ACTA ODONTOLOGICA SCANDINAVICA, 2017
VOL. 75, NO. 2, 130–136
http://dx.doi.org/10.1080/00016357.2016.1269191

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Analgesic effect of topical oral capsaicin gel in burning mouth syndrome

Mette Rose Jørgensen and Anne Marie Lynge Pedersen

Department of Odontology, Section for Oral Medicine, Clinical Oral Physiology, Oral Anatomy and Pathology, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen N, Denmark

ABSTRACT

Objective: To investigate the effectiveness of repeated topical application of oral capsaicin gel in two different concentrations for relief of burning/stinging sensations in patients with burning mouth syndrome (BMS).

Material and methods: This randomized double-blind cross-over study included 22 female patients with BMS. The patients were randomized for topical application of either 0.01% or 0.025% oral capsaicin gel on the dorsal part of tongue three times daily for 14 days, followed by 14 days wash-out period, and finally treatment with the other concentration of oral gel three times daily for 14 days. A visual analogue scale (VAS) was used to assess the severity of pain five times during the intervention period.

Results: 18 patients completed the intervention. Their VAS score at baseline was 5.5 ± 0.6 cm (mean ± SD). Treatment with the two concentrations of capsaicin gels significantly improved the burning/stinging symptoms assessed on VAS compared with baseline ($p = 0.002$). There was no statistically significant difference between the two concentrations of the gels on relieving symptoms. Four patients dropped out during the intervention period due to gastrointestinal side-effects.

Conclusions: Topical capsaicin might be an alternative for the short-term treatment of BMS. However, further studies are needed to investigate especially the gastro-intestinal side-effects which may limit its long-term use.

ARTICLE HISTORY
Received 9 August 2016
Revised 27 October 2016
Accepted 1 December 2016

KEYWORDS
Glossodynia; local anesthetics; neuropathic

Introduction

Burning mouth syndrome (BMS) is characterized by persistent oral mucosal burning pain in the absence of clinical or laboratory signs of mucosal pathology.[1,2] BMS most commonly occurs in middle-aged and often postmenopausal women.[3] Reported prevalence rates of BMS in the general populations vary from 0.7% to 4.6%.[4] The burning pain is mainly located to the tongue, hard palate and the lips and is often associated with a sensation of oral dryness (xerostomia) and altered taste perception (dysgeusia).[3,5,6] The pathogenesis and etiology of BMS are still unknown but assumed to be multifactorial, involving neurophysiological and psychological factors.[2,5,7]

A growing number of studies suggest that BMS is a form of neuropathic pain condition.[8–11] Lauria et al. [8] investigated the innervation of the epithelium of the tongue to assess whether the damage of peripheral nerve fibers could underlie the pathogenesis of BMS. The study demonstrated that patients with BMS had a significantly lower density of epithelial nerve fibers than control subjects, with a trend toward correlation with the duration of symptoms. Yilmaz et al. [12] studied the presence of the heat and capsaicin receptor TRPV1 (transient receptor potential vanilloid 1) and its regulator nerve growth factor (NGF) in patients with BMS. Immunohistochemical staining of biopsies showed a significant increase in TRPV1 and NGF positive nerve fibers in the patients, which correlated with on-going pain.

In this context, capsaicin (an alkaloid present in hot peppers like chili pepper) could offer a relevant therapeutic approach to BMS. Capsaicin (trans-8-methyl-N-vanillyl-6-nonenamide) binds to nociceptors, specifically to the TRPV1 receptor, which are located mainly on polymodal C-fibers, causing an initial neuronal excitation and release of pro-inflammatory mediators followed by enhanced sensitivity to painful thermal and mechanical stimuli (hyperalgesia).[13] However, repeated application of capsaicin causes prolonged activation of TRPV1 resulting in loss of receptor functionality, and causing impaired local nociception for prolonged periods. The mechanism for pain relief was previously believed to occur by local depletion of substance P.[13–16] However, more recent studies suggest that depletion of substance P is merely a correlate of capsaicin application, and that the causal mechanism of action is rather a process described as 'defunctionalization' of nociceptors.[17] Defunctionalization occurs due to various effects including temporary loss of membrane potential, inability to transport neurotropic factors leading to altered phenotype, and reversible retraction of nerve fiber terminals. Peripheral neuropathic hypersensitivity is mediated by diverse mechanisms that are defunctionalized

