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Original Article

Topical application in burning mouth syndrome

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Abstract *Background/purpose:* Intraoral and perioral burning sensations may be sequelae of burning mouth syndrome (BMSD) or burning mouth symptoms (BMSP), which present a diagnostic challenge. The aims of the study were to evaluate the efficacy of a topical anesthetic as a diagnostic test to differentiate BMSD from BMSP and to assess the comorbidities and responses to various pharmacologic treatments in BMSD and BMSP patients.
Materials and methods: A total of forty-four charts of patients with burning mouth that visited the Rutgers School of Dental Medicine Orofacial Pain Clinic between January 1st, 2000 and November 1st, 2014 were retrospectively reviewed. Twenty patients were diagnosed with BMSD, and 24 patients were diagnosed with BMSP attributed to local and systemic causes. The diagnosis was determined per the guidelines of the International Association for the Study of Pain and American Academy of Orofacial Pain. The main goal of this study was to evaluate the effect of topical anesthetic medication applied to the burning site.
Results: The percentage of change in pain reduction following topical anesthetic application in the BMSP group was significantly higher than that of the BMSD group ($p < 0.05$). In the BMSD group, 77% of females and 27% of males responded to clonazepam. One third of the females in the BMSP group also suffered from hypertension.
Conclusion: Topical anesthetics can be used as a simple, swift and efficient chair-side diagnostic tool to differentiate BMSD and BMSP. Females have a better response to clonazepam in BMSD.

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Introduction

Burning mouth syndrome (BMSD) is a chronic debilitating condition that can manifest as an intraoral burning pain without evident local and systemic conditions or disease.[1] Due to a lack of diagnostic criteria in the past, there is a wide variation in the reported prevalence, ranging from 0.7 to 15%.[1,2] The condition is associated with a higher prevalence in females than males.[1,2] BMSD may affect several intraoral sites, and the anterior two thirds of the tongue and the palate are the most common.[2] Burning mouth patients often describe intermittent or continuous daily pain lasting for at least 4–6 months with gradual amplification of the pain towards evening.[3] There is no change in the pain with eating or drinking, and often there is alleviation of pain with sweet food.[3,4] The pain may be accompanied by subjective changes in somatosensory perception, such as taste alterations,[5,6] taste phantoms, hyposalivation and mood alteration.[7] A burning sensation in the oral cavity may also be a sequela of various local and systemic pathologies, such as candidiasis, immune deficiency, nutritional deficiencies such as iron and vitamin B12 deficiency, infection, diabetes, trauma, medication, allergies, galvanism, xerostomia and dermatologic diseases such as lichen planus. Oral and perioral burning pain, which are attributed to specific local and systemic pathologies, are referred to as burning mouth symptoms (BMSP).[8] The diagnosis involves comprehensive clinical examination to assess the local factors and various lab tests to identify systemic factors that can cause the burning sensation. The intra- and perioral burning sensation is generally resolved by addressing the causative local or systemic factors.

Previously, BMSD was considered an idiopathic disorder. Evidence garnered from studies on BMSD patients over the last two decades suggest a neuropathic origin with varying degrees of involvement of the peripheral nervous system (PNS) and central nervous system (CNS).[8–10] This origin may involve small fiber neuropathy, subclinical pathology in lingual, mandibular, or trigeminal systems or abnormal pain processing and modulation in the CNS.[11,12] Quantitative sensory testing (QST) in these patients have confirmed variations in the sensory profile among the different phenotypes with either loss of function (hypoalgesia/hypoesthesia)[13,14] or gain of function signs in the thermal modalities.[12–14] Another common neuropathic pain hypothesis of primary BMSD relates to the gustatory system. BMSD symptoms can occur subsequent to damage to nerves, such as the chorda tympani or other innervations involved in taste. Chorda tympani hypofunction coupled with a loss of central inhibitory mechanisms exerted on the lingual nerve can lead to the evolution of the burning sensation in BMSD.[8] The findings of chorda tympani hypofunction have been validated using quantitative sensory testing.[8,15] These studies have demonstrated elevated taste detection threshold levels (via electro gustatory testing) and taste/tingling detection threshold ratios. Moreover, instances of unilateral chorda tympani dysfunction may be sufficient to produce bilateral symptoms, suggesting possible CNS mechanisms.[8] Certain individuals with an increased number of fungiform papilla often referred to as "supertasters" may be at a higher risk for development of BMSD.[2] A recently proposed comprehensive hypothesis that has been successful in explaining the majority of symptoms of BMSD suggests that an alteration in adrenal steroid physiology or severe menopausal changes combined with chronic anxiety, depression and stress often lead to a decrease in neuroprotective steroids. In the scenario of reduced neuroprotective and neuroregenerative influences, neurotoxic effects predominate and result in damage to the A-delta fibers and nigrostriatal dopamine. These factors may act independently or in combination with genetic factors that are responsible for top-down inhibition and changes in gustatory function that result in BMSD.[12]

