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Herpes zoster and post-herpetic neuralgia in the elderly: Particularities in prevention, diagnosis, and treatment

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Abstract

Herpes zoster (HZ) results from the reactivation of the varicella zoster virus latent in the sensory ganglia when cell-mediated immunity is altered. It is a frequent condition in older adults, leading to undesirable adverse outcomes. Aging is its main risk factor and the elderly may have different clinical presentations: zoster sine herpete, and a higher incidence of post-herpetic neuralgia (15%) and ophthalmic herpes (7%). Both HZ and post-herpetic neuralgia may impact the quality of life, functional status, mental health, and social interaction in older adults. Clinical trials have demonstrated that the vaccine decreases the incidence of HZ and post-herpetic neuralgia by up to 51% and 67%, respectively. When treating older adults with multi-morbidity, practitioners should consider starting low-dose drugs so they can look for potential drug-drug and drug-disease interactions. The aim of this article was to review the particularities of the risk factors, clinical presentation, complications, and treatment of HZ and post-herpetic neuralgia. (Gac Med Mex. 2017;153:84-92)

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Introduction

Herpes zoster (HZ) occurrence is the result of varicella zoster virus (VZV) latent in sensory ganglia infection reactivation, when cell-mediated immunity is altered[1]. It is a common condition in the elderly, with a life-long risk for having it of 30%, and up to 50% among 85-year old people[2,3].

Worldwide, more than 95% of adults have anti-VZV antibodies[4]. In Mexico, a seroprevalence of 85.8% was found in serum samples obtained during the National Health Survey (ENSANUT 2006) from subjects aged 1 to 70 years, between January and October 2010[5].

The incidence of HZ is similar around the world, and it is age-related: from 2-3/1000 person-years in the 20-50-year age group to 5/1000 in 60-year old people, 6-7/1000 in people aged 70-80 years and up to 1/100 in people older than 80 years[6]. However, in Mexico, as in other Latin American countries, its incidence is unknown.

The cost of the disease depends on the country and on the presence of complications. Estimated values for 2012 in US dollars (USD) consider that the cost per case, including hospitalization, for a 60-year old person is USD 500; for someone aged 70 years, USD 710; and for someone with 80 years of age or older, USD 790. In case of complications, the cost is significantly

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increased: USD 2,180 for post-herpetic neuralgia (PHN), USD 2,270 for ocular herpes, USD 4,690 for neurological complications, USD 3,060 for cutaneous complications, and up to USD 7,850 for other complications[7,8].

The purpose of this article is to review HZ and PHN risk factors, clinical presentation particularities, complications and treatment in the elderly.

Risk factors

Risk factors for the occurrence of HZ in the elderly are modified with regard to other population groups. Age-related changes in the immune system (immunosenescence) are the main risk factors related to the occurrence of HZ, in addition to other immunosuppression states[9-12]. Immune changes with aging that affect both innate immunity (decrease in type II major histocompatibility complex) expression and adaptive immunity (decreased TCD4+ lymphocyte activation against VZV and TCD8+ decreased function) result in decreased immune cell response against VZV[9,11].

Different medical conditions have been identified as risk factors for the occurrence of HZ, including rheumatoid arthritis (odds ratio [OR]: 1.46; 99% confidence interval [CI]: 1.38-1.55), chronic obstructive pulmonary disease (COPD), chronic kidney disease and depression, which have been associated with a risk higher than 10%[6]. Patients with cancer, in particular with lymphoma[14], peptic ulcer disease[14], HIV-positive subjects, transplant recipients, and those with chronic use of steroids are also at higher risk for the development of HZ[4,6]. In the specific case of patients with diabetes mellitus[6], a 2-fold risk has been reported (relative risk: 2.1; 95% CI: 1.9-2.4), while other authors have found higher risk only in patients with type 1 diabetes mellitus, but not in those with type 2[15].

Some studies report that females show a higher incidence at all ages, perhaps because they seek more medical attention with regard to the presence of PHN than males[11,16]. Ethnicity is another risk factor, which is higher for Caucasians in comparison with African Americans[17]. Psychological stress and recent trauma (less than 6 months prior) have been regarded as other risk factors for the development of HZ[17]. In a specific study of elderly subjects not vaccinated against HZ, the following risk factors were found for its occurrence: having any immunosuppression condition (hazard ratio [HR]: 1.58; 05% CI: 1.32-1.88), female gender (HR: 1.36; 95% CI: 1.30-1.43), recent diagnosis of cancer (HR: 1.35; 95% CI: 1.24-1.46) and important physical limitation in daily life activities versus none (HR: 1.33; 95% CI: 1.23-1.43), with these same risk factors being found for HZ-related hospitalization[16].

