Prognostic Factors of Postherpetic Neuralgia

The investigation was aimed to determine prognostic factors related to postherpetic neuralgia (PHN), and treatment options for preventing PHN. The data showed 34 (17.0%) out of 188 patients with herpes zoster had severe pain after 4 weeks, and 22 (11.7%) after 8 weeks, compared with 109 (58.0%) at presentation. The age (≥ 50 yr), surface area involved ($\geq 9\%$), and duration of severe pain (≥ 4 weeks) might be the main factors that lead to PHN. On the other hand, gender, dermatomal distribution, accompanied systemic conditions, and interval between initial pain and initiation of treatment might not be implicated in PHN. The subjects were orally received antiviral (valacyclovir), tricyclic antidepressant (amitriptyline), and analgesic (ibuprofen) as the standard treatment in the group 1. In addition to the standard medication, lidocaine solution was sub- and/or perilesionally injected in the group 2, while lidocaine plus prilocaine cream was topically applied to the skin lesions in the group 3. The rates of PHN in the 3 treatment groups were not significantly different, suggesting adjuvant anesthetics may not be helpful to reduce the severity of pain.

Key Words : Herpes Zoster; Pain; Neuralgia; Prognosis

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INTRODUCTION

Varicella zoster virus (VZV) that causes varicella belongs to double-stranded DNA virus, Alphaherpesviridae (1). Whereas varicella chiefly occurs in children, herpes zoster (HZ) primarily occurs in adults. The overall lifetime incidence of HZ among individuals who had varicella is known to be about 20% (2), thus 0.25% to 1.1% of population may be affected by HZ (3). VZV spreads into sensory nerve endings, and then centripetally transfers to cranial and dorsal root ganglia where it remains in a latent state. When VZV-specific cellular immunity of the host declines, VZV can be reactivated to develop HZ. The skin lesions begin as grouped vesicles on the reddish swollen base, and progress to pustules, and finally to crusts in 1 to 2 weeks. In general, characteristically intense, unilateral, and dermatomal pain is common in patients with HZ. Pain usually resolves or lessens as the lesions heal. However, 10% to 30% of patients with HZ suffer from persistent severe pain termed as postherpetic neuralgia (PHN) for a certain period varying from 1 to 3 months after the onset of rash (2, 4-9). The purpose of the present study was to evaluate the prognostic factors of PHN, and review the mechanisms of pain, and try the therapeutic options that might be expected to lower the chance of PHN.

MATERIALS AND METHODS

Patients

From September 1996 to May 2001, 188 patients with HZ (80 males and 108 females, age range 6 to 79 yr) were enrolled in the study. All participants were Koreans. They signed an informed consent document before commencing the investigation. HZ was diagnosed on the basis of clinical setting. A few cases difficult to be differentiated from herpes simplex virus infection were excluded from participation. Those who might be in a immunosuppressed state were also excluded. The patients were divided into 6 groups by age (7, 9).

Methods

Pain from HZ was assessed at week 0, 1, 2, 4, 6, 8, 12 after the onset of skin rash. The degree of intensity of pain was scored by each patient; mild, when not having substantial effects on the lifestyle; moderate, when in part affecting the normal daily life with medication not necessarily demanded; severe, when affecting the normal daily life enough to demand medication (8). It was tentatively called PHN in this article when severe pain existed for 4 weeks or longer.

Rates of PHN were compared in terms of specific derma-

tomal distribution (cranial, cervical, thoracic, and lumbosacral), accompanied systemic conditions (hypertension, diabetes mellitus, gastropathy, cardiopathy, hepatopathy, malignancy, and pulmonary diseases) (7, 8), surface area involved ($\leq 4.4\%$, 4.5–8.9%, and $\geq 9\%$ of body surface; by measuring the long and short axes of the infected erythematous area), and interval between initial pain and initiation of treatment (≤ 3 , 4–7, 8–14, and ≥ 15 days) (3).

The relationship between the treatment options for HZ and the occurrence of PHN was examined. The subjects having severe pain consisted of age-matched 3 groups ($n=30$, each group). The subjects in the group 1 were given valacyclovir (1,000 mg, tid, po), amitriptyline (10 mg tid po), and ibuprofen (400 mg tid po) as the standard treatment. Valacyclovir was administered for the first week, otherwise amitriptyline and ibuprofen were administered until pain subsided or for a maximum of 12 weeks. In addition to the standard treatment, the solution containing 2% lidocaine was sub- and/or perilesionally injected twice weekly for 2 weeks in the group 2, while the cream containing 2.5% lidocaine plus 2.5% prilocaine was topically applied to the lesion sites with non-occlusive dressing twice daily for 2 weeks in the group 3.

