J Oral Pathol Med (2004) 33: 111–4

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Systemic capsaicin for burning mouth syndrome: short-term results of a pilot study

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BACKGROUND: Burning mouth syndrome (BMS) is a major diagnostic and therapeutic problem. Systemic and topical treatments (capsaicin, lidocaine, anti-histamines, sucralfate and benzydiamine) have been tried, but they appear to be inadequate. Topical capsaicin is bitter, may cause burning and has low therapeutic efficacy. We hypothesized that systemic administration of capsaicin could reduce the limitations of topical administration and have better therapeutic efficacy; this hypothesis was tested in a controlled trial.

METHODS: Systemic oral capsaicin 0.25% was used for patients with BMS, recruited in our single centre. After the diagnosis of BMS, patients were dentally and medically examined. They were alternatively assigned to treatment with capsaicin or to a shape/smell/taste/color matched placebo. The severity of symptoms was scored at trial entry and 30 days thereafter by investigators who were unaware of the assigned intervention. The visual analogical scale (VAS) measure was used to score the severity of pain, and results for the treated and untreated groups were compared by Fisher's exact test. Analysis was performed by intention-to-treat. Statistical significance was considered for values of $P < 0.05$. Data are expressed as mean $\pm$ SD.

RESULTS: Fifty patients were enrolled (25 assigned to systemic capsaicin and 25 to placebo). The VAS score was significantly lower in treated patients (5.84 ± 1.17) as compared to the placebo-control group (6.24 ± 0.96). The use of systemic capsaicin implied significant gastric toxicity (referred gastric pain) with eight cases (32%) documented in the treatment group as compared to zero cases (0%) in the placebo control group.

CONCLUSION: Systemic capsaicin is therapeutically effective for the short-term treatment of BMS but major gastrointestinal side-effects may threaten its large-scale, long-term use. This preliminary study suggests that more, adequately powered, randomized controlled trials are necessary and worthy to come to a definitive assessment of this matter.

J Oral Pathol Med (2004) **33**: 111–4

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Accepted for publication March 18, 2003

Keywords: burning mouth syndrome; orofacial pain; stomatopyrosis; systemic capsaicin

Introduction

Burning mouth syndrome (BMS) is defined as a burning sensation of the tongue or other oral tissues in the absence of any local lesions.

According to recent data from Bergdahl & Bergdahl (1), BMS affects 3.7% of the normal population with variability relating to sex (1.6% in men; 5.5% in women). In women, BMS is more frequent during menopause, with 1% of cases occurring during the fourth to fifth decade of a woman's life (2). On the opposite, male patients are affected in an earlier phase of life, the majority of cases occurring around the age of 30 (3).

The causes and mechanisms of BMS are still a matter of debate, although abundant research has been going on, in the form of both basic science and clinical studies (4). It has been hypothesized that there is a relationship between BMS and local factors (e.g. infections, allergies, parafunctions, inadequate salivary flow) or systemic factors (vitamin deficiencies, hormone deficiencies, immunological abnormalities and drug related toxicity; 5). Although several studies have been performed, a definitive cause and pathogenetic rationale has eluded discovery, and we are still far from understanding the nature of this burning sensation in the absence of oral lesions. Further fascinating hypotheses have been reported, including the possible association between peripheral and/or central neuropathies and BMS, that is to say neural lesions or dysfunctions related to a variety of trauma of the oral district could determine BMS (2).

Both the diagnosis and treatment of BMS are controversial. In terms of diagnosis, there are still no specific tests or instruments to come to a 'diagnosis of certainty', given the absence of objective oral lesions; therefore, we still proceed by exclusion of all other possible diseases, a time-consuming process for the doctors and a stressful experience for the patients (6).

In terms of treatment options, a variety of therapeutic regimens have been tested in BMS. These include both

systemic and topical regimens. Systemic treatments include hormone administration and anti-depressant agents and have not proven to be therapeutically effective, together with the down-side of significant toxicity (7–10). Local treatments include the use of capsaicin 0.025%, lidocaine and/or antihistamines, sucralfate and benzydiamine (11–13). These have also proven to be ineffective.

Capsaicin desensitizes type C receptors for pain and reduces neurogenic inflammation (14). Topical use of capsaicin requires repeated applications of the drug, because this is quickly washed out from saliva flow and tongue movements. On the contrary, the use of systemic capsaicin, which would avoid the problem, has never been tested in a clinical trial. The evaluation of the therapeutic efficacy of systemic capsaicin in BMS was the aim of this pilot, placebo-controlled clinical trial.