CONTACT Mette Rose Jørgensenm mrj@sund.ku.dk Department of Odontology, Faculty of Health and Medical Sciences, University of Copenhagen, Noerre Allé 20, 2200 Copenhagen N, Denmark

by repeated application of topical capsaicin attenuating cutaneous hypersensitivity and reducing pain.[17]

Topical application of capsaicin has been used and found effective in a variety of chronic musculoskeletal or neuropathic pain conditions including post-herpetic neuralgia, osteoarthritis and diabetic neuropathy.[16,18,19] Likewise, capsaicin has been considered a potential treatment option in patients with BMS.[19,20] Marino et al. [21] investigated the effect of capsaicin oral rinse and found a significant reduction in scores on a visual analogue scale (VAS) in patients with BMS after two months treatment. Tabasco sauce solutions (mouth rinses in a 1:2 solution or higher) have been used in the treatment of BMS but with varying results.[3]

The aim of this study was to investigate the short-term effectiveness of repeated topical application of 0.01% and 0.025% oral capsaicin gel for relief of burning/stinging sensations in patients with BMS. The null hypothesis was that treatment with the two capsaicin gels could not alleviate the burning/stinging symptoms in the patients.

Material and methods

Study group

The participants were recruited among patients attending or referred to the Oral Medicine Clinic, Department of Odontology, Faculty of Health and Medical Sciences, University of Copenhagen from February 2009 to May 2010. A total number of 22 female patients were consecutively enrolled after informed consent consisting of verbal and written information. Inclusion criteria were: a history of oral mucosal burning/stinging pain for at least six months but without any clinical oral lesions possible responsible for the burning/stinging sensation. The diagnosis of BMS was made by exclusion of local and systemic causes of the oral burning symptoms. Exclusion criteria were: patients under 18 years of age; pregnancy; breastfeeding; pathologies that could be responsible for the oral burning/stinging sensation, e.g. oral candidiasis, lingua geographica or oral lichen planus; fertile women not using safe contraception; known hypersensitivity towards capsaicin; active infection requiring antibiotic treatment; and patients not being able to understand and sign the informed consent form.

Study design

This randomized, double-blind, cross-over study was carried out according to the recommendations of the Declaration of Helsinki and was approved by the regional scientific ethical committee, the Capital Region of Denmark (Protocol no. H-A 2008-118), and the Danish Health and Medicines Authority (No. 2612-3885). The study was registered at the Danish Data Protection Agency and ClinicalTrials.gov (NCT005245-38). The Unit for Good Clinical Practice, Copenhagen University Hospital, monitored the data throughout the study period. The computer-generated randomization allocation list was performed by an impartial person from Glostrup Pharmacy, Denmark. The gels were provided in tubes, labeled Tube 1 and Tube 2, containing 30 ml each of either 0.01% or 0.025% capsaicin gel. Both the investigators and the patients were blinded with respect to which tube that contained either 0.01% or 0.025% gel. After signing the informed consent, the patients were randomized into group 1 or 2 for: (1) treatment with either 0.01% or 0.025% capsaicin oral gel to be used three times daily for 14 days; (2) fourteen days break, followed by; (3) treatment with the other concentration of capsaicin oral gel three times a day for 14 days. The duration of the intervention was eight weeks, and the patients were seen at the clinic at baseline and at eight weeks follow-up. A flowchart of the participants is shown in Figure 1.

The primary outcome was patient assessment of oral burning/stinging sensation measured on a VAS after treatment with 0.01% and 0.025% oral capsaicin gels.

Prior to the study, the concentrations of the two gels were determined by searching the literature concerning this subject thoroughly.[16–20,22–25] To avoid fast oral clearance and to make sure the therapeutic agent stayed in the oral cavity as long as possible; the topical agent was made as a digestible capsaicin gel produced at Glostrup Pharmacy, Denmark by a pharmacist following GMP guidelines. Additionally, prior to the trial and in order to evaluate the tolerance of burning sensation after application of the gels, we performed a pilot study including ten healthy individuals; testing four different concentrations of capsaicin oral gel (0.01%, 0.025%, 0.05% and 0.10%). The individuals rated the burning sensation on a VAS following the application, and they were blinded to which concentration they were given. The gels were tested in a random order (results not shown). Based on our knowledge from the literature search and the results from the pilot study, it was decided to fabricate the gels in two the lowest concentrations, 0.01% and 0.025%.

