

Observational Report

Prevention of Post-herpetic Neuralgia from Dream to Reality: A Ten-step Model

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Herpes zoster (HZ) is a painful, blistering skin eruption in a dermatomal distribution caused by reactivation of a latent varicella zoster virus in the dorsal root ganglia (DRG). Post-herpetic neuralgia (PHN) is the most common complication of acute herpes zoster (AHZ).

Severe prodrome, greater acute pain and dermatomal injury, and the density of the eruption are the risk factors and predictors for developing PHN. PHN has a substantial effect on the quality of life; many patients develop severe physical, occupational, social, and psychosocial disabilities as a result of the unceasing pain. The long-term suffering and the limited efficacy of the currently available medications can lead to drug dependency, hopelessness, depression, and even suicide. Family and society are also affected regarding cost and lost productivity.

The pathophysiology of PHN remains unclear. Viral reactivation in the dorsal root ganglion and its spread through the affected nerve result in severe ganglionitis and neuritis, which induce a profound sympathetic stimulation and vasoconstriction of the endoneural arterioles, which decreases the blood flow in the intraneural capillary bed resulting in nerve ischemia. Our rationale is based on previous studies which have postulated that the early interventions could reduce repetitive painful stimuli and prevent vasospasm of the endoneural arterioles during the acute phase of HZ. Hence, they might attenuate the central sensitization, prevent the ischemic nerve damage, and finally account for PHN prevention.

The author introduces a new Ten-step Model for the prevention of PHN. The idea of this newly suggested approach is to increase the awareness of the health care team and the community about the nature of HZ and its complications, especially in the high-risk groups. Besides, it emphasizes the importance of the prompt antiviral therapy and the early sympathetic blockades for preventing PHN.

Key words: Acute herpes zoster, prevention, post-herpetic neuralgia, sympathetic blockade, ten-step model

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Acute herpes zoster (AHZ), also known as shingles, is expected to continue to be a serious health condition for the elderly in the next decades. The majority of the population may not be aware that shingles can lead to chronic pain lasting for months to years.

Etiology of AHZ

The primary infection from the varicella-zoster virus (VZV) causes chickenpox. After resolution of the primary infection with VZV, the virus remains latent

in the spinal dorsal root ganglia (DRG) and the cranial sensory ganglia. Over 90% of adults in the United States have contracted the chickenpox infection, have serologic evidence of VZV infection, and are susceptible to herpes zoster (HZ) infection. There is no way to predict in whom the infection will reactivate (1).

Incidence of AHZ

The annual incidence of HZ infection per 1000 was estimated to be 3.4 in the UK (2), 2.9 in the US (3), 4.6 in Iceland (4), and 4.8 in France (5). There is no

indication that the incidence has fallen with time. Increasing longevity, the number of cancer patients, and the number of immunocompromised patients may be expected to increase the incidence of HZ (6). A recent systematic review reported that the incidence of AHZ had a direct relationship to age; 6 – 8/1000 persons per years at 60 years of age had shingles which increased to 8 – 12/1000 persons per years at 80 years of age (7). The lifetime risk of HZ reactivation and the expression of a shingles episode was estimated to be approximately 30% (8).

Clinical Manifestations of HZ

HZ is a painful eruption of a rash, usually unilateral, caused by a reactivation of a latent VZV in the sensory ganglion (9). The decrease in cell-mediated immunity in some individuals allows the multiplication of the virus in the ganglia and the retrograde transport of it along peripheral or cranial nerves, producing the pain and the skin lesions characteristic of shingles (10). A prodrome of unilateral dermatomal pain typically precedes the onset of the rash by several days (1 – 5 days) (1). The rash of HZ is typically vesicular and affects a single dermatome. Pain continues after the rash onset and then resolves over the time. Healing occurs over a period of 2 to 4 weeks in most patients (1). Post-herpetic neuralgia (PHN) is the most common complication of AHZ. PHN is defined as pain 3 months after the rash appearance. The incidence of PHN has been reported to be 25% among patients over 50 years old who received antiviral therapy (11,12).

Risk Factors for AHZ and Predictors for PHN

Older aged patients, patients receiving immune suppressive agents (steroids, chemotherapy, radiotherapy) and patients who are suffering from malignancies (especially lymphoma), malnutrition, diabetes mellitus (DM), Human Immunodeficiency Virus (HIV), or chronic diseases Tuberculosis (TB) and Renal Failure (RF) are generally debilitated and much more likely to develop AHZ (10).

A recent meta-analysis study linked the risk of PHN with the severity of AHZ manifestations. Severe prodrome and greater acute pain, increased density of the eruption, and ophthalmic involvement were associated with increased risk of PHN. Moreover, immunosuppression (including HIV, currently treated for cancer, or exposed to high-dose corticosteroids) and diabetes were significantly associated with PHN (13). Patients with one or more risk factors who did not receive the

appropriate antiviral therapy are more likely to develop PHN (8,14-16). Therefore, these risk factors can be used as predictors for PHN.

