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Prevention of Postherpetic Neuralgia in Patients with Herpes Zoster Infection

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## PERMISSION

Title Prevention of Postherpetic Neuralgia in patients with Herpes Zoster infection

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### Abstract

Herpes Zoster is a viral illness caused by reactivation of the varicella-zoster virus within the human body resulting in the subsequent infection. Herpes Zoster is characterized by a painful vesicular rash which follows the dermatomal distribution pattern due to the viral activation of the underlying nerves. One of the most common and debilitating complications of Herpes Zoster is postherpetic neuralgia. Postherpetic neuralgia is defined as pain that persists following cessation of the rash for greater than 90 days. This literature review will focus on ways the acute phase of Herpes Zoster can be managed in order to reduce the incidence of postherpetic neuralgia.

The literature review of the above topic was based upon the successful completion of an objective structured clinical examination. Included in this report is the written case study from that examination which is based on a 70-year-old female patient who is diagnosed with Herpes Zoster. A research of the related literature was conducted using the PubMed and Cochrane databases with the keywords for the search used being ‘postherpetic neuralgia prevention’. Restrictions for publication date were limited to 2011-2020 with a focus placed on the evaluation in the elderly population. The literature analyzed found many common treatment modalities have been shown to have no effect on postherpetic neuralgia reduction, and more studies are needed in order to further analyze more invasive pain management techniques as well as timing of pain management initiation.

### Prevention of Post-Herpetic Neuralgia in Patients with Herpes Zoster Infection

Herpes Zoster is a viral illness commonly referred to as shingles. It results from varicella-zoster virus, the same virus that causes chickenpox, that becomes reactivated from its latent form in the human body resulting in the subsequent infection. There are approximately 1 million cases of Herpes Zoster that occur annually with roughly 30% of Americans being affected over their lifetime (Saguil, Kane, & Mercado, 2017). One of the biggest risk factors for contracting Herpes Zoster is age. As age increases, the body's T lymphocyte-specific immunity to the varicella-zoster virus decreases, leaving unvaccinated elderly patients at the greatest risk as well as immunocompromised patients (Saguil, Kane, & Mercado, 2017). The reduction of immunity allows the virus to multiply in the ganglia which leads to the retrograde transport along the nerves which then produces the pain and dermatologic presentation of herpes zoster (Makharita, 2017). Clinical presentation for herpes zoster includes a vesicular rash with hypersensitivity and pain often preceding eruption of the rash (Kennedy-Malone, Martin-Plank, & Duffy, 2019). Patients may also experience secondary symptoms including generalized malaise, anxiety, headache, fever, and other symptoms. Diagnosis is most often made by physical presentation and exam alone, but polymerase chain reaction (PCR) can be used in complex or abnormally presenting cases (Kennedy-Malone et al., 2019). Treatment includes pain control as well as antiviral therapy to slow replication of the virus, stop the formation of new lesions, and prevent ocular complications (Le & Rotheberg, 2020). Antiviral therapy is most effective if started in the first 72 hours of rash eruption and there is a relationship between acute pain being diminished at a faster rate if antiviral therapy is started within that time frame (Chen et al., 2014). The main form of prevention against individuals contracting Herpes Zoster is vaccination. The newest and most effective vaccination for prevention of Herpes Zoster is known as Shingrex and has been

found to reduce cases by 97% (Le & Rotheberg, 2020). It is approved for adults 50 years of age and older and is a 2-dose vaccination with the second administration given 2-6 months following the first dose (Le & Rotheberg, 2020).

