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ARTICLE

Liposomal topical capsaicin in post-herpetic neuralgia: a safety pilot study

Capsaicina lipossomal tópica na neuralgia pós-herpética: um estudo piloto de segurança

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ABSTRACT

Topical treatments have gained popularity for general use as an adjunct to systemic drugs in neuropathic pain, but their use produces variable clinical results and local adverse events. **Objective:** To evaluate the safety and analgesic effect of a formulation of liposomal capsaicin (LC) (0.025%) in patients with post herpetic neuralgia (PHN). **Method:** Patients who remained symptomatic after first-and second-line treatment were randomized to receive LC for six weeks in a placebo-controlled, crossover design study. Clinical assessment was performed at baseline, in the second, fourth and sixth week of treatment. **Results:** Thirteen patients completed both treatment periods. Visual Analog Scale (VAS) was significantly decreased after the end of the study (p = 0.008), however the effect of treatment was not significant (p = 0.076). There was no difference on global impression of change and other pain characteristics. LC was safe and well tolerated. However, at the concentration used, its analgesic effects were marginal and not significant.

Keywords: capsaicin, pain, neuralgia, analgesia, rash, adverse events.

RESUMO

Os tratamentos tópicos ganharam popularidade para uso geral como um adjuvante de medicamentos sistêmicos na dor neuropática, mas seu uso produz resultados clínicos variáveis e eventos adversos locais. **Objetivo:** Avaliar o efeito de segurança e analgesia de uma formulação de capsaicina lipossomal (LC) (0,025%) em pacientes com neuralgia pós-herpética. **Método:** Os pacientes que permaneceram sintomáticos após tratamento de primeira e de segunda linha foram randomizados para receber LC durante seis semanas em um estudo cruzado controlado por placebo. A avaliação clínica foi realizada no início do estudo, na segunda, quarta e sexta semana de tratamento. **Resultados:** Treze pacientes completaram dois períodos de tratamento. Escala Visual Analógica diminuiu significativamente após o final do estudo (p = 0,008), no entanto, o efeito do tratamento não era significativo (p = 0,076). Não houve diferença na impressão global de mudança e de outras características da dor. LC foi segura e bem tolerada. No entanto, para a concentração utilizada, os seus efeitos analgésicos foram marginais e não significativos.

Palavras-chave: capsaicina, dor, neuralgia, analgesia, efeitos adversos.

Neuropathic pain is present in 7% of the general population[1,2], and despite the multiple treatment approaches, its current management only provides modest pain relief[3,4]. There has been renewed interest in the development of topical treatments that can decrease pain with lower side effects[4]. However, the use of topical treatments has provided variable analgesic results[5,6] and is associated with side effects mainly related to skin reactions and pain in the application site[7,8]. One approach to increase the therapeutic index (i.e., the measurement of efficacy over toxicity) is to employ delivery systems that can release the medication to its target with fewer side effects related to local inflammation[9]. Topical capsaicin has been used in the treatment of neuropathic pain over the last few decades in different formulations with variable efficacy and side effect profiles[10]. Capsaicin, an alkaloid derived from plants of the *Solanaceae* family is commercially available in different vehicles (cream, lotion, gel, transdermal patch) at both low (< 1%) and high concentrations (capsaicin 8% patch - C8P)[8]. Capsaicin acts locally and is not distributed or absorbed systemically. Its action lasts for four to five hours. The application of capsaicin promotes the local sensation of heat and hyperemia[11]. This effect is

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dose-dependent and temporary. There is also a reduction of mechanical and thermal hyperalgesia, which increases with repeated application. Repeated exposure to capsaicin leads to a significant reduction of neuropathic pain in some patients[3]. However, there are some limitations of the use of capsaicin in clinical practice, which include the lack of efficacy in some patient groups, as well as the lack of adherence and low tolerability due to side effects, such as dermal irritation, erythema and pain at the site of application. Developing systems to improve drug delivery in order to minimize side effects and improve the local action of capsaicin could decrease such adverse events and increase tolerability. We have hypothesized that using vesicular systems, such as liposomes, to deliver capsaicin to the skin could decrease local side effects and provide pain relief[12,13,14]. The aim of this pilot proof of concept study was to evaluate the efficacy and safety of topical liposomal capsaicin (0.025%) in patients with chronic post-herpetic neuralgia. The rationale was that by using this approach we would be able to deliver smaller amounts of the drug deeper in the epidermis and nearer to its target (thin unmyelinated peptidergic nerve endings) with a better side effect profile.

