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EVIDENCE-BASED REVIEW

Update of Evidence-Based Interventional Pain Medicine According to Clinical Diagnoses

8. Herpes zoster and post herpetic neuralgia

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Abstract

Introduction: Patients suffering from postherpetic neuralgia (PHN) report unilateral chronic pain in one or more dermatomes after an acute herpes zoster (HZ) infection. The incidence of acute HZ ranges between three and five patients per 1000 person-years. In one out of four patients, acute HZ-related pain will transition into PHN. PHN can be very disabling for patients and reduce quality of life. Additionally, the treatment of PHN is characterized by high failure rates. The aim of this review is to give an update on the previous practical guideline published in 2011 and revised in 2015 (published in 2019) and to provide an overview of current interventional treatment options for HZ infection and PHN.

Methods: The literature on the diagnosis and treatment of HZ and PHN was systematically reviewed and summarized.

Results: The most important treatment for acute HZ-related pain is antiviral therapy within 72 h of symptom onset. Additional symptomatic treatment options are analgesic drugs according to the WHO pain ladder, tricyclic antidepressants (eg, nortriptyline), and antiepileptic drugs (eg, gabapentin). If pain is not sufficiently reduced, interventional treatment such as an epidural injection with local anesthetics and corticosteroids or pulsed radiofrequency of the dorsal root ganglion (DRG) are options. Treatment for PHN is preferably transdermal capsaicin, lidocaine, or oral drugs such as antidepressants or antiepileptics.

Conclusions: Treatment of acute HZ-related pain especially PHN is challenging. Besides the conventional treatment for PHN, interventional management is considered a new treatment option. PRF of DRG seems to be the most promising interventional management.

KEYWORDS
evidence-based medicine, herpes zoster, neuropathic pain, postherpetic neuralgia

INTRODUCTION

Herpes zoster (HZ) or "shingles," a reactivation of human varicella-zoster virus (VZV) ("chickenpox"), induces inflammation of the dorsal root ganglion (DRG) and corresponding nerves, causing a rash and unilateral pain following a dermatomal distribution.[1] Approximately 25% of individuals are affected by HZ at some point in their life.[2]

Three phases during an HZ reactivation are defined: acute HZ-related pain, subacute HZ-related pain, and postherpetic neuralgia (PHN). Acute HZ-related pain lasts for a maximum of 30 days. Subacute herpetic neuralgia is defined as pain that endures after the healing of the vesicles but disappears within 3 months after onset. There is still no consensus on the definition of PHN, but it is typically defined as pain that continues after 3 months of disease onset.[3] Figure 1 displays the

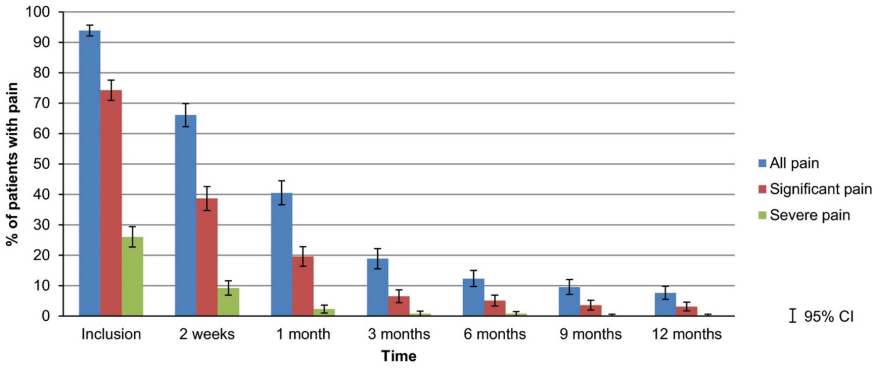

FIGURE 1 Percentage of patients with pain since the onset of herpes zoster. Clinically significant pain is defined as a VAS pain score > 30. Severe pain is defined as VAS pain score > 70.[4]

percentage of patients with any pain, significant pain, and severe pain at various time points after the onset of HZ. At 3 months, 18.8% of patients continue to have pain and at 12 months, this percentage drops to 7.6%.[4] In the literature, the prevalence of PHN varies from 5% to 30% depending on the study population and the definition of PHN used.

Acute HZ-related pain often begins with prodromal pain, starting a few days before the appearance of the rash.[5] The incidence of HZ ranges between three and five patients per 1000 person-years.[6] HZ tends to resolve spontaneously with time in most patients and leads to PHN in approximately 5%–30% of patients.[6]

Risk factors for developing PHN include older age, female sex, immunosuppression, prodromal pain, suffering from a severe rash, and greater acute pain severity.[7]

HZ-induced neuritis can have different clinical manifestations resulting in a mosaic of somatosensory symptoms.[8] Pain may be described as burning, deep, aching pain, tingling, itching, and stabbing. It is often associated with tactile and cold allodynia. It can be debilitating, having an impact on both physical and emotional functioning, and causing a decrease in quality of life (QoL).[4] It often leads to fatigue, insomnia, depression, anorexia, anxiety, and emotional distress. It is therefore important to explore methods for prevention of the development of PHN and to optimize pain treatment for both (sub)acute HZ-related pain and PHN.

The aim of this literature review is to give an update on the previous practical guideline published in 2011 and revised in 2015 (published in 2019) and to provide an overview of current interventional treatment options for HZ infection and PHN.[9,10]

Pathophysiology

Herpes Zoster

Reactivation of the VZV, usually acquired during childhood ("chicken pox"), occurs when the specific immunity to the virus decreases due to age or immune deficiency. The virus disperses from the DRG via the axon to the epidermis where it causes the characteristic unilateral rash of HZ in one, or sometimes several, dermatomes. The pain from acute HZ-related pain is primarily the result of inflammation of sensory nerves. The epidermal vesicles contain the virus, may be painful, and are infectious to people who have not (yet) built up a natural defense, often young children.

Postherpetic neuralgia

The current hypothesis is that the pathophysiology consists of two processes: sensitization (peripheral and central) and nerve damage. Abnormal sensitization occurs when peripheral nerves get damaged. Inflammatory mediators reduce the stimulus threshold of nociceptors and increase the responsiveness of nociceptors to stimulation. This results in pathological spontaneous discharges, lower thresholds for thermal and mechanical stimuli, and hyperalgesia.[11] Central sensitization is a result of peripheral nociceptor hyperactivity leading to plastic changes in the central nervous system that involve both amplification of pain signals and reduced inhibition.[11]

Nerve damage in PHN patients is the result of neuronal death due to severe inflammatory stimuli, or secondary to neuronal swelling accompanying the inflammation. This can compress the sensory ganglion in the intervertebral foramen, resulting in ischemia and nerve tissue damage.[12]

Motor defects occur in at least 0.5% of patients with HZ, observed as abdominal pseudo-hernias or motor weakness of limbs limited to the affected myotome.[13] This is thought to be caused by direct viral spread from the DRG to anterior horn cells or adjacent motor nerve roots.

Phenotypes: Several distinct phenotypes have been described for PHN, which contains treatment implications. Phenotyping may be based on several factors including physical exam findings (eg, allodynia), thermal

sensitivity (ie, through psychophysical testing), skin biopsy, and cutaneous reaction to histamine. There are several ways to classify phenotypes, one of which categorizes patients into 3 subtypes: sensory loss (the most common), thermal gain, and thermal loss with mechanical gain.[14]

In terms of mechanistic categorization, the "irritable nociceptor" phenotype is characterized by preserved sensation, profound dynamic mechanical allodynia with reduced pressure pain threshold, and relief of pain with local anesthetic infiltration. This phenotype is believed to be due to the upregulation of sodium channels and has been shown to be responsive to topical capsaicin and lidocaine, and sodium channel blockers such as oxcarbazepine.