The most important risk factor for the development of PHN is age. The incidence of PHN goes up with age. Particularly, there is only about 2% risk in those who are under the age of 50 years, while the risk is greater than 20% in those who are over 50 years old. Moreover, the incidence of PHN is 35% over the age of 80 years (4,17,18) .

The intractability of pain may also go up with age (19-21). Pain lasting more than one year has been encountered in 4% of the patients under 20 years old, 22% in those who are over 55 years old, and approximately half of the patients over 70 years old (18,22).

Impacts of PHN on the Patient and Health Care System

The impact of PHN falls on patients and health care and community resources. PHN has an important effect on patients' quality of life. Many patients develop severe physical, occupational, social, and psychosocial disabilities as a result of the unceasing pain (23). The long-term suffering and the limited efficacy of the currently available medication can lead to drug dependency, hopelessness, depression, and even suicide (5). Family and society are also affected regarding direct financial cost and lost productivity. Therefore, failure to prevent PHN engenders a significant cost for both the patient and health care system. In 1994, the annual national spending on PHN in the United Kingdom was estimated to be £4.8 – £17.9 million. The lifetime cost of managing PHN was estimated to be £770 per patient (24). In another study, the 1998 total costs of treating HZ in England and Wales was estimated to be £47.6 million (range, £33.5 – £73.8) (25). It is expected that increasing population longevity, the number of cancer patients, and the number of immunocompromised patients may increase the incidence of HZ with a subsequent rise in the total cost of HZ management. In 2007 Dworkin et al (26) estimated that the overall costs of shingles and PHN might be as high as \$1.7 billion a year, including the health care cost and the productivity losses which are expected to increase further in future.

PATHOPHYSIOLOGY OF AHZ PAIN AND PHN

During the primary infection, the virus gains entry into the sensory DRG. Reactivation of the virus occurs following depression of cell-mediated immunity and

in older aged patients. The concomitant inflammation of the peripheral nerve and the skin damage in AHZ are supposedly responsible for the acute pain (27). The tissue inflammation and destruction leads to the released inflammatory mediators that activate peripheral nociceptors directly by lowering the threshold of nociceptors, causes an ongoing discharge and hyperexcitability, leading to peripheral sensitization (28,29). Prolonged nociceptor discharge enhances the response of dorsal horn neurons to afferent stimuli and expands the dorsal horn neuron's receptive field, accounting for central sensitization, which leads to spontaneous pain and allodynia without a marked sensory loss (28,30,31). At the cellular level, evidence showed an increase in the number of subtypes of the voltage-gated sodium channels (32), alteration of voltage-gated potassium channels and upregulation of the receptors associated with pain, such as transient receptor potential vanilloid 1 (TRPV1) (33). These changes are associated with spontaneous and provoked pain due to a lowered threshold for action potentials.

Moreover, there is evidence for loss of GABAergic inhibitory interneurons at the dorsal horn, as well as loss of the descending inhibition. This alteration induces an excessive reaction of the nociceptive neurons of the spinal DRG accounting for maintaining the central nervous system (CNS) in a state of chronic sensitization (34). As a result, uninhibited and amplified activity in unmyelinated afferents lead to pain associated with PHN.

The role and contribution of sympathetic nervous system (SNS) in both AHZ and PHN pain need to be clarified and may assist in defining the role of the sympathetic blocks in the management of AHZ and prevention of PHN. Under normal physiologic conditions, the efferent sympathetic nerves function separately from the primary afferent neurons. Coupling between the 2 systems may occur in the presence of tissue damage or nerve injury. Consequently, activation of the SNS could result in the amplification of the activity of the primary afferent neurons and, therefore, increase pain(35).

In the acute phase of HZ, viral reactivation in the dorsal root ganglion and its spread through the affected nerve results in severe ganglionitis and neuritis, which induce profound sympathetic stimulation and vasoconstriction of the endoneural arterioles which decrease the blood flow in the intraneural capillary bed resulting in nerve ischemia. If ischemia is allowed to persist, endoneural edema forms, which raises the endoneural pressure and compromises the endoneural blood flow. Finally, this process will result in irreversible

nerve damage (10). This damage appears to destroy preferentially the large myelinated nerve fibers, which are metabolically more active, and to spare the small fibers (10). Disturbance of gate-control may play a role in the pathophysiology of PHN pain. Predominant loss of large myelinated afferents leads to a loss of their central inhibitory effects on pain produced by small diameter C-fiber nociceptive afferents. Therefore, C-nociceptor fiber input into the spinal cord is no longer restrained by the inhibitory influence of the large myelinated afferents. This mechanism may also explain why sympathetic neural blockade is more efficacious when used early in the course of the disease by presumably interrupting the neural ischemia before irreversible large fiber changes occur (10,36-39). Moreover, the addition of steroid to local anesthetics (LA) may counteract the inflammatory process at the level of the DRG and the distal portion of the affected nerve.

The pain, hyperalgesia, and allodynia in PHN patients can be explained by 2 different pathophysiological mechanisms: sensitization and deafferentation, which delineate 3 subtypes of PHN (30,39).

Sensitization of the peripheral and/or central nervous systems produces spontaneous pain, allodynia, and hyperalgesia. Patients complain of mechanical allodynia and normal or hyperalgesic thermal sensation due to irritable nociceptors which denotes functionally abnormal but anatomically intact primary afferent nociceptors (28,30,31,39).

