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Use of Vincristine for the Treatment of Postherpetic Neuralgia: Case Report

Uso da vincristina no tratamento de neuralgia pós-herpética: relato de caso

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Running title: Vincristine for the treatment of postherpetic neuralgia

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Abstract

Chronic pain is a condition that can cause prolonged physical and emotional suffering, affecting several aspects of an individual's life. To be considered chronic, the pain must last for at least three months and be associated with notable emotional distress and/or functional disability, which can lead to social isolation and a feeling of hopelessness. In the present study, a specific type of chronic pain is approached. The Herpes zoster virus, which causes varicella, popularly known as chickenpox, can persist in a latent state in the nervous system after a primary infection. It can later lead to an infection resulting from virus reactivation, named Herpes zoster and also known as shingles, which may be followed by postherpetic neuralgia, a persistent pain that can last for more than three months after the resolution of the skin lesions caused by the virus reactivation. This study aimed to report the possibility of treating refractory postherpetic neuralgia with the antineoplastic drug vincristine sulfate, which can be applied off-label in patients presenting with pain caused by other illnesses besides tumors. It is important to emphasize that the use of vincristine for the treatment of postherpetic neuralgia requires care and should only be performed by specialist physicians after a detailed evaluation of the patient's clinical condition.

Keywords: chronic pain; *Herpes zoster*; postherpetic neuralgia

Resumo

A dor crônica é uma condição que pode causar sofrimento físico e emocional prolongado, afetando diversos aspectos da vida do indivíduo. Para ser considerada crônica, a dor deve durar pelo menos três meses e estar associada a acentuado sofrimento emocional e/ou incapacidade funcional, podendo levar a isolamento social e sentimento de desesperança. No presente estudo, é abordado um tipo específico de dor crônica. O vírus Herpes zoster, que causa varicela-zóster, popularmente conhecida como catapora, pode persistir em estado latente no sistema nervoso após uma infecção primária. Posteriormente, pode levar a uma infecção decorrente da reativação do vírus, conhecida como herpes-zóster, que pode ser seguida por neuralgia pós-herpética, uma dor persistente que pode durar mais de três meses após a resolução das lesões de pele causadas pelo vírus. Este estudo teve como objetivo relatar a possibilidade de tratamento da neuralgia pós-herpética refratária com o medicamento antineoplásico sulfato de vincristina, que pode ser aplicado off-label em pacientes com dores causadas por outras enfermidades além das tumorações. É importante destacar que o uso de vincristina para tratamento da neuralgia pós-herpética requer cuidados e deve ser realizado apenas por médicos especialistas após uma avaliação detalhada do quadro clínico do paciente.

Palavras-chave: dor crônica; *Herpes zoster*; neuralgia pós-herpética

Introduction

Chronic pain

Pain is conceptualized as an unpleasant sensory and emotional experience, described as actual or potential tissue damage. Pain is always subjective and each individual learns and uses this term based on their experiences.¹ Given this subjectivity, it is noticeable that pain can interfere in several aspects of the individual's life, since this painful experience causes emotional, physical, economic, and social stress, restricting the capacity for family and work activities.²

Another important aspect is the characterization of pain. It is worth emphasizing that pain should be analyzed according to its extent, which may be acute or chronic. To be considered chronic, the pain must last for at least three months and be associated with notable emotional distress and/or functional disability.^{3,4} Taking into account that the intensity, duration, or location of pain proportionally interfere with the individuals' life, it is important to point out the immense damage it imposes on their quality of life, because chronic pain can trigger biological, psychological, social, and health-related problems.² Moreover, chronic pain can cause physical disability, dependence, social distancing, changes in sexuality, changes in family dynamics, hopelessness, feeling of death, among others.⁵

In addition to these aspects, another important fact regarding chronic pain is the patient's unproductive disability, likely to have individual and collective consequences that affect the country's economy. The decrease in productive capacity is so relevant that since the last century the Institute of Medicine in the United States has considered chronic pain a public health problem.⁵ On a personal level, studies have shown that individuals with chronic pain suffer from absenteeism at work and may even lose their jobs because of pain symptoms. In Spain, 24.4% of individuals presenting with chronic pain asked to leave work and 12% left or lost their jobs for the same reason.²

Varicella zoster virus

Varicella zoster virus (VZV) is an alpha herpes virus (*Herpes zoster*) that causes varicella, popularly known as chickenpox, usually in children who live in places with low vaccination rates. The major characteristic of VZV primary infection is a vesicular pruritic rash that mainly affects the trunk, head, and face. The skin lesions progress from papules to vesicles and then to crusts over a period of few days. Other symptoms can be malaise, fever, and fatigue, and the disease normally lasts about a week.⁶