A deafferentation phenotype may arise from the destruction of neurons by the virus in the DRG. This phenotype is characterized by sensory loss (including thermal and vibratory perception) without prominent thermal allodynia. However, mechanical allodynia can occur secondary to A-beta fibers activating spinothalamic pathways, known as phenotypic switches, along with pressure hyperalgesia and temporal summation, suggesting central sensitization. In one study, this phenotype was present in 10.8% of individuals. In individuals with deafferentation pain, in addition to gabapentinoids and antidepressants, neuromodulatory therapies such as repetitive transcranial magnetic stimulation may provide benefit.[15]

METHODOLOGY

The previous guideline titled "Evidence-based interventional pain medicine according to clinical diagnosis. 17. Herpes zoster and post-herpetic neuralgia" was published in 2011 and provided an overview of treatment options for acute HZ-related pain and PHN.[10] In 2015, an independent company, Kleijnen Systematic Reviews, performed a systematic review of the literature for the period 2009–2015 based on existing systematic reviews (SRs) and randomized controlled trials (RCTs).[9] For the current article, an extra search was conducted to add the period 2015–2022. This search was performed on August 10th, 2022 using the search strategy described below. In addition, on March 13th, 2024 an extra search was performed to update the section about pulsed radiofrequency (PRF) and spinal cord stimulation (SCS).

Search strategy

This review was performed to conform with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[16] For the current article an updated search was conducted for the period 2015–2022, using "herpes zoster" and "pain" associated with individual interventional pain management techniques such as "epidural" or "paravertebral" or "sympathetic block"; "radiofrequency" or "pulsed radiofrequency"; "spinal cord stimulation." Additionally, authors could select relevant missing articles from reference searches. The databases searched were PubMed and Embase. After removing duplicates, screening of the titles and abstracts was performed by one author (LA), followed by full-text screening of the selected studies by LA and JJ. Reviews and meta-analyses were excluded during full-text screening but used for cross-referencing.

Inclusion criteria were original research articles reporting on (1) treatment of acute HZ-related pain; (2) treatment of PHN; and (3) articles written in English.

The exclusion criteria were (1) conference abstracts, letters, notes, case reports, case series, reviews, and meta-analyses; (2) animal studies; and (3) vaccination studies for HZ.

Outcome measures

Outcomes of interest were measurements for pain, including scores assessed by a VAS pain score and Numeric Rating Scale (NRS) pain score, QoL, and functionality. For studies involving acute HZ-related pain, the incidence of PHN was noted when available.

Data extraction and quality assessment

Data was extracted independently by two reviewers (LA and JJ) using a standardized data extraction form. The risk of bias for selection, intervention, outcome, missing, and analysis was assessed by two independent reviewers (LA and JJ) based on the RoB-2[17] for randomized trials and ROBINS[18] for nonrandomized studies. A third person (MR) was consulted to resolve differences when there was no consensus. In Appendix A, the results of the risk of bias and data extraction are displayed. The overall risk of bias was considered low when all domains were judged as having low risk of bias. When at least one domain is scored as "high," the overall risk of bias was scored as high. When at least one domain is of moderate quality and no domain is of high risk, the overall risk of bias is considered to be moderate. The decision to include an article in this review was based on the level of evidence for the intervention. Initially, articles with a low risk of bias, often RCTs, were included. If an RCT was not available to evaluate an intervention, then articles with a lower level of evidence (eg, retrospective and observational studies) were used.

Research performed without a control group was considered to be at high risk of bias because HZ and to a lesser extent PHN, follow a natural healing course. If

the study was unblinded but still rated at least moderate quality, it is described in the results.

RESULTS

Literature screening

Figure 2 shows the flowchart of the screening and inclusion process. After screening 1271 titles and abstracts, 49 articles were included after full-text screening. Ten articles were retrospective studies, and 39 articles were prospective studies. Among prospective studies, 30 articles were RCTs.

Diagnosis

Physical examination

HZ is a clinical diagnosis based on observation of the typical rash with redness, papules, and vesicles in the painful dermatome(s). Healing vesicles may show crust formation. The rash is generally unilateral and does not cross the midline of the body.[19] In PHN patients, scarring, hyper-, and/or hypopigmentation are often visible. Allodynia is present in 45%–75% of affected patients. As described above, pseudo-hernia or motor weakness in a limb can be a motor complication occasionally detected during physical examination.

Quantitative sensory testing

In patients with PHN a mosaic of somatosensory alterations can be observed. These vary between individual patients and are an expression of underlying pathophysiological processes. Sensory alterations can manifest as hyperalgesia, allodynia, and sensory loss, which can be quantified by quantitative sensory testing (QST).[20] QST assesses somatosensory functions, such as thermal detection thresholds for the perception of cold, warmth, and paradoxical heat sensations, thermal pain thresholds for cold and hot stimuli, mechanical detection thresholds for touch and vibration, mechanical pain sensitivity, and tolerance to painful stimuli. It can provide clues regarding the underlying mechanism of pain (eg, impaired conditioned pain modulation and temporal summation suggest central sensitization) about the type of nerve damage (eg, in A-beta, A-delta, or C-fibers), and surviving afferent nerve fibers.[21] As noted above, characterizing the somatosensory phenotype of PHN is important for determining personalized treatment regimens.[22]

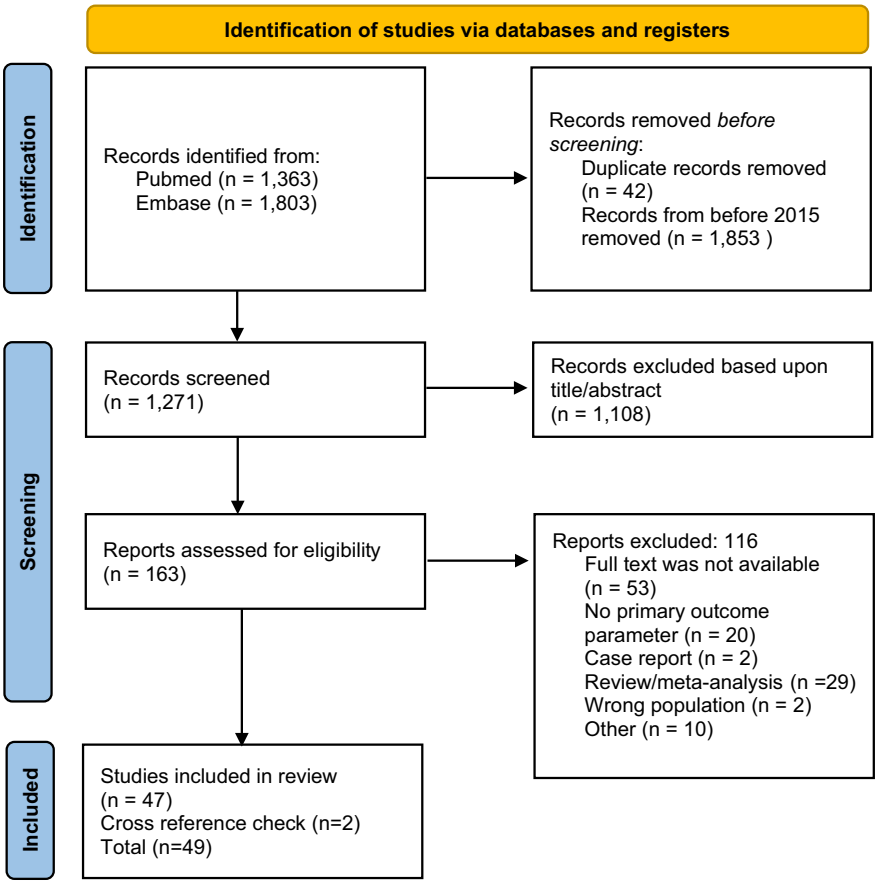

FIGURE 2 Flowchart of the literature search. Inclusion process was done according to PRISMA 2020.[16]