Clinical examination

At baseline, all the patients with BMS underwent an interview concerning their oral symptoms, current systemic diseases, medication intake and alcohol consumption; a thorough clinical examination; measurements of unstimulated and paraffin-chewing-stimulated whole saliva flow rates for 15 and 5 min, respectively;[26] a cytological smear for *Candida* taken from the dorsal part of the tongue or other oral sites by indication (the diagnosis of oral candidiasis is defined as a clinical lesion harboring *Candida* hyphae verified by *Periodic Acid-Shiff*-stained smear from the site); blood tests including hemoglobin, p-iron, p-zinc, mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), p-transferrin, p-ferritin, differential count, C-reactive protein (CRP), thyroid stimulating hormone (TSH) and blood glucose.

Intervention

At baseline, each patient was given a tube of capsaicin oral gel, 30 ml, numbered Tube 1. Each morning, midday and evening (each time at least one hour after a meal), the patients were instructed to smear 0.5 ml of the capsaicin gel

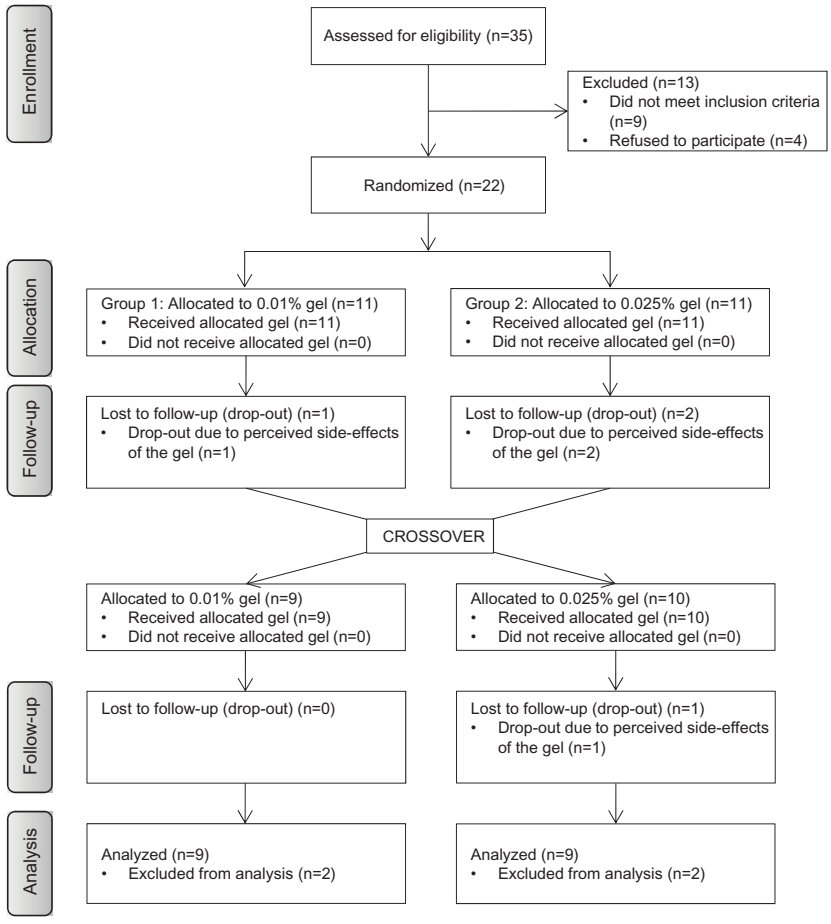

Figure 1. Flowchart of the participants.

(administered by a plastic syringe to ensure correct dosing) on the burning sites of the tongue and to spread it with a cotton bud. They were told not to consume any foods or drinks for at least half an hour after the application. The tube was used for 14 days followed by 14 days wash-out period. Then, the patient was asked to use Tube 2 also containing 30 ml capsaicin oral gel. Patients were asked to rate the severity of oral burning pain on a VAS (0 = no pain and 10 = worst imaginable pain) at baseline (Day 0), after 14 days' use of the first oral gel (Day 14), after 14 days' wash-out period with no gel used (Day 28), after 14 days' use of second gel (Day 42) and finally after 14 days' wash-out with no gel used (Day 56). Patients were also asked to fill out a diary to note if they had experienced any inconveniences when applying the gels; describe any possible side-effects; note if they had changed the dose or sustained from using the gel; note if there had been any changes in their general health or in their prescribed medication.