The evaluation of complaints of sensory nerve dysfunction is often challenging and requires special training.[16] In addition, prescribing various lab investigations for exclusion of local and systemic factors may be time consuming, expensive and may place a significant burden on healthcare resources. The cessation of pain with a topical anesthetic suggests a peripheral origin of the pain and an absence of change or increase in pain may help predict the central origin of pain and dictate the treatment plan. The objective of the present study was to evaluate if application of an intraoral topical anesthetic at the site of burning can be used as a diagnostic test for differentiating BMSD (idiopathic causes of the burning sensation) and BMSP (local or systemic causes of the burning sensation). The second objective was to assess the co-morbidities and response to treatment in BMSD and BMSP patients.

Material and methods

A retrospective chart review was conducted at the Department of Diagnostic Sciences, Rutgers School of Dental Medicine and was approved by the Institutional Review Board, Rutgers University (protocol id: 20140000697). The study was performed in accordance with the code of ethics of the World Medical Association (Helsinki Declaration of 1975 as revised in 1983). The review was conducted with charts from patients who visited the Department of Diagnostic Sciences, and a total of 44 charts of patients with burning mouth were included in the study. The diagnosis was selected per guidelines of the American Academy of Orofacial Pain (AAOP) and the International Association for the Study of Pain (IASP). The patients were divided into two groups based on the diagnosis. Patients were diagnosed with either "BMSD" or "BMSP". BMSD patients included patients with complaints of an intraoral burning sensation

in the absence of local or systemic conditions/diseases and no abnormalities in laboratory findings. BMSP patients were patients who presented with an intraoral burning sensation ascribed to specific local and/or systemic factors. The pain levels were recorded using a visual analogue scale (VAS). In brief, the chair-side test was performed by the clinician using a cotton swab containing a pea sized amount of 20% benzocaine gel. The gel was spread in the area of the burning sensation with the cotton swab. The VAS scale is a validated scale used to measure pain. The VAS scale consists of a 100 mm horizontal line with markings of "no pain" at one end and "most excruciating pain" at the other end. The patient was asked to mark a vertical line depicting the current pain level on the 100 mm horizontal line.[17] The pain intensity was evaluated using VAS before application and 2 min after application of the topical anesthetic (20% benzocaine) to the burning area.[18] The charts were reviewed in a secure private room and accessed for data collection by the principal investigator (JK) and the study coordinator (MA). Additional data recorded from the charts included co-morbidities, location of pain, treatment that was administered and effect of treatment.

Statistical analysis

Data analyses were performed using JMP Pro 13.0 statistical software (SAS Institute Inc., Cary, NC, USA). The data are reported as the mean ± standard error of mean (mean ± sem) unless otherwise specified. The outcome distribution was tested for normality using the Shapiro-Wilk test. Non-parametric analysis with the Wilcoxon rank sum test was used to compare the medians of the groups. To assess burning levels, repeated-measures ANOVAs were used with post-hoc tests if significant. P-values less than 0.05 were considered statistically significant.

Results

Age and gender

A total of forty-four charts from patients with complaints of a burning sensation met the inclusion criteria and were included in the study. Thirty females (68.2%) and 14 males (31.8%) were included in the study (female: male ratio 2.1:1). The collective age range of the subjects was 32–85 years (mean age, 62.6 years). The age range for females was 32–80 years (mean age, 61.1 years), and age range for males was 41–85 years (mean age, 61.5 years) (Table 1).

