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REVIEW ARTICLE

Herpes-zoster and post-herpetic neuralgia*

Herpes-zóster e neuralgia pós-herpética

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ABSTRACT

BACKGROUND AND OBJECTIVES: Herpes-zoster (HZ) is a vesicular painful skin rash resulting from the reactivation of varicella-zoster virus (VZV) in dorsal root ganglia or cranial nerves, which occurs decades after the primary varicella infection. However, even after skin healing, pain may persist for months or even years. This is a complication known as post-herpetic neuralgia (PHN). This review aimed at giving an overview of herpes-zoster and PHN clinical history, focusing on pain control.

CONTENTS: PHN is characterized by chronic neuropathic pain. Its incidence is higher among the elderly and immunocompromised individuals. There are several treatment options, which may be pharmacological or interventionist, both with variable efficacy.

CONCLUSION: Pain affects quality of life of patients, interfering with their daily activities. In spite of advances already obtained in the analgesic therapy for HZ and PHN, there are still difficulties in its approach. So, it is very important to prevent, diagnose and early treat HZ and its complications.

Keywords: Herpes-zoster, Post-herpetic neuralgia.

RESUMO

JUSTIFICATIVA E OBJETIVOS: O herpes-zóster (HZ) é uma erupção cutânea vesicular dolorosa resultante da reativação do vírus varicela-zóster (VVZ) nos gânglios da raiz dorsal ou nos nervos cranianos, que ocorre décadas após a infecção primária de varicela. Entretanto, mesmo após a cicatrização cutânea, a dor pode persistir por meses e até anos. Esta é uma das complicações conhecida como neuralgia pós-herpética (NPH). O objetivo desta revisão é fornecer uma visão geral da história clínica do herpes-zóster e da NPH, focando a abordagem do controle da dor.

CONTEÚDO: A NPH caracteriza-se por dor neuropática crônica. Há incidência aumentada em idosos e indivíduos imunocomprometidos. Muitas opções de tratamento estão disponíveis, podendo ser farmacológico e intervencionista, ambos apresentam eficácia variável.

CONCLUSÃO: A dor afeta a qualidade de vida dos pacientes, interfererindo nas suas atividades diárias. Apesar dos avanços já obtidos na terapia analgésica do HZ e da NPH, ainda existem inúmeras dificuldades na sua abordagem. Portanto, é muito importante prevenir, diagnosticar e tratar precocemente o HZ e suas complicações.

Descritores: Herpes-zóster, Neuralgia pós-herpética.

INTRODUCTION

Varicella-zoster virus (VZV) is a herpes virus causing varicella, which latently persists in the nervous system throughout the life of individuals after primary infection[1,2]. Herpes-zoster (HZ) is a relatively common infectious disease caused by the reactivation of VZV and is characterized by painful skin manifestations[3-6]. The disease may evolve to healing in a few weeks or pain may persist for months or even years. Post-herpetic neuralgia (PHN) is a term used to define the persistence of pain[1,7,8].

Pain is the most uncomfortable symptom for patients, both acute pain associated to HZ and PHN chronic pain[9]. Pain persistence significantly impairs quality of life (QL)[4,10] and increases health care costs[9,11]. Currently, several approaches and interventionist techniques are available to control pain. In spite of the advances of the analgesic therapy for HZ and PHN, there are still difficulties with their approach, being some patients refractory to treatment.

This study aimed at addressing an overview of the clinical history of HZ and PHN focusing on pain control.

HERPES-ZOSTER

Etiology and clinical manifestation

HZ is caused by the reactivation of VZV in cranial nerves and dorsal root ganglia, in general triggered decades after primary varicella infection[8,12]. When VZV-specific cell immunity is compromised, the disease is triggered. Reactivation is more common in individuals immunocompromised by other diseases, such as cancer, acquired immunodeficiency

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syndrome, post-transplant immunosuppression and chemotherapy[3-6,8,13,14]. There is a strong correlation between higher incidence of HZ and older age, especially above 55 years of age[2,5], because older age is associated to a decrease in T cells-mediated immune response mediated[4,6].