Statistics

All data were processed by IBM-SPSS software version 20.0 (Chicago, IL) and SAS software version 9.3 (SAS Institute Inc., NC).

With alpha set at 0.05 and beta at 0.8, 10 patients were needed in each study arm in order to detect a reduction in oral pain of 10 (difference in means) measured on a VAS scale (0–10 cm scale), anticipating that the standard deviation is 1.5 (cross-over ANOVA). The study was designed to randomize 22 patients to compensate for an expected drop-out and to include more patients to be able to estimate extra parameters e.g. a cross-over effect. Categorical variables were described by number of observations and percentage. For the demographic data, numeric variables were described by the median and minimum and maximum values. A mixed model with treatment as fixed effect and patient id-number as random effect was applied to analyze the difference in VAS scores before and after the treatment with oral gel. A pooled effect of the two concentrations of gels was estimated. If the result yielded a positive or negative result it represented an increase (worsening of pain) or decrease (improvement of pain) in VAS, respectively. The difference in the VAS scores between the two concentrations of capsaicin gels was analyzed using a similar mixed model with treatment and period as fixed effects and patient id-number as random effect. First models were run only adjusted for period, then adjusted for baseline VAS scores. To assess a possible carry-over effect (learning effect), a mixed model was used by means of the period by treatment interaction. The level of significance was $p < 0.05$.

Results

A total of 35 patients with BMS were assessed for eligibility. Nine patients did not fulfill the in- and exclusion criteria and

four patients refused the invitation to participate in the study. The inclusion was stopped when 22 patients were included.

The oral symptoms reported by the patients at baseline are shown in Table 1. The majority of patients had daily oral pain mainly characterized as a stinging and burning sensation on different oral sites, but primarily on the tongue. The type and severity of the oral symptoms varied between patients. Only one patient did not experience daily oral pain or burning. The severity of mucosal burning pain was not associated with the duration of BMS symptoms (median 2.8 years). Baseline characteristics of the patients are shown in Table 2. Fourteen (64%) patients reported systemic diseases (median 1), mainly cardiovascular or musculoskeletal conditions. Sixteen (73%) patients had a daily intake of medication (median 2), mainly from cardiovascular agents and neurologicals. None of the patients were in systemic treatment for their BMS, but some were taking analgesics for musculoskeletal disorders, e.g. osteoarthritis.

The median unstimulated salivary flow rate was 0.17 ml/min (range 0.04–0.45), and 6 (27%) patients had hyposalivation (defined as an unstimulated whole saliva flow rate of $\leq$0.1 ml/min).

None of the patients had oral candidiasis, but 13 (60%) were carriers of blastospores and/or single hyphae's. The blood tests were in general normal for all the patients but 12 (55%) patients had insignificant deviations from the reference intervals in one of the measured parameters (e.g. TSH, p-zinc and p-transferrin).

Table 1. Oral symptoms reported at baseline ($n = 22$).

Oral symptoms	
Duration of symptoms, *median (min–max), years*	2.8 (0.2–15)
Oral mucosal pain[a], *n (%)*	22 (100)
Lips (upper and lower)	13 (59)
Apical part of tongue	16 (73)
Dorsal part of tongue	11 (50)
Lateral margins of tongue	15 (68)
Anterior part of palate	11 (50)
Pharynx	3 (14)
Buccal mucosa	2 (9)
Xerostomia, *n (%)*	11 (50)
Hyposalivation (UWS)[b], *n (%)*	6 (27)
Dysgeusia[c], *n (%)*	15 (68)
Metallic taste	15 (68)
Impaired taste	13 (59)

[a]Pain described as burning, stinging, tingling, itching, feeling of excoriation. Each patient may have oral mucosal pain in more than one site.
[b]Hyposalivation is defined as UWS <0.1 ml/min (UWS = Unstimulated Whole Saliva).
[c]Each patient may experience more than one type of taste alteration.

Table 2. Baseline characteristics of the patients (n = 22).