Pain levels before and after application of a topical anesthetic

A topical local anesthetic applied intraorally at the site of burning resulted in a significant reduction in the intraoral burning sensation in the BMSP group compared to the BMSD group ($p < 0.05$). The percentage change in reduction of pain following application of the topical anesthetic in the BMSP group (47.608 ± 9.409) was significantly higher than that of the BMSD group (−30.861 ± 11.633) ($p < 0.0005$) (Fig. 1). Furthermore, a topical anesthetic applied intraorally at the site of burning resulted in a significant reduction in the intraoral burning sensation in females with BMSP. Males had significantly higher levels of pain after application of the topical medication in the BMSD group (Fig. 2, Table 2). The percentage of reduction in pain following topical anesthetic application in the BMSP group (63.986 ± 6.803) was significantly greater than that of the BMSD group (27.910 ± 16.763.400) ($p < 0.05$).

Co-morbid conditions

The co-morbidities in BMSD patients included anxiety (28.57%), cancer (14.28%), asthma (28.57%), headache

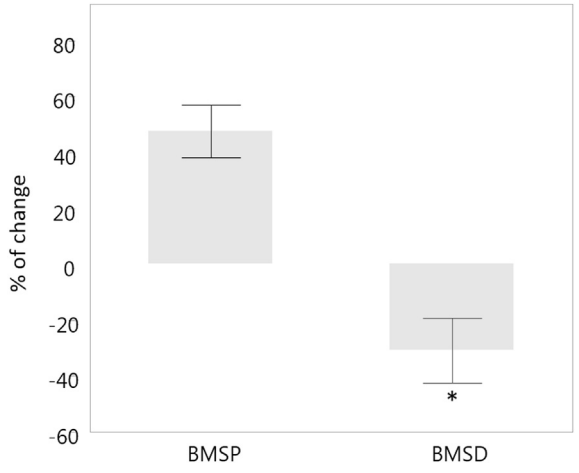

Figure 1 Percentage of change following topical anesthetic application in the BMSD (burning mouth syndrome) and BMSP (burning mouth symptoms) groups. The figure depicts that the percentage of change in reduction of pain following topical anesthetic application in the BMSP group (47.608 ± 9.409) was significantly higher than that of the BMSD group (−30.861 ± 11.633) ($p < 0.0005$).

Table 1 Demographics. A table depicting the demographic characteristics of the study population.

	Female mean age (Range)	Male mean age (Range)	Female subjects	Male subjects
[a]BMSD	62.7 (40–80)	61.8 (41–85)	12	8
[b]BMSP	59.8 (32–77)	61 (41–71)	18	6
Total	61.1 (32–80)	61.5 (41–85)	30	14

[a] Burning mouth syndrome group.
[b] Burning mouth symptoms group.

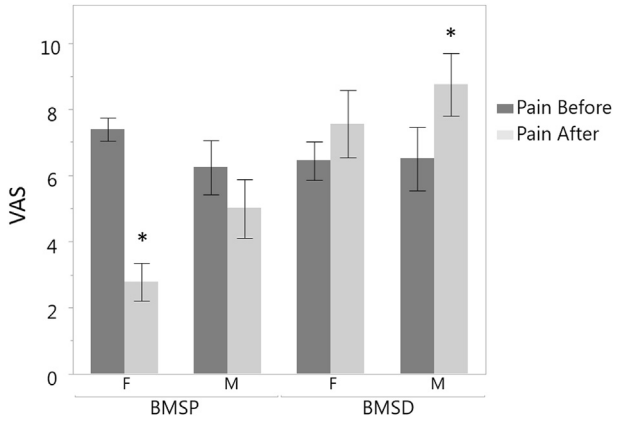

Figure 2 Effect of topical medication on pain in the BMSD (burning mouth syndrome) and BMSP (burning mouth symptoms) groups. The change in pain following topical anesthetic application in BMSD and BMSP in females and males is presented. A topical anesthetic applied intraorally at the site of burning resulted in a significant reduction in the intraoral burning sensation in females with BMSP compared to females with BMSD.

(14.28%), and diabetes (14.28%). Co-morbidities in BMSP patients included hypertension (43.57%), sleep disorder, cancer (12.50%), asthma (6.25%), headache (6.25%), diabetes (6.25%), gout (6.25%), HIV (6.25%), and anemia (6.25%).