Clinical manifestation starts with mild to moderate skin burning in a certain dermatome, often followed by fever, shivering, headache and malaise[6,9], and progresses to erythematous maculopapular rash until the final stage of crusts[2,5].

The anatomic pattern follows a peripheral distribution in the pathway of involved nerves, is normally unilateral and circumscribed to a dermatome[3,8,9,11]; however, it may involve two or more dermatomes. There is predominance on chest[6,8] and face[5,8].

Some patients may present just radicular pain, characteristic of HZ, without developing skin lesions and this manifestation is clinically called *herpes sine herpete*, which may be more severe than usual manifestations affecting different nervous system levels[5,6,8,9,15,16].

Currently, this type of disease is more easily diagnosed by the polymerase chain reaction – PCR technique to amplify VZV virus. The material used for PCR may be collected from skin biopsy, vesicular fluid, saliva or CSF[15,16]. So, VZV may reach cranial nerves and lead to major complications. Trigeminal nerve involvement may cause alterations on face, mouth, eyes or tongue[6,8]. Ramsay-Hunt syndrome is an uncommon manifestation and involves facial nerve geniculate ganglion causing earache and facial paralysis[8].

Treatment

HZ diagnosis is difficult during early stages of the disease because it may take up to three weeks for the appearance of skin lesions, thus delaying the beginning of the treatment[4,5].

The disease is treated with antiviral drugs which accelerate skin eruptions healing, decrease acute pain intensity and duration[10] and probably prevent PHN[4,6,8,17,18]. However, some patients will develop PHN even after having adequately received antiviral drugs[4,6,13,18].

The three mentioned antiviral drugs have similar success rates and are well tolerated. Most common side effects are: abdominal pain, nausea, vomiting, headache and dizziness[6-8].

Antiviral therapy is especially important for immunocompromised patients because they are at increased risk for skin and visceral dissemination and neurological complications[12].

Treatment with antiviral drugs is oral and inhibits viral replication in the doses shown in table 1.

Table 1 – Antiviral treatment of herpes-zoster.

Antiviral drugs
1. Acyclovir (800 mg), 5 times a day for 7 days
2. Famcyclovir (500 mg), 3 times a day for 7 days
3. Valacyclovir (1 g), 3 times a day for 7 days

HZ acute pain has variable intensity, going from mild to severe. In HZ active stage, common analgesics are used to control mild pain. Patients with moderate to severe pain very often need opioids[1,9,19,20]. Tricyclic antidepressants and anticonvulsants in HZ acute stage have a possible potential to help PHN relief and prophylaxis[5,6,10], but further controlled clinical trials are still needed[6].

Steroids do not seem to contribute for acute pain resolution[6] and do not prevent PHN[5,7]. In addition, the advanced age of HZ patients and their comorbidities very often contraindicate them. The combination of oral steroids and antiviral drugs may be considered an alternative for healthy elderly patients with moderate to severe pain and no contraindication for their use. It is important to remind that the use of steroids without concomitant antiviral therapy is not recommended[6].

Prognosis

For being a self-limited disease, most cases evolve to healing; however some cases may progress to complications. PHN is the most common HZ complication (Figure 1)[4,5,7,12].

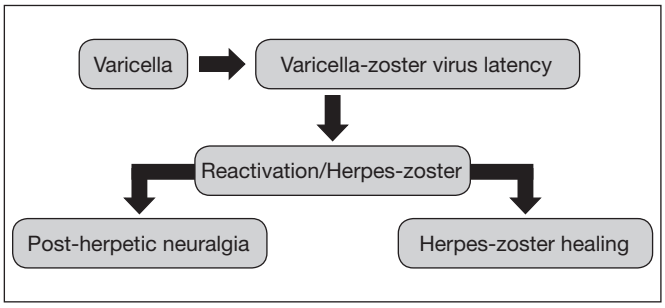

Figure 1 – Herpes-zoster evolution.

There are other HZ complications such as: encephalitis, myelitis and peripheral nerve paralysis[7]. These complications are more common in immunocompromised individuals[6]. HZ may become generalized, suggesting immune impairment or the presence of neoplasia. So, it is important to rule out such possibilities[7].