Prevention of acute HZ

The risk of HZ increases with the reduction in immunity. Vaccination can boost immunity for the VZV. Studies evaluating Shingrix, an HZ vaccine, showed that it was 97% effective in preventing HZ in patients 50–69 years old with healthy immune systems. In patients older than 70 years it was 89% effective.[23] The efficacy of Shingrix in preventing PHN development was 89%–91% in patients with healthy immune systems and 68%–91% in patients with weakened immune systems, depending on the underlying condition.[23] If a patient has had HZ in the past, Shingrix has been shown to prevent future occurrences of shingles.[23] Thus, vaccination is a promising prevention method for both HZ and PHN.

Treatment options

The objectives of treating pain from acute HZ are (1) reducing the severity and duration of pain; (2) accelerating the recovery of epidermal defects and preventing secondary infections; and (3) preventing or reducing the disease burden of PHN. The objectives of the treatment of PHN are pain alleviation and improvement in QoL.

Currently, different types of analgesic drugs, integrative therapies including psychotherapy, and procedural interventions are available. Systemic analgesic drugs include NSAIDs, opioids, anti-depressants, antiepileptics, and N-methyl-D-aspartate (NMDA) antagonists. Topical agents include capsaicin cream, lidocaine cream, and locally injected anesthetics. Additionally, there are multiple interventional treatment options such as epidural injections, PRF, nerve blocks, and SCS. At present, there is no consensus regarding the most effective treatment for PHN.

Conservative management

Pharmacological treatments

Antiviral drugs, such as acyclovir, famcyclovir, or valacyclovir, should be started within 72 h after the onset of clinical signs.[24] There is no evidence for any effectiveness after 72 h in patients who have uncomplicated HZ. In immunocompetent patients, the dosages of famciclovir and valacyclovir are 500 and 1000 mg, taken three times per day for 7 days. In immunocompromised patients, the dosage of famciclovir is 1000 mg three times per day for 10 days, while acyclovir should be given intravenously.[24] Antiviral medication accelerates the disappearance of the vesicles or crusts and healing of skin lesions and prevents new lesion formation.[25] By inhibiting viral replication, antiviral therapy is likely to reduce nerve damage, resulting in a reduced incidence of PHN. Therefore, it should be started as soon as possible.[25]

Corticosteroids in addition to antiviral medication may reduce the severity of acute zoster-related pain.[25] However, increased healing of skin lesions was not observed in one study.[12] A Cochrane review evaluated the effect of oral corticosteroids on the prevention of PHN and found they are ineffective.[26]

Opioid analgesic treatment alongside antiviral medication is a common strategy for controlling acute HZ-related pain. As reported in a previous narrative review, the use of opioids provides significant alleviation of acute HZ-related pain.[10] For acute HZ-related pain, tramadol has a number needed to treat (NNT) for 50% pain reduction of 4.7 (3.6–6.7) and strong opioids have an NNT of 4.3 (3.4–5.8).[27] Long-term use of opioids has serious side effects, such as opioid dependency and substance use disorder, and is not routinely recommended.

Methadone, an NMDA receptor antagonist, is used in acute and chronic pain management.[28] However, no RCT has been performed to determine the efficacy of methadone in acute HZ-related pain or in PHN patients. As an NMDA receptor antagonist that also inhibits the uptake of serotonin and norepinephrine, methadone can modulate pain stimuli resulting in decreased development of hyperalgesia and opioid tolerance. Despite the auspicious effects of methadone, similar to other opioids its side effects include constipation, nausea, sedation, respiratory distress, itch, endocrine-related abnormalities, and QT interval prolongation that can trigger torsade de pointes.[28,29]

Antidepressants are a first-line therapy for PHN. Both tricyclic antidepressants such as amitriptyline or nortriptyline, and serotonin and norepinephrine reuptake inhibitors (SNRIs) such as duloxetine or venlafaxine, are used. Tricyclic antidepressants have an NNT of 3. (3.0–4.4) for 50% pain reduction and SNRIs have an NNT of 6.4 (5.2–8.4) based on several controlled trials.[27]

Antiepileptics play a significant role in the treatment of acute HZ-related pain and PHN. The most common used antiepileptics are gabapentin and pregabalin. Two trials measured the effect of gabapentin on PHN and concluded that it was effective compared to placebo.[30] The pooled NNT for 50% pain reduction was 4.4 (3.3–6.1). In addition, the authors also pooled data from two trials on pregabalin versus placebo, reporting a pooled NNT for a 50% pain reduction of 4.9 (3.7–7.6).[30]

Since the previous review, one study has been published supporting the addition of prednisone to the standard of care (antiviral drugs and carbamazepine) for acute HZ-related pain. In contrast with previous studies and reviews,[26,31] the authors of this low-quality, non-randomized study found faster pain relief and earlier lesion healing compared to standard treatment.[32]

Summary

Pharmacological treatment is a well-established treatment for (sub)acute HZ-related pain and PHN. New,

high-quality evidence has been lacking since the last update of the guideline was published.

Local treatments

Topical agents for pain management have few systemic side effects, making them an attractive option in an elderly population with multiple comorbidities. Topical agents frequently used in clinical practice for the treatment of PHN are lidocaine and capsaicin cream and patches. Literature published before the previous version of the guideline showed the efficacy of capsaicin (8%) patch and lidocaine 5% plaster. Patients who received an 8% capsaicin patch experienced significant pain reduction during weeks two to eight after application compared to patients who received a control patch.[33,34] The 51.7% of the patients who received a 5% lidocaine medicated plaster achieved at least moderate pain relief after 8 weeks of treatment.[35] In the previous version of this guideline (2011 and 2015) a Cochrane review was cited showing inadequate evidence to recommend topical lidocaine as a first-line treatment for PHN. This review has been withdrawn and new evidence has emerged supporting topical lidocaine use.

Acute HZ

Intracutaneous injections are used as therapy for acute HZ-related pain.[36] The effect of a single intra-cutaneous injection with methylprednisolone combined with ropivacaine versus an injection with saline only in the affected dermatome showed a significant difference in VAS pain score 1 week (2.6 ± 2.3 vs. 4.0 ± 2.7) and 4 weeks (1.0 ± 1.9 vs. 2.1 ± 2.2) post-intervention favoring the intervention group. The treatment effect disappeared at the 12-week follow-up. Twelve weeks post-intervention the incidence of PHN in the intervention group was 10.2% versus 29.2% in the control group ($p = 0.019$). At 24 weeks post-intervention, this difference was no longer statistically significant (6.1% vs. 18.8%, $p = 0.059$). However, it could be clinically relevant.