Nevertheless, the virus persists in a latent form in the nervous system after the primary infection. The reactivation of VZV in a cranial nerve or dorsal root ganglion, triggered by compromised cell immunity, with propagation along the sensory nerve to the corresponding dermatome, leads to painful cutaneous manifestations, a condition called herpes zoster (HZ), also known as shingles.⁷ The main clinical manifestations of HZ are prodromal symptoms of pain, malaise, low fever, pruritus, and localized sensitivity. After that, a vesicular pruritic rash appears, initially as macules and papules, progressing to vesicles, pustules, and crusts. New lesions may appear 3 to 5 days after the onset despite antiviral therapy.⁸ The rash usually becomes dry and crusty within 7 to 10 days, and the lesions heal after an average period of 2 to 4 weeks.⁹

The main risk factor for HZ is increasing age, especially after age 50. Thus, unvaccinated people who live up to age 85 have a 50% risk of developing the disease.¹⁰ The mechanism that explains this higher incidence of HZ over the years is the decline in immunity that affects elderly individuals. It is known that after primary VZV infection, a progressive reduction, proportional to time, occurs in the level of T cell-mediated immunity to VZV.¹¹

Postherpetic neuralgia

Among the refractory chronic pain disorders, some are caused by underlying diseases such as postherpetic neuralgia (PHN), characterized as persistent pain for more than three months after the resolution of skin lesions that occur due to the reactivation of VZV.¹² Since chronic pain in general, and PHN in particular, significantly affects the

individual's life,⁵ it is highly important to search for treatments that help in the management and treatment of this condition.

It is widely known that individuals with suppressed immunity or who have chronic diseases are at greater risk of having HZ and PHN. In a Brazilian study that followed up 249 patients who had the first episode of HZ between 2010 and 2014, 45 (18.07%) of them had PHN. Of the patients with PHN, 62.20% were aged 60 years or older, a finding that points to a decline in immunity.¹³

The evaluation of refractory neuropathic pain is difficult to access in the literature due to the heterogeneity of studies, different definitions adopted, and distinct evaluation methods used. The classification of this type of pain has been modified with some frequency by the International Association for the Study of Pain in recent years, and may, for instance, be classified as possible, probable, and permanent.¹⁴

Therefore, it is necessary to point out the importance of the prophylactic vaccination for HZ, since immunization is still the best option to prevent the disease and its complications.¹⁵ In view of the precarious diversity of effective studies on PHN, it is mandatory to expand the research on the subject, considering the low therapeutic incidence of current treatments. Taking into account that PHN is a complex, multifactorial disorder with extensive pathophysiology, it requires a continuous approach, and the medical team in charge needs to seek therapeutic alternatives that fit this condition, despite its complexity, so that the affected patients can achieve partial or total remission of symptoms.

Vincristine

Vincristine sulfate, a drug that belongs to the mitotic inhibitor class, has traditionally been used as an anticancer drug and administered intravenously for this purpose. Although its mechanism of action is still not totally clear, in general, the substance acts specifically by inhibiting the M phase of cell division, impairing the development of various types of neoplastic tumors such as acute lymphocytic leukemia and breast cancer, and it may also interfere with the formation of some amino acids.¹⁶

Some studies suggest that vincristine can also be successfully used to treat patients presenting with refractory chronic pain of diverse etiologies.¹⁷ With regard to PHN specifically, repeated administration of vincristine to affected dermatomes permanently relieves chronic pain. The effect of this therapy probably occurs because of transganglionic degenerative atrophy of primary central sensory terminals.¹⁸

Despite the evidence that the intradermal use of vincristine in the dermatomes affected by PHN helps in pain management, its continuous intravenous infusion in rats caused chemotherapy-induced neuropathy.¹⁹ This may sound paradoxical, because the same substance that causes neuropathy can also treat it. The explanation for this is based on the principle that “poisons and remedies are often the same substances given with different intentions”.¹⁷ In this scenario, the fact is: vincristine causes degenerative atrophy of sensory terminals¹⁸ and this side effect can be positive or negative.

Based on this, vincristine was the drug chosen in this study because, although it is usually used in the treatment of tumors, its off-label application can help control PHN and substantially improve the quality of life of affected patients.