Burning location

In the BMSD group, a burning pain was reported on the lateral borders of the tongue (30.43%), roof of the mouth (20.43%), tooth areas (mainly molars, 13.04%), tip of the tongue (8.69%), back of the throat (8.69%), buccal mucosa (4.34%) and lower gums (4.34%). In the BMSP group, the burning pain was reported in tooth areas (63.63%) followed by the tip of the tongue (13.63%), upper right quadrant (9.09%), lower quadrant (4.54%), lower jaw (4.54%) and lips (4.54%).

Treatment

The majority of the BMSD subjects responded to clonazepam (61.90%), 9.52% of subjects responded to nortriptyline, duloxetine and Lyrica, and 4.76% of patients responded to lisinopril and hydrocodone. In BMSP patients, 45.45% responded to nortriptyline, 27.27% responded to steroid injection, 9.09% responded to clonazepam, 9.09% responded to Lyrica, and 9.09% responded to duloxetine. The majority of the females with BMSD responded to clonazepam (83.3%), while men with BMSD needed different medications (Table 3).

Discussion

The results of this study demonstrate that topical anesthetics may be considered a chair-side diagnostic aid to distinguish BMSD from BMSP. A topical anesthetic successfully reduced burning pain in the BMSP group; however, in the BMSD group, the application of a topical anesthetic did not have a palliative effect but, rather, aggravated the pain. Previous studies with BMSD patients using local anesthetic blocks, topical anesthetics and oral rinses suggested that BMSD may involve sensitization of both the central and peripheral nervous systems. Normally, an equilibrium in the inhibitory influences between the chorda tympani (a branch of facial nerve that supplies taste sensation to the anterior two thirds of the tongue) and the lingual nerve (branch of the mandibular division of the trigeminal nerve that supplies sensory modalities, such as thermal and mechanical modalities) maintain the balance of sensory input to the tongue. Chorda tympani hypofunction may result in loss of inhibitory control over the lingual nerve. This loss may result in the evolution of the burning sensation. An interesting observation was gender specific responses to topical anesthetics in BMSD and BMSP. Females with BMSP exhibited a significant reduction in pain following topical application of local anesthetics compared to males, whereas males with BMSD exhibited a greater pain response after application of topical anesthetic, suggesting different pathogenic mechanisms may be involved. A recently proposed comprehensive hypothesis suggests that imbalances in neuroprotective effects due to menopause, chronic anxiety and depression can lead to damage of the A-delta fibers and nigrostriatal dopamine. Independently or in genetically predisposed individuals, these factors can cause changes in pain modulatory effects and gustatory mechanisms and lead to evolution of BMSD.[12]

Female subjects with BMSD reported an intraoral burning sensation primarily in the lateral borders of the tongue followed by the roof of the mouth; however in males, the sensation was primarily located in the tooth areas around the molars followed by the tip of the tongue. In BMSP, both males and females primarily localized the burning sensation to the tooth areas around the molars. It has been previously suggested that burning complaints may be secondary to precipitating events, such as dental

Table 2 VAS before and after application of a topical anesthetic in the BMSD and BMSP groups. A table depicting the VAS before and after application of a local anesthetic in the BMSD and BMSP groups.

	[b]BMSD Females	[c]BMSP Females	[b]BMSD Males	[c]BMSP Males
[a]VAS before topical	6.44	7.38	5.57	7.4
VAS after topical	8.6	6.25	8	3.8

[a] Visual analogue scale.
[b] Burning mouth syndrome group.
[c] Burning mouth symptoms group.

Table 3 Pharmacotherapy. A table depicting the pharmacotherapy in the BMSD and BMSP groups. The majority of the females with BMSD responded to clonazepam, while men with BMSD required different medications.

