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SCIENTIFIC ARTICLE

Capsaicin topical cream (8%) for the treatment of myofascial pain syndrome

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KEYWORDS
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Topical route;
Trigger points;
Myofascial pain syndrome

Abstract
Background: Myofascial pain syndrome is a common cause of musculoskeletal pain. The objective of this study was to evaluate the potential analgesic action of 8% capsaicin cream for topical use in patients with myofascial pain syndrome.
Methods: Initially, cream formulations of PLA (Placebo) and CPS (Capsaicin 8%) were developed and approved according to the current requirements of the health authority agency. The 40 participating patients were randomly assigned to the PLA and CPS groups in a double-blind fashion. Before the creams were topically administered, according to the allocation group, the local anesthetic was used for a period of 50 minutes directly in the area of interest. The cream was applied to the area of the skin over the trigger point, represented by the area with pain at palpation, in an amount of 10 g for 30 minutes in a circular area of 24 mm diameter. Subsequently, the cream was removed and the skin tolerability parameters were evaluated. The pain was measured before and during the formulation application, as well as at 1 hour, 7 days, 30 days, and 60 days after the procedure, evaluated using a verbal numerical scale (from 0 to 10: with 0 = no pain and 10 = worst pain imaginable).
Results: No patient in PLA Group had hyperemia or burning sensation at the site of application, while 85% of patients in CPS Group had hyperemia or burning sensation at 15 minutes. These complaints disappeared 24 hours after the cream was removed. The pain score in CPS Group decreased steadily up to the 60th day of evaluation ($p < 0.0001$).

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Conclusion: Application of the formulations did not cause macroscopic acute or chronic skin lesions in patients, and the 8% capsaicin formulation was beneficial and well tolerated.

PALAVRAS-CHAVE
Capsaicina;
Administração tópica;
Pontos-gatilho;
Síndrome de dor miofascial

Creme tópico de capsaicina (8%) para o tratamento da síndrome da dor miofascial

Resumo
Justificativa: A síndrome da dor miofascial é uma causa comum de dor musculoesquelética. O objetivo deste estudo foi avaliar a potencial ação analgésica de 8% do creme de capsaicina para uso tópico em pacientes com síndrome da dor miofascial.
Métodos: Inicialmente, as formulações de creme de PLA (Placebo) e CPS (Capsaicina 8%) foram desenvolvidas e aprovadas de acordo com os requisitos atuais da agência de autoridade de saúde. Os 40 pacientes participantes foram distribuídos aleatoriamente e de forma duplo-cega para os grupos PLA e CPS. Antes dos cremes serem administrados topicamente, de acordo com o grupo de alocação, o anestésico local foi usado por um período de 50 minutos diretamente na área de interesse. A administração ocorreu na área da pele sobre o ponto-gatilho o qual apresentou a área dolorida à palpação, em uma quantidade de 10 g por 30 minutos em área circular com diâmetro de 24 mm. Posteriormente, o creme foi removido e os parâmetros de tolerabilidade à pele foram avaliados. A dor foi medida antes e durante a aplicação da formulação, bem como 1 hora, 7 dias, 30 dias e 60 dias após o procedimento avaliado pela escala numérica verbal (0 a 10, com zero sem dor e dez a pior dor imaginável).
Resultados: Nenhum paciente no grupo PLA experimentou hiperemia ou sensação de queimação no local de aplicação do creme, enquanto 85% dos que experimentaram no grupo CPS apresentaram hiperemia ou sensação de queimação 15 minutos. Estas queixas desapareceram 24 horas após a remoção do creme. O escore de dor no grupo CPS diminui de forma sustentada até o 60° dia de avaliação ($p < 0{,}0001$).
Conclusão: A administração das formulações não causou lesões cutâneas agudas ou crônicas macroscópicas nos pacientes, e a formulação de 8% de capsaicina foi benéfica e bem tolerada.