The data were analysed by SPSS for Windows (SPSS, Inc: 1999, Chicago, IL, U.S.A.) and values were calculated using chi square test. Values were compared between cohorts, with a p value of less than 0.05 considered significant.

Table 1. Duration of pain in 188 patients with HZ

Duration (week)	Intensity of pain		
	Mild	Moderate	Severe
0	20	59	109 (58.0)
1	10	40	78 (41.5)
2	6	31	51 (27.1)
4	1	18	32 (17.0)
6	0	7	25 (13.3)
8	0	2	22 (11.7)
12	0	0	17 (9.0)

HZ, herpes zoster; Patients were all on the medication; Data are given as number (%) of patients.

Table 2. Prevalence of PHN by age

Group	Age (yr)	PHN ($n=32$)	HZ[M:F] ($n=188$)
1	≤ 29	0 (0.0)	13 [8: 5]
2	30–39	2 (8.0)	25 [12: 13]
3	40–49	5 (12.2)	41 [18: 23]
4	50–59	11 (23.4)	47 [16: 31]
5	60–69	10 (21.7)	46 [20: 26]
6	≥ 70	4 (25.0)	16 [6: 10]
	< 50	7 (8.9)*	79 [38: 41]
	≥ 50	25 (22.9)*	109 [42: 67]
	Total	32 (17.0)	188 [80:108]

PHN, postherpetic neuralgia; HZ, herpes zoster; Number (%); [M:F]=[male:female]; * $p<0.05$ between above and under the age of 50 yr.

RESULTS

Of 188 patients with HZ, 109 (58.0%) had severe pain at presentation; 78 (41.5%) at week 1; 51 (27.1%) at week 2; 32 (17.0%) at week 4; 25 (13.3%) at week 6; 22 (11.7%) at week 8; 17 (9.0%) at week 12 (Table 1).

By the tentative definition of 4 weeks' duration, the prevalence of PHN in each age group ranged from 0% to 25.0%, with a roughly increasing tendency by age. In total, 32 (17.0%) out of 188 patients had PHN. The rate of PHN above the age of 50 yr (25/109, 22.9%) was significantly higher than that under the age of 50 yr (7/79, 8.9%) (Table 2). The rates of PHN in the male and female were 15.0% (12/80) and 18.5% (20/108), respectively.

The rates of HZ in the specific dermatomes were significantly different. Of 188 patients with HZ, 94 (50.0%) were infected in thoracic area, 36 (19.1%) cranial, 35 (18.6%) lumbosacral, and 30 (16.0%) cervical. However, the rates of PHN in the specific dermatomes were not significantly different; cranial (7/36, 19.4%), cervical (4/30, 13.3%), thoracic (15/94, 16.0%), and lumbosacral (6/35, 17.1%) (Table 3). Two dermatomes were simultaneously involved in the 7 patients with HZ.

Of 188 patients with HZ, 24 (12.8%) had hypertension, 20 (10.6%) diabetes mellitus, 8 (4.3%) gastropathy, 7 (3.7%) cardiopathy, 7 (3.7%) hepatopathy, 4 (2.1%) malignancy, and 3 (1.6%) pulmonary diseases. Of 32 patients with PHN, 7 (21.9%) had hypertension and 6 (18.8%) diabetes mellitus. No statistical significance was found in the rate of accompanied conditions between PHN and HZ groups (Table 4). No systemic conditions were found in 15 patients with PHN and 130 patients with HZ. The 3 patients with PHN, and the

Table 3. Dermatomal distribution

Dermatomes	PHN* ($n=32$)	HZ ($n=188$)
Cranial	7 (19.4)	36 (19.1)
Cervical	4 (13.3)	30 (16.0)
Thoracic	15 (16.0)	94 (50.0) [†]
Lumbosacral	6 (17.1)	35 (18.6)

* $p>0.05$ between the dermatomes in PHN group; [†] $p<0.05$ between thoracic and others in HZ group.

