respectively. Opioids reduced the ZAP incidence by 0.35 times more than did non-analgesics ($p = 0.037$).

Binary logistical regression with an entry method (Table 8) revealed that administration of antivirals for more than 5 days (ref. 5 days or less, $p = 0.007$) and

opioids (ref. no analgesics, p = 0.022) were risk factors for ZAP. While the administration of antivirals for more than 5 days increased ZAP occurrence, opioids decreased ZAP occurrence. Despite the lack of statistical significance, the pharmacological and non-pharmacological treatments exhibited varying correlations with ZAP incidence (Table 8). Treatment with antivirals, analgesics, and vitamins had a positive effect tendency. However, treatment with steroids, gabapentinoids, TCAs, antibiotics, and antacids had a negative effect tendency in reducing ZAP occurrence. The interventional treatment took diverse directions depending on the procedures and their combinations.

Table 8. Logistic regression for the development of ZAP with moderate/severe pain (NRS ≥ 4) (n = 581)

	B	S.E.	OR	95% CI	P value
Variable Selection Methods: Forward Selection (Conditional)					
Age 60−79 (ref. 20−39 years)	0.926	0.349	2.524	1.273−5.002	0.008*
Severe pain at administration (ref. mild pain)	0.858	0.354	2.359	1.179−4.719	0.015*
Antivirals Tx. > 5 days (ref. ≤ 5 days)	1.151	0.429	3.162	1.364−7.327	0.007*
TCAs Tx. (ref. no Tx.)	1.380	0.557	3.973	1.334−11.832	0.013*
Opioids Tx. (ref. no analgesics)	-1.063	0.510	0.346	0.127−0.939	0.037*
Variable Selection Methods: Enter					
Age 40−59 (ref. 20−39 years)	1.255	1.185	3.507	0.344−35.802	0.290
Age 60−79 (ref. 20−39 years)	2.096	1.177	8.136	0.81−81.743	0.075
Age ≥ 80 (ref. 20−39 years)	1.377	1.344	3.964	0.284−55.265	0.306
Gender: Female (ref. male)	0.338	0.371	1.402	0.677−2.903	0.363
ASA-PS II (ref. ASA-PS I)	-0.231	0.436	0.793	0.338−1.865	0.596

ASA-PS III (ref. ASA-PS I)	0.636	0.551	1.889	0.642–5.561	0.248
BMI: 23.0–24.9 (ref. ≤ 23)	-0.107	0.423	0.899	0.392–2.059	0.801
BMI: ≥ 25 (ref. ≤ 23)	-0.614	0.430	0.541	0.233–1.256	0.153
Lesion on UE (ref. lesion on HN)	-0.112	0.733	0.894	0.213–3.76	0.879
Lesion on trunk (ref. lesion on HN)	0.221	0.412	1.247	0.557–2.796	0.591
Lesion on LE (ref. lesion on HN)	-0.160	0.711	0.852	0.211–3.433	0.822
Time SLD ≥ 5 days (ref. < 5 days)	-0.141	0.621	0.868	0.257–2.934	0.820
Time PD ≥ 5 days (ref. < 5 days)	0.642	0.448	1.900	0.79–4.572	0.152
Moderate pain_ADMI (ref. mild pain)	-0.340	0.646	0.712	0.2–2.526	0.599
Severe pain_ADMI (ref. mild pain)	0.622	0.561	1.863	0.62–5.597	0.268
Antivirals Tx. (ref. no Tx.)	-2.446	1.591	0.087	0.004–1.959	0.124
Antivirals Tx. > 5 days (ref. ≤ 5 days)	1.244	0.464	3.470	1.397–8.62	0.007*
Antivirals Tx. after 3 days of rash onset (ref. ≤ 3 days)	-0.418	0.570	0.658	0.216–2.012	0.463
Steroids Tx. (ref. no Tx.)	0.206	0.408	1.229	0.553–2.733	0.613
Gabapentinoids Tx. (ref. no Tx.)	0.642	1.313	1.901	0.145–24.921	0.625
TCAs Tx. (ref. no Tx.)	1.038	0.602	2.825	0.869–9.185	0.084
Nonopioids Tx. (ref. no analgesics)	-21.111	10546.437	0.000	0–0	0.998
Opioids Tx. (ref. no analgesics)	-3.637	1.587	0.026	0.001–0.59	0.022*
Nonopioids and opioids Tx. (ref. no analgesics)	-2.439	1.654	0.087	0.003–2.232	0.140
Vitamins Tx. (ref. no Tx.)	-0.709	1.001	0.492	0.069–3.5	0.479
Antacids Tx. (ref. no Tx.)	2.199	1.312	9.013	0.688–118.023	0.094