Introduction

Myofascial Pain Syndrome (MPS), which is commonly seen in primary care clinics of various specialties, is one of the most common causes of musculoskeletal pain. Before establishing any treatment, it is very important to detect trigger points (TPs).[1] TPs represent the major source of musculoskeletal pain affecting muscles, connective tissues, and fascia, mainly in the cervical region and scapular and lumbar girdles.[2]

Currently, the diagnostic criterion for MPS is not yet defined besides the one that identifies the presence of a tension point through palpation, with or without referred pain, known as trigger point or patient's recognition of symptoms during TP palpation, associated with three findings: muscle stiffness or spasm, limitation of joint movement, worsening of stress pain, and palpation of a muscle tension zone and/or nodule associated with a TP.[3] It is accepted that functional painful syndromes expressed as localized muscle pain should be classified as MPS and, if pain is diffuse, probably classified as fibromyalgia, according to the *2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria* by Wolfe et al.[4]

MPS treatment should be multimodal with the main purpose of managing the underlying disease causing pain. It is also important to mention that treatment of existing trigger points (TPs) is critical and can be done with noninvasive approaches, such as the use of menthol aerosols, stretching, transcutaneous electrical nerve stimulation, physical therapy, and massage. However, not rarely invasive treatments with intramuscular injections of local anesthetics, corticosteroids, and botulinum toxin, as well as dry needling of TPs need to be considered.[5] Although the gold standard invasive treatment is dry needling and infiltration of these painful points with local anesthetics, these interventions can be very uncomfortable for patients. For those patients intolerant to invasive measures, lidocaine patches and topical Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) may be used, although their efficacy has not been proven. Systemic use of NSAIDs and muscle relaxants may provide some pain relief.[6] There is still a need to propose a less invasive yet effective treatment approach for MPS.

The use of capsaicin, a substance known for its analgesic properties, can be an option for these patients. Capsaicin may be used as a topical pain reliever, usually

at concentrations ranging from 0.025 to 0.075%, found in the form of creams, gels, and ointments.[7] Moreover, high-concentration capsaicin 8% patch has been approved by the American Food and Drug Administration (FDA) and European Medicines Agency (EMA) in some clinical situations, such as post-herpetic neuralgia (PHN) and HIV-associated painful neuropathy.[8] A single application lasting up to 60 minutes in patients with neuropathic pain provides effective pain relief for up to 12 weeks.[9]

In order to improve MPS treatment and offer a less invasive option, the aim of this study was to evaluate the analgesic action of a high concentration capsaicin cream, which desensitizes nociceptors and could potentially become a therapeutic option for this clinical condition.

Method

This was a prospective double-blind placebo-controlled study that met the Consort criteria. After approval by the Institutional Ethics Research Committee, the study was performed at a specialized pain clinic in a tertiary teaching hospital. Placebo (PLA) and capsaicin 8% (CPS) creams were specially formulated and developed for use in this study under standardized pharmaceutical procedures, which attested to the safety and stability, including microbiological, physical, and chemical analyzes prior to application.

Adult subjects were invited to participate in the study and were enrolled in the active or placebo group, according to a computer-generated random numbers program. Inclusion criteria were: patients undergoing regular treatment at the pain outpatient clinic; adequate adherence to prescribed medications involving conventional MPS therapy for at least one month; presence of pain severity >5 (assessed with the Verbal Numerical Scale – VNS: 0–10) caused by palpation of the most painful TP; absence of skin lesions or sores on TPs; absence of known hypersensitivity to capsaicin (subject is asked about intolerance to red pepper); abstention from red pepper ingestion six hours before cream application; absence of hypersensitivity to any component of the formula (the subject is asked about the existence of intolerance to skin creams); absence of hypertension and diabetes; and pregnancy. The patient's refusal to participate in the study immediately before the cream application was considered as an exclusion criterion. All participants agreed to participate voluntarily by giving written informed consent.

Patients were asked to point out the most painful TP during the physical examination in order to determine the topical application of the cream, according to their assigned group. This TP was demarcated by a 24 mm diameter circular mold with a stylus for use on the skin. Prior to application of study creams (PLA or CPS), patients in both groups received a commercially available topical anesthetic cream (lidocaine 4%) for 50 minutes in the area corresponding to TP, which was removed prior to PLA or CPS application, respectively, cream base or cream base with capsaicin 8%.

