Postherpetic Neuralgia: From Phenytoin to Ultrasonography-guided Blocks

**ABSTRACT**

Postherpetic neuralgia (PHN) is a painful condition affecting 2% of the patients suffering from herpes zoster (HZ). Most common risk factor for developing PHN is age. Pain has a dermatomal distribution; is confined to same dermatome as the rash. Various treatment modalities have been tried to reduce this pain and improve the quality of life of the patient. Varicella zoster vaccine has shown promising results in preventing the development of HZ as well as PHN. Early treatment with antiviral drugs within 72 hours is also helpful to decrease the incidence of PHN. There has been a gradual transition in the treatment modalities, from oral anticonvulsants, antidepressants, opioids, to combination therapies of these drugs, which reduces side-effects and improves efficacy. Now the focus has shifted to eliminate the oral route altogether. Nowadays topical applications are being used. Various topical modalities available are 5% lignocaine patch, 8% capsacian patch. Latest development is a 6% gabapentin patch. There is a combined patch which has a mix of gabapentin, ketoprofen, ketamine and lignocaine which has also been used in a case report. The most recent advance in the treatment modality is transcutaneous electrical nerve stimulation, which has shown to prevent development of PHN as well as has shown promising results to decrease the pain. When the pain is not responding to any of the treatment modalities mentioned above, ultrasonography (USG)-guided musculocutaneous peripheral nerve block has been used and it has shown positive results. Out of all the treatment modalities available in our armour, we can choose either one or a multimodal approach, depending on the patient’s condition, and provide pain relief to our patients.

**Keywords:** Anticonvulsants, Antidepressants, Postherpetic neuralgia, Transcutaneous electrical nerve stimulation, USG guided musculocutaneous peripheral nerve block.

**INTRODUCTION**

Herpes zoster (HZ) is caused due to reactivation of the varicella zoster virus (VZV) which resides dormant in the sensory nerve root ganglion whenever there is a decline in body immunity.

It usually presents with a prodromal pain along with vesicular rash. A disabling sequele to this disease is postherpetic neuralgia (PHN) which can cause serious discomfort to the patients and decreases the quality of life.

In PHN, pain can be intermittent or continuous, persisting 1 month after appearance of rash or after the rash has disappeared. This pain is usually confined to the area of original dermatomal involvement. The main risk factor for PHN is increasing age. It is uncommon in people aged <50 years, but develops in 20% of people aged 60 to 65 years who have had acute HZ, and in >30% of those people aged >80 years. Up to 2% of people with acute HZ may continue to have postherpetic pain for 5 years or more.

**MANAGEMENT**

**Antivirals and Vaccination**

Our aim should be early recognition and treatment initiated within the first 72 hours of the rash, with antiviral drugs in order to reduce both acute neuralgia (AN) and later complications and especially PHN. Treatment with oral acyclovir, famciclovir, valacyclovir has been found to be beneficial. They reduce viral shedding and accelerate resolution of symptoms.

A live, attenuated vaccine aimed at boosting immunity to VZV and reducing the risk of HZ is now available and is recommended for adults older than 60 years. The vaccine has been shown to reduce significantly the incidence of both HZ and PHN. The vaccine is well tolerated, with minor local injection site reactions being the most common adverse event.

**Oral Medications**

The other treatment modalities available for treating this pain are anticonvulsants like gabapentin, pregabalin; antidepressants like amitryptiline, nortryptiline, valnafaxine; narcotic and non-narcotic analgesics both systemic and topical.
Historically, phenytoin and carbamazepine were also used for neuropathic pain as they blocked the sodium channels which fired during bursts of pain. Sodium valproate was also used as it increased gamma-aminobutyric acid (GABA) function. Similarly benzodiazepines were also tried.

Later with the trials gabapentin was found to be effective in the management of pain due to PHN. The mechanism of action of gabapentin remains unknown. Evidence suggests that it is most likely to be the result of a complex synergy between increased GABA synthesis, non-N-methyl-D-aspartate (NMDA) receptor antagonism and binding to the α to d subunit of voltage dependent calcium channels. The latter action inhibits the release of excitatory neurotransmitters.

A recent study by Sanjay et al compared three doses of gabapentin, 300, 600 and 900 mg/day. The safety profile showed significantly more somnolence, dizziness, and gastrointestinal side-effects in dose of 900 mg/day as compared with 300 and 600 mg/day. Also the therapeutic efficacy was comparable in both 600 and 900 mg dose. This highlighted that the dose of 600 mg/day is therapeutically more effective and a safe dose. The most common side-effect was somnolence, but it was not a source of stress in patients, rather nocturnal somnolence was perceived as mark of pain relief. The results of this study show that early initiation of gabapentin can be safe and effective alternative to analgesics and tricyclics.