The allodynia and sensory loss in the affected dermatomes are associated with deafferentation, which results in dorsal horn reorganization (30). The decreased number of C-fibers of the peripheral nerves and partial loss of C-fiber input, in combination with deafferentation, induces the sprouting of AB-fibers, which normally transmit innocuous touch and pressure, to occupy synaptic space left vacant when C-nociceptors die during AHZ. AB-fibers rewiring in the DRG, which connects with the pain-transmitting spinothalamic tracts, produces dynamic and tactile allodynia (40). Therefore, patients with deafferentation type pain combined with mechanical allodynia often describe a sensory deficit (predominantly thermal) in the area of greatest pain (41).

Severe sensory loss without allodynia presumably reflects deafferentation-induced alterations in CNS structure and function and it is associated with complete primary afferent neuron disconnection and characterized by constant pain in a region of profound sensory loss (pin-prick sensation) without allodynia (39-41).

CURRENT TREATMENT OF ACUTE HZ

HZ management is challenging, as there is no established rigid guideline, up until now. Treatment modalities should consider treatment of the acute viral infection, the reduction of AHZ pain, and reduction or elimination of the possibility of PHN. Therapeutic options include antiviral therapy, corticosteroids, and pain medications.

Antiviral Therapy

Topical antiviral agents are not effective. Systemic antiviral treatment for AHZ is strongly advised as first-line treatment in the first 72 hours of rash onset for all immunocompetent patients who fulfill any of the following criteria: (1) older than 50 years, (2) suffering moderate or severe pain, (3) rash density is moderate or severe, or (4) patient presented with non-truncal involvement (42).

Antiviral drugs (acyclovir, valacyclovir, and famciclovir) inhibit viral DNA replication, reduce the severity of acute pain and its duration, hasten rash healing, and shorten the viral shedding period (43). Therefore, antiviral therapy likely reduces the viral inflammation of the nerve and ganglion; hence, this will decrease the neural damage which is thought to account prominently for the development of PHN. The usage of appropriate antiviral therapy was associated with a 50% reduction in the incidence of PHN at 6 months (11,43). Antiviral drugs are usually used for one week at a dose of 800 mg 5 times daily every 4–5 hours for acyclovir, 1000 mg 3 times daily for valacyclovir, and 500 mg 3 times daily for famciclovir. Valacyclovir and famciclovir have better bioavailability and longer intracellular half-life and are generally preferred to acyclovir due to better patient compliance. Intravenous acyclovir in a dose of 10 mg/kg every 8 hours remains the drug of choice for VZV immunocompromised patients (42). Dosage adjustment is required for patients with renal insufficiency. Nausea and headache are the most common associated side effects (42).

The safety profile of acyclovir, famciclovir, and valacyclovir accounts for a favorable balance of potential benefit versus risk. Because of their safety, we can recommend antiviral therapy, even for patients whose risk of developing PHN as well as other AHZ complications is likely to be low (young patients with mild acute pain and rash and truncal involvement). The potential values of antiviral therapy are unknown, but may be meaningful because we cannot predict which patient may develop PHN (42).

The initiation of antiviral therapy should be considered for elderly patients and severe pain patients presenting more than 72 hours after rash onset with continued new vesicle formation (indicates a continuing viral replication) or when there are cutaneous, motor, neurologic, or ocular complications. Extending the duration of the antiviral therapy for more than 7 days for these patients is also recommended (42).

Corticosteroids

Corticosteroids have anti-inflammatory effects that could be expected to decrease the nerve damage and the risk of PHN. Previous studies reported that the addition of a 3 week tapering dosage of oral steroids did not contribute significantly, beyond the benefits achieved by acyclovir alone, in reducing prolonged HZ pain (44,45). A Cochrane review found no significant difference between corticosteroids and placebo in preventing PHN (46).

However, the combination therapy (antivirals and corticosteroids) improved AHZ pain management and patient quality of life compared with acyclovir alone. It allowed a quicker return to the normal daily activities and sleep patterns (45). Steroids are associated with considerable adverse effects and have many contraindications. Therefore, the combination therapy should be considered only in patients with severe symptoms at presentation, provided no contraindications for corticosteroids exist (47).

Several studies demonstrated the inclusion of steroid therapy with LA in the neuroaxial blocks for management of AHZ (48-52). Epidural and paravertebral LA injections produce a combined somatosensory and sympathetic blockade. Steroids have a therapeutic local anti-inflammatory effect. The instillation of the steroid in combination with LA on the dorsal root ganglion and the distal portion of the affected nerve might decrease the neuronal inflammation associated with the AHZ and may exert a membrane stabilizing effect on the C-fiber transmission that produces analgesia by blocking the transmission of nociceptive input and prevents the development of ectopic neural discharge (29,30).

Topical and Analgesic Therapy

A topical tepid soak of aluminum sulfate as a drying agent of the crust in AHZ and zinc oxide ointment as a protective agent, during healing, when temperature sensitivity is the main concern, may be used. Acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) can be used for the management of AHZ pain (53).