PLA and CPS creams were applied in an amount of 10 g for 30 minutes on the demarcated skin area.[10] All necessary personal protective equipment was provided for the safety of personnel and patients (gloves, goggles, and face masks). Patients in both groups received a single treatment. After 30 minutes, the PLA and CPS formulations were removed using wet wipes, and the toxicity and tolerability parameters were evaluated. In addition, the skin demarcated area was cleaned with an anionic physiological pH cleansing gel.

Subjects were asked about the presence of burning sensation on the site (skin tolerability parameters), as well as the occurrence of skin changes during 60 minutes immediately after the cream application. When removing the creams at 30 and 60 minutes, the patients were asked to score their spontaneous pain (VNS: 0–10), that is, without TP palpation. Twenty-four hours after withdrawal of the cream formulations, patients were contacted by telephone to assess skin tolerance with questions about the presence or absence of redness and burning at the application site, as well as spontaneous pain.

Patient evaluation on the 7th day after cream application, as well as subsequent evaluations (1 and 2 months), were also made by phone calls. During these consultations, patients were asked about the presence and intensity of burning at the application site, skin changes, and also to rate the spontaneous pain felt during the last week, using the VNS in three different situations: lower pain intensity score (LPS), higher pain intensity score (HPS), and pain score at assessment time (PSA). Patients were also asked to rate their satisfaction after treatment (dissatisfied, somewhat or totally satisfied). The skin tolerability parameters to the cream applied were evaluated at four time-points (1, 15, 30, and 60 minutes).

Statistical analysis

The sample size calculation was based on the expected difference between VNS averages in the study groups, around four units of measurement. Assuming a standard deviation of 3.5 units and test power of at least 90%, we estimated that 20 patients per group were required. For the statistical analysis and verification of possible differences regarding measurement times and groups, repeated measures ANOVA was used, which enables treatment with univariate and multivariate analyzes. For comparisons involving quantitative variables, we used Student's *t*-test and comparisons between qualitative variables—the proportionality test. The significance level was set at 5%.

Results

Forty six patients were included. However, six patients were excluded during the study, as it was not possible to contact them by phone after the proposed intervention. Thus, 40 MPS patients were effectively included in this clinical trial. Twenty patients in the PLA Group (5 men and 15 women) received the cream base and 20 patients in the CPS Group (4 men and 16 women) received the capsaicin 8% cream. There was no statistically significant difference regarding age group of patients in PLA Group (57 years) and CPS Group (58 years) ($p \geq 0.05$; Student's *t*-test). Regarding the drugs actually in use, such as analgesics, anti-inflammatory drugs, muscle relaxants, and antidepressants, the results did not indicate significant difference between the two groups ($p \geq 0.05$; Student's *t*-test). The only statistically significant difference observed was in the use of benzodiazepines, anticonvulsants, and neuroleptics, which were more used in PLA

Table 1 Lower pain score in the last week evaluated using the verbal numeric scale (0–10).

Time to intervention					
Groups (n = 20)	BI	60 minutes	7 days	30 days	60 days
PLA	3.7 (1.1)	3.7 (1.7)	2.7 (2.8)	1.3 (2.9)	1.4 (3.3)
CPS	4.3 (2.2)	3.3 (2.3)	1.4 (1.4)	1.7 (1.9)	1.7 (2.9)
Mean ± SD	4.0 (1.6)	3.5 (2.0)	2.0 (2.3)	1.5 (2.4)	1.5 (3.1)

Data are presented as mean ± SD. Exposure period: BI (before intervention), 60 minutes and 7 days, 30 and 60 days after intervention ($p \geq 0.05$): comparison between periods. PLA, placebo group; CPS, capsaicin 8% group.