Demographics	
Age, median (min–max), years	61 (34–70)
Alcohol consumption, *n* (%)	
Abstainer	3 (14)
Daily	0
Weekly	11 (50)
Rarely	8 (36)
Comorbidities, median (min–max)	1 (0–5)
Medical disease/condition,[a] *n* (%)	
Gastrointestinal	4 (18)
Cardiovascular	4 (18)
Endocrine	3 (14)
Musculoskeletal	6 (27)
Neurological	2 (9)
Respiratory incl. allergy	1 (5)
ATC groups,[b] *n* (%)	
Alimentary tract (A02 A07)	6 (27)
Blood system (B01)	2 (9)
Cardiovascular system (C03, C07, C08, C09, C10)	8 (36)
Systemic hormonal preparations (H03)	1 (5)
Immuno-modulating agents (L02)	1 (5)
Musculo-skeletal system (M01, M05)	4 (18)
Nervous system (N02, N03, N05, N06)	8 (36)
Respiratory system (R03, R05, R06)	4 (18)
Postmenopausal patients, *n* (%)	20 (91)

[a]Each patient may suffer from more than one disease.
[b]Sorted by the Anatomical Therapeutic Chemical (ATC) classification system. Each patient may take more than one drug.

Effect of the oral capsaicin gel

Of the patients, 11 reported a beneficial effect on pain intensity at VAS after using the capsaicin gels. Six patients obtained pain relief in continuation of using the gels but experienced the pain returning in the 14-day washout period and five experienced continued pain relief. The VAS scorings during the intervention period of the two treatment groups (Day 0, 14, 28, 42 and 56) are shown in Table 3. The mean VAS score for both treatment groups at the first examination (baseline) was 5.5 (±0.6). There was a statistically significant positive treatment effect of the two gels with an expected decrease on VAS of 1.4 (±0.4) compared with baseline ($p = 0.002$). There was a slightly better treatment effect of gel 0.01% compared with gel 0.025% with an estimated difference on VAS of −0.5, however, this difference was not statistically significant ($p = 0.27$). Although the patients were randomly selected into the two treatment groups, a difference in VAS was reported at baseline (Table 3). However, similar results were found after statistically correction for baseline VAS scores.

There was a statistically significant correlation between pain intensity at baseline and after treatment with both concentrations of the gels; patients with a high VAS score at baseline also scored highest after the treatment ($p < 0.0001$). Patients having the longest history of symptoms showed the best improvement on VAS after treatment, however, the effect was only borderline significant ($p = 0.04$).

The VAS scores increased in both periods where the gels were not used in both treatment groups. The scores on VAS before the second treatment period was slightly lower than at baseline before the first treatment period in both groups, however, no carry-over effect was observed ($p = 0.23$).

Drop-outs and side effects

Three patients stopped therapy during the first week of treatment due to gastrointestinal side effects such as nausea and itching and another found the consistency of the gel unpleasant. One patient stopped therapy after four weeks due to soreness of the throat.

After discontinuation of the capsaicin gel, these side effects were completely reversed and were considered minor adverse events. The patients with BMS who completed the protocol reported a strong burning in the mouth after application of the gel that decreased and disappeared after 5–30 min. Other reported side effects included unpleasant taste and consistency of the gel. No major gastrointestinal side effects were reported. The patients observed a stronger localized burning sensation in the mouth after application of the 0.025% gel compared with the 0.01% gel. This burning sensation diminished after several days of exposure to capsaicin for both concentrations of the gels.

Discussion

In the present study, we investigated the effectiveness of topical capsaicin oral gel 0.01% and 0.025% in 22 patients with BMS. The participants were consecutively recruited to the study over 15 months. Of the patients, 18 completed the trial and showed good compliance to the given instructions; four dropped out due to minor adverse side effects. A pooled effect of the two concentrations of the gels proved effective in the patients with BMS as treatment led to a statistically significant reduction of the oral burning pain scored on VAS, and the null hypothesis could therefore be rejected. No patients obtained complete pain relief. Some patients obtained pain relief in continuation of using the gels but experienced the pain returning in the 14-day break and some experienced continued pain relief. These results confirm the findings of other comparable studies.[18,22] Despite the fact that the patients were randomized into the two treatment groups, a difference in VAS scores was observed at baseline. We have no simple explanation for this, however, at baseline some patients scored very high at VAS and some very low, and a random gathering of patients with higher baseline scores in one of the groups might explain this observation. However, no deviations in the results were found after statistically correction for these scores.

Initially, we intended to compare topical capsaicin gel with a placebo gel on symptoms in BMS. However, we were not able to locate a placebo-agent producing the same burning sensation after application on the tongue as the capsaicin gel. Accordingly, we would not be able to properly blind the patients. Instead, we aimed to investigate the effectiveness of two different concentrations of capsaicin gel since the threshold concentration for the effectiveness of capsaicin in BMS is unknown.