Table 4. Accompanied systemic conditions*

Dermatomes	PHN ($n=32$)	HZ ($n=188$)
Hypertension	7 (21.9)	24 (12.8)
Diabetes mellitus	6 (18.8)	20 (10.6)
Gastropathy	2 (6.3)	8 (4.3)
Cardiopathy	2 (6.3)	7 (3.7)
Hepatopathy	1 (3.0)	7 (3.7)
Malignancy	1 (3.0)	4 (2.1)
Pulmonary diseases	1 (3.0)	3 (1.6)
None	15 (46.9)	130 (69.1)

* $p>0.05$ between PHN and HZ groups; Number (%).

Table 5. Surface area involved*

Body surface	PHN (n=29)	HZ (n=163)
≤4.4%	3 (7.9)	38
4.5-8.9%	6 (11.5)	52
≥9%	20 (27.4) [†]	73

*Surface area in 3 patients with PHN and 25 patients with HZ was not measurable or measured; Number (%); [†] $p < 0.05$ between ≥9% and <9% of body surface in PHN group.

15 patients with HZ had two systemic conditions simultaneously.

The rate of PHN was significantly higher in patients with ≥9% of surface area involved than in patients with ≤4.4% or 4.5-8.9% of surface area involved, demonstrating 27.4% (20/73) vs 11.5% (6/52) or 7.9% (3/38), respectively (Table 5).

The patients whose treatment was initiated within 3 days after the initial pain had PHN at a rate of 14.0% (7/50); between 4 and 7 days, 14.9% (10/67); between 8 and 14 days, 22.2% (10/45); over 15 days, 19.2% (5/26) (Table 6). No statistical significance was found in the intervals between initial pain and initiation of treatment.

Of 30 patients in each treatment group, 7 (23.3%) had PHN in the group 1; 5 (16.7%) in the group 2; 6 (20.0%) in the group 3. No statistical significance was found in the rate of PHN between the 3 groups (Table 7).

DISCUSSION

PHN has been defined in many ways. In practice, it is defined when pain prolongs after crusts have fallen off or prolongs 4 to 12 weeks after the appearance of skin rash (4, 6). The rate of severe pain notably decreased from 58.0% to 17.0% during the first 4 weeks of treatment, whereas slightly decreased from 13.3% to 9.0% during the last 8 weeks of treatment (Table 1). The observation suggests that the reasonable period for diagnosing as PHN should be 4 weeks or longer. The rate of PHN widely ranges from 4.5% to 59% (6, 8-14), and the duration of PHN varied from 1 to 12 months in the articles (6, 8-11, 13-18). Choo et al. (6) reported the prevalence of PHN for more than 30 days was 8%, and 4.5% after 60 days. Kwon et al. (8) reported 22.8% had PHN after 8 weeks. Lepow et al. (11) reported 59% had PHN for 3 months, and 28% for more than a year. Meister et al. (13) described the incidence of PHN as 28% after 4-5 weeks. There seems to be no regional, ethnic, or gender difference in the occurrence of HZ and PHN (7, 8, 14, 15, 19).

The age has been known to be the most important risk factor for the development of the vexing complication, PHN. The age above which PHN is more likely to occur was reaffirmed to be 50 yr (Table 2). That critical age has been considered as 40 to 60 yr (8, 9, 13, 15, 19).

Certain dermatomes, for example, the cranial or sacral area,

Table 6. Interval between initial pain and initiation of treatment

Interval (days)	PHN* (n=32)	HZ (n=188)
≤3	7 (14.0)	50
4-7	10 (14.9)	67
8-14	10 (22.2)	45
≥15	5 (19.2)	26

* $p > 0.05$ between the intervals in PHN group; Number (%).

Table 7. Rate of PHN between the treatment options

Group*	PHN [†] (n=15)	HZ (n=90)
1	7 (23.3)	30
2	5 (16.7)	30
3	6 (20.0)	30

*1, Valacyclovir, amitriptyline, and ibuprofen, tid po; 2, 1 with lidocaine (2% sol) infiltration; 3, 1 with lidocaine (2.5%) plus prilocaine (2.5%) cream; [†] $p > 0.05$ between the 3 treatment groups.

have been noted to be more vulnerable to the development of PHN (12, 13, 16). In the meantime, some reports documented that there was no preference to specific dermatomes with regard to PHN (7, 9), which is compatible with the results of this study. HZ tended to occur more often in the thoracic area at a rate of 50.0% (Table 3), as described 48% or 51% in other studies (7, 9).