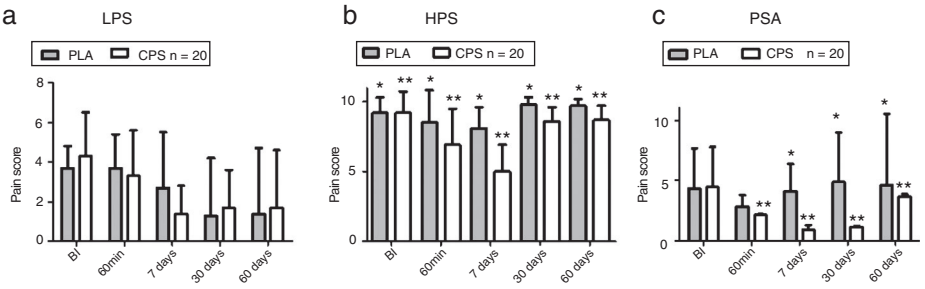

Figure 1 Pain scores evaluated using a verbal numerical scale (0–10). (a) Lower pain score (LPS) in the last week. (b) Higher pain score (HPS) in the last week. (c) Pain score at assessment time (PSA). ANOVA: results presented as mean and standard deviation. BI: before intervention; PLA: placebo group; CPS: capsaicin 8% group (*$p < 0.000$: comparison between groups; **$p < 0.001$: comparison between time points in the same group).

Table 2 Higher pain score in the last week evaluated using the verbal numeric scale (0–10).

Time to intervention					
Groups (n = 20)	BI	60 minutes	7 days	30 days	60 days
PLA	9.2 (1.1)[a]	8.5 (2.3)[a]	7.7 (2.5)	9.8 (0.5)[a]	9.7 (0.5)[a]
CPS	9.2 (1.5)	6.9 (2.6)	5.0 (1.9)[b]	8.6 (1.0)[b]	8.7 (1.0)[b]
Mean ± SD	9.2 (1.3)	7.7 (2.5)	6.5 (2.3)	9.2 (1.0)	9.2 (1.0)

Data are presented as mean ± SD. Exposure time: BI (Before Intervention), 60 minutes and 7 days, 30, and 60 days after the intervention. PLA, placebo group; CPS, capsaicin 8% group.
[a] $p < 0.0001$, comparison between groups.
[b] $p < 0.001$, comparison between time points in the same group.

Group before starting the study (80% of subjects), compared to CPS Group (50%) ($p < 0.001$: proportionality test).

Pain score evaluation in the week prior to cream application showed no statistically significant difference between groups PLA and CPS in the three considered situations (LPS, HPS, and PSA) ($p \geq 0.05$: Student's *t*-test).

There was no statistically significant difference in the level of satisfaction assessed 60 minutes after the intervention. Among patients in PLA Group, 18 subjects were fully satisfied, while in the CPS Group 20 subjects were fully satisfied ($p \geq 0.05$: proportionality test).

In CPS Group, 65% of the patients had a skin burning sensation immediately after application, while none of the PLA Group patients experienced local burning ($p < 0.0001$: Student's *t*-test). The presence of cutaneous hyperemia was seen in 47.5% of patients in CPS Group, while none of the patients in PLA Group had such alteration ($p < 0.0001$; proportionality test). Twenty four hours after the intervention, none of the 40 subjects complained of burning or local hyperemia at the application site. No other significant local or systemic side effects were seen in participants on both groups during the study observation period.

Pain scores after intervention

The lower pain scores (LPS) for both groups are shown in Table 1 and Fig. 1a. Regardless of measurement time-points, there was no significant difference between groups and times-points ($p \geq 0.05$).

Regarding the higher pain score (HPS) after intervention, subjects in PLA Group had higher pain scores compared to patients in CPS Group ($p < 0.0001$). In addition, 60 days after the intervention, there was a decrease in HPS in CPS Group, which although statistically significant had no clinical significance. These results were statistically and clinically significant for the seven and 30 day periods ($p < 0.01$) (Table 2 and Fig. 1b).

Table 3 Higher score at assessment time using the verbal numerical scale (0–0).