The effect of repetitive intracutaneous injections with ropivacaine and methylprednisolone every 48 hours for 1 week was investigated in an RCT comparing antiviral therapy plus analgesics to antiviral therapy, analgesics, and repeat injections.[37] The intervention group reported a significantly shorter duration of pain (25.7 ± 37.2 vs. 58.2 ± 66.5 days, $p = 0.005$) compared to standard of care. The VAS pain scores were significantly lower in the intervention group at all post-procedure time points (1, 2, 4, 12, and 24 weeks). The incidence of PHN 3 months after the intervention was 6.4% in the intervention group compared to 28.3% in the control group ($p = 0.005$). After 6 months, the incidence continued to be lower in the intervention group (4.3% vs. 17.4%, $p = 0.022$). A complication of repetitive intracutaneous methylprednisolone is subcutaneous fat atrophy which was not reported in this study.[38]

PHN

In a meta-analysis, the efficacy and safety of topical drugs (lidocaine, low- and high-dose capsaicin, aspirin/diethyl ether, indomethacin, and diclofenac) for PHN were investigated. This analysis found topical lidocaine had the highest possibility of being effective for PHN.[39] Two studies published after this meta-analysis confirm the efficacy of lidocaine patches for PHN. One was a large matched-control registry study comparing the effectiveness of a lidocaine 700 mg patch to first-line oral systemic medications (eg, opioids, antiepileptics, or antidepressants) in 3422 patients with PHN. It demonstrated a decrease in pain intensity in both groups, but the VAS pain score was significantly lower in the group that used the lidocaine patch at weeks 4, 12, and 24 after treatment compared to those who received oral analgesics.[40]

The efficacy of a transdermal oxycodone patch as the treatment for PHN was explored in a double-blind RCT. The oxycodone patch did not significantly reduce pain compared to the control patch.[41]

In a systematic review on the efficacy of the capsaicin 8% patch, that included 6 trials, 5 of which were available for meta-analysis ($n = 1449$), the capsaicin 8% patch reduced pain significantly more than the placebo, though the effect size was very small (mean difference NRS pain scores −8.57, 95% CI −11.98, −5.16).[42] Tan et al. performed an RCT comparing conventional therapies including analgesics, physical therapy, and paravertebral blocks to conventional therapies plus a daily lidocaine infusion for 5 days in 60 patients with subacute PHN.[43] In addition to standard medical management, the control group also received a placebo infusion of saline. Through 5-day follow-up, the NRS pain scores and the requirement for breakthrough pain medications were significantly lower in the group that received lidocaine. No long-term follow-ups were conducted.

Summary

Different local treatments are available for clinical use, with antidepressants and gabapentinoids considered first-line therapies, antivirals being effective when administered within 72 h, and opioids being efficacious but associated with a greater risk of harm. Local, non-systemic treatment has the major advantage of fewer systemic side effects in a population at high risk for side effects. There are no new studies reporting on the efficacy of capsaicin 8% for PHN, but capsaicin 8% is widely used in clinical practice, being approved in several countries for this condition. A lidocaine patch can reduce pain intensity in patients suffering from PHN and may be more beneficial in individuals with allodynia.[44] Intracutaneous injections are helpful for short time periods in HZ while repetitive injections

with local anesthetic and steroid may reduce VAS pain scores for up to 6 months, but can cause subcutaneous fat atrophy.

Interventional management

Epidural and paravertebral injection (eg, of local anesthetics and/or glucocorticoids)

In the previous guideline, epidural injection with corticosteroids and local anesthetic as an add-on therapy was found to be superior to standard care alone (oral antiviral and analgesic medications) for up to 1 month in the management of acute HZ-related pain.[10] An additional RCT published since the previous guidelines demonstrated no difference between interlaminar and transforaminal epidural steroid injections for up to 3 months after the procedure.[45]

The previous guideline reported high-quality evidence that paravertebral injections of corticosteroids with local anesthetics reduce pain during the active phase of HZ.[10,46,47]

Acute HZ

A trial comparing the efficacy of repetitive paravertebral blocks with ropivacaine versus dexmedetomidine to prevent PHN showed that the incidence of zoster-related pain was significantly lower 1 month after therapy in the patient group receiving paravertebral block with dexmedetomidine.[48] After 3 months, the effect was still significant in favor of dexmedetomidine.

In an RCT performed in 40 patients, no difference was observed in the occurrence of PHN after an epidural steroid injection administered via the interlaminar versus transforaminal approach.[45] In both groups, VAS pain scores were significantly lower at 1- and 3-month follow-up compared to baseline. This could be in line with the natural course of HZ.

Subacute HZ

In a retrospective study, transforaminal epidural injections administered for acute HZ-related pain were associated with a significantly shorter time to pain relief compared to transforaminal epidural injections performed in the subacute phase.[49] An RCT found that a continuous epidural block combined with opioids and gabapentin reduced NRS pain scores more than analgesic drug treatment alone during a 30-day follow-up.[50] However, both of these studies were deemed to be of low quality.

PHN

A small RCT demonstrated a decrease in NRS pain scores 6-month post-treatment initiation for repeat versus single (15 mg vs. 5 mg dexamethasone) epidural steroid injections administered over 24 days.[51] This trial also found an increased likelihood of complete remission during 6-month follow-up in the group receiving repeat epidural dexamethasone. However, this study was of low quality.

Summary

Epidural or paravertebral injection(s) of local anesthetics and/or glucocorticoids could be considered in the treatment of acute HZ-related pain. For the treatment of subacute PHN, there was low-quality evidence supporting epidural injections. For the treatment of PHN, the evidence supporting a continuous epidural infusion was of low quality. None of the included studies for HZ or PHN investigated whether epidural or paravertebral injections result in a decrease in pain compared to standard therapy.

Pulsed radiofrequency

The previous guideline asserted that there was moderate-quality evidence that PRF of the intercostal nerve reduces pain for 6 months in patients suffering from PHN.[10,52] There was also very low-quality evidence that PRF to the DRG reduces pain for 6 months in patients suffering from PHN.[53] Since the publication of the previous guideline, multiple studies have been published assessing the efficacy of PRF.

Acute HZ

An RCT was performed in which 60 patients were treated by high voltage, bipolar PRF of the cervical sympathetic chain or sham treatment.[54] The same treatment was repeated in both groups after 3 days. The VAS pain scores of the PRF group at each postinterventional point (1 day, 2 days, 1 month, 2 months, and 3 months) were significantly lower than the VAS pain scores in the sham group. At 3 months postintervention, the incidence of PHN was 16.7% in the PRF group compared to 40.0% ($p < 0.05$) in the sham group.

Another RCT evaluating high-voltage, long-duration PRF of the Gasserian ganglion was performed in 96 patients with (sub)acute herpes-related trigeminal neuralgia. This study found decreased VAS pain scores at all postinterventional time points (3, 7, 14 days, 1, 3, and 6 months) compared to the sham group.[55]

Subacute HZ

In a randomized, comparative-effectiveness study performed in 120 patients with (sub)acute trigeminal HZ, a single application of high-voltage PRF applied to the Gasserian ganglion was compared to 3 cycles of conventional PRF.[56] The authors found that the mean VAS pain scores at different time points for up to 6 months during follow-up were significantly lower in the high-voltage PRF group. In an RCT comparing PRF to short-term SCS (stSCS), a decrease in pain and improved 36-Item Short Form Health Survey (SF-36) scores were observed in both groups at 6-month follow-up.[57] In an RCT performed in 72 patients, PRF of spinal nerves or peripheral branches of cranial nerves combined with a 5-day infusion of intravenous lidocaine initiated 5 days post-PRF treatment resulted in greater pain reduction, less rescue analgesic usage, and reduced inflammatory cytokines at 2 months compared to PRF combined with saline infusions. The

lidocaine group also experienced a lower incidence of PHN than the saline group.[58] A major limitation in these studies is that they did not account for the high natural recovery rate.

