REVIEW ARTICLE

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Burning measure for burning mouth syndrome: a systematic review

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Abstract (J Korean Assoc Oral Maxillofac Surg 2024;50:63-69)

This current systematic review aimed to evaluate the current evidence on the effect of topical capsaicin application to alleviate symptoms related to burning mouth syndrome (BMS). PubMed, Ovid SP, and Cochrane were searched from 1980 to 2022 to identify relevant literature. A total of 942 titles (PubMed, 84; Ovid SP, 839; Cochrane, 19) was retrieved, of which 936 were excluded based on the title and abstract. A total of 11 studies were further evaluated for full text analysis, of which 7 were excluded. As a result, 4 articles were included for qualitative synthesis of data. Capsaicin as a mouthwash can have potential application in the treatment of symptoms related to burning mouth. The quality of available studies is moderate to low, and a well-designed randomized multicentric study comparing capsaicin with other active agents is planned to obtain more definitive conclusions.

Key words: Burning mouth syndrome, Capsaicin, Pain, Orofacial pain

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I. Introduction

Burning mouth syndrome (BMS) is a burning, stinging, or itching sensation of the lips, tongue, and the oral mucosa with no evidence of oral lesions[1]. This condition is also referred to as stomatopyrosis, glossopyrosis, glosodynia, scalded mouth syndrome, stomatodynia, sore tongue, burning lips syndrome, glossalgia, oral dysesthesia, and sore mouth. BMS has a common triad of symptoms of burning oral mucosa, dysgeusia (altered taste sensation), and xerostomia (dry mouth). The prevalence of BMS ranges from 1.73% in the worldwide general population to 7.72% in the clinical population. Females older than 50 years are more likely to develop BMS[2]. The disease is multi-factorial, and no single etiopathogenesis has been discovered. Recent research has discussed possible causes as neuropathic, affecting both the general and special sensory components of the trigeminal nerve and the nigrostriatal dopaminergic pathway dysfunction, causing damage to the taste pathway[3-8]. Anxiety, depression, and sleep deprivation are co-morbidities associated with BMS[9]. Other co-factors associated with BMS include gastroesophageal reflux disease, hypertension, hypercholesterolemia, hyperhomocysteinemia, and hypothyroidism[10,11]. Treatment of BMS is complex and requires a custom-made multidisciplinary approach for each patient. Treatment includes a combination of systemic, behavioral, and topical treatments such as antidepressants, anticonvulsants (clonazepam, gabapentin, pregabalin), antipsychotics, vitamins or dietary supplements (alpha-lipoic acid), analgesics, mouthwashes (benzydamine hydrochloride & clonazepam), and hormone replacements for postmenopausal women[12]. Herbal agents are gaining popularity recently for the treatment of BMS. Ultramicronized palmitoylethanolamide, herbal catuama, hypericum perforatum, and lycopene-enriched extra virgin oil are being evaluated for treatment of BMS.

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Recent research has demonstrated that the capsaicin component present in pepper has an analgesic effect and is proposed for conditions such as neuralgias, arthritis, and diabetic neuropathy. Capsaicin produces a burning sensation in contacted tissues as a result of neuronal excitation in the polymodal C fiber where it binds to the nociceptor TRPV1. Repeated application of capsaicin acts through three pathways: (1) temporary loss of membrane potential, (2) inability to transport neurotrophic factors, and (3) altered phenotype and reversible retraction of the terminals of the epidermal and dermal nerve fibers, leading to dysfunctioning and reduced pain and burning sensation[13,14].

Systemic capsaicin has been shown to have a beneficial effect in reduction of symptoms related to BMS, but the side effects include gastrointestinal irritation[15]. Some studies have reported beneficial uses of topical capsaicin in the reduction of symptoms related to BMS. The aim of this current systematic review is to evaluate the effect of topical capsaicin in reducing the symptoms of BMS.