One of the most common and debilitating complications of Herpes zoster is post-herpetic neuralgia. Postherpetic neuralgia occurs in roughly 20% of patients with Herpes zoster and 80% of postherpetic neuralgia cases occur in patients 50 years of age and older. Postherpetic neuralgia is defined as pain that follows the dermatomal distribution and is present for at least 90 days following cessation of the rash (Saugil et al., 2017). As the virus replicates within the nerve during a Herpes Zoster outbreak, this often causes an inflammatory response and subsequent damage to the nerve therefore causing the pain and negative effects of postherpetic neuralgia (Saugil et al., 2017). The pain caused by postherpetic neuralgia is often described as sharp, burning, and debilitating by patients and for many the pain is non-refractory to treatment and has the potential to persist for years (Nakamura et al., 2017). Current treatment options for patients suffering from postherpetic neuralgia include acetaminophen, NSAIDS, topical capsaicin or lidocaine, or weak opioids for mild pain and stronger opioids, gabapentin, amitriptyline, or anticonvulsants for moderate-severe pain (Le & Rotheberg, 2020). As expected, postherpetic neuralgia has negative effects on quality of life for patients as well as being costly. A study based in Japan was able to conclude that Herpes Zoster has a substantial financial burden on the healthcare system as a result of high costs related directly to clinic visits, prescriptions and OTC medications, and hospitalizations. It was also found that both societal and healthcare payer costs were substantially higher in those individuals who suffered from postherpetic neuralgia (Nakamura, 2017). Postherpetic neuralgia has negative effects on patient's physically, socially, functionally, and

psychologically, making preventing this complication something that should be made a priority for all patients.

The purpose of this report is to gain insight into both prevention and management of one of the most common complications of Herpes Zoster, post-herpetic neuralgia. Included in this paper is a case report of a 70-year-old female who was diagnosed with Herpes Zoster. While this was the initial evaluation of the patient and post-herpetic neuralgia was not identified, she is at higher risk of this occurring due to her age as well as immunocompromised status with a history of rheumatoid arthritis. This is also discussed as a need for follow-up and education was provided in order to further assess for complications including postherpetic neuralgia and emergencies such as herpes ophthalmicus as well as to evaluate at that time for cessation of the rash and adequate pain management.

### **Case Report**

A 70-year old female presented to the clinic with a chief complaint of right-sided low back pain for 2 days. She denied any trauma to the area or change in activity level that brought on the pain. She rated the pain 6/10 which was aggravated by movement and touch and relieved with ice to the area. She described the pain as sharp and burning and non-radiating in nature. She denied any numbness or tingling as well. Upon presentation to the clinic, she was afebrile with a mildly elevated blood pressure at 154/90. All other vital signs were stable. Her past medical history includes hypertension and rheumatoid arthritis. She takes 20mg Lisinopril daily as well as prednisone PRN, which she reported to taking daily at this time. She has also been taking PRN Tylenol for her back pain and this has been ineffective. No other relevant family, surgical, or social history was reported. She reported no history of previous back pain episodes similar to

this one, no numbness or tingling down the affected leg, she denied any bowel or bladder dysfunction, and she denied any genitourinary symptoms including dysuria, suprapubic tenderness, frequency, urgency, CVA tenderness and other concerns. She reports she did receive a flu vaccination this season but denies receiving the Shingrex or Zostavax vaccinations for shingles in the past. All other vaccinations were reported as up to date. Upon examination, her lower right-lumbar region is tender with palpation and this pain does not radiate. There is no bony tenderness along the cervical, thoracic, or lumbar spine. There is no CVA tenderness. Upon examination of the skin, a roughly 7.5cm oblong erythematous lesion with fluid-filled blisters was visualized to the right lower back. No other lesions visualized as the lesion did not cross the midline along with following a pattern along the T12/L1 dermatome. Patient reports she was unaware of a rash or blisters to that region and is not sure how long it has been there. The remainder of the exam was unremarkable.

Diagnosis of Herpes Zoster was discussed with the patient based on the findings from the physical assessment. Different treatment modalities and antiviral therapy were presented as well, and it was agreed upon to treat with valacyclovir 1000mg PO Q8h for 7 days as opposed to acyclovir which requires dosing 5 times a day for 7 days (Le & Rotheberg, 2020). The patient was also advised to trial topical therapy modalities including lidocaine 5% patches for the pain and to continue with ice as this was effective as well as Tylenol PRN. The patient was advised that she will be contagious as long as the blisters are present, and she will stop being contagious once they have crusted over. She was advised to keep area covered during the contagious period and avoid having others come in direct contact with the affected area and specifically the vesicular fluid. Things such as dressings and clothing that may come into contact with the fluid should be handled with caution. Education was provided on monitoring area for any spreading



and potential serious complications including any lesions that present to the face especially near the eyes requiring immediate medical attention. If this were to occur, she was advised to seek immediate care at the nearest emergency room. Follow-up was scheduled in one weeks' time for reassessment of pain control, potential for postherpetic neuralgia, and to ensure improvement of rash with no new eruptions. The patient verbalized understanding of the above recommendations. Her mildly elevated blood pressure was not addressed and at this point attributed to her 6/10 pain and would be reevaluated at her next visit as well.

