Postherpetic Neuralgia: A Review

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Abstract

Postherpetic neuralgia, a complication of herpes zoster, is a neuropathic pain syndrome which results from a combination of inflammatory and viral damage to primary afferent fibers of sensory nerves. Postherpetic neuralgia is often diagnosed when pain persists in a dermatomal pattern weeks after the herpes zoster vesicular eruption has healed. The pain of postherpetic neuralgia can be debilitating, severely affecting patients' quality of life. Unfortunately, no treatment has been shown to completely prevent postherpetic neuralgia, yet some treatments may shorten the duration or lessen the severity of symptoms. The pathophysiology, incidence, epidemiology, and treatment options for postherpetic neuralgia are presented.

PATHOPHYSIOLOGY

Postherpetic neuralgia, a complication of herpes zoster, is a neuropathic pain syndrome resulting from a combination of inflammatory and viral damage to primary afferent fibers of sensory nerves. After resolution of a primary infection of varicella, the virus remains dormant in the sensory ganglia[1]. The virus is reactivated, presenting as acute herpes zoster, and is associated with damage to the ganglion, the primary afferent nerve, and skin.[1] Histopathological studies have demonstrated fibrosis and neuronal loss (in the dorsal ganglion), scarring as well as axon and myelin loss (in the affected peripheral nerve), atrophy (of the dorsal horn of the spinal cord), and inflammation (around the spinal cord) with infiltration and accumulation of lymphocytes[2,3]. Furthermore, there is a reduction of large inhibitory nerves and an increase in small, excitatory neurons in the peripheral nerve[4]. Two different pathophysiological mechanisms, sensitization and deafferentation, can explain the pain of postherpetic neuralgia[1]. Peripheral sensitization: subsequent to tissue injury, nociceptors become sensitized, resulting in spontaneous discharge activity and hyperexcitability[1]. Central sensitization: the exaggeration of dorsal horn neurons response to afferent stimuli and the expansion of their receptive fields by prolonged nociceptor discharge may lead to allodynia without sensory loss[1]. Deafferentation pain: reactivation of the varicella zoster virus results in neural damage and inflammation with subsequent edema[1]. Other mechanisms for postherpetic neuralgia pain include neuroma formation or neuronal sprouting, and local axons reinnervating previously denervated areas[5].

EPIDEMIOLOGY

Postherpetic neuralgia, a chronic pain syndrome, is often diagnosed when pain persists in a dermatomal pattern 4-6 weeks after the herpes zoster vesicular eruption has healed[6]. The definition of postherpetic neuralgia varies in the defined time period of the persistence of pain after the resolution of the rash (4-24 weeks) and thus the actual incidence is not known. Approximately 1,000,000 cases of herpes zoster occur in the United States per year,[7] and this incidence can likely increase as our population ages. Of those patients with herpes zoster, approximately 9%-34% develop postherpetic neuralgia[8]. Approximately 80-85% of postherpetic neuralgia develops in herpes zoster patients more than 50 years of age[7]. Increased age, increased severity of acute pain, greater extent of the rash, and the presence of a prodrome of dermatomal pain before the onset of the rash of herpes zoster will increase postherpetic neuralgia development[9] and severity (50%-75% have persisting pain six months after the rash)[10]. The incidence of postherpetic neuralgia is reduced by 66.5% in immunocompetent individuals 60 years of age or older vaccinated by live attenuated varicella-zoster virus[11].

CLINICAL PRESENTATION

The pain of postherpetic neuralgia can persists for weeks, months, and on occasion for years. Postherpetic neuralgia persisted one year or longer in 6% of those 50 years of age or older in a population-based study[7]. The pain has been described as mild to excruciating in severity, constant, intermittent, lasting from a few minutes to being constant daily or almost daily[12]. The pain can be constant, deep,

burning pain with an intermittent sharp, stabbing, shooting pain. These patients may also have allodynia, may be unable to have clothing in the area of allodynia, and, thus, dressing, bathing, grooming, and mobility may be effected[13] . The severity of the pain of postherpetic neuralgia can have a significant negative impact on a person's quality of life and can be very debilitating. Postherpetic neuralgia patients can experience chronic fatigue, anorexia, weight loss, and depression[12]. Their social role may change from an active person in the community to an individual who rarely leaves their home[14]. Postherpetic neuralgia has been stated to be one of the most common causes of pain-related suicide in the elderly[14].