Antidepressants may be useful adjuncts for AHZ pain. They help to alleviate the significant sleep disturbance, mood-elevation, and decrease the incidence of PHN (54). A 50% reduction in pain prevalence at 6 months has been reported, if amitriptyline is started within 48 hours of the onset of the rash, but the study was not replicated (54). Antidepressants are contraindicated in cardiac patients, those who are suffering from glaucoma, and in patients with senile prostate enlargement, which are common associations with AHZ in the elderly.

Anticonvulsants may also be of value as an adjunct to sympathetic neural blockade in the management of pain from AHZ. They may be particularly useful in relieving the persistent paresthesia, dysesthesia, and allodynia. The use of pregabalin as an adjunct medication to the sympathetic blockade for treatment of AHZ pain in a dose of 150 mg/12 hours was associated with drowsiness in 54.8% of patients during the first week of treatment. Meanwhile, an average dose of 75 mg/12 hours in the second week was associated with 6.5% drowsiness (55). In 2011, the Food and Drug Administration (FDA) approved the usage of gastro-retentive gabapentin as an extended-release formulation of gabapentin for the treatment of PHN (56). Gastro-retentive gabapentin is characterized by the ability of the tablet to be retained in the stomach. This property is due to the implementation of a polymer-based technology that allows the tablet to swell to a size that promotes gastric retention following oral administration with a meal (57,58). The tablets are retained in the stomach for approximately 15 hours and its peak blood level is at 8 – 9 hours. Subsequently, this provides a steady and continuous release of gabapentin, which rectifies the absorption by its transporters, located mainly in the upper small intestine. This results in improved pharmacokinetics and more convenient dose proportionality and bioavailability, which facilitates a once-daily dosing. Thus, a better titration of the therapeutic dosages could be accomplished. Over 90% of patients reach the target recommended dose of 1,800 mg/day gastroretentive gabapentin within 2 weeks (56,58,59). While, only 14% of patients reached the recommended therapeutic 1,800 mg/day dosage in, on average, 10 weeks, according to a retrospective database analysis of patients with PHN who were administered immediate-release gabapentin tid (60). Gastro-retentive gabapentin was associated with fewer adverse events in clinical trials (11% for dizziness and 5% for somnolence) (59). Clinical investigation of the use of gastro-retentive gab-

apentin in the treatment of AHZ pain is recommended.

If carbamazepine is used, rigid monitoring for hematologic parameters, especially in patients undergoing chemotherapy or radiation therapy, is indicated(53).

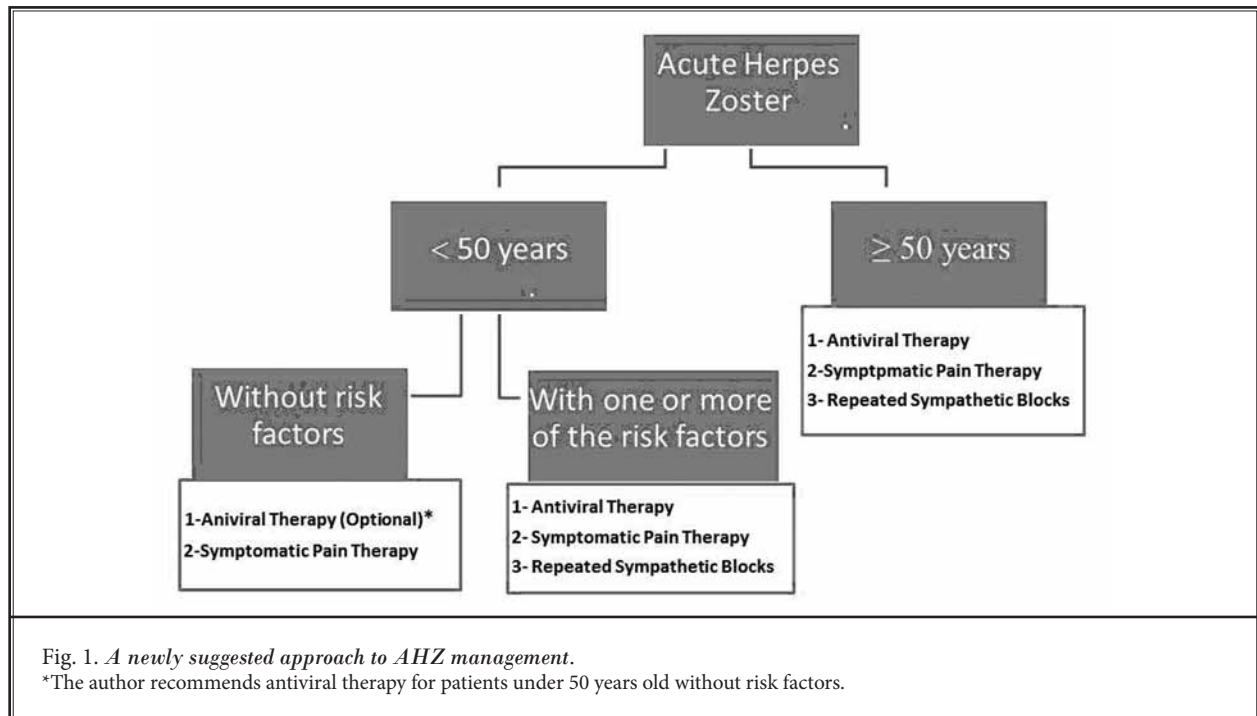
Opioid medications are mainstays for the short-term treatment of severe pain. There must be a clear understanding that opioids are to be used for a limited term in cases of severe non-cancer pain. For AHZ pain, tramadol and oxycodone can be used (42,61).

