Evidence-Based Case Report

The Prevention and Management of Postherpetic Neuralgia With Emphasis on Interventional Procedures

Honorio T. Benzon, MD, Kiran Chekka, MD, Amit Darnule, MD, Brian Chung, MD, Oscar Wille, MD, and Khalid Malik, MD

Objective: A patient with postherpetic neuralgia (PHN) did not respond to medications, either singly or in combination, or to intrathecal methylprednisolone but responded to intrathecal alcohol. This evidenced-based case management article evaluates and grades the evidence for the prevention and treatment of PHN.

Methods: A search of published English-language studies on the prevention and treatment of PHN was made.

Results: Randomized clinical studies showed the efficacy of antiviral agents in the prevention of PHN and the use of anticonvulsants, antidepressants, opioids, and Lidoderm patch in the treatment of PHN (level A evidence). The role of epidural local anesthetic and steroid injections in preventing PHN has not been completely established (level B evidence). Intrathecal steroid injections and topical capsaicin may be effective in PHN (level B evidence). No randomized controlled study supports the usefulness of spinal cord stimulation and intrathecal alcohol.

Conclusions: Postherpetic neuralgia should be managed pharmacologically. If not effective, intrathecal steroid injections or nerve blocks may be tried. Spinal cord stimulation or intrathecal alcohol should be used only as a last resort.

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Postherpetic neuralgia (PHN) can be extremely difficult to manage. We present a patient whose pain did not respond to most of the available drugs for PHN and to intrathecal methylprednisolone. A combination of pregabalin and methadone was partially effective, but the patient could not tolerate the drugs. The patient responded to intrathecal alcohol. We discuss the evidence-based prevention and management of PHN including pharmacological management, peripheral and neuraxial blocks, and interventional procedures.

CASE REPORT

The patient is a 91-year-old woman who developed a right T6 to T8 herpes zoster 2 years before she was seen in our pain clinic. She had pain during the acute stage, which became persistent; epidural blocks were not performed during the acute stage of her shingles. She saw several physicians who prescribed gabapentin, pregabalin, nortriptyline, duloxetine, and fentanyl patch from which she had very mild and insignificant relief from the medications, that is, a decrease in her pain score from 9 of 10 to a range of 8 to 9 of 10. When seen, the patient stated that her pain radiated from her spine to her anterior axillary line, along her right T6 to T8 dermatomes. The pain was described as constant, sharp, and burning in character and was rated at 8 to 9 of 10. Her medical history included hypertension, for which she took verapamil and lisinopril, elevated cholesterol level, and bladder cancer. Physical examination results showed allodynia in her right T6 to T8 dermatomes; there were few barely visible healed herpetic scars in the affected areas. The rest of the neurologic examination results was normal. The patient preferred an injection and requested that medications not be tried. After informed consent, 3 intrathecal injections of 80 mg methylprednisolone and 50 mg lidocaine were administered at 2-week intervals; the sensory level was T8 after each injection. The patient did not experience any relief in her pain or in her allodynia after the intrathecal injection of methylprednisolone.

She individually took the previous medications for her PHN, so we tried combination of the drugs. We started pregabalin, 75 mg twice a day, and added methadone, 5 mg twice a day, 1 week later. Her pain score decreased to a range of 4 to 5 of 10, but she had to stop the pregabalin because of the swelling of her legs. Her residual pain score increased to 7 of 10 with the methadone alone; the patient had to stop the methadone 2 months later because of nausea and vomiting and because of a 10-lb weight loss due to loss of appetite. Lidoderm patch mildly decreased her allodynia. Doxepin, 20 mg at night, did not give her any relief and was discontinued by the patient because of sedation. Memantine, 5 mg twice a day initially then increased to 15 mg/d, decreased her pain score from a range of 8 to 9 of 10 to 5 of 10 after 2 weeks, but her pain score later increased to a range of 7 to 8 of 10. Our patient tried all the medications, either solely or in combination, but experienced either no relief or minimal relief or had to stop the medication because of their adverse effect(s). We discussed the risks and benefits of spinal cord stimulation (SCS) and intrathecal alcohol, and the patient preferred the intrathecal alcohol injection.

The intrathecal alcohol injection was performed in the operating room under fluoroscopy to confirm correct vertebral levels. The patient was placed in the left lateral decubitus position with a 30- to 45-degree forward tilt, and in a slightly Trendelenburg position, the operating room table was flexed so that the right T6 to T8 levels were highest in relation to her body. Under aseptic conditions, 22-gauge spinal needles were inserted at the T5 to T6 and T6 to T7 interspaces (because the nerve roots arise from the spinal cord 1-2 levels above the vertebral level).[1] The needle was stopped as soon as cerebrospinal fluid (CSF) was aspirated. Three and a half milliliters of CSF was slowly

From the Department of Anesthesiology, Northwestern University Feinberg School of Medicine, Chicago, IL.
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Address correspondence to: Honorio T. Benzon, MD, Department of Anesthesiology, Northwestern University Feinberg School of Medicine, Feinberg Pavilion, Suite 5-704, 251 E Huron, Chicago, IL 60611 (e-mail: hbenzon@nmff.org).
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aspirated to decrease the volume of CSF around the nerve roots,[1] and 0.3 mL of 100% alcohol was injected per needle at 0.1-mL incremental injections every 30 secs. A total of 0.6 mL of the hypobaric alcohol was injected during a 3-min period. The stylet was reinserted, no fluid (local anesthetic or saline) or air was injected, and the needles were removed 10 mins later. Sedation for the procedure included 1 mg midazolam and 25 μg fentanyl, and the patient's vital signs remained stable throughout the procedure. The patient remained in the left lateral decubitus position for 1 hr. The patient was then brought to the recovery room and remained supine for another hour. She was discharged neurologically intact and with stable vital signs. On follow-up by telephone 3 days later, the patient stated that her allodynia was less and that her pain score decreased to a range of 4 to 5 of 10. Seven days later, her pain score decreased to a range of 0 to 1 of 10, and her allodynia was completely relieved. Seen 3 weeks after the intrathecal alcohol injection, she confirmed that her pain score was in a range of 0 to 1 of 10. There was no sensory deficit or allodynia on physical examination. She still has minimal pain (visual analog scale, 0–1/10) 6 months after the intrathecal alcohol injection.