PREVENTION/TREATMENT

No treatment has been shown to completely prevent postherpetic neuralgia, yet some treatments may shorten the duration or lessen the severity of symptoms.

ANTIVIRAL AGENTS

The use of antiviral agents within the first 72 hours of the onset of the rash of herpes zoster can reduce the duration of the rash and the duration of postherpetic neuralgia[15-18]. The antiviral agents acyclovir, valacyclovir, and famcyclovir are highly selective for thymidine kinase, an enzyme encoded by the herpes zoster virus, and ultimately inhibit viral replication. By inhibiting viral replication, the duration of viral shedding and lesion formation, the time to rash healing, the severity and duration of acute pain from zoster, and the risk for progression to postherpetic neuralgia are reduced. Acyclovir (800mg po 5 times daily for 7-10 days), valacyclovir (1 gm po tid for 7 days), and famcyclovir (500 mg po tid for 7 days) can cause the following side-effects: nausea, vomiting, diarrhea, abdominal pain, and headache. A meta-analysis of four double-blind, randomized, placebo-controlled trials of oral acyclovir for herpes zoster demonstrated an acceleration in the resolution of zoster-associated pain and a reduction by at least 50% in the prevalence of postherpetic neuralgia at 3 and 6 months in patients who received

acyclovir[15]. These benefits of acyclovir therapy were greatest for patients 50 years of age or older[15]. Valacyclovir accelerated the resolution of herpes zoster-associated pain and postherpetic neuralgia, reduced the proportion of patients with pain persisting for at least 6 months[16] .Valacyclovir reduces the duration of pain (51 days with acyclovir vs. 38 days with valacyclovir) and reduces the pain at 6 months (26% of patients taking acyclovir vs. 19% of patients taking valacyclovir) more than acyclovir[16] . In a double-blind, randomized comparison of valacyclovir and high dose famcyclovir in acute herpes zoster, valacyclovir treatment is comparable to famcyclovir treatment in speeding the resolution of zoster associated pain and postherpetic neuralgia[17]. Postherpetic neuralgia resolves two times faster in patients taking famcyclovir than those receiving the placebo with a 3.5 month reduction in the average duration of pain[18] .

Therefore, the antiviral agents acyclovir, valacyclovir, and famcyclovir reduce the duration of the rash and the duration of postherpetic neuralgia[15-18] Valacyclovir reduces the duration of pain and reduces the pain at 6 months more than acyclovir[16]. Valacyclovir treatment is comparable to famcyclovir treatment in speeding the resolution of zoster associated pain and postherpetic neuralgia[17].

ANTICONVULSANTS

Gabapentin, an anticonvulsant, has been used to treat neuropathic pain. In a multicenter, randomized, double-blind, placebo-controlled, parallel design, 8-week trial, gabapentin (titrated to a maximum of 3600mg/day) significantly reduced postherpetic neuralgia pain (a reduction in mean daily pain score from 6.3 to 4.2 with gabapentin vs. a reduction with placebo from 6.5 to 6) and associated sleep disturbance with an improvement in mood and quality of life[19] . Yet, the patients in this study who received gabapentin had side effects occurring at higher incidences than in the placebo group such as somnolence, dizziness, ataxia, peripheral edema, and infection[19]. In a multicentre, double-blind, randomized, placebo controlled 7-week study, gabapentin (1800 and 2400 mg/day) significantly reduced postherpetic neuralgia pain with the most common side effects of dizziness and somnolence[20]. Although there is no standard dosing regimen, treatment can be initiated at 900mg/day (300mg po day 1, 300mg po bid day 2, 300mg po tid day 3) with an additional titration to 1800mg/day for additional efficacy as tolerated[21]. Some patients may require doses up to 3600mg/day[21]. Dosage adjustment in patients with renal insufficiency is necessary. The mechanism of analgesic action of gabapentin is unclear. Most likely, gabapentin binds to the $alpha_2$ -$delta_1$ subunit of voltage-gated calcium channels decreasing calcium influx, and inhibiting the release of excitatory neurotransmitters[22] and also acts directly in the brainstem via a glutamate-dependent mechanism to stimulate descending inhibition to produce antihypersensitivity after peripheral nerve injury[23].