Clinical presentation

During the prodromal episode of the disease, patients refer headache, photophobia and general discomfort, but rarely do they experience fever[1].

Typically, HZ presents with pain and rash with vesicles that follow the trajectory of a dermatoma[18], which can appear on the face, trunk or limbs, but that never crosses the midline[19]. It can affect up to 3 contiguous dermatomas, which is considered to be rare in immunocompetent patients[1]. Atypical rashes can occur in elderly patients[20]; more extended rashes or hemorrhagic or necrotic lesions have been reported more frequently in patients older than 70 years[21].

The lesions progress from discrete erythema patches to a cluster of vesicles, with subsequent pustules and scabs for 7 to 10 days, but that may take up to one month to heal. Frequently, they are associated with anti-esthetic scars, pigmentation changes and pain. Rash duration is longer in older patients and it is age-correlated[19].

Most patients report deep, pungent or pricking pain, paresthesias, dysesthesias or an exaggerated pain response to stimuli that usually are not painful (allodynia) and electric-shock-like pain[22].

Pain is HZ most common symptom and it always precedes rash by days or weeks[22]; occasionally, it is the only manifestation (zoster sine herpete)[19]. Zoster sine herpete remains a controversial aspect of the disease; although the incidence of zoster sine herpete is still unknown in young and older people, it should be suspected at the presence of persistent radicular pain, labyrinthitis, facial palsy without vesicles present, unilateral ophthalmic neuralgia or presence of ophthalmoplegia, painful muscle paresis of unknown origin[23], or acute, sub-acute or chronic cerebral or spinal disease of unknown origin, especially when accompanied by pleocytosis[24].

Diagnosis

In case of suspected zoster sine herpete or any other atypical presentation of the disease, the diagnosis should be confirmed by real-time polymerase chain

reaction (RT-PCR) for VZV in sample of saliva, of the vesicles fluid content (obtained with a cotton swab), Tzanck smear, dry scabs or skin biopsy; VZV direct staining with antibodies in infected cells or in a smear of the base of a lesion can also be used, although it is less sensitive than RT-PCR[25,26]. In case of acute cerebral disease, in addition to RT-PCR, determination of IgG against VZV in cerebrospinal fluid can also be useful; in this situation diagnosis is important, since these patients may respond to intravenous antiviral treatment[24].

Complications

As a consequence of cell-mediated immunity failure, viruses travel to major organs, where they can elicit the development of complications[12], which appear in 13-40% of cases and increase with age[27]. Complications can be divided in 4 groups: cutaneous, visceral, neurologic and ocular[1,28]. The most common cutaneous complication in the elderly is bacterial overinfection. In case of visceral dissemination, hepatitis, arthritis, myocarditis and pericarditis can be found. Neurologic complications are among the most serious, and the main in the elderly is PHN, but aseptic meningitis, meningoencephalitis, transverse myelitis, peripheral nerve palsy and vestibular dysfunction can also occur. Ocular complications are the second more common in the elderly and will be further addressed later[28].

PHN

Although all complications have great impact on the individual, PHN is the most important, since about 15% of patients will experience it for more than 3 months and it will be more serious in HIV-positive subjects or in those with diabetes mellitus[29,30]. Pain prevalence and duration increase with age, accordingly to aging-related immune response decrease. Few children develop PHN, whereas 27%, 47% and 73% of untreated adults older than 55, 60 and 70 years, respectively, will experience it. The persistence of pain also increases with age: up to 48% of patients older than 70 years experience pain that will endure for more than 1 year[22].

Ophthalmic HZ

It is HZ second most common complication in the elderly; it accounts for 10-25% of all cases of HZ[31], and its frequency increases with age, since it has been reported to range from 5.5% in the 70-74-year age-group to up to 9.0% in the group older than 85 years[21]. It occurs when there is VZV reactivation on trigeminal nerve ganglia compromising the ophthalmic branch. Most patients show periorbital vesicular rash in the trajectory of the involved dermatome[32]. A minority can develop conjunctivitis, keratitis, uveitis and other cranial nerves' (III, IV and VI) paralysis[33]. Ophthalmic herpes is present in up to 7% of cases[34]. Ophthalmic HZ permanent sequels are important in the elderly, since they can overlap with other common conditions (glaucoma, maculopathy, diabetic retinopathy, etc.); these may include chronic ocular inflammation, vision loss and PHN.