PHN

In patients with PHN involving the thoracolumbar region, Xiong et al. randomized 78 patients to receive PRF of the DRG combined with oral analgesic treatment or oral analgesic treatment (gabapentin) alone.[59] NRS pain scores of both groups decreased significantly over time (at 1, 4, 8, and 12 weeks after treatment). The decrease in NRS pain scores at 12-week follow-up in the group ($n = 39$) who received PRF was significantly greater compared to those who received only oral analgesic treatment (mean 7.5 to 2.8 vs. 7.6 to 4.2).

Makharita et al.[60] conducted an RCT in 50 patients in which PRF of the intercostal nerves was compared to sham PRF, reporting significantly lower VAS pain scores through 12-month follow-up in the treatment group. Significant improvements favoring PRF were also found for QoL and analgesic reduction.

Two retrospective studies evaluating PRF for PHN found high-voltage PRF to be beneficial through at least 12 months after PRF treatment compared to conventional PRF settings.[61,62]

One retrospective study evaluating PRF targeting peripheral facial nerves (supraorbital nerve, infraorbital nerve, and mental nerve) versus PRF of the Gasserian ganglion in patients suffering from trigeminal PHN was performed.[63]

Multiple studies compared PRF as an add-on therapy to other treatment options versus PRF alone, other treatments alone, or compared PRF with other interventional therapies. PRF has been combined with nerve blocks,[64] methylene blue paravertebral nerve block,[65] and dexamethasone injection for trigeminal PHN,[66] with positive results being reported at various time points in these uncontrolled or poorly controlled studies.[65,66] PRF has also been shown to provide comparable effectiveness to botulinum toxin type A,[67] and superiority for some outcome measures against stellate ganglion blocks at 6-month follow-up.[68] Drawing conclusions from these studies is difficult given the lack of control groups, small sample sizes, and a myriad of other methodological shortcomings.

Summary

PRF provides significant pain relief lasting over 3 months in patients with (sub)acute HZ and PHN. Since few studies have compared PRF with sham treatments, it is not possible to calculate an accurate NNT. There are no comparative studies comparing PRF of the intercostal nerves to PRF of the DRG, but both preclinical and clinical studies including one performed for post-thoracotomy neuropathic pain (the most common site for HZ and PHN), demonstrate superiority for the latter.[69–71]

Spinal cord stimulation

The previous guideline found very low-quality evidence that SCS provides prolonged pain reduction in patients with PHN at long-term follow-up (29 months).[72]

Subacute HZ

As described above, in (sub)acute HZ-related pain a 10-day SCS course decreased NRS pain score and improved SF-36 scores for both groups up to 6 months, with significant differences favoring SCS at 30 and 180 days, but not at 90 days.[57]

PHN

An RCT performed in 70 elderly patients with PHN compared high voltage, long duration PRF of the DRG to SCS.[73] At 12-month follow-up, VAS pain scores decreased significantly in both groups but were lower at 3-, 6-, and 12-month post-treatment in the SCS group. In another RCT conducted in 44 PHN patients in which patients were allocated to an 8-day course of SCS or PRF of the DRG, both groups improved, with greater improvement noted in pain scores (mean VAS pain score 2.0, interquartile range (IQR) 1.0–2.3 vs. 4.0, IQR 4.0–4.3) and QoL in the SCS group observed through 6-month follow-up.[74] The lack of a placebo or true control groups in both studies are major limitation.

An RCT performed in 160 PHN patients with a disease duration between 6 months and 1 year compared short-term SCS (7–14 days) with temporary spinal nerve root stimulation, finding improvement in pain scores and QoL in both groups during 3-month follow-up, with no between-group differences noted.[75]

Summary

Since the evidence for the efficacy of SCS in PHN patients is of low quality and SCS is an invasive treatment, more research is needed before recommending SCS as a routine treatment for PHN.

Sympathetic nerve block

In the previous update, low-quality evidence was found that sympathetic (stellate ganglion) nerve blocks reduce the duration of acute HZ-related pain.[46,76] There was also very low-quality evidence that sympathetic nerve blocks provide no meaningful pain relief in patients with PHN.[46] In the previous guideline, a double-blind study was described comparing pain relief and the incidence of PHN in 64 patients with acute HZ who were randomized to stellate ganglion blocks with local anesthetic and corticosteroid or a saline placebo group. All patients received pregabalin and acetaminophen for rescue medication. The authors found lower pain scores, higher satisfaction rates, and a lower incidence of PHN through 6-month follow-up in the intervention group.[76]

Summary

There is low-quality evidence for the use of sympathetic blocks to treat acute HZ-related pain, but there is no evidence for the use of sympathetic blocks to treat PHN.

Intrathecal injection

In the previous guideline update, the intrathecal administration of corticosteroids for PHN was evaluated. An RCT describing four weekly intrathecal injections of methylprednisolone acetate dissolved in lidocaine was stopped early due to futility, with increased pain reported in patients in the intervention group.[77] At the same time, evidence emerged on the toxicity of intrathecal methylprednisolone acetate.[77,78] This RCT in combination with updated safety data provided contradictory evidence to an earlier controversial study suggesting efficacy for intrathecal methylprednisolone acetate.[79]

Summary

Considering the risks of treatment and unclear clinical benefits, the intrathecal administration of methylprednisolone acetate in PHN patients is not recommended.[80]

Other interventional treatments

Multiple other interventions for zoster-related pain have been described. There is a randomized, placebo-controlled study performed in 140 patients with acute cervical HZ showing that nerve root blocks with a mixture of lidocaine, triamcinolone, and cobamamide resulted in a lower burden of illness than the placebo group.[81]

An RCT performed in 90 PHN patients compared transcutaneous electrical nerve stimulation (TENS) in combination with local lidocaine, local cobalamin, or local lidocaine in combination with cobalamin injections. The authors found that the addition of cobalamin injection, with or without lidocaine, resulted in significantly lower VAS pain scores than TENS combined only with local lidocaine injections.[82]

Complications of interventional pain management

Epidural or paravertebral injection of local anesthetics and/or corticosteroids carries the risk of mild complications such as puncture of the dura, nerve damage, bleeding, and infections.[83] The drugs used during the injections can have side effects as well. No serious complications were observed in the studies included in this review.[45,49–51] In one study, patients complained of dizziness, drowsiness, nausea, and dry mouth.[50]

Performing PRF of the DRG or intercostal nerves can cause serious side effects like pneumothorax, hematoma, or infection. When an injectate is administered into the foramen, a spinal cord infarct has been reported, but this may also occur secondary to trauma to radiculomedullary arteries.[83,84] In the studies included in this guideline, the main adverse reactions observed were pain, tachycardia, nausea, local swelling, and increased blood pressure. No serious adverse effects were noted.[54,55,60–62,85]

During SCS, no serious complications, such as hematoma at the puncture site, infection, pneumothorax, spinal cord injury, peripheral nerve injury, cerebrospinal fluid leakage, or electrode displacement, were reported. However because SCS complications are therapy-, not indication-driven, the rate of complications is expected to be similar to the incidence for other SCS indications.[73]

In the initial review, sympathetic nerve block complications were described. Hypotension can be the result of vasodilatation which occurs when sympathetic nerves are blocked. Intrathecal injections with methylprednisolone acetate may result in neurotoxicity.[77]

Overall summary

Treatment of acute HZ-related pain and PHN is challenging. The most important treatment for acute HZ-related pain is antiviral therapy instituted within 72 h of the onset of symptoms. Additional symptomatic treatment options include analgesic drugs according to the WHO pain ladder, tricyclic antidepressants (eg, nortriptyline), and antiepileptic drugs (eg, gabapentin). If pain is not reduced, interventional treatments such as epidural injections with local anesthetic and corticosteroid or PRF of the DRG are options.

