Therapeutic Options for Post Herpetic Neuralgia

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Abstract

Background: Post herpetic neuralgia (PHN) is the most frequent chronic complication of herpes zoster and the most common neuropathic pain resulting from infection. It is conventionally defined as dermatomal pain persisting at least 90 days after the appearance of the acute herpes zoster rash. PHN causes considerable suffering and results in a health care burden at both the individual and social levels. Treatment approaches include nonsteroidal anti-inflammatory drugs, gabapentin, opioids, and tricyclic antidepressants (TCA) as well as other treatments. Herein, we will summarize the different therapeutic options for PHN.

Keywords: Post Herpetic Neuralgia, tricyclic antidepressants, corticosteroids.

Post herpetic Neuralgia

Definition

Post herpetic neuralgia defined as dermatomal pain persisting at least 90 days after the appearance of the acute herpes zoster rash. PHN causes considerable suffering and results in a health care burden at both the individual and social levels. It is the most frequent chronic complication of herpes zoster and the most common neuropathic pain resulting from infection (1).

Herpes zoster (HZ) is a viral infection that usually presents as a childhood infection of varicella. The pathogen is human herpesvirus-3 (HHV-3), also known as the varicella zoster virus (VZV). Following the acute phase, the virus enters the sensory nervous system, where it is harbored in the geniculate, trigeminal, or dorsal root ganglia and remains dormant for many years. With advancing age or immunocompromised states, the virus reactivates and an eruption of HZ occurs. Even after the acute rash subsides, pain can persist or recur in zoster-affected areas. This condition is known as PHN (2).
Epidemiology:
Frequency one month and 3 months after onset of HZ is 9-14.3% and about 5% respectively (2). Helgason et al. (3) demonstrated variations in risk of PHN associated with different age groups. No patient younger than 50 years described severe pain at any time. Patients older than 60 years described severe pain: 6% at 1 month and 4% at 3 months from the onset of zoster. Older age appears to be the most significant risk factor for developing PHN. No predilection for developing PHN is known. The association between greater age and PHN is strong. At age 60 years, approximately 60% of patients with shingles develop PHN, and at age 70 years, 75% develop PHN.

Pathophysiology:
Varicella Zoster Virus is a highly contagious DNA virus that remains latent within the sensory ganglia following resolution of chickenpox, which usually occurs during childhood (4). During HZ, VZV is reactivated, travels back along the affected neurons away from the sensory ganglia, and propagates in the epidermis. A hallmark of HZ is that it is typically unilateral (ie, not crossing the midline), and in most cases only a single dermatome is affected. The erythematous maculopapular HZ rash is usually accompanied by pain and dysesthesia. The rash progresses to clear vesicles similar to the original chickenpox outbreak. Then, over a period of 48–72 hours, pustules form, ulcerate, and eventually scab over. Scabs fall off in 2–3 weeks and scarring may occur (4).

Diagnosis of post herpetic neuralgia:
History:
A painful vesicular eruption in a dermatomal distribution is typical of HZ. With resolution of the eruption, pain that continues for 3 months or more is defined as post herpetic neuralgia. HZ can reactivate sub clinically with pain in a dermatomal distribution without rash. This condition is known as zoster sine herpete and may be more complicated, affecting multiple levels of the nervous system and causing multiple cranial neuropathies, polyneuritis, myelitis, or aseptic meningitis (5).

Symptoms:
With resolution of the HZ eruption, pain that continues for three months or more is defined as PHN.
Pain is variable, from discomfort to very severe, and may be described as burning, stabbing, or gnawing (5).

**Signs:**
Area of previous HZ may show evidence of cutaneous scarring. Sensation may be altered over the areas involved, in the form of either hypersensitivity or decreased sensation. In rare cases, the patient might also experience muscle weakness, tremor, or paralysis if the nerves involved also control muscle movement (5).

**Laboratory studies:**
No laboratory work is usually necessary in cases of PHN. Results of cerebrospinal fluid (CSF) evaluation are abnormal in 61%. Pleocytosis is observed in 46%, elevated protein in 26%, and VZV DNA in 22%. These findings are not predictive of the PHN clinical course (5).

**Treatment options for PHN**
Post herpetic neuralgia may persist for years and is difficult to treat. The safety and tolerability of pharmacologic therapies are important issues to consider as PHN affects primarily an older population (4). Once PHN has been diagnosed, treatment should be directed at pain control and minimizing treatment-related adverse events. No single best treatment has been identified (6). Current guidelines recommend treatment of PHN with calcium channel α2-δ ligands (gabapentin and pregabalin), TCAs (amitriptyline, nortriptyline, or desipramine), or topical lidocaine patches as first-line drugs; opioids and topical capsaicin patch or cream as second- or third-line treatment options (7).

1- **Anticonvulsants**
Since the 1960s antiepileptic drugs (also known as anti-convulsant) have been used in pain management, though their use is mainly confined to neuropathic pain. Anticonvulsants like gabapentin and pregabalin are recommended and approved by the Food and Drug Administration (FDA) as the first line of treatment for PHN (8).

a- **Gabapentin:** Gabapentin is structurally related to GABA neurotransmitter. It acts by binding to the α2-δ site of voltage-gated calcium channels, modulating the influx of calcium and thereby resulting in the reduced release of excitatory neurotransmitters (9).
b- **Pregabalin**
It acts similarly to that of gabapentin, binding to calcium channels, modulating the influx of calcium, and influencing neurotransmitter release. It is more potent than gabapentin, so it is used at a lower dose (10).