Another oral medication used is pregabalin, which binds with high affinity to the α2-δ subunit protein of voltage-gated calcium channels and, thereby, reduces release of excitatory neurotransmitters. One recent study was done by Guan et al where they conducted a double blinded placebo controlled study, in which one group of patients received pregabalin 150 to 600 mg/day and the other group received placebo for 8 weeks. On completion of the study, end point change in mean daily pain rating scale (DPRS) score was noted and it was seen that treatment with pregabalin resulted in significant improvement compared with results with placebo. Study results suggested that relative to placebo, pregabalin in daily doses of 150 to 600 mg/day was effective and well tolerated.

Moving on to our next class of drug, the tricyclic antidepressants (TCAs), block sodium, calcium, and NMDA receptors and inhibit serotonin and norepinephrine reuptake, therefore could act in a similar way as the anticonvulsants by blocking the conduction of painful impulses. Earlier amitriptyline, nortriptyline, desipramine and imipramine were the TCAs that had shown to be effective for the symptomatic relief of PHN. Serotonin noradrenaline reuptake inhibitors (SNRIs), such as venlafaxine and duloxetine have been shown to be very promising for the treatment of PHN with fewer adverse effects than TCAs. Selective serotonin reuptake inhibitors (SSRIs) were shown in a number of studies to have some efficacy in relieving PHN-related pain, yet other studies of the SSRIs have demonstrated conflicting outcomes.

In a recent study on venlafaxine for PHN, it was found that venlafaxine was reasonably well-tolerated drug in the dose of 75 to 122 mg/day and may be of some benefit in people who cannot tolerate other antidepressants or anticonvulsant drugs that are more widely prescribed to people with neuropathic pain.

Due to incomplete efficacy and dose limiting side-effects of oral medications as monotherapy there were many trials to compare the efficacy of combined drug regimen compared to monotherapy. One such trial by Gilron et al studied the effects of nortryptiline and gabapentin alone and in combination for neuropathic pain. It showed that combined therapy was superior to monotherapy with either drug. The combination had lower mean daily pain intensity, significant improvement in sleep interference, increased percentage change in pain. However, the maximal tolerated dose of each drug was reduced but greater efficacy was achieved with smaller doses. So they recommend combined gabapentin and nortryptiline therapy for patients with partial response to even one and who seek additional pain benefit.

Another class of oral medication explored were the opioids. Opioids are μ-receptor agonists and have been shown to alleviate certain neuropathies. The conventionally used opioids include morphine and tramadol. Raja et al investigated two oral agents by comparing TCAs (nortriptyline 89 mg or desipramine 63 mg) and opioids (morphine 91 mg or methadone 15 mg) and placebo. In his screening of 103 patients, he found that TCAs decreased pain by 32%, while opioids showed mildly better with a 38% improvement. Earlier evidences were high in favor of TCAs for pain management in PHN but latest RCTs support opioids over them for better results.

Topical Medications

Due to the side-effects associated with oral medications, the focus was shifted to topical medications. The advantages of topical formulation are first of all a convenient and pain-free self-administration for the patient. Moreover, there is a reduced frequency of dosing administration and a reduced systemic exposure to drug. Last but not least there is an enhancement in the patient compliance and the topical application is able to target specific pathophysiologic events that in the periphery generate or maintain pain.
One such formulation is the lidocaine 5% patch which is a safe, manageable, efficient option in case of localized neuropathic pain (LNP). Lidocaine inhibits voltage gated sodium channels which are in the functional state: these ion channels play a major role in determining excitability properties of neurons. The lidocaine acts by blockade of abnormally functioning (synthesitized) Nav 1.7 and Nav 1.8 channels along with the consequent stabilization of the neuronal membrane potential, through A-beta and C fibers, managing to reduce ectopic discharges.

The first-line treatment in LNP is the lidocaine patch: in 1999, this patch was approved by the US Food and Drug Administration (FDA) for the treatment of PHN.

The lidocaine patch is a targeted peripheral analgesic, which consists of a 10 × 14 cm, nonwoven, polyethylene backing and medication-containing adhesive of 5% lidocaine (700 mg/patch). A maximum of three lidocaine patch may be applied to the intact patient skin, left in place for 12 hours and removed for 12 hours each day with these formulations only 2 to 3% of the dose is absorbed and reach the systemic circulation: the maximum concentration of lidocaine remain well under the clinical-relevant concentration even when the maximum recommended dose is exceeded.7,8

In a recent study, Delorme et al evaluated the efficacy and tolerability of lidocaine 5% patch in patient with PHN (20%) or LNP (80%), demonstrating the stable reduction of pain for more than 24 months: this persistent analgesic effect suggests that the analgesic efficacy of the patch is not influenced by time, in contrast with the other systemic analgesic treatment which showed the development of a tolerance during time, limiting the therapeutic possibility only to a short period. Considering the high profile of safety, tolerability and efficacy, the lidocaine 5% patch is a promising and first chosen treatment in case of local neuropathic pain.9