Antibiotics Tx. (ref. no Tx.)	0.674	0.427	1.963	0.849–4.536	0.115
ILI, NBs, or LLLT (ref. no interventions)	-0.256	1.022	0.774	0.105–5.734	0.802
NBs and LLLT (ref. no interventions)	0.203	0.933	1.225	0.197–7.632	0.828
ILI and LLLT (ref. no interventions)	-0.023	1.056	0.978	0.123–7.742	0.983
ILI, NBs, and LLLT (ref. no interventions)	0.100	1.122	1.106	0.123–9.975	0.929

ADMI, at administration; ASA-PS, American Society of Anesthesiologists physical status; B, unstandardized beta; BMI, body mass index; CI, confidence intervals; HN, head and neck; ILI, Intralesional injection; LE, lower extremity; LLLT, low level laser therapy; LOS, length of stays; NB, nerve block; NRS, numeric rating scale; OR, odds ratio; PD, pain duration; S.E., standard error; SLD, skin lesion duration; Tx, treatment; UE, upper extremity; ZAP, zoster-associated pain.

6. Factors influencing for decision of pharmacological and non-pharmacological treatments

The binary logistic regression with a forward selection (Conditional) method using the demographic data and NRS during hospitalization revealed no factors influencing the selection of intravenous antivirals and interventional treatments, in (Table 7). The skin lesion location was a factor influencing steroid selection, and lesions on the upper extremity, trunk, and lower extremity decreased the selection of steroids 0.16 times, 0.18 times, 0.15 times more than lesions on the head and neck ($p < 0.001$, $p < 0.001$, $p < 0.001$, respectively, Table 9). ASA-PS and BMI were factors influencing gabapentinoids selection. The ASA-PS III and III reduced gabapentinoids selection 0.09 times and 0.04 times than the ASA-PS I ($p = 0.022$, $p = 0.004$, respectively), and BMI $\geq$ 25 increased gabapentinoids selection 3.5 times than BMI $\leq$ 23 ($p = 0.051$) (Table 9). NRS was a factor influencing the selection of TCAs, and patients with severe pain during administration increased the selection of TCAs 1.6 time more than patients who had mild pain ($p = 0.001$, Table 9). ASA-PS and NRS were factors influencing the selection of analgesics. The ASA-PS III reduced the selection of

analgesics by 0.1 times compared with that associated with ASA-PS I (p = 0.008). Similarly, patients with moderate or severe pain during administration exhibited an increased selection of analgesics, by 5.2 times and by more than 10 times than that in patients with mild pain (p = 0.067 and p = 0.993, respectively) (Table 9).

Table 9. Factors influencing for decision of pharmacological and non-pharmacological treatments (n = 581)

	Antivirals		Steroids		Gabapentinoids		TCAs		Analgesics		Interventional treatments	
	Adj. OR	P value	Adj. OR	P value	Adj. OR	P value	Adj. OR	P value	Adj. OR	P value	Adj. OR	P value
Variable Selection Methods: Forward Selection (Conditional) [a]												
ASA-PS II (ref. I)					0.091	0.022						
ASA-PS III (ref. I)					0.042	0.004			0.100	0.008		
BMI: ≥ 25 (ref. ≤ 23)					3.546	0.051						
Lesion on UE (ref. HN)			0.156	< 0.001								
Lesion on trunk (ref. HN)			0.175	< 0.001								
Lesion on LE (ref. HN)			0.153	< 0.001								
Moderate pain_ADMI (ref. mild pain)									5.159	0.067		
Severe pain_ADMI (ref. mild pain)							1.640	0.010	8×10^{7}	0.993		

Binary logistic regression was applied with a forward selection (Conditional) method using the demographic data and NRS at administration. Variables were converted into dummy variables of age, sex, ASA-PS, BMI, skin lesion, SLD, PD, and NRS at administration were used. Adj. OR, adjusted odds ratio; ADMI, at administration; ASA-PS, American Society of Anesthesiologists physical status; BMI, body mass index; HN, head and neck; LE, lower extremity; NRS, numeric rating scale; PD, pain duration; SLD, skin lesion duration; UE, upper extremity.