METHODS

Search Procedure

Relevant articles were sought using the following search phrases: (*a*) "prevention of postherpetic neuralgia," with 177 citations, mostly review articles, editorials, commentaries, and the role of antiviral medications and the vaccine; (*b*) "nerve blocks for prevention of PHN," with 19 citations; (*c*) "pharmacological management of PHN," with 10 citations, all review articles; (*d*) "antidepressants for PHN," with 165 citations; (*e*) "anticonvulsants for PHN," with 158 citations; (*f*) "opioids for PHN," with 100 citations; (*g*) "SCS for PHN," with 16 citations but only 4 dealt with PHN; and (*h*) "intrathecal alcohol," with 1 citation. In addition, we identified randomized and controlled articles through book chapters and review articles on the topic.

Evaluation of the Evidence and Discussion of Efficacy

The levels of evidence were based on the criteria set by van Tulder et al[2] and adapted by Niemisto et al[3] and Malik and Benzon[4] (Table 1). We will discuss the epidemiology of acute herpes zoster, the prevention of PHN, and the interventional and pharmacological treatments of PHN. We focus on the interventional managements because most review articles dealt with the pharmacological management of PHN.

TABLE 1. Classification of Levels of Evidence

Level A: Strong research-based evidence provided by generally consistent findings in multiple, high-quality, randomized clinical trials
Level B: Moderately strong research-based evidence provided by generally consistent findings in 1 high-quality randomized clinical trial plus 1 or more low-quality randomized clinical trials or generally consistent findings in low-quality randomized clinical trials
Level C: Limited or conflicting research-based evidence provided by 1 randomized clinical trial (either high or low quality) or inconsistent findings in multiple randomized clinical trials
Level D: No research-based evidence, ie, no randomized clinical trials

DISCUSSION

Acute Herpes Zoster and PHN

After immediate exposure to varicella-zoster virus (VZV), through either chickenpox or VZV vaccination, the VZV remains latent in the dorsal root ganglia. The 2 major risk factors for reactivation and resultant herpes zoster are advanced age and immune compromise. In a population-based study, it was noted that the incidence of herpes zoster increased from 1.9 cases per 1000 person-years in the 25- to 34-year-olds to 14.2 cases per 1000 person-years in those older than 75 years.[5] The prevalence of pain that lasts more than 1 month after the appearance of rash increases from 0% in those aged 0 to 29 years to 34% in adults older than 80 years.[6] Disease, age, and drug-related compromise of cellular immunity further increase the incidence of herpes zoster. In immune-compromised patients, the frequency of herpes zoster increases 20- to 100-fold when compared with immunocompetent populations.[7] Other lesser-risk factors include white race, psychologic stress, and physical trauma.

Prevention of PHN With Antiviral Agents or a Vaccine

Research has been aimed at the prevention of PHN including the use of a vaccine and the role of the following treatments during the acute phase of the disease: (*a*) antiviral agents, (*b*) oral antidepressants, and (*c*) neuraxial and peripheral nerve blocks. Randomized controlled double-blind trials have shown that initiation of antiviral therapy within 72 hrs of the onset of rash reduces the acute pain and the duration of the postherpetic pain,[8,9] with acyclovir, famciclovir, and valacyclovir having similar efficacy. All 3 drugs are nucleoside analogs that disrupt viral DNA polymerase and limit VZV's ability to replicate. In a multicenter, double-blind, placebo-controlled trial,[10] patients were randomized into 3 treatment groups within 72 hrs of the onset of rash: (*a*) placebo, (*b*) oral 500 mg famciclovir 3 times a day, and (*c*) 750 mg famciclovir 3 times a day. The medications were administered for 7 days. In both famciclovir groups, the median duration of PHN was 63 days compared with 119 days in the placebo group. A direct comparison between valacyclovir and famciclovir was conducted in immunocompetent patients older than 50 years.[11] Both drugs had similar rates of healing of the rash and were equally effective in decreasing the duration of PHN. Postherpetic neuralgia occurs in 20% to 30% of patients even with optimum preventive therapy.[12]

A new development in the prevention of the long-term sequelae and disability from the disease is the herpes zoster vaccine. The Shingles Prevention Study examined 38,456 immunocompetent adults older than 60 years with a history of chickenpox and randomized them into zoster vaccine or placebo.[13] The vaccine was a live attenuated Oka/Merk VZV vaccine. The subjects were observed for a mean of 3.5 years, during which a total of 957 confirmed cases of herpes zoster occurred, 315 were from the vaccine group and 642 were from the placebo group. Postherpetic neuralgia occurred in 107 subjects, of which 27 were from the vaccine group and 80 were from the placebo group. The burden of illness due to herpes zoster, which was a measure affected by the incidence, severity, and duration of associated pain and discomfort, was the investigators' primary end point. The use of a vaccine resulted in a 61% reduction in zoster burden-of-illness score ($P < 0.001$), a 51% reduction in herpes zoster incidence ($P < 0.001$), and a 66.5% reduction in the incidence of PHN ($P < 0.001$). The most common adverse reactions to the vaccine were localized

tenderness, warmth, and erythema at the site of injection that occurred in almost 50% of patients. Several unanswered questions about the vaccine include the duration of protection provided by the vaccine, its usefulness for patients younger than 60 years, and its effect on patients who have an unknown history of chickenpox or who already had herpes zoster.[7]

Prevention of PHN With Amitriptyline Prescribed During the Acute Stage of Herpes Zoster

Amitriptyline administered during the acute stage of herpes zoster may decrease the incidence of PHN. In a randomized, double-blind, placebo-controlled trial, Bowsher[14] showed that patients older than 60 years who were administered 25 mg amitriptyline daily, within 48 hrs of the rash, had 16% incidence of PHN compared with 35% in the patients who were administered placebo.