Other complications

Stroke is another ophthalmic HZ (infrequent) complication in the elderly. It is secondary to internal carotid artery granulomatous arteritis. Its incidence decreases 6 months after initial rash onset[35]. Antiviral treatment should be started within the first 72 hours after rash onset, and opportune treatment by the ophthalmologist is critical to limit sequels[33].

HZ and comorbidity

A HZ episode can cause an unbalance of other conditions in the elderly and jeopardize the health status of patients with diabetes, COPD or cardiovascular disease[36], as well as of frail elders[21].

HZ, wellbeing, quality of life and functionality

Previous studies have demonstrated that both HZ and PHN impact on quality of life, both at acute and chronic phases[37]. PHN can cause intense pain and compromise the performance of basic daily life activities[37], psychological wellbeing (depression, anxiety, distress, fear, difficulty to concentrate and enjoy life) and social interaction (leisure activities, going out)[21,38], in addition to eliciting other conditions such as fatigue, anorexia, decreased mobility and sleep disorders[38]. Some people have been shown to be likely to experience a permanent sensation of dependence and not to return to their previous lifestyle after HZ occurrence[38]. In the oldest individuals (older than 85 years), poor quality of life and physical performance has been reported, as well as

Table 1. Indications, contraindications and adverse effects of the vaccine against HZ43

Indications and use
1. HZ prevention in people older than 50 years.
2. Not indicated for the treatment of HZ o PHN.
3. Not indicated for the prevention of primary infection with varicella
   Can be simultaneously applied with the use of topical or inhaled steroids or with the use of low-dose systemic steroids or steroids as replacement therapy.

Contraindications
1. History of hypersensitivity to any component of the vaccine, including gelatin.
2. History of anaphylactic or anaphylactoid reaction to neomycin.
3. States of primary or acquired immunodeficiency owing to:
   a. Acute or chronic leukemia.
   b. Lymphoma.
   c. Other disorders that affect the bone marrow or the lymphatic system.
   d. HIV/AIDS-related immunosuppression.
   e. Cell immunity deficiencies.
4. Immunosuppressant treatments (including high-dose corticosteroids).
5. Untreated active tuberculosis.
6. Pregnancy.

Adverse effects
1. Erythema, pain, hypersensitivity, edema, pruritus, hematoma, burning or heat sensation may occur in the vaccine application site.
2. Headache.

an increased presence of depression associated with HZ-related pain[21].

The presence of 50 vesicles or more, being a male and the appearance of severe pain, as measured by the visual analogue scale, have been reported to be factors of worse prognosis for the occurrence of PHN[39].

Opportune treatment of pain and use of antiviral agents once acute symptoms are present have demonstrated a decreased incidence of PHN[1,40].

Primary prevention

A recent advance in primary prevention has been the development of the vaccine for HZ and PHN. This vaccine has been approved in Mexico for people older than 50 years[41], while in the USA and Australia it is recommended for 60-year old and older people and in the United Kingdom it is available for 70-year old and older people[6]. The protection time of this vaccine can range from 7 to 12 years, although this period is not known with certainty and it is likely to decrease over time; to this moment, boost is not recommended[8].

The vaccine, prepared with the OKA strain, has a higher number of live, attenuated viruses than the vaccine against varicella (not less than 19,400 plaque forming units)[42]. This vaccine has been shown to reduce the incidence of HZ and PHN by 51% and 67%, respectively, in elderly people[43]; however, there are controversial studies with regard to its efficacy to reduce PHN in people older than 60 years[44]. Those who in spite of having received the vaccine develop HZ have lower duration and seriousness of the disease in comparison with those who received placebo[42]. Its indications, contraindications and adverse effects are shown in table 1. The vaccine against HZ can be administered simultaneously with other vaccines such as influenza, tetanus and anti-pneumococcus, but it should be applied with a different syringe and on another anatomical site[43].