II. Protocol and Registration

The protocol was registered in Prospero with the registration number CRD42022379471.

1. Framework

The PICO strategy framework was adapted based on the pre-formulated question, "Is topical capsaicin application effective in reducing symptoms related to Burning Mouth Syndrome?" The search strategy of the systematic review is as follows: (P) patient: any patient with established diagnosis of BMS; (I) intervention: topical capsaicin application either as mouthwash or a gel; (C) comparison: placebo or any other agent; and (O) outcome: mitigation of symptoms related to BMS.

2. Search strategy

Thorough electronic searches were performed in PubMed, Ovid SP, and Cochrane for studies from January 1980 until December 2022. Grey literature was searched in the LILACS database for related relevant articles. No restrictions were applied to the language as long as it was translatable into English. The search was performed using search terms (Capsaicin) AND (Burning mouth).

3. Eligibility criteria

Clinical trials that evaluated local application of capsaicin in topical form (mouthwash, gel) were included. Case reports, narrative and systematic reviews, and articles that could not be translated into English were excluded. Any clinical study that evaluated topical capsaicin with or without a control agent for treatment of BMS were included in the current review. The article titles were carefully screened and then further evaluated by reviewing their abstracts. Articles deemed fit were subjected to full-text evaluation and then further processed for qualitative analysis. Two reviewers independently evaluated quantitative and qualitative data. If there was any discrepancy, a third independent reviewer became involved to resolve the issue.

4. Risk of bias evaluation

Two independent reviewers assessed the methodological quality of the included articles using the ROBINS-I (Risk Of Bias In Non-randomized Studies of Interventions) Cochrane criteria.

III. Results

1. Study selection

A total of 942 titles (PubMed, 84; Ovid SP, 839; Cochrane, 19) was retrieved, of which 936 were excluded based on the title and abstract. A total of 11 studies was further evaluated for full text analysis, of which 7 were excluded[15-21] (Table 1),

Table 1. Table showing excluded articles and reasons for exclusion

No.	Excluded articles	Reasons for exclusion
1	Azzi et al.[16] (2017)	Standardized preparation not performed in the study.
2	Scardina et al.[20] (2006)	Model study for identifying pathophysiology of burning mouth syndrome.
3	Epstein and Marcoe[17] (1994)	Capsaicin is used for neuropathic pain and trigeminal neuralgia.
4	Petruzzi et al.[15] (2004)	Systemic rather than topical administration of capsaicin.
5	Peppin and Pappagallo[18] (2014)	Capsaicin is used for neuropathic pain.
6	Romero et al.[19] (2019)	Capsaicin is used for myofascial pain.
7	Teixeira et al.[21] (2015)	Capsaicin in post-herpetic neuralgia.

Sunny Priyatham Tirupathi et al: Burning measure for burning mouth syndrome: a systematic review. J Korean Assoc Oral Maxillofac Surg 2024