2- **Antidepressants**
Many anti-depressants have been used for neuropathic pain caused by PHN since the early 1980s at a lower dose which provides the only analgesia and not relief from depression (8). Tricyclic antidepressants such as amitriptyline, nortriptyline, and desipramine, have been studied and commonly used as an off-label treatment for patients with PHN, although not approved by the FDA (11). Tricyclic antidepressants provide analgesia by inhibiting the reuptake of serotonin and norepinephrine neurotransmitters at the presynaptic nerve terminals thereby decreasing the sensory perception between the brainstem and spinal cord. They also act by blocking the sodium channels and α-adrenergic receptors modulating the descending pain pathway (12).

3- **Topical lidocaine**
Lidocaine is a local anesthetic and can provide surface analgesia when applied topically. To facilitate transfer across the uninjured skin, lidocaine is formulated as a plaster for the treatment of chronic pain such as PHN (13).

4- **Topical capsaicin**
Capsaicin is an irritant ingredient found in hot chili peppers of the genus Capsicum. It is a selective agonist of TRPV1 channels located in the nociceptors nerve fibers of the skin. Exposure to capsaicin activates TRPV1 which causes an influx of calcium and also inhibits the electron-chain transport resulting in a loss of cellular integrity and de-functionalization of nociceptor nerve fibers for a prolonged period (14).
It was approved by the FDA for PHN treatment and must be applied by trained professionals in health care centers. A 2017 Cochrane review reported that high concentration topical capsaicin proved to be more efficient than the low concentrations in achieving excellent pain relief in people with PHN, after a single application (13).

5- **Opioids**
Despite its good analgesic effect, the use of opioids to treat neuropathic pain such as PHN is controversial owing to concerns about misuse, overdose, dependence, and addiction. Opioids are used as second-line or third-line agents for PHN (8).

Opioids provide analgesia by modulating pain via various opioid receptors of the mu, kappa, and delta classes that are present both centrally and peripherally during an inflammatory response. These receptors coupled with inhibitory G-proteins, when activated, causes closure of voltage-gated calcium channels leading to potassium efflux and hyperpolarization, and decreases the production of cyclic adenosine monophosphate. These mechanisms result in a reduction of neuronal cell excitability and transmission of nociceptive impulses, thereby altering the response to pain (12).

6- Tramadol

Tramadol acts as a centrally acting weak opioid at the μ receptor. It also inhibits the reuptake of serotonin and norepinephrine (15). Tramadol is considered a mild opioid and has proven to be less effective in pain relief in PHN than other opioids, but it is better tolerated and a safer alternative. A multi-center, double-blind RCT conducted in 2003 demonstrated a higher efficacy and safety for tramadol than the placebo (16).

7- Botulinum Toxin A

Botulinum Toxin A, a toxin secreted by clostridium botulinum has been used clinically for the treatment of various diseases for decades. BTX-A can be used for treating dystonia, spasticity, brain paralysis, strabismus, and cosmetic procedures. BTX-A is also used for the management of chronic pain of a different origin. Studies have demonstrated the use of BTX-A in the treatment of neuropathic pain including PHN (8,17).

The mechanism of action in BTX-A in relieving pain is not fully understood; however, there are several theories regarding its mechanism. It mainly acts by inhibiting the release of pain mediators from the nerve terminals and dorsal root ganglions, reducing inflammation around the nerve endings, deactivating sodium channels, and exhibiting axonal transport (18).

8- Nerve block

Systematic review conducted in Korea summarized that an early nerve block cannot only relieve acute HZ pain, but can also prevent its sequelae, PHN (19). In this study, the authors concluded that among the various nerve blocks, stellate ganglion blocks had a lesser effect.
in reducing the occurrence of PHN. However, somatic blocks including repeated or continuous epidural and para-vertebral blocks prevented PHN and reduced its incidence (19).

9- Neuromodulation:
Another treatment option, which is used recently for chronic pain conditions after the conservative management has failed, is neuromodulation. Neuromodulation via various methods including transcutaneous electrical nerve stimulation (TENS) (20), peripheral nerve stimulation (PNS), Spinal Cord Stimulation (SCS), and radiofrequency in combination with conservative treatment has contributed to the prevention of PHN (21). Spinal Cord Stimulation is reported to be useful in treatment and prevention of PHN (19). The higher medical cost of SCS and difficulty in providing appropriate stimulation is its major setback, especially in the thoracic region where the level of CSF is deep. Pulsed radiofrequency (PRF) is considered more useful in comparison to continuous radiofrequency (CRF) in spite of its effectiveness in pain relief. In CRF treatment, due to prolonged exposure of the nerves to a higher temperature, there is an increased risk of thermal or nerve injuries. PRF with pulsed/short bursts of RF is used with the temperature of the probe maintained at 42°C to overcome these complications (19).

10- Vaccination
Administration of zoster vaccine in immunocompetent adults aged 60 or older is recommended by the United States Advisory Committees on Immunization Practices (ACIP) to reduce the incidence of HZ and prevention of PHN (22).

11- Intraleisonal of corticosteroids:
Corticosteroids have a potent anti-inflammatory action, which it has been suggested might minimize nerve damage and thereby relieve or prevent the pain experienced by people suffering from PHN (23).

References


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