Prevention of PHN With Sympathetic, Peripheral, or Neuraxial Blocks

Most of the published studies on the role of nerve blocks to prevent or treat PHN are case series or retrospective studies with its inherent defects.[15–17] Even the studies with a control group have problems in experimental design. In a double-blind, placebo-controlled study, patients with acute herpes zoster were administered either 4 stellate ganglion blocks with bupivacaine or placebo; the blocks were performed daily for 4 consecutive days.[18] Nine (90%) of the 10 patients who were administered bupivacaine were pain-free compared with 2 (20%) in the saline group. Unfortunately, 7 of the 10 patients who had no pain relief after the placebo injections received a set of stellate ganglion blocks with a local anesthetic,[18] thus effectively losing the "control" nature of the group. Two studies used a historical control: one compared the effects of stellate ganglion blocks and epidural mepivacaine/methylprednisolone acetate injections with a thesis published 20 years before the study,[19] whereas another study compared the effects of nerve blocks (stellate ganglion blocks with bupivacaine, epidural bupivacaine, or local infiltration with bupivacaine with or without triamcinolone acetonide) with an article published 27 years earlier.[20] Another study had no real control group[21]; that is, both groups had sympathetic blockade: the blocks were done in 1 group as soon as the patients had pain suggestive of herpes zoster, before the skin eruptions, whereas the other group had the blocks within 10 days of the skin lesions. The incidence of PHN in the 3 studies cited[19–21] was the same in the treatment and the control groups.

Although most studies used sympathetic (stellate) or epidural blocks during the acute stage of herpes,[18–21] a report on 2 patients noted the efficacy of occipital nerve blocks and deep cervical plexus block in relieving the pain of herpes zoster.[22] Neither 1 of the 2 elderly patients reported developed PHN.[22]

A retrospective study by Winnie and Hartwell[23] showed that 100% of patients who had the sympathetic (stellate, epidural) or intercostal blocks within 2 weeks of the onset of rash had complete pain relief compared with 92% when the blocks were performed between 2 weeks and 1 month of the onset of acute herpes and 80% when the blocks were performed between 1 and 2 months. The success rates decreased to 18%, 21%, and 4% when the blocks were performed between 2 and 6 months, between 6 months and 1 year, and after 1 year, respectively.[23] It thus seems that sympathetic blocks are most effective in relieving the pain of acute herpes zoster when performed within 2 weeks of the onset of herpes zoster. Because the relationship between the severity of pain of acute herpes and the incidence of PHN is well established,[24] nerve blocks may reduce the incidence of PHN by decreasing the intensity of the pain of acute herpes zoster.

There are 2 randomized and controlled studies on the effect of neuraxial blocks in the prevention of PHN, and their results are contradictory. The study by Pasqualucci et al[25] involved 569 patients who were older than 55 years, had acute herpes zoster of less than 7 days in duration, and were randomized into 1 of 2 groups: intravenous acyclovir (10 mg/kg 3 times a day) for 9 days plus prednisolone (60 mg/d with progressive reduction) for 21 days or epidural injections of 6 to 12 mL of 0.25% bupivacaine every 6 to 8 or 12 hrs plus methylprednisolone 40 mg every 3 to 4 days by epidural catheter for a period ranging from 7 to 21 days. The cycle of epidural injections was repeated, after a 1-day break, if the pain persisted. The mean number of epidural bupivacaine injections was 2.4; the exact number of epidural methylprednisolone injections was not stated, although at least 2 injections were administered per patient. Efficacy was noted at 1, 3, 6, and 12 months. The incidence of pain after 1 year, in the 485 patients who completed the study, was 22% (51/230 patients) after the medications and 1.6% (4/255 patients) in the epidural group. The incidence of abnormal sensations was 12% in the medications group and 4% in the epidural group (Table 2). The results of the study by Pasqualucci et al[25] were not confirmed in a later study. van Wijck et al[26] randomly assigned 598 patients into 1 of 2 groups: standard therapy (oral antivirals and analgesics) and standard therapy plus 1 epidural steroid injection of 80 mg methylprednisolone and 10 mg bupivacaine. The patients were older than 50 years who had acute herpes rash of less than 7 days. The oral antiviral medications were 800 mg acyclovir 5 times a day, 500 mg famciclovir 3 times a day, or 1000 mg valacyclovir 3 times daily. At the 1-month follow-up, the percentage of patients who had pain in the epidural group was significantly less (48% vs 58%). However, the results were not significantly different at the 3-month (21% vs 24%) and 6-month follow-ups (15% vs 17%).

Prevention of PHN With Combination of Nerve Blocks and Antiviral Agents

A nonrandomized study showed that the combination of epidural injections with medical management has been shown to decrease the pain of acute herpes zoster. Epidural injections of local anesthetic and steroid (bolus of 5–7 mL of 0.25% bupivacaine and 40 mg methylprednisolone followed by an infusion of 2 mL/hr of 0.125% bupivacaine) and intravenous acyclovir (5 mg/kg 3 times a day) for 7 days were noted to be more effective than intravenous acyclovir alone in shortening the days it took for the pain to significantly decrease.[27] The study was not randomized, and the patients in the acyclovir group were treated 6 months earlier.[27] In another study,[28] the same group of investigators compared epidural injections and oral famciclovir (250 mg/d) for 7 days to their previous group of epidural injections and intravenous acyclovir.[27] They noted that the duration of pain (decrease in the intensity of pain from 100 to 50 or 100 to 10) was less in the epidural and famciclovir groups, but the total duration of pain (decrease in the intensity of pain from 100 to 0) was similar in both groups.[28] In both studies,[27,28] all the patients continued their amitriptyline therapy.