Pregabalin, an anticonvulsant, also has been used to treat neuropathic pain. In a multicenter, parallel-group, double-blind, placebo-controlled, 8-week, randomized clinical trial, pregabalin (600mg/day or 300mg/day based on renal clearance) significantly reduced postherpetic pain beginning the first day of treatment (50% of patients treated with pregabalin and 20% of patients treated with placebo had equal to or greater than 50% decrease in their pain) and improved sleep in patients with postherpetic neuralgia beginning the end of the first week of treatment[24]. Dizziness and somnolence were the most significant side effects of pregabalin treatment in this study[24]. In a randomized, double-blind, multicentre, placebo-controlled, parallel-group design to evaluate the efficacy and safety of twice a day flexible (15-600 mg/day) or fixed-dose (600mg/day) pregabalin in patients with postherpetic neuralgia or diabetic neuropathy, a significant reduction of pain and improvement in sleep over placebo was demonstrated[25]. In a 4-week randomized trial comparing flexibly-dosed pregabalin (150-600mg/day), fixed-dose pregabalin (300mg/day), and placebo, pregabalin fixed- and flexible-dose regimens produced significant reductions in pain in 1.5 and 3.5 days respectively in patients with postherpetic neuralgia and a reduction in allodynia after one week[26]. Discontinuation rates due to adverse events were more frequent in the fixed-dose group [26]. In another randomized, double-blind, multicentre, placebo-controlled trial, pregabalin was also shown to significantly reduce pain, improve sleep, mood disturbances, and health-related quality of life measures in patients with postherpetic neuralgia[27].

Pregabalin, like gabapentin, binds to the $alpha_2$ -$delta_1$ subunit of voltage-gated calcium channels decreasing calcium influx, and inhibiting the release of excitatory neurotransmitters[22].

Pregabalin binds to the $alpha_2$ -$delta_1$ subunit with six times greater affinity than gabapentin[28]. Both gabapentin and pregabalin have a high correlation between plasma clearance and renal function, similar elimination half-lives, no inhibition of the cytochrome P450 enzymes, minimal drug-drug interactions, and a similar adverse effect profile. Pregabalin, however, has a higher bioavailability independent of dose (90% with pregabalin versus 33-66% with gabapentin which is saturable and dose-dependent), is rapidly absorbed (peaks one hour versus 3-4 hours with gabapentin), increases its plasma concentrations linearly with increasing doses, and has low intersubject pharmacokinetic variability[29]. In a retrospective study, patients with postherpetic neuralgia in the usual-care setting, there was increased opioid use after the initiation of gabapentin and decreased opioid use after the initiation of pregabalin[30].

In summary, both gabapentin and pregabalin significantly reduce postherpetic neuralgia pain, associated sleep disturbance with an improvement in mood and quality of life[19,27]. Pregabalin, however, has a higher bioavailability independent of dose, is rapidly absorbed, increases its plasma concentrations linearly with increasing doses, and has low

intersubject pharmacokinetic variability[29]. Both a fixed- and flexible-dose of pregabalin regimen appear to be effective[26]. When opioids are combined with gabapentin or pregabalin, there was increased opioid use after the initiation of gabapentin and decreased opioid use after the initiation of pregabalin[30].