Ⅳ. DISCUSSION

The incidence of PHN ranges from 1% to more than 30% [6, 7, 11-14], varying with the follow-up duration, being 19.5% and 13.7% after 1 and 3 months following HZ treatment, respectively [14]. Zhang et al. [6] reported that 19.4% of 732 patients had PHN that lasted for more than 1 month after HZ. Schmidt-Ott et al. [13] reported that 11.9% of HZ patients developed PHN at 3 months, with moderate-to-severe pain and that the incidence increased to 14.3% in patients over 80 years old. Immunocompromised patients are more susceptible to HZ and PHN. Therefore, excluding immunocompromised patients, immunocompetent patients have a lower PHN frequency, and the incidence of PHN at 1 and 3 months after HZ treatment reduces reduced by 9.4% and 7.2%, respectively [14]. Inpatients were readmitted 5.4% of the time for any reason within 30 days after discharge, and postherpetic neuralgia was diagnosed in 8.2% of hospitalizations [15]. During the 6 months following discharge, 17.9% of patients had ZAP above NRS 1, and 7.6% had ZAP with moderate-to-severe pain. However, in a study that used more stringent criteria of ZAP or PHN, which was more than 4 NRS score and the administration of neuropathic pain relievers/except NSAIDs [7]. This study identified ZAP incidence of 17.7%, 3.3%, and 1.2%, and 7.2%, 0.7%, and 0.7% at 1, 3, and 6 months with a cutoff NRS ≥ 1 or moderate-to-severe pain, respectively, indicating the incidence of PHN varies based on the PHN definition, inclusion criteria, and observation duration. Therefore, these aspects should be considered when interpreting the PHN incidence rate.

Numerous risk factors can affect the occurrence of ZAP or PHN, and recognizing and managing these risk factors can help anticipate and prevent ZAP or PHN. Female sex, older age, increased pain intensity, larger and multiple skin lesions, longer time delay from rash onset to treatment initiation, presence of comorbidities, history of antiviral medication, and an immunosuppressive state were identified as risk factors [6, 7, 12, 16-23]. They reported that the development of PHN was uncommon in patients without acute pain. However, it was significantly more common in patients with

moderate-to-severe pain or in the prodromal phase. The independent risk factors identified in a meta-analysis were age ≥60 years (OR = 1.59; ref. age <60), acute severe pain in the herpes stage (odds ratio [OR] = 1.49), presence of prodromal symptoms (OR = 2.00), and severe rash (OR = 2.40) [12]. The incidence of postherpetic neuralgia was higher in patients aged 70-74 years (OR = 3.51; ref. 60-64 years), immunosuppressive status or therapy (OR = 6.44), severe pain (OR = 3.08) and rash (OR = 3.46; ref. no rash) [23]. Schmidt-Ott et al. [13] identified the pain severity at treatment initiation as the only statistically significant predictor of PHN, with an estimated OR of 5.6 for moderate pain versus mild pain and 10.9 for severe pain versus mild pain [13]. Female sex is a reported risk factor for PHN, with the incidence being higher in women (29.5%) than in men (6.03%) [6]. However, several studies have found no statistically significant difference a higher incidence in men [12, 15, 23]. In this study, HZ caused more hospitalization in women, old age, head/neck/truck lesions, and moderate-to-severe pain. Increased age, severe pain intensity, and the severity of skin lesions were identified as risk factors for ZAP or PHN in this study. However, sex was not determined as a risk factor for ZAP or PHN. Amicizia et al. [24] investigated the age-sex interaction in the development of PHN. They reported no significant interaction in women with increasing age, while men showed a higher incidence of PHN with increasing age. Therefore, the effect of sex on PHN resulted in controversy due to the influence of age-sex interaction.