Management of Established PHN With Peripheral and Neuraxial Blocks

Nerve blocks may still have a role in established PHN when combined with pharmacological management. A prospective case series of 22 patients showed that the combination of nerve

TABLE 2. Randomized Controlled Studies on the Effects of Neuraxial Steroid/Local Anesthetic Injections and Nerve Blocks in the Prevention and Treatment of PHN

Study	Type of Study	Duration of Acute Herpes/PHN	Treatment Group	Control Group(s)	Results
Prevention of PHN					
Pasqualucci et al[25]	P, R, C	<7 d	Epidural injection of 40 mg MP and local anesthetic injections (at least 2 injections), 290 patients	IV injection of acyclovir and oral prednisolone, 279 patients	Incidence of PHN at 1 y: 22% after medications and 1.6% after epidural
van Wijck et al[26]	P, R, C	<7 d	Standard treatment and 1 epidural injection of 80 mg MP and bupivacaine injection, 301 patients	Standard therapy (oral antivirals and analgesics), 297 patients	Significantly less number of patients in the epidural group had pain at 1 mo but not at 3 and 6 mo
Treatment of PHN					
Kikucki et al[32]	P, R, C	PHN for >1 y	IT injection of 60 mg MP and 3 mL of 2% lidocaine, 13 patients	Epidural injection of 60 mg MP and 5 mL of 2% lidocaine 12 patients	Relief in the IT group
Kotani et al[31]	P, R, C, B	PHN for at least 1 y	IT injection of 60 mg MP and 3 mL of 3% lidocaine once a week for up to 4 wk, 89 patients	(*a*) IT injection of lidocaine, 91 patients (*b*) No treatment, 90 patients	90% of patients in IT MP/lidocaine group had good or excellent relief compared with 15% in the IT lidocaine group
Catala et al[30]	P, R, C	PHN for 3 mo to 2 y	Blocks (stellate or paravertebral) twice a week to a maximum of 6 blocks, 15 patients	IV lidocaine (3 mg/kg) for 2 hrs on 15 consecutive d, 15 patients	At 12 mo of F/U, better pain control in the nerve block group

B indicates blinded; C, controlled; F/U, follow-up; IT, intrathecal; IV, intravenous; MP, methylprednisolone; P, prospective; R, randomized.

blocks with bupivacaine and methylprednisolone (epidural, intercostal, supraorbital, supratrochlear, and infraorbital) and amitriptyline, 50 to 100 mg/d, resulted in greater than 50% relief of pain in 59% of patients and acceptable pain relief in 73% of the patients who were observed.[29] The mean duration of PHN in the patients when the blocks were performed was 4.6 months with a range of 1 to 13 months.[29] In another study,[30] patients were randomized into 2 treatment groups, either nerve blocks (stellate or paravertebral blocks, 2 times a week to a maximum of 6 blocks and a mean of 4.5 blocks) or intravenous lidocaine infusion (3 mg/kg for 2 hrs on 15 consecutive days). At the 3- and 12-month follow-ups, the patients who had the sympathetic blocks experienced better pain control. The mean pain scores in the nerve block group decreased from a baseline of 8.1 to 2.4 at 3 months and 1.6 at 12 months. In comparison, the corresponding scores in the intravenous lidocaine group were 8.3, 5.7, and 4.4 (Table 2).

Intrathecal steroid and local anesthetic injections were reported to be effective in some resistant cases of PHN. In a randomized and blinded trial, Kotani et al[31] showed that 90% of the patients who had up to 4 weekly intrathecal injections of 60 mg methylprednisolone acetate and 3 mL of 3% lidocaine had a good or excellent pain relief (Table 2). Ninety-one percent of the patients in the methylprednisolone-lidocaine group had good or excellent global pain relief compared with 15% in the lidocaine-only group and less than 4% in the no-treatment group. Epidural injections of methylprednisolone and lidocaine are not as effective as intrathecal methylprednisolone-lidocaine injections.[32] The decreases in the IL-8 concentrations seen in the intrathecal injections are not seen in the epidural steroid injections.[32] Arachnoiditis may be a consequence of subarachnoid methylprednisolone injections, secondary to the polyethylene glycol in the steroid preparation. However,[33] the concentration of polyethylene glycol that causes depression of the compound action potentials of the A, B, and C nerve fibers is greater than 20%, whereas the concentration of the vehicle in the depot steroid is only 2.9%.

Interventional Treatments of PHN Including SCS and Intrathecal Alcohol

The interventional treatments of PHN include SCS[34–37] and intrathecal alcohol.[38] Studies on SCS were all case series, either retrospective[34–36] or prospective,[37] with a small number of patients that ranged from 4 patients[35] to 28 patients.[37] The mean duration of follow-up in the studies ranged from 15 months[34] to 97.6 months,[36] and long-term success rates (pain relief of at least 50%) ranged from 21%[36] to 82%.[37] The study by Harke et al[37] was the only prospective study; they assessed the efficacy of the treatment by turning the SCS off and noted the recurrence of the patients' pain. Eight patients discontinued their SCS permanently after 3 to 66 months because of low levels of their pain. Interestingly, the authors placed temporary SCS bipolar electrodes in 4 patients with severe acute herpes zoster. The patients had relief of their pain from 9 to 1 of 10, and the SCS was discontinued after a median period of 2.5 months because of cessation of the patients' pain.

There is only 1 previous report on the use of intrathecal alcohol in PHN. Lauretti et al[38] reported 5 patients with long-standing history of refractory PHN who responded to subarachnoid alcohol. They injected isobaric 0.5% bupivacaine in

volumes that ranged from 0.3 to 0.8 mL and observed their patients' responses. Subarachnoid alcohol, in doses of 0.4 to 0.6 mL, was injected 1 week after injection of the bupivacaine. In contrast, we proceeded with our intrathecal alcohol injection to limit the number of thoracic subarachnoid needle placements and decrease the risk of spinal cord injury. We decided not to inject a local anesthetic just before the alcohol because we were not sure that the spread of the injected local anesthetic would be limited to the nerve roots that we were interested in blocking. We were also worried about the cardiovascular consequences of the intrathecal local anesthetic. We did not inject saline or air to compensate for the dead space in the needle because we did not want the saline to dilute the alcohol or the air to cause headache. We felt that inserting the stylet and keeping the needle for another 10 mins were adequate. In contrast, Lauretti et al[38] injected 0.3 mL of normal saline before pulling their needle out. We kept our patient in the same position for 1 hr after injection of the alcohol, whereas Lauretti et al[38] kept their patients in the same position for 30 mins. Moore[1] recommended keeping the patient for additional 30 to 45 mins, whereas Matsuki et al[39] and Cousins[40] commented that the patient may be repositioned 15 to 20 mins after the alcohol injection. We injected a total of 0.6 mL of intrathecal alcohol, whereas Moore[1] recommended limiting the total dose to 0.5 to 0.7 mL in an ambulatory patient whose pain is limited to 1 or 2 dermatomes. Injections of 1 mL or greater are reserved for patients who are bedridden and in whom there is little concern for bowel or bladder incontinence.[1]

The risks of intrathecal alcohol include motor paresis, loss of bowel or bladder sphincter function, dysesthesias, impairment of touch and proprioception, meningitis, and postmeningeal puncture headache.[40,41] Our patient did not have any complication and had very good relief of her pain and allodynia at the time of this writing, 6 months after the intrathecal injection. It should be noted that the patients of Lauretti et al[38] had pain relief that lasted 10 to 13 months.