PREVENTION OF POST-HERPETIC NEURALGIA

The main therapies for prevention of PHN include primary varicella vaccine, zoster vaccine for the elderly, antiviral therapy, and sympathetic blockades for the high-risk groups. Optimal antiviral therapy can provide 50% reduction in the incidence of PHN (11,43). The role of varicella vaccine and early sympathetic blockades need to be explained. A new approach to AHZ management aiming at prevention of PHN is suggested (Fig. 1). Education for both the health care providers and the patients and their families is the most important step in the prevention of PHN.

Varicella Zoster Vaccinations

A primary varicella vaccine is a live attenuated VZV vaccine using the Oka/ Merck strain. Vaccination given during the childhood period decreases the incidence of chickenpox, subsequent HZ reactivation, and AHZ infection, therefore, accounts for the reduction of PHN. The vaccine virus is less likely able to establish latency and reactivate than the wild-type VZV (62). Vaccination increases cell-mediated immunity and, therefore, can reduce the incidence and severity of the AHZ infection with subsequent reduction in the incidence and severity of PHN. The adoption of a universal chickenpox vaccination in the United States in 1995 resulted in a reduction in the incidence of VZV infection by 90% to 95% in children aged 1 to 9 years (63). Elimination of the initial varicella infection in children can potentially reduce the future shingles incidence in the adult population. Oxman et al (64), investigated the value of VZV vaccine (zoster vaccine) in a double-blind, randomized, placebo-controlled study involving approximately 38,000 healthy adults older than 60 years, and reported that the zoster vaccine reduced the incidence of AHZ by 51.3% and the risk of PHN by 66.5%. The zoster vaccine for prevention of HZ (shingles) in adults aged ≥ 60 years received approval by the FDA in 2006 and was recommended by the Advisory Committee on Immunization Practices (ACIP) in 2008 (65). In March 2011, the FDA



approved the use of the zoster vaccine for adults age 50 through 59 years regardless previous varicella exposure (66). In June 2011, owing to the limited data on the long-term protection afforded by HZ vaccine among adults aged 50 through 59, the ACIP declined to recommend the vaccine for this age group and reaffirmed its recommendation for adults aged 60 years and older (66).

Sympathetic Block for Acute Herpes Zoster

SNS blockade is the target of many interventional procedures used for the management of AHZ pain. Viral reactivation in the dorsal root ganglion and its spread through the corresponding nerve results in severe ganglionitis and neuritis, which induces profound stimulation of SNS. This stimulation reduces intraneural blood flow, resulting in neuronal ischemia and eventual death. Our rationale was that early interventions that reduce the repetitive painful stimuli and prevent vasospasm of the endoneural arterioles during the acute phase of HZ may attenuate the central sensitization, prevent ischemic nerve damage, and finally account for PHN prevention. Early treatment of AHZ with sympathetic blocks is thought to attenuate vasospasm and prevent the irreversible nerve damage (10). Failure to use different forms of sympathetic blocks early and aggressively, especially in the elderly and the high-risk

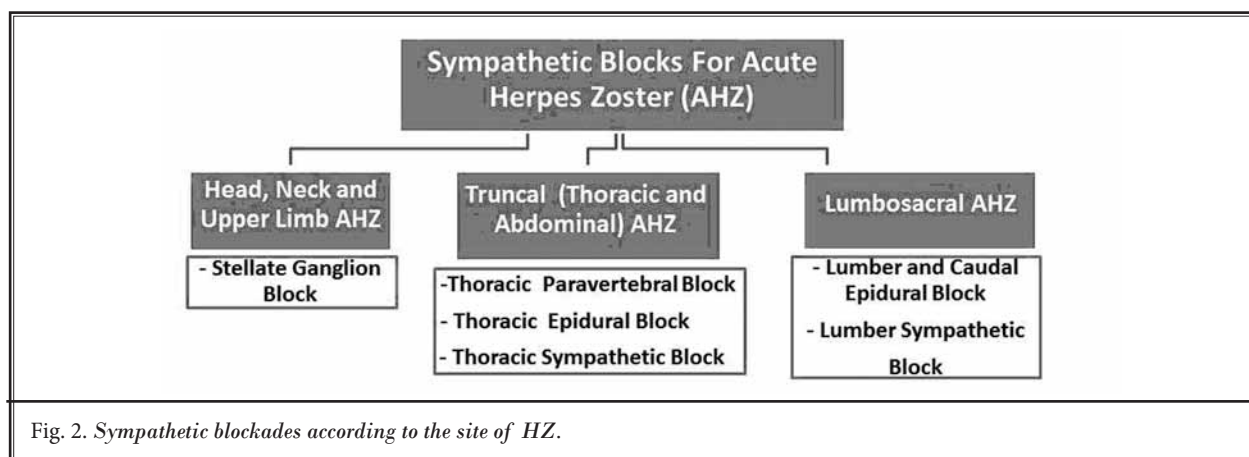
groups, may sentence the patients to a lifetime of suffering (53).