In any medical treatment or clinical trial, the psychobiological placebo effect can affect the therapeutic outcome due to care, concern and thorough examinations.[27] This is especially relevant in the group of patients with BMS, who often have been examined and treated by several specialists in the medical healthcare systems often without any positive outcome regarding reduction in their symptoms. The placebo effect regarding this study is almost inevitable first of all due to the fact that the participants knew they were being treated with an active agent during the entire intervention period, secondly due to the extra care and concern, as mentioned above. This placebo effect is a major shortcoming, and the positive results obtained in the study therefore have to be interpreted with precaution.

BMS is a disabling pain condition that often has major negative impacts on the patient's quality of life. The management of BMS is challenging and our search for effective and safe therapeutic approaches is important. The treatment options of BMS reflect the fact that the pathogenesis and etiology behind the disease are still largely unknown. A variety of therapeutic approaches has been proposed to relieve symptoms, but with limited effect.[5,23] Both systemic and topical treatments have been studied in attempt to alleviate the symptoms in the patients. Antidepressants such as paroxetine,[28] the benzodiazepine clonazepam,[29,30] the antioxidant alpha-lipoic acid [31–35] and local bupivacaine anesthetic [36] have all shown some efficacy but with no convincing effectiveness.

Capsaicin has been used in the management of post-herpetic neuralgia demonstrating promising results.[37] However, only a few clinical trials have investigated the efficacy of capsaicin on pain relief in patients with BMS. In 1994, Epstein and Marcoe [19] (case study) reported the use of topical capsaicin for the management of BMS. They documented the therapeutic efficacy of a 0.025% topical capsaicin gel in treatment of two patients with BMS. Petruzzi et al. [20] proved the efficacy of systemic capsaicin 0.25% in treating BMS patients over a short-term period, but the systemic administration of capsaicin was associated with significant gastric pain.

The mucosal burning sensation at the time of application of the capsaicin gel is commonly reported in studies using topical capsaicin.[18,19,22,24] However, the burning pain diminished the more times the gel was used. This could be

Table 3. VAS Scoring of the two treatment groups at baseline and during the intervention period. *Mean* (*SD*).

	1. Treatment period			2. Treatment period			
Group/(order of received gels)	Baseline Day 0	After use of first gel Day 14	VAS diff (FU1-BL)[a]	After 14 days' wash-out Day 28	After use of second gel Day 42	VAS diff (FU3-BL)[a]	After 14 days' wash-out Day 56
1/(0.01%;0.025%) ($n = 9$)	6.4 (2.0)	4.7 (2.7)	−1.7 (2.3)	5.9 (3.2)	5.1 (3.0)	−1.0 (1.7)	6.0 (2.7)
2/(0.025%;0.01%) ($n = 9$)	4.6 (2.6)	3.6 (2.8)	−1.0 (2.8)	3.5 (2.8)	3.0 (2.9)	−1.6 (2.3)	3.2 (3.1)

Patients were asked to rate the severity of oral burning pain on a VAS (0 = no pain and 10 = worst imaginable pain) at baseline, after 14 days' use of the first oral gel (either 0.01% or 0.025%), after 14 days' wash-out period without the use of any gel, after 14 days' use of second gel (either 0.01% or 0.025%) and finally after 14 days' wash-out period without the use of any gel.

[a]VAS diff: Mean (SD) difference in VAS scores before and after the treatment with oral gels; BL: Baseline; FU1: Follow-up1 (after use of the first gel); FU3: Follow-up3 (after use of the second gel).

explained by the fact that the TRPV1 receptor activation itself produces pain, but repeated application desensitizes the receptor, thus blocking the signal to the primary afferent. Capsaicin application also produces a release of substance P and calcitonin gene-related peptide (CGRP) in the skin and continued application depletes peripheral terminals of these pro-nociceptive substances.[38] We found no statistically significant difference in the effectiveness between the 0.01% and 0.025% oral gels on the BMS symptoms. This could imply that the 0.01% concentration of the capsaicin gel is high enough to activate the TRPV1 receptor, thereby producing pain relief in the patients. Another advantage of the 0.01% concentration is that it produces fewer side effects in the form of less burning sensation on the tongue after application compared with the 0.025% gel.