ANTIDEPRESSANTS

In a randomized, double-blind, parallel design trial comparing desipramine (titrated to a maximum dose of 150mg/day), amitriptyline (titrated to a maximum dose of 150mg/day, and fluoxetine (titrated to a maximum of 60mg/day) in patients with postherpetic neuralgia, all three agents reduced daily diary pain or end-treatment pain relief category with desipramine producing relief in 80% of those treated[31]. Adding fluphenazine to amitriptyline does not significantly provide more pain relief than amitriptyline alone[32]. Tricyclic antidepressants, such as desipramine and amitriptyline, inhibit the reuptake of norepinephrine and serotonin[33], block N-methyl-D-aspartate (NMDA) receptors [34], block sodium channels[35,36], and block calcium channels[37]. The selective serotonin reuptake inhibitors (SSRIs) inhibit serotonin reuptake without action on noradrenaline reuptake[33]. Fluoxetine blocks sodium channels, unlike other SSRIs, yet the blockade seems to be different than that of tricyclic antidepressants[36] . Side effects of tricyclic antidepressants include dry mouth, sweating, dizziness, orthostatic hypotension, fatigue, constipation, problems with micturition, and cardiac disturbances. The SSRI's may cause nausea, vomiting, and dyspepsia. Of interest, topical use of tricyclic antidepressants has been studied. In a randomized, placebo-controlled crossover study in the study of neuropathic pain, topical 5% amitriptyline and 5% lidocaine were compared showing that topical 5% lidocaine reduced pain intensity and topical 5% amitriptyline was not effective in reducing pain intensity[38]. Furthermore, a randomized trial of patients (>60 years of age) diagnosed with herpes zoster

initiated 25mg of amitriptyline or placebo within 48 hours of rash onset and continued the treatment for 90 days[39]. The amitriptyline group, in this study, showed a 50% decrease in pain prevalence at 6 months[39].

In summary, desipramine, amitriptyline, and fluoxetine reduced the pain in patients with postherpetic neuralgia, with desipramine producing relief in 80% of those treated treated[31]. Adding fluphenazine to amitriptyline does not significantly provide more pain relief than amitriptyline alone[32]. Furthermore, topical 5% amitriptyline was not effective in decreasing neuropathic pain[38].

LIDOCAINE PATCH

The 5% lidocaine patch relieves the pain and allodynia of patients with postherpetic neuralgia[40]. The patch is a topical adhesive patch containing 700 mg of lidocaine and up

to three patches can be applied simultaneously for 12 hours per day. One to three patches or a portion of a patch can be placed over the painful area[41]. The mechanism of the patch is believed to be the reduction of aberrant firing of sodium channels on damaged pain nerve fibers directly under the patch[41]. Systemic lidocaine levels remain well within a safe range with doses of up to 4 patches on for 24 hours[41]. Adverse reactions are rare, mild, and mostly topical[41]. The lidocaine patch is contraindicated in advanced liver failure because of the decreased metabolism of lidocaine[41]. In a prospective, randomized, placebo-controlled, two-way, cross-over study in three medical hospitals, the topical application of 5% lidocaine patch effectively relieved pain and allodynia in postherpetic neuralgia patients[42]. A cost comparison study in the United States found that, on average, patients receiving the lidocaine patch spent $1780 per patient-year less on health care than patients receiving branded gabapentin as an analgesic and spent $1330 less than those receiving generic gabapentin[43]. So, 5% lidocaine patch is effective on relieving the pain and allodynia of patients with postherpetic neuralgia[40].

TOPICAL CAPSAICIN

As another treatment for postherpetic neuralgia, capsaicin is an agonist at transient receptor potential vanilloid 1 which is present on primary nociceptive afferent terminals.

Topical capsaicin cream (0.075%), as a treatment for postherpetic neuralgia, statistically improved the number of patients experiencing pain relief versus placebo[44,45]. In these studies, 0.075% capsaicin cream was applied four times daily and the main side effect, burning or stinging, diminished after the first week[44,45].