European consensus-based (S2k) guidelines recommended the management of HZ infection [9]. Oral and intravenous antiviral medicine is strongly advised for patients over 50 years old, head and neck lesions, moderate-to-severe pain, complicated and multi-segment lesions, immunocompromised state, and other complicated risk factors [9]. The essential treatment of HZ is early antiviral and analgesic intervention [2]. The antiviral medication should be started as early as possible, within 72 hours after symptom onset [9]. However, it can be initiated later as long as new vesicles appear in patients at risk of a complicated course or with obvious complications and those with an immunocompromised state [9]. For pain management, early initiation of analgesia has been recommended according to the World Health Organization pain ladder and,

antidepressant or antiepileptic medications has been recommended in patients with moderate-to-severe pain or risk factors for PHN [9]. Mild opioids (32%) were the most commonly administered analgesic for first-line acute HZ pain, while pregabalin (37%) was the most commonly prescribed analgesic agent as the second-line for HZ pain [25]. This study also showed that 55.9% of patients received antiviral medication within 72 hours of rash development, and the average duration of antiviral treatment was 6.7 days (95% CI, 6.5 - 6.9) with 62.7% of antiviral medication over 5 days. All hospitalized patients in this study received antiviral medication (99.5% of intravenous acyclovir), analgesics (99%, mainly opioids), therapeutic interventions (93.5%), gabapentinoids (97.1%), TCAs (74.2%), and steroids (46.8%) were additionally administered according to their symptoms.

As previously stated, reducing PHN or ZAP, and treating HZ, are important. Therefore, the effects of medications and interventions on PHN or ZAP reduction have been analyzed in patients with HZ. Antivirals showed a controversial effect on preventing PHN [26, 27]. Mounsey et al. [28] reported that antivirals had the advantage of decreasing the symptom period; but had no effect on reducing overall PHN incidence. Cochran's review of the antivirals documented that oral acyclovir was ineffective in considerably reducing the incidence of PHN after reviewing high-quality evidence [26]. Insufficient evidence supports the effect of other antivirals on preventing PHN and this requires further well-designed RCTs with specific subgroups [26]. The present study could not determine whether antivirals can prevent PHN or ZAP since all patients received antivirals. Corticosteroids have been used to treat HZ and to prevent PHN due to its anti-inflammatory effects. The combination of corticosteroids and antivirals significantly improves patients' quality of life by hastening normal activity return and sleep, although this combination does not affect the healing of infected lesions [28]. However, a literature review reported that corticosteroids administered by oral, intramuscular, or intravenous routes within 7 days after rash onset could not be definitively stated to prevent PHN because of moderate-quality evidence, even though corticosteroids are recommended for relieving acute ZAP symptoms [29, 30]. The early co-administration of gabapentinoids with antiviral medication and analgesics neither

provides significant relief from acute ZAP symptoms, nor does it prevent PHN [31]. TCAs do not affect PHN; however, they can significantly decrease the pain intensity of PHN if TCAs are initiated as soon as possible within 48 hours of the rash onset and are continued for several months [28]. This study identified the administration antivirals for more than 5 days and TCAs as stronger risk factors in increasing PHN or ZAP occurrence than the administration of antivirals for 4 days or less and non-TCA treatment. Moreover, administering opioids more strongly correlated with decreasing PHN or ZAP occurrence than was non-analgesic treatment, in logistic regression analysis. This suggests that administering antivirals for more than 5 days and TCAs effectively improve HZ and quality of life but neither affect PHN nor prevent ZAP. However, this may indicate that PHN or ZAP incidence is determined by demographics and clinical features rather than by treatment, except for analgesics. Thus, further research is required to evaluate these medications' efficacy in preventing PHN.

Several studies have reported that active interventional treatments, such as repetitive intralesional and paravertebral injections, epidural blocks, and other sympathetic blocks, can help prevent or reduce the occurrence of PHN [32-39]. However, the effectiveness of sympathetic interventions (stellate ganglion, paravertebral, epidural, and other sympathetic blocks) on the PHN occurrence remains controversial because of insufficient evidence, including the lack of control groups [40]. This study also showed that the therapeutic interventions had no benefit for the prevention of PHN or ZAP. Therefore, neither medications nor interventional treatment provide a complete preventive effect of postherpetic neuralgia. However, some may shorten the disease duration or lessen the symptom severity [28].

Evaluation of the effectiveness of each medication and interventional treatments on PHN or ZAP prevention is also important. However, most patients receive multidisciplinary treatment. A meta-analysis reported that combination therapy with antivirals and various interventions was more effective in decreasing the risk of PHN and duration of neuralgic pain after HZ, compared with the outcomes associated with antiviral medication and analgesics [32]. Kim et al. [8] demonstrated that the incidence