Methods

This was a comparative, single centre, triple blind (participants, investigators, outcome assessors), 'intention-to-treat' trial of oral capsaicin administered as 0.25% capsules t.i.d. for 4 weeks compared to shape-/taste-/smell-/colour-matched placebo. The trial was performed according to the Declaration of Helsinki. Local ethics authorities were queried and approved the original protocol, and written consent was obtained from all participants. All men and women aged 20–80 years who presented BMS (defined as a burning sensation of the tongue or other oral tissues in the absence of local lesions) were dentally and medically examined according to the protocol for the management of patients with BMS proposed by Bergdahl & Anneroth (15), provided they had never been previously treated for BMS. The protocol outlined by Bergdahl and Anneroth implies a complete medical history plus a medical and dental examination (including an estimation of saliva secretion rate and candidal investigation). Laboratory work-up included haemoglobin, mean corpuscular volume, white blood cell count, platelet count, serum iron, serum ferritin, serum transferring, serum vitamin B12 and serum folic acid.

At the initial visit, visual analogical scale (VAS) score was taken for all subjects, then patients were alternately assigned to either treatment with oral capsaicin 0.25% capsules t.i.d. for 1 month or shape/test/smell/colour-matched placebo. Treatment assignment, evaluation of BMS with VAS score, toxicity and tolerability of the drug and assessment of outcomes and data-analysis were independently carried out by sets of separate investigators to guarantee triple blinding. Patients were requested to contact the investigators by phone every week. The investigator asked and recorded any adverse events (gastric pain, itching, dysgeusia) at each phone call. Given the short duration of the study and the known non-harmful potential of this agent, there was no reason to investigate serious adverse events such as withdrawals for serious medical conditions, death and other major morbid events or hospital admission for any reason, but it was planned that these data would be collected if they occurred. This would be a reason for immediate termination of the study.

Patients were re-examined at day 30 after assignment to the treatment groups by investigators who were blinded to treatment allocation. The VAS score was taken at that time.

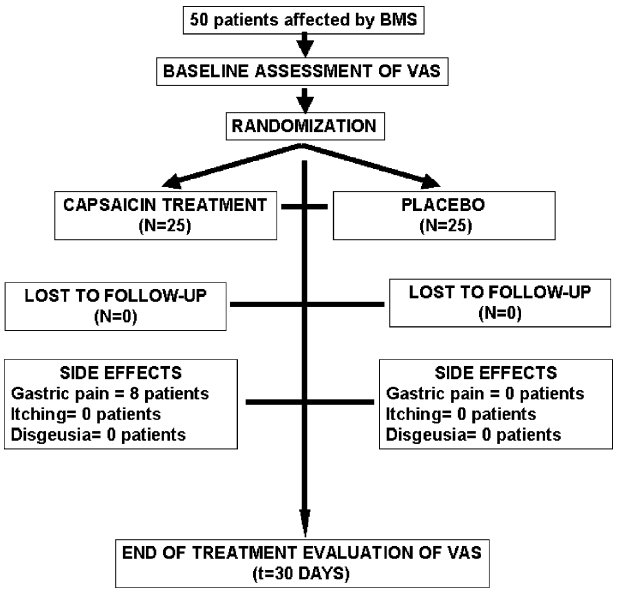

Figure 1 Patient's flow throughout the study and study methodology.

Compliance to treatment medication was assessed by residual pill counting (number of tables returned, divided by number of tablets expected to be taken).

Statistical analysis

Data were analysed independently by two separate outcome assessors. The mean value of VAS at the beginning and at the end of treatment was plotted and compared with Fisher's exact test. Statistical significance was as stated for a value of $P < 0.05$. Data are expressed as mean $\pm$ SD.

Results

Fifty patients were alternately assigned to active treatment (oral capsaicin 0.25% capsules t.i.d. for 1 month) or placebo (Fig. 1). After allocation, the two groups were comparable for age, sex, duration of the disease and VAS score (Table 1).