Pulsed radiofrequency lesioning of peripheral nerves and the dorsal root ganglion has been reported for chronic pain conditions from noncancer etiology. This modality has not been tried in patients with PHN.[4,42] Our clinical experience with pulsed radiofrequency is that the benefit does not last for more than a few weeks, at the most.

Pharmacological Management of PHN

The studies showing the efficacy of the different drugs will not be discussed in detail since the pharmacological management of PHN was recently reviewed[43]; only general comments will be made. The numbers needed to treat (NNTs), numbers needed to harm (NNH),[43,44] and the adverse effects of the different drugs are shown in Table 3. The anticonvulsants are effective[45–49] and are the most commonly prescribed drugs in PHN because of their efficacy and benign adverse effect profile. Although the tricyclic antidepressants are effective in PHN,[50–55] their use is limited by their adverse effects. Nortriptyline is probably the ideal antidepressant for PHN because it is as effective and is better tolerated than amitriptyline.[56] Opioids, specifically oxycodone,[57] morphine,[54] methadone,[54] and tramadol,[58] are also effective in PHN. However, addiction and regulatory issues, coupled with the benign adverse effect profile of anticonvulsants, make opioids a secondary choice in PHN.[59] A combination of an anticonvulsant and an opioid[60] has been noted to be more effective than either agent administered singly.

Local Anesthetics (Intravenous, Mexiletine, Patch) for the Treatment of PHN

Intravenous lidocaine, in doses of 5 mg/kg, was noted to be superior to placebo[61,62] especially in reducing the area of allodynia.[62] Intravenous lidocaine, 3 mg/kg for 2 hrs, administered daily for 15 days, was noted to be less effective than sympathetic blocks.[30] Mexiletine was noted to have no significant effect on the area of allodynia or on spontaneous or evoked pain in patients with PHN.[63] Lidocaine patch has been

TABLE 3. NNT, NNH, and Adverse Effects of Selected Drugs for PHN

Drug	NNT (95% CI)	NNH (95% CI)	Specific/Common Adverse Effects
Amitriptyline	1.6 (1.2–2.4)[50] 4.2 (2.13–81.6)[51]	Minor harm: 8 (2.5–22) Major harm: 24 (8–36)	Sedation, dry mouth, tachycardia, constipation, urinary retention, weight gain, prolonged QT interval
Desipramine	1.9 (1.3–3.7)	Minor harm: 4.8 (2.5–36.7) Major harm: 13*	
Nortriptyline	3.7 (2.4–8)	ND	
Gabapentin	4.4 (3.3–6.1)	Minor harm: 4.1 (3.2–5.7) Major harm: 12.3 (7.7–30.2)	Somnolence, dry mouth, weight gain, peripheral edema, ataxia
Pregabalin	4.9 (3.7–7.6)	Minor harm: 4.3 (2.8–9.2) Major harm: ND	Dizziness, somnolence, peripheral edema
Oxycodone	2.5 (1.7–4.4)	Minor harm: 3.6 (2.2–10.2) Major harm: 6.3 (4.2–12.8)	Immune suppression, loss of libido, endocrine dysfunction
Morphine-controlled release or methadone	2.8 (2–4.6)	ND	
Tramadol	4.8 (3.5–6.0)	Minor harm: 7.2* Major harm: 10.8*	Somnolence, constipation, nausea and vomiting, seizures, serotonin syndrome when combined with SSRIs and MAO inhibitors
Lidocaine patch	2 (1.4–3.3)	Minor harm: ND	Burning sensation in area of application
Topical capsaicin	2.3 (1.4–6)	Minor harm: 3.9 (2.5–8.6)	Burning sensation in area of application

The values for NNTs and NNH were adapted from Hempenstall et al[44] and Wu and Raja.[43] The NNTs for amitriptyline were based on studies by Watson et al[50] and Max et al.[51]

*The 95% confidence interval (CI) could not be determined by Hempenstall et al[44] or by Wu and Raja.[43]

ND indicates could not be determined by Hempenstall et al[44]; SSRIs, selective serotonin reuptake inhibitors; MAO, monoamine oxidase.

TABLE 4. Levels of Evidence Supporting the Interventions for the Prevention and Treatment of PHN

Drug/Intervention	Level of Evidence	Reference(s)	Comments
Prevention of PHN			
Antiviral medications	A	8–11	RCTs support efficacy
Amitriptyline	B	14	RCT[14] showed efficacy of amitriptyline in decreasing incidence of PHN when administered within 48 hrs of rash
Sympathetic blocks	C	18	Other studies had historical control[19,20] or no real[21] control group
Neuraxial local anesthetic and steroid	B	25, 26	One RCT showed efficacy,[25] whereas another RCT[26] showed difference only at the 1-mo follow-up
Treatment of PHN			
Nerve blocks	C	30	A case series[29] showed efficacy of nerve blocks when combined with amitriptyline
Intrathecal steroid injection	B	31, 32	Two RCTs support efficacy
SCS	D	34–37	Case series
Intrathecal alcohol	D	38	Case series
Antidepressants	A	50–55	RCTs support efficacy
Anticonvulsants	A	45–49	RCTs support efficacy
Opioids	A	54, 57, 58	RCTs support efficacy
Lidocaine patch	A	64–67	RCTs support efficacy
Topical capsaicin	B*	68, 69	RCTs support efficacy

*Two studies showed the efficacy of topical capsaicin, but the magnitude of pain relief may not be clinically important.[75]
RCT indicates randomized controlled trial.

shown to be effective in several prospective randomized trials.[64–67]