The role of sympathetic blockades for treatment of AHZ can be traced to as early as 1969 when Colding described the use of regional sympathetic blocks for zoster treatment (67). Wu et al (35) reviewed 6 observational studies that assessed the effect of sympathetic nerve blocks during acute HZ and its role in preventing PHN (67-72) and concluded that the effect of sympathetic blocks on the occurrence of PHN remains controversial mainly because none of the studies included a control group.

SNS blockades for AHZ can be done at different sites (Fig. 2) using different methods and techniques. Direct SNS blockade spares sensory and motor function while indirect SNS blockade, such as in the epidural space or paravertebral space, can temporarily block sensory and motor function(53).

A stellate ganglion block is a type of direct SNS block, which has been used successfully for the management of AHZ. Salvaggio et al (73) reported successful treatment of facial pain due to AHZ ophthalmicus with no residual pain at 6 and 12 months in five patients if stellate ganglion blocks were performed early, within 15 days of pain onset.

Makharita et al (55) conducted a randomized, placebo-controlled study, which included 64 patients



over 50 years of age. The study included patients with acute HZ of the face for fewer than 2 weeks and received appropriate antiviral therapy. Patients received 2 stellate ganglion injections under fluoroscopy one week apart, using either 6 mL bupivacaine 0.125% + 8 mg dexamethasone in a total volume of 8 mL or 8 mL saline as placebo. A significantly lower incidence of PHN was reported in the active group after 3 and 6 months than the control (placebo) group (6.5% vs 26.7% at 3 months, $P = 0.043$) and (0% versus 13.3% at 6 months, $P = 0.035$). The authors have concluded that early stellate ganglion blockade, in combination with an antiviral agent, is a very effective treatment modality, as it dramatically decreases the intensity of acute pain, shortens its duration, and reduces the incidence of PHN.

Thoracic sympathetic block is a type of direct SNS block which is technically difficult, needs a skillful pain physician, and its anatomic location makes pneumothorax a primary risk factor. Therefore, indirect SNS blocks for thoracic HZ (epidural and paravertebral) can be used easily for the management of thoracic HZ.

Epidural blockade can be performed in a blind manner using "loss of resistance" or under the guidance of ultrasound or fluoroscopy. The epidural sympathetic block can be used to treat AHZ.

Several studies reported a successful reduction in the incidence of PHN with the use of epidural injection (48-50). Hwang et al (48) included 65 patients with AHZ within 14 days after the onset of the rash in a prospective, non-randomized study. Patients were enrolled and divided into 2 groups. The control group received intravenous acyclovir at a dose of 5 mg/kg 3 times a day for 7 days. While the active group received intravenous acyclovir at a dose of 5 mg/kg 3 times a day for

7 days, plus continuous epidural infusion for 7 days via an epidural catheter (2 mL/hour 0.125% bupivacaine) after a bolus dose of 5 – 7 mL 0.25% bupivacaine plus 40 mg of methylprednisolone acetate. Amitriptyline and acetaminophen were allowed in both groups. Although all patients in both groups had complete relief of pain within 10 weeks, which persisted during the 12 – 18-month follow-up, patients with the epidural blockade showed a more rapid resolution of pain than those in the control group. The average total duration of pain was shorter in the epidural group (18.5 vs. 31.6 days).

Pasqualucci et al (49), at 2 study centers, evaluated the efficacy of repeated epidural injection of LA and steroid in the prevention of PHN. Six hundred patients above the age of 55 with severe HZ pain and had skin rash for fewer than 7 days were enrolled in a randomized clinical trial. The patients received either acyclovir and prednisolone intravenously (control group) or methylprednisolone and bupivacaine via a fluoroscopically guided inserted epidural catheter for a period ranging from 7 to 21 days. Successful reduction in the incidence of PHN was reported in patients who received epidural injection (7.6%, 5.4%, 3.6%, and 1.6% after one, 3, 6, and 12 months vs 40.5%, 29.6%, 22%, and 22.2%, respectively). Therefore, early repeated epidural blockades via epidural catheter had a potential preventive effect on PHN. The results of this randomized clinical trial consolidate the results of the non-randomized, non-blinded study of Hwang et al (48).

In a large randomized, multicenter clinical trial involving 598 patients (the PINE study), 300 family doctors in different regions in the Netherlands recruited patients who suffered from AHZ within 7 days after the onset of the rash, older than 50 years, with dermatomal distribution below C6 to be allocated into two groups.