Time to intervention					
Groups (n = 20)	BI	60 minutes	7 days	30 days	60 days
PLA	6.7 (2.0)	3.5 (2.2)	5.7 (2.5)[a]	7.8 (2.0)[a]	8.8 (0.5)[a]
CPS	6.8 (2.1)	2.2 (2.1)	0.7 (1.2)[b]	1.1 (1.2)[b]	3.8 (3.4)[b]
Mean ± SD	6.7 (2.0)	2.8 (2.2)	3.2 (3.2)	4.4 (3.7)	6.3 (3.5)

Data presented as mean ± SD. Exposure time: BI (before intervention), 60 minutes and 7 days, 30, and 60 days after intervention. PLA: placebo group; CPS: capsaicin 8% group.
[a] $p < 0.0001$: comparison between groups.
[b] $p < 0.001$: comparison between time points in the same group.

There was no statistically significant difference between the two groups regarding pain score at assessment time (PSA) in the first 60 minutes after intervention. However, at seven, 30, and 60 days post-intervention, a LPS was seen in CPS group ($p < 0.0001$). In PLA Group, pain increased over time compared to the time before intervention, as shown in Table 3 and Fig. 1c, which did not occur in subjects in CPS Group.

Discussion

Capsaicin has a recognized analgesic effect when topically applied. Despite studies with contradictory results regarding its use in MPS, there are no studies addressing the use of capsaicin in high concentrations, as it has been used to treat peripheral neuropathic pain in this specific clinical situation. However, it is known that the capsaicin concentrations commonly used clinically have been associated with short-term pain relief and poor adherence to continued use due to side effects, particularly burning sensation after application. The benefit of capsaicin has been associated with a concentration-related phenomenon. Thus, MPS patients may benefit from improved pain relief over a longer period using the high-concentration capsaicin.[11]

The clinical characteristics of patients with MPS included in this study were similar to those of subjects included in other publications. Studies performed in pain centers and multi-specialty clinics reported MPS incidence of 21%–93% in individuals with generalized pain complaints.[12] The average age of patients participating in this study was 57–58 years. One study showed that there was a higher prevalence of MPS in patients aged 50–74 years.[13] These data are consistent with other studies and suggest that working-age individuals are the most affected by MPS. However, most patients who agreed to participate in this study were about 50 years old. In Brazil, middle-aged women are more likely to suffer from MPS (3:1) compared to men, particularly in the age group of 30 to 49 years.[14]

It is also noteworthy that most of the subjects in both groups in this study were female. A clinical epidemiology study performed at Hospital das Clínicas, University of São Paulo Medical School, reported a higher prevalence of MPS in females. In most individuals, the involvement occurred in more than one body segment.[15]

Notable aspects such as pain, disability caused by MPS, condition chronicity, and some frustrating therapeutic experiences tend to make the patient more resistant to new treatment proposals, especially when its efficacy cannot be guaranteed with a relative degree of confidence. Several patients invited to participate in this study declined because there was no guarantee that the intervention would solve their problem. Moreover, patients are skeptical that applying a pepper derivative could relieve pain resulting from MPS.

The subjects who agreed and were admitted to the study expressed great hope that something unknown would be administered and could alleviate their pain. However, it is known that for every 10 patients treated with capsaicin one tends to give up treatment due to the onset of local signs and symptoms.[16] In addition, because of these localized effects, it is difficult to perform clinical studies with this drug due to the difficulty in blinding the study.

Patients in this study were already receiving drug therapy prescribed for their diagnosis. The most commonly prescribed drugs were analgesics, NSAIDs, antidepressants, benzodiazepines, muscle relaxants, anticonvulsants, and neuroleptics. However, there is not enough evidence in the medical literature to support the use of capsaicin, benzodiazepines, and NSAIDs in MPS.[17]

Capsaicinoids (capsaicin and dihydrocapsaicin) are the substances of the capsicum pepper responsible for the spicy taste and irritability of skin and mucous membranes resulting from its topical use.[18] Capsaicin binds to the vanilloid receptor Type 1 present in the peripheral nerves, leading to an influx of calcium and release of inflammatory neuropeptides, which is associated with capsaicin irritating properties.[19] Moreover, the acute release of substance P, which also occurs, results in initial hyperalgesia that, with continued treatment, is followed by this substance depletion and consequent analgesia.