Other Drugs in the Treatment of PHN: Topical Capsaicin, *N*-Methyl-D-Aspartic Acid–Blocking Agents

Topical capsaicin, although shown to be effective in PHN,[68,69] is not used widely probably because it causes a burning sensation in the area of application and because of the efficacy of lidocaine patch. Ketamine, an *N*-methyl-D-aspartic acid–blocking agent, has been shown in several case reports to decrease the pain, allodynia, and hyperpathia associated with PHN,[70–72] although dizziness, fatigue, and altered visual and auditory acuity occurred in most patients. Memantine was shown to be effective in diabetic neuropathy but not in PHN.[73,74]

Recommendations Based on Levels of Evidence

On the basis of the criteria used by several investigators,[2–4] antiviral agents are effective in preventing PHN (Table 4). The role of epidural local anesthetic and steroid injections has not been completely established because 1 study[25] showed the efficacy of the intervention, whereas another study showed efficacy only at the 1-month follow-up.[26] Anticonvulsants, antidepressants, opioids, and lidocaine patch have level A evidence supporting their use in PHN. Intrathecal steroid injections, nerve blocks, and topical capsaicin may be effective in PHN (level B evidence). No randomized controlled study supports the efficacy of SCS and intrathecal alcohol. Our levels of evidence are in agreement with the assessments of the Quality Standards Subcommittee of the American Academy of Neurology.[75]

There is a need for randomized controlled studies on the efficacy of interventional treatments of PHN either because drugs are not always effective, as shown in our case report, or because their adverse effects limit their dose. Intrathecal alcohol should be considered only in resistant cases of PHN. The choice between SCS and intrathecal alcohol depends on the experience of the interventional pain physician; the patient should be fully informed of the risks of the 2 procedures.

REFERENCES

1. Moore DC. Spinal (subarachnoid) block with absolute alcohol. In: Moore DC. *Regional Block. A Handbook for Use in the Clinical Practice of Medicine and Surgery.* 4th ed. Springfield, IL: Charles C. Thomas; 1965:485–490.
2. van Tulder M, Malmivaara A, Esmail R, Koes B. Exercise therapy for low back pain. *Spine*. 2000;25:2784–2796.
3. Niemisto L, Kalso E, Malmivaara A, Seitsalso S, Hurri H. Radiofrequency denervation for neck and back pain: a systemic review within the framework of the Cochrane collaboration back review group. *Spine*. 2003;28:1877–1888.
4. Malik K, Benzon HT. Radiofrequency applications to dorsal root ganglia: a literature review. *Anesthesiology*. 2008;109:527–542.
5. Donahue JG, Choo PW, Manson JE, Platt R. The incidence of herpes zoster. *Arch Intern Med*. 1995;155:1605–1609.
6. Hope-Simpson RE. Postherpetic neuralgia. *J Royal Coll Gen Pract*. 1975;25:571–575.
7. Gnann J. Vaccination to prevent herpes zoster in older adults. *J Pain*. 2008;9:S31–S36.
8. Balfour HH, Bean B, Laskin OL, Ambinder RF, Meyers JD, Wade JC, et al; and the Burroughs Wellcome Collaborative Acyclovir Study Group. Acyclovir halts progression of herpes zoster in immunocompromised patients. *N Engl J Med*. 1983;308: 1448–1453.
9. Wood MJ, Johnson RW, McKendrick MW, Taylor J, Mandal BK, Crooks J. A randomized trial of acyclovir for 7 days or 21 days with and without prednisolone for treatment of acute herpes zoster. *N Engl J Med*. 1994;330:896–900.
10. Tyring SK, Barbarash RA, Nahlik JE, Cunningham A, Marley J, Heng M, et al. Famciclovir for the treatment of acute herpes zoster:

effects on disease and postherpetic neuralgia. *Ann Int Med*. 1995; 123:89–96.