Although controversial, studies indicate that the incidence of PHN increases in proportion and severity when the acute stage is inadequately treated[20]. HZ recurrence is very uncommon and affects approximately 5% of patients. One explanation is that HZ would stimulate an important immune response, thus preventing subsequent episodes[21].

POST-HERPETIC NEURALGIA

Definition

PHN is characterized by chronic neuropathic pain[14,17] persisting at least one month in the pathway of the affected nerve, starting between one and six months after skin rash healing and may last for years. The incidence of PHN varies from 10% to 20% in immunocompetent adults[7,22,23]. There is no predominance with regard to gender[5]. Age is a major PHN predictor because prevalence significantly increases with age[4,19].

Pain may be divided into three different stages: acute, subacute and chronic. The acute stage is defined as pain starting within 30 days after the appearance of skin rashes. The

sub-acute stage is characterized by pain persisting beyond the acute stage, but resolved before PHN diagnosis[4,5,9,10]. The third stage is PHN itself, with pain persisting for 120 days or more after the exanthema[19].

Clinical manifestation and diagnosis

PHN may manifest with different types of pain[13,14] and sensory symptoms[9]. Pain is chronic, characterized by burning or pricking and may be associated to hyperalgesia, hyperesthesia or allodynia[14]. Excruciating, pinching or stabbing pain has been more often reported in acute HZ, and burning pain is more common in PHN[4,5,7,8].

The anatomic distribution of PHN follows the pattern of dermatomes involved with HZ, being dermatomes from T_3 to L_3 more commonly involved[7]. HZ affects chest and face in 50% to 60% of cases and sacral dermatomes are involved in just 5%, thus being a more uncommon site for the appearance of PHN[8,24].

HZ and PHN diagnosis is clinical. Differential diagnosis will depend on pain clinical characteristics and location of the affected nerve. Differential diagnosis includes: cardiac diseases, Bell paralysis and trigeminal neuralgia, among others[7,8].

Risk factors for PHN are: more advanced age, higher intensity of pain and exanthema in the acute stage, presence of negative sensory signals, presentation of polyneuropathy on active HZ and psychological aspects. The impact on personal and social life of patients is considerable because it affects sleep and the ability to work and perform physical activities, thus affecting their QL[4,8,10]. PHN may significantly affect several aspects of the life of a patient, causing chronic fatigue, sleep disorders, difficulty to concentrate, depression and anxiety, anorexia, weight loss and social withdrawal[4].

Treatment

Treatment should be with drugs to control and relieve pain. First line drugs to treat PHN are anticonvulsants (gabapentin and pregabalin) and tricyclic antidepressants (especially amitriptyline). Opioids are classified as second line analgesics and may also be used[4,8,10,23].

Although there are several pharmacological treatments for symptomatic relief of neuropathic pain, many times these agents do not offer satisfactory relief for all patients[21]. The complex and heterogeneous nature of PHN suggests that adequate pain relief with a single medication is unlikely. Analgesic combinations are used in the clinical practice for pain relief[4].

Pharmacological treatment

Tricyclic antidepressants

Low dose tricyclic antidepressants are used for PHN as single therapy or associated to other drugs[5,10,14,23]. Your use demand 3 monts to positive effect[10]. Action mechanism is the blockade of serotonin and norepinephrine reuptake and also the inhibition of voltage-dependent sodium channels[5,10,23].

Amitriptyline is the most common drug[17], however all drugs have similar therapeutic efficacy. Tricyclic antidepressants prescribed for HZ include amitriptyline, nortriptyline, imipramine and desipramine[10].

Tricyclic antidepressants should be selected based on the particularities of drugs and comorbidities of each patient. A special concern are elderly patients, more susceptible to having pharmacological interactions[4,10]. A limiting factor for the clinical use are adverse effects such as dry mouth, blurred vision, dizziness, fatigue, sedation, urinary retention, constipation, weight gain, palpitations, orthostatic hypotension and prolonged QT interval. Although there is no formal recommendation to request an electrocardiogram (ECG) before starting therapy with tricyclic antidepressants, it is prudent to get an ECG from patients with cardiac disease[10,23].