METHOD

The study was approved by our local institutional review board (#0078/11). All patients provided written informed consent before being included in the study.

Patients

Post-herpetic neuralgia (PHN) patients from the Pain Center of the *Hospital das Clínicas, Universidade de São Paulo*, Brazil were prospectively screened for the study. The inclusion criteria were chronic ($>$ 6 months) symptomatic PHN non-responsive (visual analog scale (VAS) $>$ 4) to systemic neuropathic pain drugs (e.g., tricyclic antidepressants, anticonvulsants and opioids) and being able to inform adequately. PHN, was defined as definite neuropathic pain according to current criteria[15]. The exclusion criteria excluded patients with major systemic or psychiatric disease and the presence of other pain syndromes that could bias the assessment, such as primary headache or painful peripheral neuropathy.

Study design

This study was a double-blind, crossover randomized trial divided into two periods. All participants received either 0.025% liposomal capsaicin or placebo for six weeks (first period). Non-ionic cream (capsaicin) or vehicle (placebo) was applied two or three times per day. Then, after a withdrawal period of two weeks, they underwent a second six-week treatment period in a crossover design. The systemic pain medication used in the beginning of the study was maintained in all patients until the end of the second treatment period. Acute pain medications were not allowed, except for the use of paracetamol at a maximum dose of 3 g/day.

Clinical assessment

All participants were evaluated in the beginning of each treatment period and after the second, fourth and sixth (end) week of each treatment period. All clinical assessments were similar, were performed by a blinded researcher and included the following tools: (1) spontaneous pain (SP) intensity by the VAS [0-100 mm]; (2) the Category Verbal Scale (CVS), which classified the average pain in the last two weeks as mild, moderate, and severe pain in intensity[16]; (3) the intensity of evoked pain (EP), and static and dynamic mechanical allodynia intensity in the painful area were used to study EP through the contact and movement of a cotton swab; (4) pain relief scale after treatment (better, worse or no change) by direct questioning; (5) McGill Pain Questionnaire (MPQ)[17]; (6) quality of life by the SF-36 questionnaire[18]; and (7) adverse events by direct questioning patients on the presence of new symptoms presenting during treatment and direct examination by a blinded researcher.

Data analysis

Each participant's baseline characteristics were expressed as descriptive statistics as the mean ± standard deviation, and analyzed using Student's t-test, Fisher's exact test and Chi-squared test when indicated. The treatment response was analyzed by ANOVA with treatment (liposomal capsaicin and placebo) as the factor and time before and after treatment as within-group variables. In all instances, the level of significance was set at $p < 0.05$.

RESULTS

Patient characteristics

Nineteen patients with neuropathic pain secondary to PHN were screened for participation in the study. Fourteen were included and thirteen completed the two treatment phases. One patient dropped out due to a change (dose decrease) in the baseline treatment for PHN during the first treatment period. The mean age of patients treated with capsaicin was 71.94 ± 10.5 years. The patients experienced pain in thoracic dermatomes in 66% of the cases, followed by the trigeminal and cervical areas.

Pain characteristics

The mean duration of pain was 33.4 ± 21.0 months. The intensity of spontaneous pain measured by VAS ranged from 7.00 ± 2.17 to 5.31 ± 2.65 in the after capsaicin and from