Case report

A 73-year-old female patient sought medical care at our service due to a herpetic lesion located in the lower region of the left breast, sensory level at T5 dermatome, complaining of extreme local pain and discomfort. After clinical evaluation and the confirmation of the diagnosis of PHN, we adopted we adopted the following medications: duloxetine, pregabalin, buprenorphine, codeine, and tramadol. However, after exhausting the pharmacotherapeutic options with no improvements, we opted for the intradermal treatment with vincristine sulfate, an antineoplastic drug commonly used in various dermatological diseases and several types of cancer.

The protocol consisted of eight sessions of 0.1-mL vincristine solution intradermal applications at intervals of 0.5 cm, along the entire length of the herpetic lesion, every 30 days. This solution was first obtained by diluting 1 mL vincristine to 10 mL saline

and then 1 mL of the product so obtained was diluted again to 1000 mL saline.^a Both the periodicity and the total number of sessions were determined according to the needs of the patient.

Due to allodynia in the affected area, the patient was taken to the operating room and sedated before the procedure, after defining the area to be treated. Adverse reactions reported by this patient were mild, including discomfort and redness in the treated area, which lasted about a week. No significant complications or side effects were observed.

The visual analog scale (VAS), a self-reported pain rating scale ranging from 0 (“no pain”) to 10 (“worst pain”), was used prior to the procedure, after each session in follow-up appointments, and at the completion of the treatment. According to the patient, PHN decreased from 10 (preintervention) to 2 (postintervention), showing that the treatment with vincristine was highly effective in controlling her pain.

Thus, this method can be a safe and effective option for the treatment of PHN, as long as it is carried out with caution and constant monitoring by a specialized professional. It is crucial that each case is evaluated individually, and also that the choice of treatment is based on an adequate and individualized clinical evaluation, considering the characteristics of the patient and the lesion, in addition to the risks and benefits of each therapeutic option.

During the entire treatment, our team closely monitored the patient, advising on care and possible side effects of vincristine sulfate applications. After the sessions, the patient reported significant improvement in the lesion and in PHN and her satisfaction with the results. The treatment was found to be safe and effective in this case.

In summary, the patient experienced temporary local discomfort and redness following the sessions, but had no severe complications or systemic reactions after the procedure. Although the treatment with intradermal vincristine solution resulted in considerable improvement in PHN, as assessed by VAS, suggesting that this approach may be a safe and efficient therapeutic option for the treatment of this type of pain in elderly patients, more research is needed to evaluate its effectiveness and safety in a larger sample of patients.

^aPersonal communication Prof. Dr. José Oswaldo de Oliveira Júnior, São Paulo, SP.

Discussion

Chronic refractory pain is a debilitating condition that affects millions of people worldwide, with significant deleterious effects on quality of life and economic losses.²⁰ It is characterized as a persistent pain that is often difficult to treat with conventional therapies,²¹ and therefore it can lead to a range of physical and psychological complications.²²

Managing refractory chronic pain requires a multidisciplinary approach, involving physicians, physiotherapists, psychologists, and other health professionals.²³ In addition, treatment options must be individualized, tailored to the needs and preferences of each patient, and monitored by a pain specialist.²⁴

A specific condition of refractory chronic pain is PHN, a painful complication that can remain even after the resolution of HZ lesions. Given that more than 1 million new cases of HZ occur in the United States each year, and approximately 30% of all Americans will have HZ in their lifetime,²⁵ the scenario is worrying.

Based on the fact that chronic pain substantially impairs the quality of life of patients, several studies have investigated options for the management of neuropathic pain. In the past, traditional categories of drugs were more analyzed for this purpose such as anticonvulsants and antidepressants. Currently, a tendency is observed towards the use of new classes of drugs or the innovative use of existing drugs such as antineoplastic drugs.¹⁷

Some studies have been conducted with the aim of investigating treatment options for PHN, including antiviral therapies and other drugs such as vincristine.²⁶ Although vincristine is commonly used as an antineoplastic agent,¹⁶ it is an example of a drug with promising results for the off-label treatment of refractory chronic pain.¹⁷ Paradoxical as it may seem, some studies have demonstrated that by causing

degenerative atrophy of the sensory terminals, the intradermal administration of vincristine in the dermatomes affected by PHN permanently relieves chronic pain.¹⁸

Conclusion

It is important to emphasize that every patient is unique and that the treatments must be tailored to their individual needs. The treatment of patients diagnosed with PHN with vincristine should be carefully supervised by a physician specialized in pain, especially in elderly patients with underlying health conditions. Despite indications that vincristine may be a promising treatment option for patients presenting with PHN, more research is needed to evaluate its effectiveness and safety for the treatment of this painful condition in a larger sample of patients.

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