Anticonvulsants

Anticonvulsant drugs have been used for different conditions inducing neuropathic pain[14,18]. Gabapentin and pregabalin are drugs analog to gamma aminobutyric acid (GABA), however they do not act on GABA receptor. Gabapentin action mechanism is unclear, but it is believed that it acts on the α-2-δ sub-unit of voltage-dependent calcium channels, decreasing calcium flow and inhibiting excitatory neurotransmitters release on primary afferents of spinal cord dorsal horn, similarly to pregabalin[5,10,23].

It is possible that gabapentin has effect on N-methyl-D-aspartate type receptors (NMDA), decreasing glutamate levels to better control allodynia. Daily gabapentin dose may vary from 1800-2400 mg[14]. It is totally excreted by the urine. Major side effects are: sleepiness, dizziness, ataxia and peripheral edema[5,10]. The combination of gabapentin and an opioid, both in lower doses, induces superior analgesia as compared to each drug used as single agent[10].

Pregabalin is effective and safe for PHN because it controls pain and has minor interaction with other drugs. Recommended dose is 300-600 mg/day[10,14]. Its side effects are in general not severe, but may happen, such as peripheral edema, dizziness and sleepiness[10].

Carbamazepine acts by antagonizing sodium channels, stabilizing pre and post-synaptic neuronal membranes. It is used for several diseases inducing neuropathic pain[5,17]. It is very effective for paroxysmal[5,8] and excruciating pain and less effective for burning pain and allodynia. Recommended dose is 600-1600 mg/day divided in 2 to 3 doses[8]. Adverse effects associated to carbamazepine are dizziness, blurred vision, nausea and vomiting[23]. There might be skin rash, however severe reactions such as Stevens-Johnson and toxic epidermal necrolysis are uncommon[3,5].

Opioids

Several studies have shown that opioids are effective to treat neuropathic pain, especially if pain is moderate to severe; however some considerations must be done, such as dose titration to minimize side effects, drug tolerance and abuse. Opioids should be rationally used[4,5]. Adverse effects, such as nausea, vomiting, obstipation, dizziness and sedation should

be taken into consideration[10]. A common recommendation is to use codeine (30-60 mg) every 6 hours, when needed[25]. Codeine may be associated to paracetamol[17]. Other opioids (morphine, oxycodone, methadone) are also used[10].

Tramadol analgesic action occurs in μ-agonist opioid receptors and in norepinephrine and serotonin reuptake inhibition, promoting pain relief and improved QL[10,14]. In cases of difficult pain management, a combination of tramadol and amitriptyline has been used[18].

Capsaicin

Capsaicin is a pepper-derived alkaloid (*Capsicum frutescens)* acting on neuropathic pain induced by substance P peripheral sensitization on primary peripheral receptors, leading to painful symptoms. Capsaicin stimulates a peripheral discharge of substance P, leading to its storage depletion. The unavailability of substance P on primary afferent fibers (C fibers) inhibits the generation of the painful phenomenon[23]. During early topical treatment with capsaicin there is increased pain, especially burning pain, due to substance P discharge before its depletion. Very often this impairs adherence to treatment. However, this inconvenient effect decreases or disappears with time[5,8,10,26]. It has been shown that topic capsaicin provides significant pain relief in randomized clinical trials[4,14].

Topic capsaicin in low concentration (0.025%-0.075%) has been used for decades as second line treatment for PHN, however with diverging results[26-28]. Recently, 8% topical capsaicin has been developed and approved for the treatment of PHN, based on two randomized and controlled studies which have shown the efficacy and safety of 1-hour application for PHN[27]. It is applied by transdermal route on the painful area for 30 minutes on feet and for 60 minutes on remaining body areas.

Treatment may be repeated every 3 months and its adverse effects are pain and erythema on application site, so it needs topic anesthesia before application. It should not be applied to injured or inflamed skin[28]. This treatment may decrease pain for several months; however 8% capsaicin patch has not been studied for trigeminal PHN and for face and head application[27]. 8% capsaicin is not available in Brazil.