6.38 ± 2.50 to 6.0 ± 2.64 under placebo. This difference was statistically significant (p = 0.008) concerning the effects of time, but was not related to the treatment factor (p = 0.076), (interacion p = 0.581) (Figure). Measurements of spontaneous pain by the category verbal scale showed that it was considered mild in 10%, moderate in 30% and intense in 60% of patients treated with capsaicin. Spontaneous pain was moderate in 44.4% and intense in 55.5% of the patients treated with the placebo before treatment. At the end of the treatment, pain became mild in 30% of patients treated with capsaicin but not in any of the placebo-treated patients; pain remained intense in 50% of patients treated with capsaicin and 62.50% of the placebo-treated patients, however, these differences did not reach statistical significance. Dynamic mechanical allodynia was severe or moderate in 83.3% of patients before treatment and decreased to 38.46% after the use of capsaicin. In the group that received the placebo, severe or moderate allodynia was present in 61.54% at the beginning of the study and remained unchanged after treatment. None of these differences were statistically significant (p = 0.434). The reporting of pain in general did not differ between patients treated with capsaicin or placebo (p = 0.381), nor did the pain relief score. The improvement in symptoms occurred in 55.63% of patients treated with capsaicin and in 48.85% of patients treated with placebo (p = 0.260.) The index of the McGill Pain Questionnaire changed from 21.6 ± 13.5 to 19.5 ± 14.2) after the active and from 25.44 ± 13.7 to 23.40 ± 12.8 after the placebo treatment (p = 0.118). Quality of life scores increased after both treatments, going from (15.20 to 23.8) in the active and from 23.97 to 27.22 in the placebo treatment group (p = 0.382).

Side effects

The adverse effects of treatment were expressed at most in 87.5% of patients treated with capsaicin and in 60% of patients treated with placebo. At the end of treatment 56.25% of patients treated with capsaicin and 60% of patients treated with placebo reported discomfort (p = 1.00).

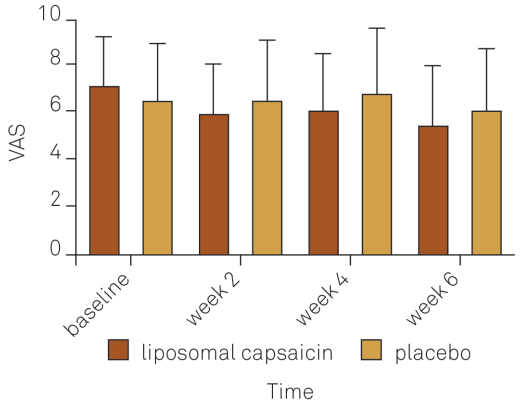

Figure. Visual analog scale (VAS) at baseline, 2nd, 4th and 6th week of treatment after the liposomal capsaicin and placebo treatment.

DISCUSSION

In the present study, pain intensity (VAS) was significantly decreased compared to baseline, however, the effect of treatment was not significant. Other pain characteristics, intensity of allodynia and quality of life were not influenced by the treatment.

Low-dose capsaicin (0.075%) has been shown to be effective for the relief of neuropathic pain with a modest effect. On the other hand, a meta-analysis that pooled data from seven studies comparing low dose capsaicin and 8% patches for treatment of neuropathic pain showed the superiority of the higher dose in most studies, which was observed via the reduction of spontaneous pain, but the higher dose had higher rates of mild and self-limited side effects, such as application-site erythema, application-site pain, application-site pruritus, and application-site papules[19,20]. Possible advantages of a liposomal formulation used in this study include optimal penetration and absorption, slow release of the drug, longer lasting analgesic effect, the need for smaller doses and therefore a lower rate of side effects[21,22]. In fact, no major side effects were reported in this study, which demonstrates the safety and tolerability of the liposomal formulation at the concentration used. There are two major subsets of unmyelinated primary afferent nociceptors. The first is a transient receptor potential vanilloid-1-positive nociceptor. The second is a non-peptidergic nociceptor that binds isolectin B4 and expresses the Mrg family of G-protein-coupled receptors. These subsets innervate different epidermal layers and can be differentially activated by peripheral noxious stimuli and engage different ascending circuits. Whereas peptidergic fibers are responsible for noxious heat, nonpeptidergic afferents selectively contribute to mechanical pain behaviors[23,24]. We hypothesized that LC would be able to reach the deeper section of the epidermis and reach its receptor with lesser side effects. The treatment was devoid of local or systemic side-effects but ineffective in the concentration used.

In conclusions, liposomal capsaicin was safe and well tolerated. At the concentration used, its analgesic effects were marginal and not significant. This was a pilot, safety study assessing the effects of lipossomal capsaicin as an ad-on treatment to patients already taking at least two different types of medication. We suggest that higher concentrations of liposomal capsaicin should be tested in larger studies of PHN patients to determine its clinical efficacy.

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