### **Literature Review**

This literature review is focused on the effectiveness of pain management strategies and different modalities to prevent the complication of post-herpetic neuralgia in patients following Herpes Zoster infection. There are currently a wide range of agents, both non-invasive and invasive, used for the treatment of postherpetic neuralgia as well as the acute pain present with Herpes Zoster infection. The question brought about by this literature review and the studies mentioned is are any modalities or combination of treatment options that are more effective in reducing the incidence of postherpetic neuralgia?

### **Pain Management Techniques**

**Corticosteroids.** Corticosteroids are effective in a wide range of conditions for assistance with reduction of inflammation and subsequent relief of pain. The hypothesis regarding this medication is that its use in the acute phase of Herpes Zoster infection can help in reducing the inflammation and subsequent nerve damage that leads to postherpetic neuralgia. According to the American Family Physician, both prednisolone and prednisone are effective adjunctive therapy for Herpes Zoster and are associated with a reduction in healing time of lesions as well

as reduction in pain, but have no effect on the prevention of postherpetic neuralgia (Saugil et al., 2017). This is further supported by the 2013 Cochrane Review based on a moderate quality of evidence (Han et al., 2013) as well as a 2019 review showing no benefit in postherpetic neuralgia prevention (Kowalsky & Wolfson, 2019b). While corticosteroids may be an effective choice for some patients during the acute phase of Herpes Zoster, their use has not been shown to decrease the incidence of postherpetic neuralgia.

**Invasive therapies.** Invasive pain management techniques encompass both intracutaneous injections and subcutaneous injections with an analgesic agent as well as a steroid. These therapies are utilized for severe pain during the acute phase of Herpes Zoster infections as well as for pain that does not respond to typical treatment modalities for patients already suffering from postherpetic neuralgia. A 2017 randomized clinical trial looked at the efficacy of subcutaneous injections of triamcinolone and lidocaine and found a statistically significant reduction in neuropathic pain at both 3 and 6 months after rash eruption when compared to the control group (Ni et al., 2017). An additional study looked at single cutaneous injections of ropivacaine and methylprednisone within 14 days of rash eruption in addition to the antiviral therapy of acyclovir and pregabalin as well as PRN Tylenol for breakthrough pain. This treatment protocol led to statistically significant lowered pain intensity and duration, and decreased time to rash clearance as opposed to the control group. The researchers however were unable to formally conclude that the incidence of postherpetic neuralgia was decreased, only suggesting that this may occur and that more studies are needed (Cui et al., 2018). While these single studies do show promise in invasive pain management techniques in preventing postherpetic neuralgia, more studies are needed to determine their true effectiveness. Cost-

effectiveness as well as potential for increased complications and must be considered with the above strategies as well as more invasive ones.

**Anticonvulsants.** Gabapentin is the most commonly used anticonvulsant as a treatment for the neuropathic pain in Herpes Zoster. Gabapentin is also frequently used to treat chronic neuropathic pain in adults with a wide array of conditions including diabetic neuropathy and fibromyalgia. It is also used as an anticonvulsant for a variety of seizure disorders and neurological disorders. Researchers hypothesized that the prevention of central sensitization and antihypersensitivity actions in dorsal horn neurons during the acute phase of Herpes Zoster may help to prevent postherpetic neuralgia (Rullan et al., 2017). The results however are not consistent with this hypothesis with majority showing no effectiveness in the prevention of postherpetic neuralgia at a wide variety of doses and titrating strategies (Bulilete et al., 2019). While this medication has been shown to be effective in pain reduction and is a well-established option (Rullan et al., 2017), current evidence shows that the addition of gabapentin as a treatment modality for the acute pain of Herpes Zoster has not been shown to reduce the incidence or prevent postherpetic neuralgia.