Lidocaine

Topical lidocaine is a first line drug to treat PHN. It acts by blocking sodium channels and decreasing abnormal ectopic discharges[4,5,10,26,28,29]. It is used as 5% lidocaine skin patches or as a cream, such as the Eutectic Mixture of Local Anesthetics (EMLA) containing 2.5% prilocaine and 2.5% lidocaine. 5% lidocaine patch is licensed for PHN patients in the USA. The patch has 750 mg lidocaine, of which just 5% are released[26,30]. Topical lidocaine is effective and safe, with low incidence of systemic adverse reactions and few side effects; in general, patients have mild local reactions[17,26,28,30]. Even with multiple lidocaine applications, systemic levels of this drug remain low. 5% lidocaine should be applied in the painful skin area for a maximum period of 12h per day[26,28,30]. It may be used in association with anticonvulsants, opioids and tricyclic antidepressants[17].

Interventionist treatment

There are many interventionist options as strategy to treat PHN, however some with uncertain efficacy.

Neural blocks

Sympathetic neural blocks may also be considered to relief HZ and PHN acute pain[3,10,11,31]. Although the precise mechanisms through which sympathetic nervous system contributes to neuropathic pain are not clear, data indicate an abnormal activation of alpha-adrenergic receptors in primary afferent neurons.

Neural blocks have been used to relief pain in PHN patients, although with less analgesic efficacy as compared to HZ. When the blockade is induced during HZ acute stage, in addition to decreasing pain intensity, it theoretically prevents the development of PHN[4,10].

Local anesthetics promote pain relief for 12-24 hours. In the long term, relief may be achieved by weekly performing the procedure in early stages of the disease[7]. The incidence of severe complications induced by the blockade is low and depends on the location of the blocked nerve[10]. A single administration in the epidural space of a steroid associated to local anesthetic during HZ acute stage may decrease pain for one month, but it is not effective for the long term prevention of PHN[6,10].

Several observational and prospective studies suggest that epidural block in combination with oral administration of an antiviral drug is very effective to treat acute HZ, decreasing pain duration and severity. Other nervous blocks, such as intercostal nerve block, have been used to relieve PHN pain[10].

Although subarachnoid injection of methylprednisolone acetate relieves PHN pain, its safety has been questioned, since it contains benzyl alcohol and polyethylene glycol as preservatives[4,10].

Spinal cord stimulation

Spinal cord stimulation has been used to treat chronic neuropathic pain, but its action mechanism is still unclear[10,14]. Its action is based on the pain control gate theory, where the stimulation of myelinated Aβ fibers interferes with the transmission of nociceptive stimuli conducted by C and Aδ fibers from the periphery to the spinal cord dorsal horn. The electric impulse is transmitted as from a generator implanted in the subcutaneous to electrodes placed in the epidural space. Spinal cord stimulation has complication rates varying from 30% to 40%.

Major complications are: hardware problems, especially electrodes migration, infection and painful stimulation. Complications are more significant when associated to neurological injuries due to root or spinal cord injury in the perioperative period. In the attempt to prevent infection, a strict sterile technique and venous antibiotics are used before the procedure. There may be accidental dura-mater puncture during the implant of the spinal cord stimulator, resulting in postdural puncture headache. The first option is the conservative treatment; however for refractory cases it is recommended an

epidural blood patch. When there is painful stimulation, one should reposition or remove the electrode[32]. Current literature evidences suggest that spinal cord stimulation is effective to handle certain types of neuropathic pain. For some patients, it may promote long term pain relief in up to 60% to 80%[10,23], with improved patients' QL and satisfaction.

Surgical excision

Preliminary studies have tried to show that surgical skin excision of the area affected by PHN is an option to decrease pain, eliminate tactile allodynia and decrease the use of analgesics in up to one year after surgery, but follow up has revealed constant pain increase, exceeding pre-surgical levels. Authors have concluded that surgical skin resection of the affected area is not recommended to treat PHN[5,8,10].