In other studies, maximum pain relief was achieved after 4–5 weeks' therapy.[18,20,22] In our study, the treatment period was 14 days, which might not be sufficient time to obtain the desired treatment effect compared with the other studies. It cannot be ruled out that some of the non-responders in this study might benefit from higher doses of capsaicin or prolonged therapy.

In this study, we experienced some reluctance to enroll (estimated to approximately 30%) either because the burning sensation had diminished spontaneously (regularly controlled patients) or because the patients did not wish to participate in clinical trials. Moreover, only 18 patients completed the intervention, which might make this study underpowered as we were not able to perform the final statistical analysis on the required number of participants suggested by the power analysis.

In conclusion, within the limitations and shortcomings of this study, topical capsaicin might be a useful short-term alternative to treat BMS, but further clinically controlled studies are necessary for further definition of its usefulness in the management of BMS.

Acknowledgements

The authors gratefully thank Glostrup Pharmacy, especially pharmacist Steen Mejlgaard, for their corporation, skilled planning and production of the capsaicin gels. We also would like to thank Claus Jensen for statistical consultation.

Disclosure statement

The authors have no conflict of interests to report.

Funding

This study was implemented with financial support from the Danish Dental Association, The Danish Council for Independent Research and A.P. Møller og Hustru Chastine Mc-Kinney Møllers Fond til Lægevidenskabens Fremme.

References

[1] Forssell H, Jääskeläinen S, Tenovuo O, et al. Sensory dysfunction in burning mouth syndrome. Pain. 2002;99:41–47.

[2] Sun A, Wu KM, Wang YP, et al. Burning mouth syndrome: a review and update. J Oral Pathol Med.2013;42:649–655.

[3] Grushka M, Epstein JB, Gorsky M. Burning mouth syndrome. Am Fam Physician. 2002;65:615–620.

[4] Scala A, Checchi L, Montevecchi M, et al. Update on burning mouth syndrome: overview and patient management. Crit Rev Oral Biol Med. 2003;14:275–291.

[5] Pedersen AML, Smidt D, Nauntofte B, et al. Burning mouth syndrome: aetiopathogenic mechanisms, symptomatology, diagnosis and therapeutic approaches. Oral Biosci Med. 2004;1:3–19.

[6] de Moraes M, do Amaral Bezerra BA, da Rocha Neto PC, et al. Randomized trials for the treatment of burning mouth syndrome: an evidence-based review of the literature. J Oral Pathol Med.2012;41:281–287.

[7] Forssell H, Jääskeläinen S, List T, et al. An update on pathophysiological mechanisms related to idiopathic oro-facial pain conditions with implications for management. J Oral Rehabil. 2015;42:300–342.

[8] Lauria G, Majorana A, Borgna M, et al. Trigeminal small-fiber sensory neuropathy causes burning mouth syndrome. Pain. 2005;115:332–337.

[9] Albuquerque RJ, de Leeuw R, Carlson CR, et al. Cerebral activation during thermal stimulation of patients who have burning mouth disorder: an fMRI study. Pain. 2006;122:223–234.

[10] Just T, Steiner S, Pau HW. Oral pain perception and taste in burning mouth syndrome. J Oral Pathol Med. 2010;39:22–27.

[11] Puhakka A, Forssell H, Soinila S, et al. Peripheral nervous system involvement in primary burning mouth syndrome – results of a pilot study. Oral Dis. 2016;22:338–344.

[12] Yilmaz Z, Renton T, Yiangou Y, et al. Burning mouth syndrome as a trigeminal small fibre neuropathy: increased heat and capsaicin receptor TRPV1 in nerve fibres correlates with pain score. J Clin Neurosci. 2007;14:864–871.

[13] Mason L, Moore RA, Derry S, et al. Systematic review of topical capsaicin for the treatment of chronic pain. Bmj. 2004;328:991.

[14] Holzer P. Capsaicin: cellular targets, mechanisms of action, and selectivity for thin sensory neurons. Pharmacol Rev. 1991;43:143–201.

[15] Woolf CJ, Mannion RJ. Neuropathic pain: aetiology, symptoms, mechanisms, and management. Lancet. 1999;353:1959–1964.

[16] Kissin I. Vanilloid-induced conduction analgesia: selective, dose-dependent, long-lasting, with a low level of potential neurotoxicity. Anesth Analg. 2008;107:271–281.