Pharmacotherapy	Total	[a]BMSD Females	[b]BMSP Females	[a]BMSD Males	[b]BMSP Males
Clonazepam	14	10	1	3	0
Nortriptyline	7	1	5	1	0
Duloxetine	3	0	1	2	0
Lyrica	3	0	1	2	0
Steroid injection	3	0	3	0	0
Lisinopril	1	0	0	1	0
Hydrocodone	1	0	0	1	0
OTC (Tylenol/Ibuprofen)	0	0	0	0	0

[a] Burning mouth Syndrome group.
[b] Burning mouth symptoms group.

treatment or mechanical or facial trauma.[19] Systemic comorbidities had a higher prevalence in BMSP patients, especially among females. The presence of systemic co-morbidities such as cancer and diabetes in BMSD patients has been previously documented.[19] Patients with diabetes may have a dry mouth, which may cause insufficient lubrication and increase mucosal sensitivity and induce a burning sensation.[19] In addition, candida infections are more common in diabetics and may act as a local factor in BMSP. Small fiber peripheral neuropathies are more common in diabetics, and a similar mechanism may be in play in BMSD patients with diabetes.[20] It has been hypothesized that hyperglycemia and insulin deficiency may cause micro vasculitis leading to ischemic injury. These events may cause demyelination of peripheral nerves and axonal atrophy or loss resulting in polyneuropathy. In addition, constant peripheral pain inputs due to changes in mucosa induced by dry mouth, chronic irritation by intraoral prosthesis and changes in salivary composition may result in evolution of peripherally maintained central sensitization. Patients with cancer or HIV may complain of a burning sensation due to effects of the disease or side effects of treatment. Metastasis or local invasion by malignant cells and release of inflammatory and pain mediators may result in reduction of detection thresholds or may induce nerve damage and elevate the detection threshold. Xerostomia, dry mouth, changes in salivary flow and composition, increased sensitivity of oral mucosa, irritation by dental prosthesis and mucositis can induce a burning sensation during or subsequent to radiation/chemo therapy. Opportunistic infections such as candidiasis have a higher prevalence in patients with HIV and patients with xerostomia and can act as local factors in BMSP. Chemotherapy and antiretroviral therapy can also induce peripheral neuropathies; however, whether a similar situation occurs in BMSD patients with HIV and the relations between BMSD and the duration of the symptoms and between BMSD and the retroviral therapy needs to be explored in a prospective manner with a larger sample.

Hypertension was an important comorbidity seen in BMSP patients, primarily females. Medications such as diuretics commonly used in hypertensive patients may have an effect on salivary flow and induce xerostomia. Dry mucosa may be more susceptible to damage by ill-fitting prostheses or traumatic ulcerations and cause a burning sensation. Taste receptor function has been reported to be similar in hypertensive and normotensive rats, suggesting that BMSP may be related to the local effects of the medication rather than the condition itself.[21] Anxiety was also a co-morbidity in BMSD subjects, which has been previously documented and fits in the comprehensive theory of BMSD.[12,19] Although systemic co-morbidities may be found in BMSD, they are often inconsistent and the burning sensation may not reduce despite treatment or control of the systemic conditions.[22] In such instances when doubt exists in the mind of the clinician, local anesthetics may act as a simple chair-side diagnostic aid to discern whether the burning sensation is due to mechanisms involved in BMSD (peripheral or central) or is more likely to be the cause of BMSP. Early recognition and prompt referral in cases of primary BMSD may help in reducing the distress, disease burden, and development of co-morbid depression due to repeated failure in diagnosis and management.

An important finding of this study was the gender specific response to medications in BMSD. The response to clonazepam was more specific in females. Males required different categories of medications such as tricyclic antidepressants, SSRIs, SNRIs and anti-convulsants, suggesting different and heterogeneous mechanisms in males. A recent meta-analysis on symptom remission in BMSD using topical and systemic clonazepam concluded that both routes are effective for reducing burning symptoms.[23] Whether there is a higher gender specific response to clonazepam can be explored in future prospective studies. Some of the patients with BMSP also responded to neuropathic medications, suggesting that peripheral sensitization may be present and may be related to certain systemic conditions. The dosage and duration of drug intake should have been taken into consideration and is a limitation of the present study. We did not explore this issue, and further studies are required to fully understand the roles of dosage and duration.

In conclusion, topical anesthetics may act as a simple adjunct, chair-side diagnostic aid in differentiating BMSD and BMSP. Their use may reduce the ambiguity in diagnosis faced by general dentists and enable clinicians to look for local factors in cases of BMSP or to initiate early referrals to tertiary care centers in cases of primary BMSD.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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