Treatment

Antiviral agents

Systemic antiviral drugs can reduce rash seriousness and limit acute pain. However, the decrease in PHN incidence is still under debate[1]. In the USA, 3 antiviral drugs have been approved for the treatment of HZ: acyclovir, valacyclovir and famciclovir. The use of these antiviral drugs is recommended in patients older than 50 years who have HZ without complications within the first 72 hours of symptom onset in order to potentiate treatment benefit, and in case this time period is exceeded, treatment should be also initiated in those who at the moment of consultation exhibit new lesions, which implies there is viral replication[45]. Its

Table 2. Use of antiviral drugs for HZ in the elderly[54]

	Dosage	Treatment duration	Interactions	Adverse effects	Renal function-adjusted dosage
Acyclovir	800 mg 5 times per day	7-10 days	Foscarnet, tizanidine, valproic acid, phenytoin, sodium mycophenolate mofetil, ataluren, meperidine, zidovudine	Contact dermatitis (topical cream, 2%), diarrhea 2.4-3.2%, nausea 2.7-4.8%, vomiting, headache 2.2%, malaise 11.5%	Creatinine clearance ≥ 25 ml/min No adjustment required; 10-24 ml 800 mg/8 h; ≤ 10 ml/min 800 mg/12 h
Valacyclovir	500 mg 3 times per day	7 days	Tacrolimus, cidofovir, sirolimus, amikacin, ampicillin, abacavir, zidovudine, lamivudine, adefovir, carboplatin, tenofovir, cyclosporines, clofarabine, cisplatin, iodipamine, gentamicin, foscarnet, meperidine, methotrexate, neomycin, oxyplatin, pentamidine, streptomycin, tobramycin	Rash 8%, abdominal pain 1-11%, nausea 5-15%, vomiting 1-6%, leukocytopenia, thrombocytopenic purpura, AST (SGOT) elevation 1-4%, agitation, aseptic meningitis, chorea, confusion, delirium, dizziness, encephalopathy, hallucinations, headache, psychotic disorder, acute renal failure, hemolytic uremic syndrome, fatigue	Creatinine clearance ≥ 50 ml/min No adjustment required; 30-49 ml/min 1 g/12 h; 10-29 ml/min 1 g/24 h; ≤ 10 ml/min 500 mg/24 h
Famciclovir	1000 mg 3 times per day	7 days	Entecavir, pemetrexed. Ampicillin, colchicine	Diarrhea 1.8-9%, flatulence 0.6-4.8%, nausea 2.2-12.5%, vomiting 1.2-4.8%, headache 9.7-39.3%, dysmenorrhea 0.9-7.6%, erythema multiforme, Stevens-Johnson syndrome	Creatinine clearance ≥ 60 ml/min No adjustments required; 40-59 ml/min 500 mg/12 h; 20-39 ml/min 500 mg/24 h; ≤ 20 ml/min 250 mg/24 h

opportune use is also recommended in seriously immunocompromised patients or post-transplantation, even 72 hours after symptom onset. In the cases of disseminated zoster, the patient should be hospitalized to receive intravenous treatment with acyclovir[46]. There are no contraindications for the use of these drugs in elderly subjects, but doses should always be adjusted according to directly or indirectly calculated renal function[1] (Table 2).

Owing to the convenience of lower number of doses per day (owing to its high availability), less frequency of drug-drug and drug-disease interactions and adverse reactions, the use of valacyclovir or famciclovir is preferred in comparison with acyclovir[47]. Treatment selection should be also influenced by its cost. Table 2 shows antiviral drugs different properties.

Use of corticosteroids

Systemic corticosteroids administered within the first 72 hours of rash onset have demonstrated important benefit in the treatment of acute pain, except for PHN[40]. Their use in combination with acyclovir has been shown to improve the quality of life of healthy adults older than 50 years with localized HZ, since they decrease pain faster during the acute phase and improve interrupted sleep, help patients to return sooner to their daily activities and require using analgesics for shorter time[48]. However, there are no differences in the disease evolution 6 months after initial rash occurrence[40]. In the presence of uveitis or corneal inflammation in ophthalmic HZ, ophthalmic in combination with oral steroids have to be prescribed by the specialist[40].

Possible adverse effects have to be considered when steroids are used in the elderly: hypertension, glucose intolerance, osteoporosis and secondary bacterial infection, among others. Possible comorbidity present in the population also has to be taken into account and contraindicate their use (diabetes mellitus, hypertension, osteoporosis, glaucoma).

Treatment of pain

The choice of analgesic treatment for acute neuralgia or PHN in the elderly has to take comorbidity, use of other medications and pain severity into account[37].