11. Tyring SK, Beutner KR, Tucker BA, Anderson WC, Crooks RJ. Antiviral therapy for herpes zoster. *Arch Fam Med*. 2000;9:863–869.
12. Dworkin RH, Johnson RW, Breuer J, Gnann JW, Levin MJ, Backonja M, et al. Recommendations for the management of herpes zoster. *Clin Infect Dis*. 2007;44:S1–S26.
13. Oxman MN, Levin MJ, Johnson GR, Schmader KE, Straus SE, Gelb LD, et al, for the Shingles Prevention Study Group. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. *N Engl J Med*. 2005;325:2271–2284.
14. Bowsher D. The effects of pre-emptive treatment of postherpetic neuralgia with amitriptyline: a randomized, double-blind, placebo-controlled trial. *J Pain Symptom Manage*. 1997;13:327–331.
15. Kumar V, Krone K, Mathieu A. Neuraxial and sympathetic blocks in herpes zoster and postherpetic neuralgia: an appraisal of current evidence. *Reg Anesth Pain Med*. 2004;454–461.
16. Ali NM. Does sympathetic ganglionic block prevent postherpetic neuralgia? Literature review. *Reg Anesth*. 1995;20:227–233.
17. Wu CL, Marsh A, Dworkin RH. The role of sympathetic nerve blocks in herpes zoster and postherpetic neuralgia. *Pain*. 2000;87: 121–129.
18. Tenicella R, Lovasik D, Eaglstein W. Treatment of herpes zoster with sympathetic blocks. *Clin J Pain*. 1985;1:63–67.
19. Rutgers MJ, Dirksen R. The prevention of postherpetic neuralgia: a retrospective review of patients treated in the acute phase of herpes zoster. *Br J Clin Pract*. 1988;42:412–414.
20. Riopelle JM, Naraghi M, Grush KP. Chronic neuralgia incidence following local anesthetic and steroid for relief of pain secondary to herpes zoster. *Arch Dermatol*. 1984;120:747–750.
21. Yanagida H, Suwa K, Corssen G. No prophylactic effect of early sympathetic blockade on postherpetic neuralgia. *Anesthesiology.* 1987;66:73–76.
22. Hardy D. Relief of pain in acute herpes zoster by nerve blocks and possible prevention of post-herpetic neuralgia. *Can J Anaesth*. 2005;52:186–190.
23. Winnie AP, Hartwell PW. Relationship between time of treatment of acute herpes zoster with sympathetic blockade and prevention of post-herpetic neuralgia: clinical support for a new theory of the mechanism by which sympathetic blockade provides therapeutic benefit. *Reg Anesth*. 1993;18:277–282.
24. Schmader KE, Dworkin RH. Natural history and treatment of herpes zoster. *J Pain*. 2008;9:S3–S9.
25. Pasqualucci A, Pasqualucci V, Galla F, De Angelis V, Marzocchi V, Colussi R, et al. Prevention of postherpetic neuralgia: acyclovir and prednisolone versus epidural local anesthetic and methylprednisolone. *Acta Anaesthesiol Scand*. 2000;44:910–918.
26. van Wijck AJM, Opstelten W, Moons KGM, van Essen GA, Stolker RJ, Kalkman CJ, et al. The PINE study of epidural steroids and local anaesthetics to prevent postherpetic neuralgia: a randomized controlled trial. *Lancet*. 2006;367:219–224.
27. Hwang SM, Kang YC, Lee YB, Yoon KB, Ahn SK, Choi EH. The effects of epidural blockade on the acute pain in herpes zoster. *Arch Dermatol*. 1999;135:1359–1364.
28. Ahn HJ, Lim HK, Lee YB, Hwang SM, Lee WS, Ahn SK, et al. The effects of famciclovir and epidural blockade in the treatment of herpes zoster. *J Dermatol*. 2001;28:208–216.
29. Dureja GP, Bhalla AP. Multimodality regimen for the management of postherpetic neuralgia. *Pain Clin*. 1992;5:15–19.
30. Catala E, Ferrandiz M, Aliaga L, Serra R, Castro MA, Villar LJM. Intravenous lidocaine compared with sympathetic blocks as treatment for post-herpetic neuralgia. *Pain Clin*. 1994;7:205–210.
31. Kotani N, Kushikata T, Hashimoto H, Kimura F, Muraoka N, Yodono M, et al. Intrathecal methylprednisolone for intractable postherpetic neuralgia. *N Engl J Med*. 2000;343:1514–1519.
32. Kikucki A, Kotani N, Sato T, Takamura K, Sakai I, Matsuki A. Comparative therapeutic evaluation of intrathecal versus epidural methylprednisolone for long-term analgesia in patients with intractable postherpetic neuralgia. *Reg Anesth Pain Med*. 1999;24:287–293.
33. Benzon HT, Gissen AJ, Strichartz GR, Avram MJ, Covino BG. The effect of polyethylene glycol on mammalian nerve impulses. *Anesth Analg*. 1987;66:553–559.
34. Meglio M, Cioni B, Prezioso A, Talamonti G. Spinal cord stimulation in the treatment of postherpetic pain. *Acta Neurochir Suppl (Wien)*. 1989;46:65–66.
35. Sanchez-Ledesma MJ, Garcia-March G, Diaz-Cascajo P, Gomez-Moreta J, Broseta J. Spinal cord stimulation in deafferentation pain. *Stereotact Funct Neurosurg*. 1989;53:40–45.
36. Kumar K, Hunter G, Demeria D. Spinal cord stimulation in treatment of chronic benign pain: challenges in treatment planning and present status, a 22-year experience. *Neurosurgery.* 2006;58:481–496.
37. Harke H, Gretenkort P, Ladleif HU, Koester P, Rahman S. Spinal cord stimulation in postherpetic neuralgia and in acute herpes zoster pain. *Anesth Analg*. 2002;94:694–700.
38. Lauretti GR, Trevelin WR, Frade LP, Lima CPR. Spinal alcohol neurolysis for intractable thoracic postherpetic neuralgia after test bupivacaine spinal analgesia. *Anesthesiology.* 2004;101:244–247.
39. Matsuki K, Kato Y, Ichiyanagi K. Progressive changes in the concentration of ethyl alcohol in the human and canine subarachnoid spaces. *Anesthesiology.* 1972;36:617–621.
40. Cousins MJ. Chronic pain and neurolytic neural blockade. In: Cousins MJ, Bridenbaugh PO, eds. *Neural Blockade in Clinical Anesthesia and Management of Pain*. 2nd ed. Philadelphia, PA: Lippincott-Raven Publishers; 1988:1053–1062.
41. Benzon HT. Complications associated with neurolytic blocks. In: Neal JM, Rathmell JP, eds. *Complications in Regional Anesthesia and Pain Medicine*. Philadelphia: Saunders Elsevier; 2007:273–283.
42. Malik K, Benzon HT. Pulsed radiofrequency: a critical review of its efficacy. *Anaesth Intensive Care*. 2007;35:863–873.
43. Wu CL, Raja SN. An update on the treatment of postherpetic neuralgia. *J Pain*. 2008;9:S19–S30.
44. Hempenstall K, Nurmikko TJ, Johnson RW, A'Hern RP, Rice AS. Analgesic therapy in postherpetic neuralgia: a quantitative systematic review. *PLoS Med*. 2005;2:e164.
45. Rowbotham M, Harden N, Stacey B, Bernstein P, Magnus-Miller L. Gabapentin for the treatment of postherpetic neuralgia: a randomized controlled trial. *JAMA*. 1998;280:1837–1842.
46. Rice AS, Maton S. Gabapentin in postherpetic neuralgia: a randomized double-blind, placebo-controlled study. *Pain*. 2001;94:215–224.
47. Dworkin RH, Corbin AE, Young JP, Sharma U, LaMoreaux L, Bockbrader H, et al. Pregabalin for the treatment of postherpetic neuralgia. *Neurology.* 2003;60:1274–1283.
48. Sabatowski R, Galvez R, Cherry DA, Jacquot F, Vincent E, Maisonobe P, et al. The 1008-045 Study Group. Pregabalin reduces pain and improves sleep and mood disturbances in patients with post-herpetic neuralgia: results of a randomised, placebo-controlled clinical trial. *Pain*. 2004;109:26–35.
49. Freynhagen R, Strojek K, Griesling T, Whalen E, Balkenohl M. Efficacy of pregabalin in neuropathic pain evaluated in a 12-week, randomised, double-blind, multicentre, placebo-controlled trial of flexible- and fixed-dose regimens. *Pain*. 2005;115:254–263.
50. Watson CP, Evans RJ, Reed K, Merskey H, Goldsmith I, Warsh J. Amitriptyline versus placebo in postherpetic neuralgia. *Neurology.* 1982;32:671–673.