Acupuncture

This is a therapy considered effective to control pain. In spite of several documented cases about its use for HZ and PHN, samples are small. It is very useful when jointly used with conventional PHN therapies[4,7,8].

Psychological treatment and behavioral therapies

The association of emotional and biological factors is extremely important for PHN maintenance and modulation[5]. So, potential benefits of psychological support for PHN patients should not be ignored[4,5]. Behavioral therapies, such as relaxation, meditation and massages have also been used with positive effects for PHN[4,8].

Prevention

The number of HZ and PHN patients may increase in the future, because general population is ageing, which may increase the incidence of HZ and its complications[9].

A prophylactic vaccine able to improve specific immunity of T cells against VZV is a promising clinical approach to limit HZ and its debilitating complications, including PHN. In fact, HZ is associated to increase in specific cell immunity for VZV, being uncommon recurrences of HZ in immunocompetent indivuals[19].

The study about HZ prevention, Shingles Prevention Study (SPS), has evaluated the efficacy of an attenuated live virus vaccine to decrease the incidence and/or severity of HZ and PHN in a sample of 38546 individuals aged ≥ 60 years. The vaccine is effective to prevent HZ and promotes 66.5% decrease in the incidence of PHN and of 51.3% in the incidence of HZ[21,29].

This vaccine was approved by the FDA (US Food and Drug Administration) and by EMA (European Medicines Agency). The vaccine is indicated to prevent HZ in individuals aged ≥ 60 years (USA) or ≥ 50 years (Europe), being contraindicated for immunocompromised patients, children and pregnant women[4,21]. In the future, vaccines against varicella and HZ may change HZ and PHN epidemiology and natural history[6]. However, vaccine against HZ is still not available in Brazil[33].

CONCLUSION

Acute pain is the symptom afflicting HZ patients the most. Early use of antiviral drugs accelerates the healing of skin rashes and decreases pain intensity. Early HZ diagnosis and treatment are important in the attempt to optimize pain management in the acute stage and to prevent complications, such as PHN. Several therapeutic options are available to treat PHN, however with variable efficacy. Optimal pain control is difficult and no treatment is completely effective for all patients.

Analgesic combinations are used in the clinical practice for pain relief. However, randomized and controlled clinical trials are needed to better evaluate drug combinations and new therapies, aiming at developing new strategies to manage PHN. A prophylactic vaccine against VZV is a promising approach to decrease the incidence of HZ and PHN.