In a recent study, an 8% capsaicin patch was used. This patch is an adhesive patch containing a high concentration (8% w/w) of synthetic capsaicin, a selective agonist of transient receptor potential vanilloid 1 channel. It is approved for treatment of peripheral neuropathic pain in adults either alone or in combination with other medicinal products for pain. In two randomized trials, a single 60 minutes application of the capsaicin 8% patch reduced pain scores significantly more than a low-concentration (0.04 %) capsaicin control patch in patients with PHN. Capsaicin 8% patch treatment was noninferior to pregabalin (optimized dosage) in a randomized trial in patients with nondiabetic peripheral neuropathic pain. The capsaicin 8% patch was associated with expected, transient, capsaicin-related application-site adverse events such as erythema and pain.10

There is a case report by Kenneth et al in which topical and intranasal analgesic pharmacotherapy was used instead of oral medications. It was found that a patient-specific, stepped approach to topical and intranasal analgesic pharmacotherapy was effective in reducing refractory PHN not responding to the current standard of care for PHN. The use of topical analgesic therapy allowed for higher concentrations of medication locally while reducing the likelihood of systemic side-effects common to the drugs used. No adverse effects were noted for either topical or intranasal drug therapy. The patient-specific, stepped approach resulted in clinically significant decreases in pain on visual analog scale (VAS). The formulation used was intranasal ketamine 10% solution and topical gabapentin 6%, ketoprofen 10%, lidocaine 5%, and ketamine 10% cream.11

Another interesting recent advance in the treatment of PHN was the development of topical gabapentin patches. In a study by Hiom et al, in 2015, they studied the efficacy of topical gabapentin for neuropathic pain. It was based on the fact that some patients cannot tolerate oral gabapentin and have significant side-effects. Only those patients who could not tolerate oral gabapentin were included in the study and they were given gabapentin patches, which contained 6% w/w gabapentin gel. The pain scores were assessed pre and postoperatively. The pain scores decreased significantly up to 1 month after treatment and patients reported 30 to 80% pain relief. Topical gabapentin resulted in rapid improvement of symptoms (<1 month) when compared to the gradual titration required with oral administration (<8 weeks). Results support anecdotal evidence that topical gabapentin is safe and efficacious for use in refractory focal peripheral neuropathic pain.12

**Transcutaneous Electrical Nerve Stimulation**

After having exhausted all the options, the researchers have come up with some novel techniques. One such recent advance in the management of PHN includes transcutaneous electrical nerve stimulation (TENS).

In a pilot study by Ing et al, the patients refractory to medical treatment were treated with TENS. In this study, patients were divided into two groups. One group treated with a sham device and other with the true device. After every two treatments with the sham and true device, the patients were required to fill out a standard neuropathic pain scale score. The patients were allowed to select the other device after three consecutive treatments if they felt an inadequate decrease in their pain. The true device was chosen over the sham device by all patients. The patients with TENS reported a significant decrease in pain score.
This study paved way for many more to follow.\textsuperscript{13}

The earlier studies were aimed at treating the pain after PHN had occurred. There was a study by Stepanovic et al which focussed on prevention of development of PHN through electrical nerve stimulation. They compared the development of pain after herpes in four groups, TENS, antiviral drugs, TENS+ antiviral drugs, and a control group. They found that PHN cannot be completely prevented. TENS as a single therapy was found the most successful among the tested treatments in reducing the incidence of subacute herpetic neuralgia.\textsuperscript{14}

A similar study was done in which TENS was combined with local injection of cobalamine alone, with lidocaine alone, and in combination with cobalamine and lidocaine for 8 weeks. The pain scores, pain reduction, worst pain and quality of life were measured in the patients. And it was concluded that Transcutaneous nerve stimulation combined with local injection of cobalamine and lidocaine provided the greatest pain relief.\textsuperscript{15}

\textbf{Ultrasound-guided Musculocutaneous Peripheral Nerve Block}

Having talked about the oral medications to topical ones to newer techniques like TENS, we would like to shed light upon another technique cited in a case report by Kuo et al where they used ultrasound-guided musculocutaneous peripheral nerve block to relieve intractable pain due to herpes. Patient who was not responding to any of the treatment modalities was selected who was in excruciating pain. Following the block, symptoms remained controlled at 1 month follow-up. Ultrasound was applied to improve the accuracy and efficiency of peripheral nerve block as it is currently widely used to evaluate the musculoskeletal system in clinical settings.

\textbf{CONCLUSION}

Postherpetic neuralgia is a biopsychosocial condition. Since it has a significant impact on patient’s psychological and social well-being and physical functioning, patient education becomes important. Besides the use of therapeutic agents and their combinations in the management of PHN pain, interventional pain management techniques are also gaining importance. Still in the absence of any particular guidelines, and given the refractoriness and heterogeneity of the disease, clinicians who treat patients with PHN should be familiar with the entire spectrum of therapeutic options and their appropriate application for specific types of symptoms.

\textbf{REFERENCES}