### **Timing of Pain Management Initiation**

Pain management is an important aspect of Herpes Zoster treatment. While antiviral therapy initiation has been regarded as a time-sensitive component with increased effectiveness noted when administered within the first 72 hours of rash eruption (Kennedy-Malone, Martin-Plank, & Duffy, 2019), there are currently no guidelines regarding initiation of pain management. Pain is a completely subjective experience for the patient and varies with each case and situation. Recent studies have been able to show a correlation between timing of pain

management initiation and incidence of postherpetic neuralgia. A study by Xing, Sun, & Yan (2020) was able to show that in elderly patients with moderate-severe Herpes-associated pain, when pain management strategies were initiated and controlled within the first 2 weeks of rash onset that postherpetic neuralgia incidence was decreased. The researchers hypothesized that by providing adequate pain control in the acute period, central hyperexcitability would be reduced in the initiation period and allow normal central processing to not be damaged by subsequent factors (Xing et al., 2020). A 2017 meta-analysis looking at 9 different RCTs and the timing of pain management supplementation was able to support this finding showing a statistically significant decrease in the incidence of postherpetic neuralgia with early pain management (Xing, Zhou, Zhang, & Yan, 2017). Even with these findings, more quality studies are needed to further support this conclusion and allow it to be applied to practice.

### **Antiviral Therapy**

Antiviral therapy is an important component of Herpes Zoster treatment, especially in those high-risk populations such as the elderly or those who are immunocompromised. It has been shown that antiviral therapy such as acyclovir, famciclovir, and valacyclovir when started within the first 72 hour of rash eruption are effective in reducing the acute pain associated with Herpes Zoster (Kennedy-Malone, Martin-Plank, & Duffy, 2019). It is hypothesized by researchers that reducing the viral load and viral replication during the acute phase of Herpes Zoster would reduce the incidence and prevent postherpetic neuralgia due to the reduced damage caused by the virus to the underlying nerves. According to the 2014 Cochrane Review, researchers were able to conclude based on high quality of evidence that oral acyclovir did not significantly prevent postherpetic neuralgia and more research is needed on the effectiveness of

postherpetic neuralgia prevention with both famciclovir and valacyclovir (Chen et al., 2014). This was further supported by the 2019 review again showing no benefit in preventing postherpetic neuralgia with the use of any form of antiviral therapy (Kowalsky, Wolfson, & Zehtabchi, 2019a).

### **Vaccinations**

There are currently two vaccinations available for the prevention of Herpes Zoster; the live attenuated vaccine Zostavax and recombinant vaccine Shingrex (CDC, 2018). Zostavax was first offered in 2006 and Shingrex was first offered in 2017. Shingrex is offered as a 2-vaccine series and has become the preferred vaccine choice since becoming available to the public due to its increased effectiveness (CDC, 2018). Even if an individual has been previously vaccinated with Zostavax, the Shingrex series is recommended. Shingrex has been found to be 97% effective in preventing Herpes Zoster and 91% effective in preventing postherpetic neuralgia in adults 50-69 years of age and 91% effective in preventing Herpes Zoster and 89% effective in preventing postherpetic neuralgia adults 70 years of age and older (CDC, 2018). A 2011 Cochrane review found that there was insufficient evidence to show a direct correlation between vaccination (Zostavax) and postherpetic neuralgia reduction beyond its effect in the reduction of Herpes Zoster (Chen et al., 2011). Even with the Cochrane Review showing no direct correlation with Zostavax vaccination and postherpetic neuralgia reduction, data from the CDC supports the claim that Shingrex vaccination does aid in postherpetic neuralgia prevention. There is currently no updated Cochrane review assessing the potential for postherpetic neuralgia incidence reduction with the Shingrex vaccination, but data from the CDC does support this correlation.

### Learning Points

- Herpes zoster and the complication of postherpetic neuralgia can have debilitating effects on patients' physically, socially, and psychologically as well as being costly for the healthcare system and patient.
- Corticosteroid use, antiviral therapy, and gabapentin use during the acute phase of Herpes Zoster outbreak was found to be ineffective in reducing postherpetic neuralgia incidence.
- The most effective and reliable way to prevent postherpetic neuralgia is to prevent Herpes Zoster by vaccination with the 2-dose vaccination series of Shingrex.
- Invasive pain management techniques and the timing of pain management initiation both show promise in postherpetic neuralgia prevention, but more studies are needed in order to confirm or deny efficacy.

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