Effective treatments for PHN include topical capsaicin and lidocaine, and oral drugs such as antidepressants or antiepileptics. The most promising interventional management for PHN is PRF of the DRG or Gasserian ganglion.

The average quality of the newly published studies is low, and a substantial number of studies have a moderate to high risk of bias.

Table 1 summarizes the newly found evidence on interventional treatment for (sub)acute HZ-related pain and PHN.

Techniques

Epidural and paravertebral injection

Both epidural and paravertebral injections are performed as close to the affected level as possible. For transforaminal epidural injections, the needle tip is positioned under the pedicle in the intervertebral foramen.[45] The position is checked with fluoroscopic imaging, with contrast injection showing the injectate bathing the DRG and extending into the epidural cavity.[49] For a continuous epidural nerve block, an epidural catheter is positioned using an interlaminar approach, delivering a continuous local anesthetic infusion.[50]

For paravertebral injections, a needle is positioned in the paravertebral space under fluoroscopic or CT guidance and medications are injected.[48]

TABLE 1 Summary of the new evidence on interventional treatment of (sub)acute HZ-related pain and PHN.

	Level of evidence	Recommendations/findings
Interventional treatment of acute herpes zoster		
Epidural and paravertebral injection (eg, of local anesthetic and/or glucocorticosteroid)	Low/moderate	A paravertebral block with dexmedetomidine yields improvement of pain scores for up to 3 months[48] Interlaminar and transforaminal epidural steroid injections result in lower pain scores for up to 3 months (no control group)[45]
Pulsed radiofrequency	Moderate	PRF treatment reduces pain scores more than sham for up to 3-month follow-up[54] High-voltage, long-duration PRF reduces VAS pain scores to a greater extent than sham treatment for up to 6 months[55] PRF of the dorsal root and Gasserian ganglia provides better outcomes than PRF of peripheral nerves[56] High-voltage, long-duration PRF reduces VAS pain scores significantly more compared to baseline[75]
Interventional treatment of subacute herpes zoster		
Epidural and paravertebral injection (eg, of local anesthetic and/or glucocorticosteroid)	Low	Transforaminal epidural injections reduce acute HZ-related pain more than subacute or chronic HZ-related pain for up to 6 months[49] Continuous epidural nerve block combined with analgesic treatment reduces pain scores more than analgesic treatment alone for up to 30 days[50]
Pulsed radiofrequency	Low	High-voltage PRF results in lower pain scores than conventional PRF settings for up to 6 months[56]
Interventional treatment of postherpetic neuralgia		
Epidural and paravertebral injection of local anesthetic and/or corticosteroid	Low	Continuous epidural infusion with local anesthetic and dexamethasone reduces pain scores more than an infusion without dexamethasone for up to 6 months[51]
Pulsed radiofrequency	Low/moderate	PRF of the DRG reduces pain scores for up to 12 weeks[59] PRF of the intercostal nerves reduces pain scores High-voltage PRF is more beneficial compared to conventional PRF for up to 12 months[60-62] PRF of the Gasserian ganglion provides greater pain reduction than PRF of peripheral nerves for up to 1 year in patients with trigeminal PHN[63]
Spinal cord stimulation	Low	SCS provides greater pain reduction compared to PRF through 12-month follow-up[73] Short-term SCS vs. traditional SCS shows reduced VAS pain scores during 3 month follow-up[75]

Pulsed radiofrequency of the DRG

During PRF at the cervical, low thoracic, and lumbar levels, an electrode with an active tip is inserted near the DRG using a transforaminal approach.[53] The correct needle position is ascertained using fluoroscopic guidance. The tip should be situated behind the upper lateral part of the facet column in an anteroposterior view. When the electrode is stimulated at 50-Hz, thresholds ≤0.5 volt should elicit paresthesia in the affected dermatome, thereby confirming the correct needle position. During a pain mapping, multiple needles at adjacent levels may be stimulated to assess whether these levels are contributing to the patient's pain. During PRF treatment, an electrical field is created near the DRG by a radiofrequency generator, with the dimensions being similar to that of conventional RF ablation (ie, enveloping the active tip). The temperature at the needle tip should never exceed 42°C. Other parameters include voltages ranging between 40 and 60 volt[69]; pulse frequency and durations between 1 and 2 Hz and 120–900 s (2–15 min), respectively; and pulse width between 10 and 20 ms in a 500 ms cycle, allowing for dissipation of heat. The typical resistance during PRF is 330–350 ohm. The number of PRF cycles varies between one and 3 cycles.

Conclusion and recommendations

Treatment of acute HZ-related pain and PHN is challenging. Pain in the acute phase of HZ is often severe with a high percentage of patients seeking healthcare. Fortunately, the majority of patients recover due to the natural course of the disease. It is, however, difficult to predict who will not recover, how long pain will persist, and which treatment regimen will prove effective in patients suffering from PHN. Recommendations are summarized in Figure 3.

The most important *treatment for acute HZ-related pain* is antiviral therapy implemented within 72 hours of the onset of symptoms. Additional symptomatic treatment options include analgesic drugs according to the