After repeated applications for varying periods, the site presents reduced sensitivity and increased blockade of painful stimuli, resulting in desensitization (reversible upon treatment discontinuation) or reversible fiber injury, depending on the dose and duration of exposure.[20]

Most commercially available capsaicin formulations are in the form of an ointment containing 0.025% or 0.075% active ingredients.[21] For pain relief, low concentration capsaicin formulations require several weeks of application. However, due to local skin reactions, such as redness, burning and erythema, many patients abandon treatment before this time.

The use of dermal patch containing capsaicin concentrations similar to those employed in this study is indicated for treating pain associated with post-herpetic neuralgia and

has been approved by the FDA. The most common adverse effects related to this formulation containing high concentration of capsaicin are transient erythema, pruritus and pain. These skin reactions are not severe and disappear spontaneously seven days after application.[11]

In this study, we observed the occurrence of burning and local cutaneous hyperemia in 48% of patients 15 minutes after the administration of CPS formulation, even with the previous application of topical local anesthetic. These skin reactions disappeared 24 h after administration without complications. Patients who received the PLA formulation had no skin disorder.

The amount of cream administered was approximately 10 g for each patient, applied to the previously demarcated TP, using a 24 mm diameter plastic mold. No antidote for capsaicin is known.[11]

In capsaicin toxicity studies, exposure times greater than 30 minutes were used in rats, mice, and pigs without toxicity being observed. Dermal absorption of capsaicin in rats has been shown to be greater than that observed when human skin is exposed. In humans, about 70% of the capsaicin present in the patch is transferred to skin and other tissues.[22] In the present study, systemic toxicity or phototoxicity was seen during or after application of PLA and CPS formulations. Capsaicin's phototoxic potential was not seen in rats.[23]

Capsaicin is typically an analgesic drug used to treat neuropathic pain, such as diabetic neuropathy and post-herpetic neuralgia, as well as osteoarthritis, rheumatoid arthritis, and symptomatic psoriasis.[24] The authors did not find studies using capsaicin at high concentrations in MPS patients.

The results of this study corroborate the pharmacodynamic activity of capsaicin,[20] as some patients showed a decrease in pain intensity up to 60 days after application and may have experienced a possible reversible pain desensitization.

Pain intensity was evaluated in this study before and after VNS application and showed reductions in pain scores after 60 minutes of application, which persisted until the beginning of 60 days of observation. There is evidence that capsaicin may possibly decrease the density of epidermal nerve fibers after a single application of a high concentration adhesive. This effect is reversible, since after cessation of exposure there is reinnervation of the epidermis with functional recovery of nerve fibers.[25]

To our knowledge, this study was the first using capsaicin 8% topically in MPS treatment. As a limitation, it is important to note that post-application evaluations were performed through phone interviews and no pressure algometer was used in the evaluation of the most painful TG, both in the inclusion phase of participants and in subsequent evaluations.

The concentration in the CPS formulation was significantly higher than the concentration used in capsaicin topical products patented in Brazil. A single 60-minute application of the CPS formulation may have resulted in a significant reduction in epidermal nerve fiber density, which was not measured in this study by immunohistochemical analysis. Although data from immunohistochemical studies suggest that capsaicin may interfere with nociceptive nerve fibers,[26] it is worth mentioning that axonal degeneration is probably not the only mechanism responsible for the pain relief seen in this study. A reduction in neuronal excitability, which disrupts rapid axonal transport or intrinsic desensitization of receptors, probably contributed to the therapeutic effect.[27] Sixty days after application, all patients experienced pain de novo, although less severe; the reversible mechanism of CPS action was prescribed.

Conclusion

Capsaicin 8%, as topically applied in this clinical study in patients with MPS, showed significant analgesic effect. This analgesia persisted for almost two months after a single application without producing significant adverse effects.

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Conflicts of interest

The authors declare no conflicts of interest.

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