OPIOID ANALGESICS

Opioid analgesics have been used for the treatment of nociceptive and cancer pain, yet their role in the management of nonmalignant neuropathic pain, such as postherpetic neuralgia, has been controversial. Also, other factors, such as opioid-related side effects, development of tolerance, and fear of addiction contribute to the controversy of using opioids for the treatment of nonmalignant neuropathic pain. Despite these controversies, studies demonstrate the effectiveness of opioids in the treatment of neuropathic pain, particularly postherpetic neuralgia[46-49]. In a double-blind, placebo-controlled, randomized, controlled trial, intravenous infusions of morphine or lidocaine provided significant pain relief in patients with postherpetic neuralgia[46]. In the majority of subjects who reported pain relief, allodynia also disappeared[46]. In a double-blind, placebo-controlled, randomized trial, controlled-release oxycodone (titrated to a maximum dosage of 60mg per day) provided significant benefits with respect to pain, disability, and allodynia compared with placebo[47]. Controlled-released oxycodone demonstrated rapid onset of pain control, superior efficacy in relieving both moderate and severe postherpetic neuralgia pain, a good safety profile, and a decrease in the concomitant use of three-ladder analgesics[48]. In a double-blind , placebo-controlled, randomized three-period crossover study, treatment with oral morphine (mean daily dose 91mg), tricyclic antidepressants (mean daily dose nortriptyline 89mg and desipramine 63mg), and placebo in patients with postherpetic neuralgia were compared[49]. The efficacy of opioids and tricyclic antidepressants for pain relief were similar and more than placebo, yet the patients preferred treatment with opioid analgesics, despite a greater incidence of side effects during opioid treatment[49]. In a double-blind dose-response trial, a postherpetic neuralgia subgroup examining the use of opioids (levorphanol)for the treatment of neuropathic pain showed a greater reduction in pain with higher doses rather than lower doses of opioids[50] . Despite receiving 12 months of treatment with oral morphine for chronic non-cancer pain, patients in a long-term prospective study did not demonstrate impairment in neuropsychological tests[51]. The most common side effects of opioid analgesic therapy include constipation, sedation, and nausea. Opioid analgesics must be used cautiously in patients with a history of substance abuse.

In summary, in terms of the use of opioids for the treatment of postherpetic neuralgia, both intravenous and oral

administration of opiods have been shown to provide significant relief of pain and allodynia[46,47]. Higher doses rather than lower doses of

0pioids provided a greater reduction of pain in patients being treated for neuropathic pain[50]. Finally, despite patients receiving long-term treatment with oral morphine, there was not an impairment noted in neuropsychological testing[51].

TRAMADOL

The analgesic actions of tramadol are mediated by its opioid agonist activity at the mu receptor and the inhibition of the reuptake of norepinephrine and serotonin. In a multicenter, randomized, double-blind, parallel-group study, six weeks of treatment with tramadol (100-400mg/day) for postherpetic neuralgia was associated with a reduction in pain [52] .

INTERVENTIONAL STRATEGIES

Interventional treatment options for postherpetic neuralgia have been examined as potential treatments of postherpetic neuralgia. These treatment options include sympathetic blocks, epidural and intrathecal methylprednisolone, and spinal cord stimulators.

SYMPATHETIC NERVE BLOCKS

Sympathetic nerve blocks have been utilized as a treatment modality in patients with postherpetic neuralgia. In studies evaluating the effectiveness of sympathetic nerve blocks in treating postherpetic neuralgia and preventing postherpetic neuralgia, there are significant methodological issues which effect the evaluation of the role of sympathetic blocks in postherpetic neuralgia[53]. These methodological issues include lack of control groups, varying definitions of postherpetic neuralgia, inadequate assessments of pain severity and relief, lack of appropriate follow up, adequate sample size, and lack of double-blind, randomized, controlled trials[53]. Sympathetic blocks may be effective in relieving pain during acute herpes zoster, yet they do not seem to provide long term relief in patients in patients with long-standing postherpetic neuralgia[54,55]. If sympathetic blocks reduce the severity of the acute pain, a risk factor for increasing the development of postherpetic neuralgia[9], then they may theoretically prevent the development of postherpetic neuralgia.