Acetaminophen should be started in patients with mild pain, either alone or in combination (if highly necessary) with some opiate (codeine or tramadol). The use of non-steroid anti-inflammatory drugs should be restricted to short periods of time due to their nephrotoxicity and possible gastrointestinal damage. Adverse effects of either short or long-acting opiate analgesics include somnolence, cognitive slowing, nausea, constipation and pruritus, which may occur more frequently in the elderly[49]. They should be used cautiously in patients with addictions.

There are different options for the treatment of pain in PHN owing to the lack of response observed in some cases: tricyclic antidepressants, gabapentin, pregabalin and lidocaine or capsaicin patches[50].

Tricyclic antidepressants have been used for the treatment of PHN. The most commonly used is amitriptyline, although there are also reports on the use of nortriptilin and desimipramine, both the latter with fewer adverse effects[51]. Amtriptyline-associated adverse effects include orthostatic hypotension, sedation, xerostomia, urinary retention, arrhythmias (A-V block) and electrocardiographic abnormalities (QT prolongation), which limits its use in elderly subjects[51].

Anticonvulsants such as gabapentin and pregabalin have been reported to decrease pain severity in PHN. There is no standard dose for gabapentin, but studies suggest that young patients can be started with a dose of 900 mg/day, with escalation to up to 1800 mg/day (in 7-10 days) only in case of lack of response[52]. Gabapentin is usually well tolerated by elderly patients. Its adverse effects include somnolence, dizziness and peripheral edema; in addition, it can increase gait and balance alterations in elderly patients, especially in those who are frail[37]. Initial dose should be half than that for young patients and should be gradually increased (dose-response).

Pregabalin has few drug interactions, but its use in combination with benzodiazepines produces dizziness, somnolence, difficulty to concentrate and judgment and thought alterations[53,54]. In some studies in young subjects, a dosage of 150-600 mg/day has been shown to be efficacious by reducing pain in PHN[55]. Very cautious use is recommended in the elderly, since it has very similar adverse effects to those of gabapentin; however, it offers faster clinical effect than gabapentin. Both gabapentin and pregabalin should be adjusted in patients with decreased renal function[50].

Topical analgesics are often prescribed for the treatment of PHN. The lidocaine patch 5% can have analgesic effect for PHN lasting up to 12 hours, with mild or no adverse effects, when it is effective[56]. Topical capsaicin in 0.025% cream applied up to four times a day has been reported to be able to decrease pain, but it is tolerated only by 30% of patients owing to intolerable pain, similar to a burn, it may produce, which limits its usefulness[57]. One option can be the capsaicin 8% patch formulation, applied for 60 minutes, which has been reported to decrease pain in up to 30% of patients with PHN[58] (Table 3).

Combination therapy may have the following advantages: increase of single medications partial response, increased rapidness when a medication that requires time to reach effective dose is used and better analgesia at lower doses. However, potential disadvantages of combined therapy in elderly patients include an increase in the risk for adverse effects with increased number of medications, which even makes it difficult to know which one of them is causing the adverse effects, in addition to increasing the cost of treatment[3].

Non-pharmacological treatment

There are other options for the treatment of PHN that still require further study to demonstrate their efficacy. These options include:

- Invasive techniques, such as nerve blocks and local anesthetics or glucocorticoids intrathecal administration.
- Botulinum toxin type A application.
- Surgery: thalamus electrical stimulation, anterolateral cordotomy and dorsal roots electrocoagulation.
- Others: transcutaneous electrical nerve stimulation (TENS), acupuncture, cryotherapy, psychological therapy, percutaneous electrical nerve stimulation.

Table 3. Treatment of PHN pain (consider adverse effects and drug interactions for use in the elderly[54]