Effect of systemic capsaicin on VAS

Treatment with systemic capsaicin induced a statistically significant reduction of VAS at the end of study period

Table 1 Baseline characteristics of patients enrolled in the comparative study of systemic capsaicin vs. placebo and variation of VAS score at the end of treatment

	Capsaicin	*Placebo*
No. of patients	25	25
Age (years)	55.6 ± 6	57.4 ± 7
Male (*n*)	8	6
Female (*n*)	17	19
Duration of BMS (months)	11 ± 1	12 ± 1.4
Baseline VAS	8–10/15	8–10/13
(range/no. of patients)	4–7/8	4–7/7
	0–3/2	0–3/5
End of treatment VAS	8–10/1	8–10/13
(range/no. of patients)	4–7/3	4–7/6
	0–3/21	0–3/6

($P < 0.001$). Of 15 patients who initially presented a value of VAS between 8 and 10, only 1 was in this range at the end of 1-month treatment with systemic capsaicin. Among eight patients presenting a value of VAS between 4 and 7, three did not present any improvement. In the placebo group, no patient presented a significant improvement of the VAS score, when the base line value was between 8 and 10. Of seven patients whose baseline VAS value was between 4 and 7, only one improved (Table 1).

Toxicity and tolerability

There were eight reports of minor adverse events (gastric pain) and no other specific events. The number of complaints reported by patients at weekly phone conferences increased progressively from week 1 to week 4. Specifically, gastric pain was reported by zero patients at week 1, one patient at week 2, three patients at week 3 and four patients at week 4 for a total of eight cases (32%) in the capsaicin treated group as compared to zero cases in the group receiving placebo.

No patient withdrew for any reason, including a wish not to continue with the trial. Compliance with trial medication was 100% according to residual pill counting.

Discussion

Based on the present findings, the use of systemic capsaicin 0.25% is effective in treatment of BMS-related symptoms over a short-term duration of 1 month. Yet, systemic administration of capsaicin is associated with significant gastric pain, and the number of complaints relating to this side-effect seem to increase with time on treatment.

Topical capsaicin has been used as treatment for neuropathic pain of the facial and oral district, including the management of the temporomandibular pain and oral mucositis following radio-chemotherapy (16, 17). In general, it has proven to be ineffective although it has been tested in small numbers of patients and with often inadequate study designs.

Epstein & Marcoe (11) firstly 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.

The results of the present study are particularly important, given the limitations of topical capsaicin use; topical use of this agent has in fact shown to be poorly effective, and capsaicin has a bitter taste, which reduces compliance to topical treatment. Further, topical use implies multiple applications to avoid clearance related to the salivary flow and tongue movements. We propose the use of systemic capsaicin capsules as a means to reduce non-compliance and improve therapeutic effects. Contrary to several other studies in the area of BMS treatment, this is a comparative randomized trial in which both participants, investigators and outcome assessors, were blinded and no patients were lost to follow-up. The methods used in this pilot study represent a major strength of our analysis.

However, the study does have limitations. First, alternation was used to randomly allocate patients to treatment groups ('pseudo' randomization) because this was only intended as a pilot trial. Second, and for the same reason, the sample size was small, a minus that was partly counterbalanced by the absence of patients lost at follow-up. Even in this case, the small sample size may underpower the statistical estimate of the true treatment effects.

Finally, the outcomes were measured just after 1 month, which is a short time frame for evaluation of symptoms of BMS.

The study has strong implications for clinical practice and particularly research: the therapeutic efficacy of systemic capsaicin in BMS strengthens the hypothesis that this disease might have a neurogenic origin, even though this study and in general any trial addressing an intervention will not be adequate to provide an assessment of the causes and mechanisms of the disease and further studies are necessary to find these as well as the best treatment options (18, 19). As yet, our study indicates the possibility that systemic capsaicin may be a reliable treatment option, but implies the need for further, properly randomized and concealed trials (sequentially labelled, sealed, opaque envelopes or central/pharmacy randomization) enrolling larger number of patients over a longer period of time, which would determine a conclusive assessment of not only the effects of oral capsaicin in reducing symptoms of BMS but also its toxicity and tolerability.

In conclusion, given that BMS is significantly prevalent in the general population, and in the absence of a thorough understanding of its cause and mechanism, the search for therapeutic approaches, which are effective, is fundamental. In this study, we tested one such treatment, which proved to be effective even with the outlined limitations and toxicity.

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Acknowledgements

We are strongly indebted to the anonymous reviewers of the study for precious suggestions.