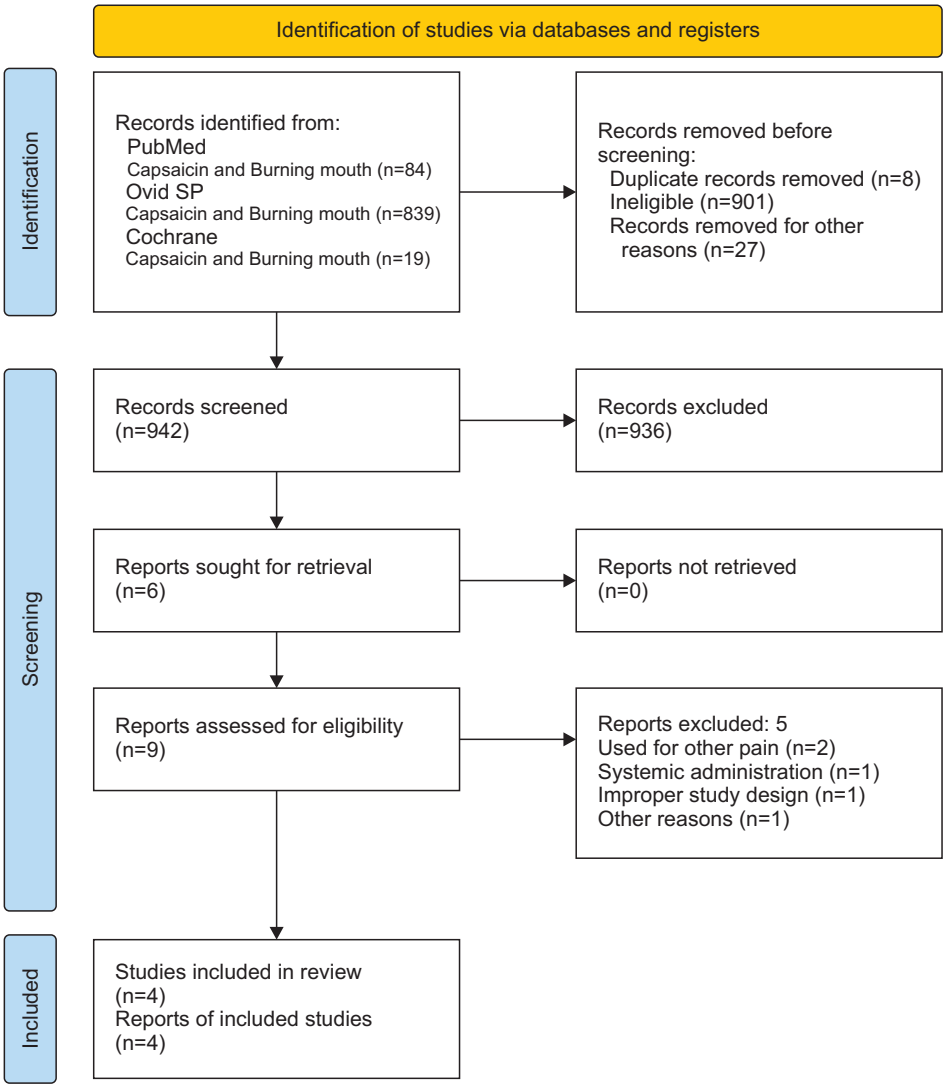

Fig. 1. Prisma flowchart.
Sunny Priyatham Tirupathi et al: Burning measure for burning mouth syndrome: a systematic review. J Korean Assoc Oral Maxillofac Surg 2024

leaving 4 articles for the qualitative analysis.(Fig. 1, Table 2) Critical appraisal of included articles: The four included articles were subjected to quality appraisal and deemed to be of low to moderate quality (average score=11).(Table 3)

2. Overall risk of bias

The overall risk of bias among the four included studies ranged from moderate to serious. Four studies were included for the final qualitative analysis. All were interventional studies published between 2012 and 2021[22-25]. The age range of participants in the included studies was 30-90 years.(Fig. 2, 3) In the studies included, capsaicin was used in topical preparation form (mouthwash form), where the concentration was between 0.01% and 0.025%. The frequency of usage of mouthwash ranged from a thrice a week regimen to 28 days of continuous use. Capsaicin was used singly or in combination with other agents. No control was used in the studies by Jørgensen and Pedersen[23] and Ricken et al.[24]. Placebo rinse was used in the study by Silvestre et al.[25]. Subjective pain was measured using a visual analog scale (VAS) among all groups.