The control group received the standard treatment for HZ (analgesia as needed and oral antiviral therapy) by the family doctors; while, the epidural injection group received the standard treatment plus a single epidural injection of LA and steroid using blind techniques (loss of resistance or the hanging drop techniques) by anesthesiologists in the 22 cooperating local hospitals. After one month, 48% in the epidural group compared to 58% in the control group reported pain ($P = 0.02$). After three months, persistent pain was reported in 21% vs 24% of the patients in the epidural and the control groups respectively ($P = 0.47$), and at six months in 15% vs 17% of the epidural and the control groups participants, respectively ($P = 0.43$). The noticed lower efficacy of epidurals in the prevention of PHN in the PINE study may be attributed to the use of single shot injection using a blind technique (50).

Paravertebral block (PVB) is a type of an indirect SNS blockade. The sympathetic chain lies on either side in the paravertebral gutter.

The effectiveness of repetitive paravertebral injections with LA and steroids for the prevention of PHN had been investigated in a randomized, controlled study by Ji et al (51). One hundred thirty-two patients with AHZ within 7 days after the onset of the rash, older than 50 years, with dermatomal distribution below C6 were enrolled into 2 groups. The control group received the current standard treatment for herpes (oral acyclovir 800 mg, 5 times daily for 7 days, and analgesics as needed). The paravertebral group's patients received the same standard treatment plus repetitive paravertebral injections with a mixture of 10 mL 0.25% bupivacaine added to 40 mg methylprednisolone acetate every 48 hours for a week (a total of 4 injections). A significant reduction in the incidence of PHN was reported with the use of repetitive paravertebral injections over one week at three months (7% vs 30%, $P < 0.001$), 6 months (4% vs. 22%, $P = 0.001$), and at a one-year follow-up (2% vs. 16%, $P = 0.017$).

Recently, Makharita et al (52) investigated the effect of a single paravertebral block on the incidence of PHN in a randomized, placebo-controlled study with 143 patients over the age of 50 with AHZ which had been affecting the chest wall for less than one week. Patients had moderate and severe pain and were under appropriate antiviral therapy. Patients were randomly assigned to receive either paravertebral block using either 10 mL saline as placebo under fluoroscopy (placebo group) or 25 mg bupivacaine 0.5%, plus 8 mg dexamethasone in a total volume of 10 mL under

fluoroscopy (active group). Significantly shorter duration of pain was noticed in the active group compared with placebo (24.6 vs. 35.9 days). A significantly shorter duration of the herpetic eruption and rapid skin healing were reported in the active group (23.3 vs. 31.2 days). The active group displayed a lower incidence of PHN than the placebo group after 3 months; however, this was not statistically significant (11.4% vs. 22.1%, $P = 0.094$). A significantly lower incidence of PHN was encountered in the active group after six months (5.7% vs. 16.2%, $P = 0.048$).

Therefore, the authors reported that a single paravertebral blockade was a safe and effective treatment modality. It shortened the duration of pain and skin eruption, and reduced the incidence of PHN.

The block quality of paravertebral blockade is unique; it provides a high-quality sympathetic block compared to the central neural block which is desired for AHZ treatment. Being a unilateral block, it may be associated with a lower incidence of cardiovascular adverse effects in terms of hypotension and bradycardia (74).

For lumbosacral AHZ, no study reported the use of lumbar sympathetic block for management of AHZ. However, many of the above-mentioned studies reported the inclusion of patients suffering from lumbar and sacral AHZ with successful reduction of PHN incidence (48-51).

The evidence for different interventional techniques in the prevention of PHN was evaluated by van Wijck et al in 2011 (75). The recommendations were based on "Grading Strength of Recommendations and Quality of Evidence in Clinical Guidelines" described by Guyatt et al (76). It was 2 B- for one time epidural injection, 2 C+ for repeated paravertebral injections, and 2 C+ for sympathetic nerve block. In the light of the recently available randomized, placebo-controlled clinical trials (52,55), the evidence must be re-evaluated.

From the previous studies, we can notice that steroid injection must be under a cover of strong antiviral therapy and the number and extent of the sympathetic blockade vary between the providers. We can infer that the longer the duration of the sympathetic blockade, the lower the incidence of PHN encountered. A new approach to the management of AHZ aiming at prevention of PHN is suggested (Fig. 1).

The incidence of PHN is at least 10 times more often in patients above 50 years of age. Therefore, the preventive strategy should focus on the patients with AHZ aged above 50 years. On the other hand, early pre-

diction of PHN below the age of 50 years accompanied by a more aggressive treatment in the presence of the mentioned risk factors are paramount.

In this approach, the patients suffering from AHZ will be stratified into one of 3 groups:

- a- Patients < 50 years without risk factors will receive optimal antiviral therapy (optional) + symptomatic pain therapy. The author recommends antiviral therapy for patients under 50 years old without risk factors.
- b- Patients < 50 years with one or more of the risk factors will receive optimal antiviral therapy + early repeated sympathetic blocks + symptomatic pain therapy.
- c- Patients \geq 50 years will receive optimal antiviral therapy + early repeated sympathetic blocks + symptomatic pain therapy.

Further studies are required to detect the optimal duration of sympathetic blockade needed to prevent PHN.