INTRATHECAL AND EPIDURAL METHYLPREDNISOLONE

Patients who have had postherpetic neuralgia have inflammation around the spinal cord with infiltration and accumulation of lymphocytes[2] and high concentrations of interleukin-8 in the cerebrospinal fluid[56] . Patients with intractable postherpetic neuralgia for at least one year, in a randomized, controlled study, revealed that an intrathecal injection of methylprednisolone and lidocaine (versus lidocaine alone or no treatment) significantly decreased pain, the area of pain, the use of diclofenac (by 70% 4 weeks at the end of treatment), and allodynia[57] . In the intrathecal methylprednisolone and lidocaine group, the cerebrospinal fluid (CSF) concentration of interleukin-8 decreased by 50% and this decrease correlated with the duration of neuralgia before treatment and with global pain relief [57]. Intrathecal administration of methylprednisolone appears to provide greater relief and lower CSF levels of interleukin-8 compared to epidural methylprednisolone[56]. Additional studies are needed to determine the safety of intrathecal methylprednisolone since it has been associated with neurological complications such as arachnoiditis[57,58,59].

SPINAL CORD STIMULATOR

Spinal cord stimulation is an interventional treatment option for some types of neuropathic pain[60]. For patients with postherpetic neuralgia with pain more than two years duration with preserved sensory function refractory to conventional pharmacotherapy, spinal cord stimulation provided 82% of the patients with long-term relief[61] .The mechanism of spinal cord stimulation is unclear. Postulated mechanisms include the stimulation of large myelinated A-beta fibers interfering with the transmission

of nociceptive information carried by small unmyelinated C and myelinated A-delta fibers from the periphery, suppression of sympathetic overdrive, and inhibition of nociceptive processing via GABA-ergic interneurons[60,61].

CONCLUSION

Postherpetic neuralgia, a complication of herpes zoster, can be a debilitating painful condition most commonly affecting the elderly. Unfortunately, no treatment has been shown to completely prevent postherpetic neuralgia, yet some treatments may shorten the duration or lessen the severity of symptoms. Education to improve early detection of herpes zoster will allow the opportunity to use antiviral medication within the first 72 hours to reduce the duration of the rash and of postherpetic neuralgia. A review of the literature suggests that there is evidence of lessening symptom severity in established postherpetic neuralgia for the following orally administered therapies: tricyclic antidepressants, opioids, gabapentin, pregabalin and

tramadol. There is also some evidence for topical agents with analgesic efficacy for postherpetic neuralgia: 5% lidocaine patch and capsaicin. Intrathecal methylprednisolone and lidocaine provide analgesia in these patients as well; however the safety of intrathecal methylprednisolone still needs further evaluation. Psychological support along with the above treatments may be considered in this often debilitating condition.

Since more than one mechanism of action of postherpetic neuralgia seems to be involved, the concomitant use of two or more analgesics with different mechanisms of action may cover these mechanisms and provide greater relief than one single agent. This may produce fewer adverse events, since lower doses of each analgesic may be utilized. The advantages of using drug combinations must be weighed against complications resulting from drug interactions which can be life-threatening (e.g. tramadol with tricyclic antidepressants).

The prevention of postherpetic neuralgia would ideally be a first step in reducing the number of patients afflicted with herpes zoster and, thus, postherpetic neuralgia pain. The vaccination of young children is effective in preventing varicella. In May 2008, the US Centers for Disease Control and Prevention recommended vaccinating immunocompetent adults greater or equal to 60 years of age, against herpes zoster, including those who previously have had shingles. It is still unclear whether childhood varicella vaccination will result in increase in herpes zoster incidence (reduced varicella among children may deprive seropositive adults of exogenous boosting from contact with infected children) and whether adult zoster vaccination will produce long-standing immunity for the recipients.

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