[17] Anand P, Bley K. Topical capsaicin for pain management: therapeutic potential and mechanisms of action of the new high-concentration capsaicin 8% patch. Br J Anaesth. 2011;107:490–502.

[18] Peikert A, Hentrich M, Ochs G. Topical 0.025% capsaicin in chronic post-herpetic neuralgia: efficacy, predictors of response and long-term course. J Neurol. 1991;238:452–456.

[19] Epstein JB, Marcoe JH. Topical application of capsaicin for treatment of oral neuropathic pain and trigeminal neuralgia. Oral Surg Oral Med Oral Pathol. 1994;77:135–140.

[20] Petruzzi M, Lauritano D, De Benedittis M, et al. Systemic capsaicin for burning mouth syndrome: short-term results of a pilot study. J Oral Pathol Med. 2004;33:111–114.

[21] Marino R, Torretta S, Capaccio P, et al. Different therapeutic strategies for burning mouth syndrome: preliminary data. J Oral Pathol Med. 2010;39:611–616.

[22] Bernstein JE, Bickers DR, Dahl MV, et al. Treatment of chronic postherpetic neuralgia with topical capsaicin. A preliminary study. J Am Acad Dermatol. 1987;17:93–96.

[23] Zakrzewska JM, Forssell H, Glenny AM. Interventions for the treatment of burning mouth syndrome. Cochrane Database Syst Rev. 2005;1:CD002779.

[24] McBurney DH, Balaban CD, Popp JR, et al. Adaptation to capsaicin burn: effects of concentration and individual differences. Physiol Behav. 2001;72:205–216.

[25] Green BG, Rentmeister-Bryant H. Temporal characteristics of capsaicin desensitization and stimulus-induced recovery in the oral cavity. Physiol Behav. 1998;65:141–149.

[26] Pedersen AM, Reibel J, Nauntofte B. Primary Sjögren's syndrome (pSS): subjective symptoms and salivary findings . J Oral Pathol Med. 1999;28:303–311.
[27] Benedetti F, Mayberg HS, Wager TD, et al. Neurobiological mechanisms of the placebo effect. J Neurosci. 2005;25:10390–10402.
[28] Yamazaki Y, Hata H, Kitamori S, et al. An open-label, noncomparative, dose escalation pilot study of the effect of paroxetine in treatment of burning mouth syndrome. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2009;107:e6–e11.
[29] Grushka M, Epstein J, Mott A. An open-label, dose escalation pilot study of the effect of clonazepam in burning mouth syndrome. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1998;86:557–561.
[30] Gremeau-Richard C, Woda A, Navez ML, et al. Topical clonazepam in stomatodynia: a randomised placebo-controlled study. Pain. 2004;108:51–57.
[31] Femiano F, Gombos F, Scully C, et al. Burning mouth syndrome (BMS): controlled open trial of the efficacy of alpha-lipoic acid (thioctic acid) on symptomatology. Oral Dis. 2000;6:274–277.
[32] Carbone M, Pentenero M, Carrozzo M, et al. Lack of efficacy of alpha-lipoic acid in burning mouth syndrome: a double-blind, randomized, placebo-controlled study. Eur J Pain. 2009;13:492–496.
[33] Cavalcanti DR, da Silveira FR. Alpha lipoic acid in burning mouth syndrome – a randomized double-blind placebo-controlled trial. J Oral Pathol Med. 2009;38:254–261.
[34] López-Jornet P, Camacho-Alonso F, Leon-Espinosa S. Efficacy of alpha lipoic acid in burning mouth syndrome: a randomized, placebo-treatment study. J Oral Rehabil. 2009;36:52–57.
[35] Palacios-Sánchez B, Moreno-López LA, Cerero-Lapiedra R, et al. Alpha lipoic acid efficacy in burning mouth syndrome. A controlled clinical trial. Med Oral Patol Oral Cir Bucal. 2015;20: e435–e440.
[36] Treldal C, Jacobsen CB, Mogensen S, et al. Effect of a local anesthetic lozenge in relief of symptoms in burning mouth syndrome. Oral Dis. 2016;22:123–131.
[37] Burness CB, McCormack PL. Capsaicin 8 % patch: a review in peripheral neuropathic pain. Drugs. 2016;76:123–134.
[38] Roberts LA, Connor M. TRPV1 antagonists as a potential treatment for hyperalgesia. Recent Pat CNS Drug Discov. 2006;1:65–76.