The author thinks there is a narrow time span to perform sympathetic blocks aiming at prevention of PHN, which is related to the first week after the eruption. Moreover, this block must continue for at least 2 weeks to avoid re-spasm of the endoneural arterioles. The aim of the repeated sympathetic blocks after one week until one month is to reduce the incidence and severity of PHN. For patients presented to the pain clinic after one month until the third month, we perform only one injection that may be of benefit. Therefore, the earlier the treatment, the less likely the incidence of PHN.

EDUCATION

Physician Education

Early interventional treatment is very effective, it can provide rapid and often complete pain relief and reduce the incidence of PHN. Because of the time issues, patients and physicians must be educated in the value of early and aggressive treatment. Too often, some physicians tell their patient that "nothing can be done" and "the rash will go away on its own." Sending the patient for treatment after the lesions have healed is a terrible disservice to the patients. Unfortunately, we cannot predict which patient will develop PHN, however, it's still a potential risk. General practitioners (GP), family doctors, dermatologists, and specialists dealing

with the high-risk groups have to be educated by pain physicians regarding the optimal antiviral therapy and the value of the early intervention for AHZ and its impact as a preventive strategy on the incidence of PHN. The health care provider staff needs to be sensitized to the criticality of the intervention time and the disastrous sequelae of HZ infection in the patients at risk. Frequent lectures to family doctors, GPs, and dermatologists are an effective tool to spread our rational as well as the new strategy for prevention of PHN. Identification of the high-risk groups for the development of PHN is crucial in this preventive strategy.

Patient Awareness

General awareness of the population about AHZ and its complications, especially among the elderly, must be raised, aiming at encouraging patients with a painful unilateral eruption to consult their physician as soon as possible. In 1994, 236 patients were involved in a European survey. Approximately half of them reported that they would have consulted sooner asking for help if they had received knowledge about HZ and its complications (77). Therefore, once the shingles diagnosis is made, a careful explanation of the nature of HZ infection and its sequelae is paramount. The awareness of the potential for the occurrence of chronic pain lasting months to years known as PHN is essential. An important step in the management plan is the discussion of the treatment options including the newly suggested strategy to prevent PHN. The use of media, television, internet, and written articles for the newspaper on the topic can help in dissemination of knowledge about HZ and the importance of the early medical consultation.

Finally, the author suggests a Ten-step Model as a new comprehensive strategy for the prevention of PHN. The idea of the newly suggested model is to raise the awareness of the health care providers and the community about the critical nature of time and the disastrous sequelae of HZ infection, especially among the high-risk groups. This model focuses on the importance of the early antiviral therapy and sympathetic blockades for the prevention of PHN.

SUGGESTED APPROACH TO POST-HERPETIC NEURALGIA PREVENTION: A TEN-STEP MODEL

1. Awareness of the population and education of the health care providers about the nature of HZ infection and its complications.
2. Vaccination for children and high-risk groups.

3. Early diagnosis of the AHZ infection.
4. Early use of the antiviral therapy in optimal dose and optimal duration.
5. Identification of the high risk-groups for the development of PHN.
6. Stratification of AHZ patients into one of 3 groups
 - a. < 50 years without risk factors (antiviral therapy [optional]* + symptomatic pain therapy). *The author recommends antiviral therapy for patients under 50 years old without risk factors.
 - b. < 50 years with one or more of the risk factors (antiviral therapy + repeated sympathetic blocks + symptomatic pain therapy).
 - c. ≥ 50 years (antiviral therapy + repeated sympathetic blocks + symptomatic pain therapy).
7. Early sympathetic blocks according to the anatomical location of HZ (repeated injection of at least two blocks or continuous blockade for at least 2 weeks).
8. Optimization of the symptomatic pain therapy.
9. Follow-up of the patients and detection of any complications.
10. Good reporting, filing, collection, and analysis of the patients' data.

RECOMMENDATIONS

PHN is one of the most intractable pain disorders. It is often accompanied by severe physical, occupational, social, and psychosocial disabilities, and increased health care utilization. Unfortunately, the treatment of

PHN to date has been quite disappointing. Efforts are being directed toward preventing PHN. The sympathetic blockades have been commonly used for the treatment of AHZ pain and the prevention of PHN. Despite the presence of few randomized controlled studies, the evidence for the efficacy of the early sympathetic blockades in the prevention of PHN is growing. This must encourage more investigators to conduct more research on this topic. Further studies should address not only the pain and the incidence of PHN but also the quality of life and the cost-effectiveness. Moreover, previous studies showed that the number and extent of the sympathetic blockades vary between providers. Therefore, we recommend further studies to determine the optimal duration of sympathetic blockades that prevents or maximally reduces the incidence of PHN, especially in the high-risk groups. Early diagnosis and tailoring a treatment plan based on the identification of the high-risk groups hold the key to establishing a preventive strategy for PHN. We suggest a Ten-step Model as a new approach for the prevention of PHN. A Ten-step Model is clearly a multi-disciplinary approach to the problem. Health education for the community, clinical education for the physicians dealing with the disease, and the proper rapid clinical decision are the core of this model, as well as the ultimate goal of it. Future clinical research is expected to investigate the efficacy of a Ten-step Model as a comprehensive approach to prevent PHN.

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