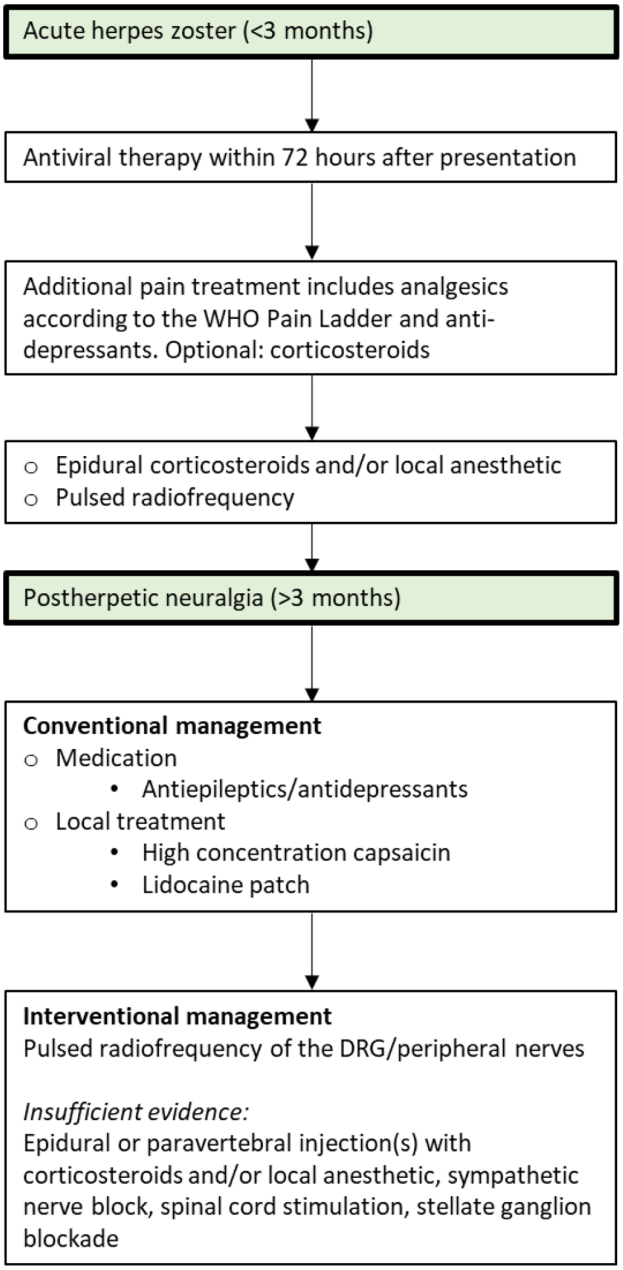

FIGURE 3 Practice algorithm for treatment of acute herpes zoster-related pain and PHN.

WHO pain ladder, tricyclic antidepressants (eg, nortriptyline) and antiepileptic drugs (eg, gabapentin and pregabalin).[86] Local therapies such as lidocaine cream and capsaicin are not viable options during the active rash phase and the presence of skin lesions. There is some evidence that adding corticosteroids to the above-mentioned analgesic drugs might reduce zoster-related pain. However, it does not appear to speed up the healing of the lesions. If pain reduction is not sufficient, interventional treatments such as an epidural injection with local anesthetic, corticosteroid or PRF of the DRG, or stellate ganglion blockade could be considered as therapeutic options.

PHN is preferably treated with the least invasive, safest treatment options, for instance, topical medications such as capsaicin 8% or a lidocaine patch. For more diffuse pain or when localized pain does not respond to topical analgesics, systemic analgesics such as antidepressants or antiepileptics are recommended. Longer follow-up periods that can last weeks or even over 1 month with longer titration schedules, may be needed to assess effectiveness.

If conventional management of PHN is inadequate and pain is interfering with functionality and/or QoL, interventional management is recommended. The strongest evidence (low to moderate) is for PRF of the DRG, while low-quality evidence supports PRF of the intercostal or other peripheral nerves. Epidural or paravertebral injection(s) represent a second-line interventional management strategy, with lower levels of evidence. SCS is invasive with only three studies suggesting a beneficial effect for PHN. More research is therefore needed to assess whether SCS has a place in the treatment algorithm for PHN. There is no evidence that sympathetic nerve blocks result in meaningful pain relief in patients suffering from PHN. We strongly advise against the use of intrathecal injections with methylprednisolone acetate for PHN, as substantial preclinical safety data demonstrate toxicity.

ALGORITHM

Figure 3 shows a summary of the treatment algorithm based on the latest literature.

CONSIDERATIONS

In this review, we updated the previous guideline published in 2011 and revised in 2015 (published in 2019).[9,10] The average quality of the newly published studies is low, with a substantial number having a moderate to high risk of bias. This risk of bias is often the result of a study lacking a control group, including cohort studies and comparative-effectiveness studies devoid of a group that receives an inactive treatment or no treatment, which itself poses a risk of bias. Since acute HZ-related pain tends to resolve spontaneously with time, this makes studies devoid of a control group difficult to interpret.

The time points chosen to measure the primary outcome measure vary, making comparisons between studies, and meta-analyses challenging. Well-designed studies, preferably RCTs, with a large number of participants, a control arm, a double-blinded design, and a follow-up time of at least 3 months are lacking.

The IMMPACT guidelines have put forth suggestions for improvement in study design.[87-89] One of the recommendations is to carefully phenotype patients with

chronic pain to reduce the heterogeneity of the study population. Clinical phenotyping may be performed by assessing patterns of sensory symptoms, and combining these with social, psychological, and demographic data.[22,90] Different sensory symptoms may reflect the extent and type of damage to the somatosensory nervous system. This varies between individuals with PHN, resulting in a variety of pathophysiological processes such as conduction blocks, deafferentation, ectopic impulse generation, peripheral sensitization, spinal and cortical reorganization, and/or central sensitization.[22,90] Recent studies indicate that QST allows for detecting three subsets of PHN patients who may display specific phenotypes (that may overlap): sensory loss, mechanical hyperalgesia, or thermal hyperalgesia.[22,91] Different underlying mechanisms are likely responsible for the generation and maintenance of pain in these subsets.[22,90] All of the studies mentioned in this review did not distinguish between different phenotypes in the treatment of patients suffering from PHN. This may be of great interest since studies indicate that distinct subsets of patients may respond differently to pain treatments.[22] However, before treatment effects within subsets of patients can be reliably studied, phenotyping needs to be improved. Psychological comorbidities, coping strategies, functionality, and sleep, among other variables, should be included in clinical phenotyping before individualized pain therapy can be implemented for patients suffering from PHN.[21]

AUTHOR CONTRIBUTIONS

Elisabeth Adriaansen contributed to the conception and design of the study, data collection, risk of bias assessment, analysis, and interpretation of the data, and drafting and revising the manuscript. Julien Jacobs contributed to data collection, risk of bias assessment, and critical revision of the manuscript for important intellectual content. Lisette Vernooij was involved in the design of the study, risk of bias assessment, statistical analysis, and critical revision of the manuscript for important intellectual content. Albert van Wijck was involved in the critical revision of the manuscript for important intellectual content. Steven Cohen was involved in the critical revision of the manuscript for important intellectual content. Frank Huygen contributed to the conception and design of the study, data analysis, and interpretation of the data, and drafting and revising the manuscript. Mienke Rijsdijk contributed to the conception and design of the study, data collection, risk of bias assessment, analysis, and interpretation of the data, and drafting and revising the manuscript. All authors have read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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CONFLICT OF INTEREST STATEMENT

Prof. Dr. Frank Huygen is an Editorial Board member of Pain Practice and a co-author of this article. To minimize bias, they were excluded from all editorial decision-making related to the acceptance of this article for publication.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

PATIENT CONSENT

No patient consent statement was necessary for this literature review.