	Lidocaine patches	Capsaicin	Gabapentin	Pregabalin	Opioids	Amtriptylin	Tramadol
Mechanism of action	Amino-amide anesthetic	Affects P-substance storage, transportation and release	Gamma-aminobutyric acid analogue	Gamma-aminobutyric acid analogue	Mu opioid receptor agonists	Tricyclic antidepressant	Mu opioid receptor agonist
Dose	Up to 3 patches on the painful area, for 12 hours	Cream: not available in Mexico; apply on painful area 3 or 4 times a day. Patch 8%: apply one patch for 60 minutes, up to 4 patches every 3 months	300 mg on day 1, 300 mg twice on day 2, 300 thrice on day 3; can be increased to up to 1800 mg divided in 3 doses	75 mg twice daily or 50 mg thrice daily; can be increased to up to 300 mg per day, over a 1-week period, based on efficacy and tolerability	Morphine-equivalents start with 2.5-15 mg every 4 h, after 1-2 weeks convert total daily dose and continue with shorter half-life drugs if required	10-25 mg by night; dose can be increased in weekly doses up to a maximum dose of 150-200 mg per day	Start with 50 mg once daily, increase 50 mg every day, in divided doses every 3-7 days, if tolerated, to up to a maximum dose of 400 mg/day; in patients older than 75 years, up to 300 mg/day in divided doses
Adverse effects	Burning sensation, skin reddening or rash	Erythema, pain, pruritus, rash, nausea, nasopharyngitis, hypertension	Peripheral edema, nausea, vomiting, ataxia, nystagmus, Stevens-Johnson syndrome, dizziness, somnolence, thought alterations	Peripheral edema, increased appetite, weight gain, constipation, xerostomia, asthenia, ataxia, dizziness, headache, lack of coordination, somnolence, tremor, blurry vision, diplopia, thought alterations, euphoria, nasopharingitis, fatigue, jaundice, hypersensitivity reactions, creatinine elevation, suicidal ideation, angioedema	Constipation, sedation, nausea, vomiting, respiratory depression, pruritus, somnolence, headache, dizziness, cardiac arrest, orthostatic hypotension, syncope, myoclonus, coma, seizures, dependence	Weight gain, xerostomia, constipation, dizziness, headache, somnolence, blurry vision, cardiac arrhythmias, electrocardiographic abnormalities, myocardial infarction, QT interval prolongation, agranulocytosis, hepatotoxicity, jaundice, neuroleptic malignant syndrome, seizures, depression, suicidal ideation	Reddening, pruritus, constipation, nausea, vomiting, xerostomia, dizziness, headache, insomnia, somnolence, myocardial infarction, pancreatitis, anaphylactic reactions, seizures, dyspnea, respiratory depression, serotoninergic syndrome
Interactions	Amiodarone, donepezil	Angiotensin-converting enzyme inhibitors	Morphine, antacids, hydrocodone	Benzodiazepines, propoxyphene, buprenorphine, ethanol, diphenhydramine, chlorpheniramine, telmisartan, valsartan	Anticholinergic drugs, hypnotic sedative drugs, benzodiazepines, cytochrome P450 inhibitors, muscle relaxants	Phenothiazines, antipsychotic drugs, anticholinergic drugs, serotonin reuptake inhibitors, hypnotic sedative drugs, anti-arrhythmic drugs, monoamine oxidase inhibitors	Naltrexone, rasagiline, selegiline, venlaflaxine, linezolid, benzodiazepines, serotonin reuptake inhibitors, chlorimipramine, haloperidol, fentanyl, cytochrome P450 inhibitors, hypnotic sedative drugs

Sympathetic blocks can be helpful in the treatment of HZ or PHN-related pain. Delicate surgeries have been practiced for PHN-related treatment-refractory pain, including electrical stimulation of the thalamus (neuromodulation), anterolateral cordotomy and dorsal root electrocoagulation, which entail risks for permanent neurological deficits. No consistent benefits have been demonstrated in the treatment of PHN-related pain[59].

Evidence for beneficial effects of intrathecal and epidural administration of local anesthetics plus steroids appears to be consistent if they are applied within the first 2 months of HZ onset; however, since it is an invasive procedure, it should be assessed on an individual basis, due to possible neurological sequels: aseptic meningitis, transverse myelitis, cauda equina syndrome, lumbar radiculitis, headache, urinary retention and arachnoiditis[59,60]. Epidural administration of local anesthetics plus steroids reduces the incidence of PHN within the first month after application, but the effect decreases once 3 months have elapsed[61]. Although generally useful, the evidence for the use of sympathetic blocks in HZ and PHN still requires further randomized controlled trials for validation[62].

Botulinum toxin type A administration is still under study for the treatment of PHN[63]. Cryotherapy[64], TENS and acupuncture efficacy for the treatment of pain in PHN has not been demonstrated due to the lack of well controlled studies[59].

Percutaneous electrical nerve stimulation, administered thrice-weekly for 2 weeks in patients with HZ was shown to be useful for some, but not at all acutely painful points; it decreases PHN seriousness, but not its incidence[65].

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