51. Max MB, Schafer SC, Culnane M, Smoller B, Dubner R, Gracely RH. Amitriptyline, but not lorazepam, relieves postherpetic neuralgia. *Neurology.* 1988;38:1427–1432.
52. Kishore-Kumar R, Max MB, Schafer SC, Gaughan AM, Smoller B, Gracely RH, et al. Desipramine relieves postherpetic neuralgia. *Clin Pharmacol Ther.* 1990;47:305–312.
53. Watson CP, Chipman M, Reed K, Evans RJ, Birkett N. Amitriptyline versus maprotiline in postherpetic neuralgia. A randomized, double-blind crossover trial. *Pain*. 1992;48:29–36.
54. Raja SN, Haythornthwaite JA, Papagallo M, Clark MR, Travison TG, Sabeen S, et al. Opioids versus antidepressants in postherpetic neuralgia: a randomized, placebo-controlled trial. *Neurology.* 2002;59:1015–1021.
55. Rowbotham MC, Reisner LA, Davies PS, Fields HL. Treatment response in antidepressant naive postherpetic neuralgia patients: double-blind, randomized trial. *J Pain*. 2005;6:741–746.
56. Watson CP, Vernich L, Chipman M, Reed K. Nortriptyline versus amitriptyline in postherpetic neuralgia: a randomized trial. *Neurology.* 1998;51:1166–1171.
57. Watson CP, Babul N. Efficacy of oxycodone in neuropathic pain: a randomized trial in postherpetic neuralgia. *Neurology.* 1998;50: 1837–1841.
58. Boureau F, Legallicier P, Kabir-Ahmadi M. Tramadol in post-herpetic neuralgia: a randomized double-blind, placebo-controlled trial. *Pain*. 2003;104:323–331.
59. Finnerup NB, Otto M, McQuay HJ, Jensen TS, Sindrup SH. Algorithm for neuropathic pain: an evidence-based proposal. *Pain*. 2005;118: 289–305.
60. Gilron I, Bailey JM, Tu D, Holden RR, Weaver DF, Houlden RL. Morphine, gabapentin, or their combination for neuropathic pain. *N Engl J Med*. 2005;352:1324–1334.
61. Rowbotham MC, Reisner-Keller LA, Fields HL. Both intravenous lidocaine and morphine reduce the pain of postherpetic neuralgia. *Neurology.* 1991;41:1024–1028.
62. Baranowski AP, De Courcey J, Bonello E. A trial of intravenous lidocaine on the pain and allodynia of postherpetic neuralgia. *J Pain Symptom Manage*. 1999;17:429–433.
63. Wallace MS, Magnuson S, Ridgeway B. Efficacy of oral mexiletine for neuropathic pain with allodynia: a double-blind, placebo-controlled, crossover study. *Reg Anesth Pain Med*. 2000;25:459–467.
64. Rowbotham MC, Davies PS, Verkempinck C, Galer BS. Lidocaine patch: double-blind controlled study of a new treatment method for postherpetic neuralgia. *Pain*. 1996;65:39–44.
65. Galer BS, Rowbotham MC, Perander J, Friedman E. Topical lidocaine patch relieves postherpetic neuralgia more effectively than a vehicle topical patch: results of an enriched enrollment study. *Pain*. 1999;80:533–538.
66. Meier T, Wasner G, Faust M, Kuntzer T, Ochsner F, Hueppe M, et al. Efficacy of lidocaine patch 5% in the treatment of focal neuropathic pain syndromes: a randomized double-blind placebo-controlled study. *Pain*. 2003;106:151–158.
67. Galer BS, Jensen MP, Ma T, Davies PS, Rowbotham MC. The lidocaine patch 5% effectively treats all neuropathic pain qualities: results of a randomized double-blind, vehicle-controlled, 3-week efficacy study with use of the neuropathic pain scale. *Clin J Pain*. 2002;18:297–301.
68. Bernstein JE, Korman NJ, Bickers DR, Dahl MV, Miilikan LE. Topical capsaicin treatment of chronic postherpetic neuralgia. *J Am Acad Dermatol*. 1989;21:265–270.
69. Watson CP, Tyler KL, Bickers DR, Millikan LE, Smith S, Coleman E. A randomized vehicle-controlled trial of topical capsaicin in the treatment of postherpetic neuralgia. *Clin Ther.* 1993;15:510–526.
70. Eide PK, Jorum E, Stubhaug A, Bremmes J, Breivik H. Relief of postherpetic neuralgia with the *N*-methyl-D-aspartic acid receptor antagonist ketamine: a double-blind, cross-over comparison with morphine and placebo. *Pain*. 1994;58:347–354.
71. Eide PK, Stubhaug A, Oye I, Breivik H. Continuous subcutaneous administration of the *N*-methyl-D-aspartic acid (NMDA) receptor antagonist ketamine in the treatment of postherpetic neuralgia. *Pain*. 1995;61:221–228.
72. Hoffman V, Coppejans H, Vercauteren M, Adriaensen H. Successful treatment of postherpetic neuralgia with oral ketamine. *Clin J Pain*. 1994;10:240–242.
73. Eisenberg E, Kleiser A, Dortort A, Haim T, Yarnitsky D. The NMDA (*N*-methyl-D-aspartate) receptor antagonist memantine in the treatment of postherpetic neuralgia: a double-blind placebo-controlled study. *Eur J Pain*. 1998;2:321–327.
74. Sang CN, Booher S, Gilron I, Parada S, Max MB. Dextromethorphan and memantine in painful diabetic neuropathy and postherpetic neuralgia: efficacy and dose-response trials. *Anesthesiology.* 2002;96:1053–1061.
75. Dubinsky RM, Kabbani H, El-Chami Z, Boutwell C, Ali H. Practice parameter: treatment of postherpetic neuralgia. *Neurology.* 2004;63: 959–965.