of PHN at 3 months was most low in patients receiving epidural block followed by antiviral/intralesional injections, antiviral/antiepileptic/sympathetic block, antiviral/antiepileptic/paravertebral block. This network meta-analysis revealed no preventive effect of antiviral alone compared to that associated with a placebo, but a combination therapy of antivirals with intralesional injections exhibited beneficial effects [8]. They reported that the incidence of PHN at 3 months after HZ infection was lower with intensive epidural block than with the combination therapies with antivirals and intralesional injections [8]. Early stellate ganglion block combined with antivirals is effective enough to dramatically decrease the acute pain intensity, shorten pain duration, and reduce the occurrence of PHN [37]. Ma et al. [41] suggested that early repetitive paravertebral block prevents PHN development compared to that associated with antiviral therapy alone. According to Doo et al. [42], an early selective nerve root block seemingly decreases the incidence and shortens the duration of PHN [43]. Thus, all pharmacological and non-pharmacological treatments should be implemented as soon as possible. Moreover, combination therapy, along with antiviral drugs, will be effective in preventing PHN or ZAP occurrence. However, this study failed to analyze this combination therapy. Nevertheless, this study did not analyze this combination therapy since the sample size was insufficient for the assessment of the combination of each medication and interventional treatment.

A new point of interest is that this study analyzed the factors considered when selecting pharmacological and non-pharmaceutical treatments for the treatment of HZ. Corticosteroids were likely to be used significantly higher in patients with lesions on the head and neck than in those with lesions in other sites. Gabapentinoids were likely to be significantly more frequently administered in patients with ASA-PS I than they were in patients with ASA-PS II and III and with BMI $\geq$ 25 rather than BMI $\leq$ 23. TCAs were likely to be significantly higher in patients with severe pain during administration than in patients with mild pain. The selection of analgesics was shown to be significantly preferred ASA-PS I rather than ASA-PS II and III and BMI $\geq$ 25 rather than BMI $\leq$ 23. The selection of TCAs was significantly preferred by patients with severe pain during administration rather than patients with mild pain. Analgesics

were likely to be administered significantly more in patients with ASA-PS I than in patients with ASA-PS III, with NRS 4–6 and patients with severe pain during administration rather than patients with mild pain. Similarly, corticosteroids were selected for complications after HZ, and gabapentinoids, TCAs, and analgesics were selected for managing patients' systemic conditions and pain sensitivity during hospitalization.

This study had several limitations. First, since it was a retrospective study, it might not have produced results comparable to those that would have been obtained from a well-designed prospective randomized control study. Second, the preventive effects of pharmacological and non-pharmacological treatments for HZ could not be included in the subgroup analysis on the incidence of PHN. The sample size was sufficient for a trend analysis of therapeutic medications and interventional treatments. However, there were numerous combinations between medications and interventional treatments for treating HZ in patients enrolled in this study and the sample size classified as these subgroups was insufficient to analyze the preventive effect of PHN. Furthermore, weak correlations were observed between pharmacological and non-pharmacological treatment and the prevention of ZAP or PHN, even though these were not addressed in this paper. Therefore, no modalities or HZ-related treatments for the prevention of ZAP or PHN can be recommended based on this study's results. Moreover, further research should analyze whether medications, interventional treatments, and combination therapies have a preventive effect on PHN occurrence based using large-scale data and a larger sample size. Finally, the results of this study only identify the therapeutic trend of HZ and the incidence of PHN at a single institute and may thus not reflect the situation at other institutes.

Ⅴ. CONCLUSIONS

Commencing antivirals within 72 hours after the onset of rash was 55.9%, and administration of antivirals for more than 5 days was 62.7%. Antivirals, gabapentinoids, TCAs, steroids, and interventional treatments effectively reduce the NRS at discharge. However, ZAP with moderate-to-severe pain during the 6 months after discharge were 17.9% and 7.6%, respectively. Patients with trunk lesions and severe pain intensity and the requirement of antiviral treatment for more than 5 days and antibiotic treatment contributed to increasing the incidence of ZAP with remained pain. Older adult patients with severe pain intensity and patients requiring antiviral treatment and TCA treatment for more than 5 days contributed to increasing the incidence of ZAP with moderate-to-severe pain. However, opioids indicated lower ZAP incidence with moderate-to-severe pain than that associated with non-analgesics. However, further research of subgroups receiving combinations of various treatments is needed to evaluate the synergistic effect or additive effect on preventing PHN or ZAP in the pharmacological and non-pharmacological treatments for HZ.

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Legends for Tables

Legend for Figure

Fig. 1. Flowchart of the study. ASA-PS, American Society of Anesthesiologists - Physical Status; NRS: Numeric rating scale.