REFERENCES

1. Pearce JM. Post herpetic neuralgia. J Neurol Neurosurg Psychiatry. 2005;76(4):572.
2. Thyregod HG, Rowbotham MC, Peters M, et al. Natural history of pain following herpes zoster. Pain. 2007;128(1-2):148-56.
3. Garcia JB, Ferro LS, Carvalho AB, et al. Severe carbamazepine-induced cutaneous reaction in the treatment of post-herpetic neuralgia. Case report. Rev Bras Anestesiol. 2010;60(4):429-37.
4. Johnson RW, McElhaney J. Postherpetic neuralgia in the elderly. Int J Clin Pract. 2009;63(9):1386-91.
5. Naylor RM. Neuralgia pós-herpética. Aspectos gerais. São Paulo: Segmento Farma; 2004. p. 5-39.
6. Schmader KE, Dworkin RH. Natural history and treatment of herpes zoster. J Pain. 2008;9(1 Suppl 1):S3-9.
7. Roxas M. Herpes zoster and postherpetic neuralgia: diagnosis and therapeutic considerations. Altern Med Rev. 2006;11(2):102-13.
8. Portella AVT, Gomes JMA, Marques HG, et al. Neuralgia pós-herpética em área anatômica pouco usual. Relato de caso. Rev Dor. 2012;13(2):187-90.
9. Dworkin RH, Grann JW Jr, Oaklander AL, et al. Diagnosis and assessment of pain associated with herpes zoster and postherpetic neuralgia. J Pain. 2008;9(1 Suppl 1):S37-44.
10. Wu CL, Raja SN. An update on the treatment of postherpetic neuralgia. J Pain. 2008;9(1):19-30.
11. Stankus SJ, Dlugopolski M, Packer D. Management of herpes zoster (shingles) and postherpetic neuralgia. Am Fam Physician. 2000;61(8):2437-44.
12. Opstelten W, Eekhof J, Neven AK, et al. Treatment of herpes zoster. Can Fam Physician. 2008;54(3):373-7.
13. Dworkin RH. Recent advances in reducing the burden of herpes zoster and postherpetic neuralgia. J Pain. 2008;9(1):1-2.
14. Hempenstall K, Nurmikko TJ, Johnson RW, et al. Analgesic therapy in postherpetic neuralgia: a quantitative systematic review. PLoS Med. 2005;2(7):e164.
15. Gilden D, Cohrs RJ, Mahalingam R, et al. Neurological disease produced by varicella zoster virus reactivation without rash. Curr Top Microbiol Immunol. 2010;342:243-53.
16. Vena GA,1 , Doriana Apruzzi Apruzzi D,1 , Michelangelo Vestita Vestita M,1 et al. , Agata CalvarioZoster... "a lmost"... sine herpete: diagnostic utility of real time-polymerase chain reaction. New Microbiol. 2010;33(4):409-10.
17. Hall GC, Carroll D, McQuay HJ. Primary care incidence and treatment of four neuropathic pain conditions: descriptive study, 2002-2005. BMC Fam Pract. 2008; 9(26):1-9.
18. Ursini T, Tontodonati M, Manzoli L, et al. Acupuncture for the treatment of severe acute pain in herpes zoster: results of a nested, open-label, randomized trial in the VZV pain study. BMC Complement Altern Med. 2011;11(46):1-8.
19. Watson CP. Herpes zoster and postherpetic neuralgia. CMAJ. 2010;182(16):1713-4.
20. Dworkin RH. Post herpetic neuralgia. Herpes. 2006;13(1):21A-27A.
21. Gnann JW Jr. Vaccination to prevent herpes zoster in older adults. J Pain. 2008;9(1):S31-6.
22. Spátola A. Neuralgia pós-herpética – tratamento da dor neuropática com uso da toxina botulínica tipo A – apresentação de um caso. Med Reabil. 2010;29(3):74-5.
23. Zin CS, Nissen LM, Smith MT, et al. An update on the pharmacological management of post-herpetic neuralgia and painful diabetic neuropathy. CNS Drugs. 2008;22(5):417-42.
24. Bjekic M, Markovic M, Sipetic S. Penile herpes zoster: an unusual location for a com-

mon disease. Braz J Infect Dis. 2011;15(6):599-600.
25. Gilden DH, Kleinschmidt-DeMasters BK, LaGuardia JJ, et al. Neurologic complications of the reactivation of varicella-zoster virus. N Engl J Med. 2000;342(9):635-45.
26. Flores MP, Castro APCR, Nascimento JS. Analgésicos tópicos. Rev Bras Anestesiol. 2012;62(2):244-52.
27. Sayanlar J, Guleyupoglu N, Portenoy R, et al. Trigeminal postherpetic neuralgia responsive to treatment with capsaicin 8% topical patch: a case report. J Headache Pain. 2012;13(7):587-9.
28. Teotónio R, Brinca A, Cardoso JC, et al. Tratamento da neuralgia pós-herpética. Rev SPDV. 2012;70(4):451-7.
29. Bennett GJ, Watson CP. Herpes zoster and postherpetic neuralgia: past, present and future. Pain Res Manag. 2009;14(4):275-82.
30. Delorme C, Navez ML, Legout V, et al. Treatment of neuropathic pain with 5% lidocaine-medicated plaster: five years of clinical experience. Pain Res Manag. 2011;16(4):259-63.
31. Cunningham AL, Dworkin RH. The management of post-herpetic neuralgia. BMJ. 2000;321(7264):778-9.
32. Jeon YH. Spinal cord stimulation in pain management: a review. Korean J Pain. 2012; 25(3):143-50.
33. Pasternak J. Vacina contra herpes-zóster. Einstein. 2013;11(1):133-4.