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APPENDIX A

Title	Author	Year		1. Participant selection	2. Randomization process	3. Intervention	4. Classification of interventions	5. Confounding	6. Outcome	7. Missing outcome data	8. Reported result
Combined high-voltage pulsed radiofrequency and ozone therapy versus ozone therapy alone in treating postherpetic neualgia: a retrospective comparison	Zhang	2023	H								
Efficacy and Safety of Botulinum Toxin A and Pulsed Radiofrequency on Postherpetic Neuralgia: A Randomized Clinical Trial	Chen	2022	H								
Clinical Observation of CT-Guided Intervertebral Foramen Puncture and Radiofrequency Thermocoagulation for the Treatment of Refractory PHN in the Superior Thoracic Segment	Du	2022	H								
Efficacy of Internal Heat Acupuncture Combined with High-Voltage Long-Duration Pulsed Radiofrequency on Subacute Postherpetic Neuralgia: A Retrospective Study	Fei	2022	H								
Pulsed Radiofrequency Combined With Methylene Blue Paravertebral Nerve Block Effectively Treats Thoracic Postherpetic Neuralgia	Ji	2022	U								
The Therapeutic Efficacy of Pulsed Radiofrequency Alone Versus a Dexamethasone and Pulsed Radiofrequency Combination in Patients With Trigeminal Postherpetic Neuralgia: A Double-blind, Randomized Controlled Trial	Li	2022	U								
Novel Bipolar High-Voltage Pulsed Radiofrequency Targeting the Cervical Sympathetic Chain for Treating Acute Herpetic Neuralgia	Lin	2022	H								
Treatment Efficacy and Technical Advantages of Temporary Spinal Nerve Root Stimulation Compared to Traditional Spinal Cord Stimulation for Postherpetic Neuralgia	Huang	2022	H								
Safety and Efficacy of CT-Guided Pulsed Radiofrequency Combined with Steroid and Ozone Injection-Treated Cervical 3-8 Herpes Zoster Neuralgia Using a Posterior and Upper Quarter of the Cervical Foramina Puncture Approach	Ma	2022	H								
Short-Term Spinal Cord Stimulation or Pulsed Radiofrequency for Elderly Patients with Postherpetic Neuralgia: A Prospective Randomized Controlled Trial	Sheng	2022	H								
Lidocaine 700 mg medicated plaster for postherpetic neuralgia: real-world data from the German Pain e-Registry	Überall	2022	L								
The effectiveness of repetitive paravertebral block with ropivacaine and dexmedetomidine for the prevention of postherpetic neuralgia in patients with acute herpes zoster	Yang	2022	U								
Clinical Efficacy of Pulsed Radiofrequency Combined with Intravenous Lidocaine Infusion in the Treatment of Subacute Herpes Zoster Neuralgia	Zhang	2022	U								
Evaluation of the efficacy of unipolar and bipolar spinal dorsal root ganglion radiofrequency thermocoagulation in the treatment of postherpetic neuralgia	Zhu	2022	H								
Comparison of therapeutic effects of continuous epidural nerve block combined with drugs on postherpetic neuralgia	Dong	2021	H								
Efficacy of dorsal root ganglion pulsed radiofrequency combined with paravertebral injection of recombinant human interferon-α2b in herpetic neuralgia	Fei	2021	H								
Efficacy and safety of pulsed radiofrequency modulation of thoracic dorsal root ganglion or intercostal nerve on postherpetic neuralgia in aged patients: a retrospective study	Huang	2021	H								
Effective Treatment of Postherpetic Neuralgia at the First Branch of the Trigeminal Nerve by High-Voltage Pulsed Radiofrequency	Li	2021	U								
Pulsed Radiofrequency of the Trigeminal Ganglion for Treating Postherpetic Neuralgia of the Ophthalmic Branch	Liu	2021	H								
Comparison of Two Different Pulsed Radiofrequency Modes for Prevention of Postherpetic Neuralgia in Elderly Patients with Acute/Subacute Trigeminal Herpes Zoster	Wan	2021	U								
Efficacy of Pulsed Radiofrequency or Short-Term Spinal Cord Stimulation for Acute/Subacute Zoster-Related Pain: A Randomized, Double-Blinded, Controlled Trial	Wan	2021	U								
Efficacy of intermittent epidural dexamethasone bolus for zoster-associated pain beyond the acute phase	Choi	2020	H								
Efficacy of Pulsed Radiofrequency to Cervical Nerve Root for Postherpetic Neuralgia in Upper Extremity	Ding	2020	H								
CT-Guided Pulsed Radiofrequency at Different Voltages in the Treatment of Postherpetic Neuralgia	Han	2020	U								
Subcutaneous botulinum toxin-A injection for treating postherpetic neuralgia	Hu	2020	H								
A clinical study on the treatment of postherpetic neuralgia with pulsed radiofrequency of the dorsal root ganglion with pain management	Xiong	2020	H								
Efficacy of CT guided pulsed radiofrequency treatment for trigeminal postherpetic neuralgia	Ding	2019	H								
Efficacy and Safety of Computed Tomography-Guided Pulsed Radiofrequency Modulation of Thoracic Dorsal Root Ganglion on Herpes Zoster Neuralgia	Ding	2019	U								
CT-Guided Stellate Ganglion Pulsed Radiofrequency Stimulation for Facial and Upper Limb Postherpetic Neuralgia	Ding	2019	H								
Intravenous infusion of lidocaine enhances the efficacy of conventional treatment of postherpetic neuralgia	Tan	2019	U								
High-Voltage, Long-Duration Pulsed Radiofrequency on Gasserian Ganglion Improves Acute/Subacute Zoster-Related Trigeminal Neuralgia: A Randomized, Double-Blinded, Controlled Trial	Wan	2019	U								
A clinical study of paraspinal nerve block on treatment of herpes zoster under ultrasonic guidance	Zhao	2019	H								
Clinical Study of Ultrasound-Guided Methylene Blue Thoracic Paravertebral Nerve Block for the Treatment of Postherpetic Neuralgia	Zhao	2019	H								
Effect of Single Intra-cutaneous Injection for Acute Thoracic Herpes Zoster and Incidence of Postherpetic Neuralgia	Cui	2018	U								
Transforaminal vs Interlaminar Epidural Steroid Injection for Acute-Phase Shingles: A Randomized, Prospective Trial	Fujiwarea	2018	H								
Clinical efficacy of transforaminal epidural injection for management of zoster-associated pain: a retrospective analysis	Kim	2018	H								
Combined therapy of pulsed radiofrequency and nerve block in postherpetic neuralgia patients: a randomized clinical trial	Li	2018	H								
Ultrasound-guided Pulsed Radiofrequency in the Management of Thoracic Postherpetic Neuralgia: A Randomized, Double-blinded, Controlled Trial	Makharita	2018	H								
Transcutaneous electrical nerve stimulation in combination with cobalamin injection for postherpetic neuralgia	Xu	2018	H								
Effect of Repetitive Intracutaneous Injections with Local Anesthetics and Steroids for Acute Thoracic Herpes Zoster and Incidence of Postherpetic Neuralgia	Cui	2017	H								
Comparison of efficacy of continuous epidural block and pulsed radiofrequency to the dorsal root ganglion for management of pain persisting beyond the acute phase of herpes zoster	Kim	2017	H								
PainVision® Apparatus for Assessment of Efficacy of Pulsed Radiofrequency Combined with Pharmacological Therapy in the Treatment of Postherpetic Neuralgia and Correlations with Measurements	Wang	2017	H								
Bipolar High-Voltage, Long-Duration Pulsed Radiofrequency Improves Pain Relief in Postherpetic Neuralgia	Wan	2016	H								
Effect of corticosteroid therapy in acute pain edema caused by Herpes Zoster	Zhang	2016	H								
Transcutaneous electrical nerve stimulation for chronic post-herpetic neuralgia	Ing	2015	U								
Treatment of postherpetic neuralgia using DREZotomy guided by spinal cord stimulation	Liu	2015	H								
Single paravertebral injection for acute thoracic herpes zoster: a randomized controlled trial	Makharita	2015	U								
Ultrasound-guided cervical nerve root block for the treatment of acute cervical herpes zoster: a randomized controlled clinical study.	Zheng	2019	U								
Transdermal oxycodone patch for the treatment of postherpetic neuralgia: a randomized, double-blind, controlled trial	Gavin	2017	L								