Immunocompromising conditions such as the elderly, organ transplants with immunosuppressives, malignancy with chemotherapy, HIV infection, or long-term corticosteroid use contribute to the increased incidence of HZ and possibly PHN (6, 12). Researchers have investigated whether the systemic disorders other than immunosuppressed conditions might be associated with HZ. Some authors reported hypertension (20%) and diabetes mellitus (26%) were the two most common combined conditions with HZ, but did not mention their association with PHN (7, 8). The difference was not significant in the rate of hypertension (21.9% vs 12.8%) or diabetes mellitus (18.8% vs 10.6%) between PHN and HZ groups (Table 4).

Attention has been paid to the extent of rash, severity of initial pain, interval between initial pain and initiation of treatment, and duration of intense pain in relation to the risk factors for PHN (3, 8, 12, 13, 15, 16, 19-21). The number of vesicles has been used as an index of cutaneous dissemination and visceral involvement (3) or as an indicator of PHN (12). It appears to be sometimes hard to count the vesicles since the lesions can be fast changeable into coalescence and ulceration. So, the method of evaluating the extent of burn, known as the rule of 9, was applied to this research. Whitley et al. (19) stated time to initiating treatment after rash onset did not influence pain outcome. On the contrary, Watson (20) insisted on the possibility of prevention of PHN by early treatment within the first 72 hr. The data demonstrated that longer than 4 weeks of severe pain or wider than

9% of surface area involved might be associated with the higher probability of PHN, however earlier initiation of treatment might not guarantee a prevention of PHN. Besides, the prodromal symptoms such as loss of the tactile sense (12, 16, 19), and psychopathological impairment (11) have been the clinical predictors of PHN, albeit not connected with the length of PHN. A positive association of development of PHN with the HLA class I antigens was recognized, suggesting that HLA class I gene may control the immune response against VZV in the pathogenesis of PHN (22).

The pathogenetic mechanisms of PHN have not been clearly understood. To date, pathologic interaction between impaired function of afferent A beta-fiber, impaired response of axon reflex, damaged C fiber, and spinal cord hyperreflexity may play a role in HZ pain as well as PHN (4, 23, 24). These interactions act via excitatory amino acids and neuropeptides, including norepinephrine, released from sympathetic terminals and newly expressed receptors on the afferent neuronal membrane (24). The recent article gave a clue that the relative contributions of peripheral and central mechanisms to the pathology of pain may differ among subjects and vary over the course of PHN (21). Also, the density of epidermal innervation may provide an objective correlate for the presence or absence of pain (17). In these contexts, amitriptyline acts as a norepinephrine reuptake blocker, and lidocaine provides pain-relief by blocking neuronal sodium channels and dampening peripheral nociceptor sensitization and CNS hyperexcitability (25).

At present, there is no ideal drug that completely eliminates herpetic pain, whether acute or chronic. Systemic administration of antiviral, tricyclic antidepressant and analgesic agents has been accepted as the conventional therapy (25). It is controversial that conventional therapy alone or in combination with systemic corticosteroids and/or nerve block may be of some benefit for preventing PHN. Chiarello (26) challenged tumescent infiltration of corticosteroids, lidocaine, and epinephrine into dermatomes, with overall positive results for acute herpetic pain but inconstant results for PHN. The concentration of lidocaine he used was diluted to 0.05% with 1:1,000,000 epinephrine in a normal saline solution, and the amount of anesthetic solution injected was from 100 to 1,000 mL. Unlike that formula, 2% lidocaine solution without triamcinolone or epinephrine was chosen in this trial to find out the unique action of anesthetics on reduction of herpetic pain, and the amount of solution did not exceed 1 to 2 mL per injection. Kanazi et al. (25) reported patients with PHN were successfully treated with topical 5% lidocaine patches. Meanwhile, Attal et al. (27) reported a eutectic mixture of local anesthetics cream produced an anesthetic effect without reducing spontaneous ongoing pain and mechanical allodynia in the acute situation, but reduction of paroxysmal pain and hyperalgesia in the long run. The same topical agent was chosen in this trial. According to the findings of this investigation, adjuvant anesthetics, via injection or

topical application, added to the medication could not affect the duration of pain (Table 7). No remarkable adverse events save drowsiness or gastrointestinal discomfort in a few subjects occurred during the treatment. Further investigations employing new treatment trials with a larger number of patients are required.

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