IV. Discussion

Four studies were included for the final qualitative synthesis of data. None had a randomized design, and all were interventional studies of topical capsaicin application[22-25]. Capsaicin was used at concentrations ranging from 0.01% to 0.025% among the included studies. Topical application of capsaicin was delivered in gel form in the studies by Jørgensen and Pedersen[23] and Ricken et al.[24] and in mouthwash form at a concentration of 0.02% in the studies by Jankovskis and Selga[22] and Silvestre et al.[25]. Capsaicin was used alone

Table 2. Characteristics of included studies

Study	Study design	Sample characteristics	Intervention and form	Application protocol.	Control	Measurement scale	Outcome	Adverse effects
Ricken et al.[24] (2021)	Interventional study	18 patients aged 30-69 years were recruited for application of capsaicin in a burning mouth region. Duration: 90 days	0.025% capsaicin gel applied to the affected area. Application protocol: thrice daily for one month, twice daily every alternate day for the second month, once daily for three days per week	Application protocol: thrice daily in gel form for one month, twice daily every alternate day for the second month, once daily for three days a week	No control	Subjective pain scores and quality of life using the OHIP-14 scale	Topical application of capsaicin is effective in reducing the intensity of burning sensation.	7 patients (38%) reported xerostomia. 2 patients reported erythema on the lip and jugal mucosa.
Jørgensen and Pedersen[23] (2017)	Interventional study, randomized double-blind crossover study	22 female patients aged 34-70 years were recruited, of which 18 completed the study, crossover design application of capsaicin in the burning region.	0.025% and 0.01% capsaicin gels were applied on the dorsal part of the tongue.	Capsaicin gel was applied three times a day for 14 days followed by a 14-day washout period. For the next 14 days, the other concentration was applied.	No control	Subjective pain scores using VAS	There was a significant decrease in both the capsaicin groups (0.01% and 0.025%) and the VAS score in comparison to baseline. The VAS score at baseline was 5.5±0.6, and there was a decrease of VAS by 1.4±0.4. VAS scores increased in the wash out period. There was no significant difference in either of the concentration groups.	4 patients reporting minor side effects were deferred from treatment. Side effects were mostly related to gastrointestinal symptoms such as nausea, itching, and sore throat. All side effects were reversible.
Silvestre et al.[25] (2012)	Interventional study, randomized double-blind crossover study	30 patients were recruited for the study including 23 individuals aged 40-90 years. Crossover design	0.02% capsaicin rinse for 7 days	The total duration was three weeks. Mouthwash administered thrice daily for one week, followed by a one-week washout period and then subjection to the control placebo mouthwash.	Placebo rinse	Subjective pain scores using VAS	There was a significant decrease in the VAS score in the capsaicin group.	7 dropouts Side effects ranged from intense burning sensation in 30% of subjects ranging up to 30 minutes after application of the rinse.
Jankovskis and Selga[22] (2021)	Interventional study	89 patients, of which 20 were allocated to the capsaicin mouthwash group.	0.02% capsaicin rinse	The total duration of therapy was three weeks. The patient was subjected to capsaicin mouth rinse three times a day for three weeks.	Zinc and vitamin B_{12} supplementation	Subjective pain scores using VAS	Capsaicin mouth rinse in conjunction with B_{12} and zinc supplementation is effective in reducing VAS scores related to burning mouth syndrome.	-

(OHIP-14: Oral Health Impact Profile-14, VAS: visual analog scale)

Table 3. Quality assessment of the included studies

Study	Aim	Inclusion	Data collection	Endpoint	Evaluation bias	Follow-up period	Loss to follow-up	Sample size	Total score
Ricken et al.[24] (2021)	2	2	1	2	0	2	2	0	11
Jørgensen and Pedersen[23] (2017)	2	2	1	2	0	2	2	0	11
Silvestre et al.[25] (2012)	2	2	1	2	0	2	2	0	11
Jankovskis and Selga[22] (2021)	2	2	1	2	0	2	2	0	11

Score: 0=not reported, 1=reported but inadequate, 2=reported and adequate.
Ideal score is 16 for non-comparative studies and 24 for comparative studies.
Sunny Priyatham Tirupathi et al: Burning measure for burning mouth syndrome: a systematic review. J Korean Assoc Oral Maxillofac Surg 2024

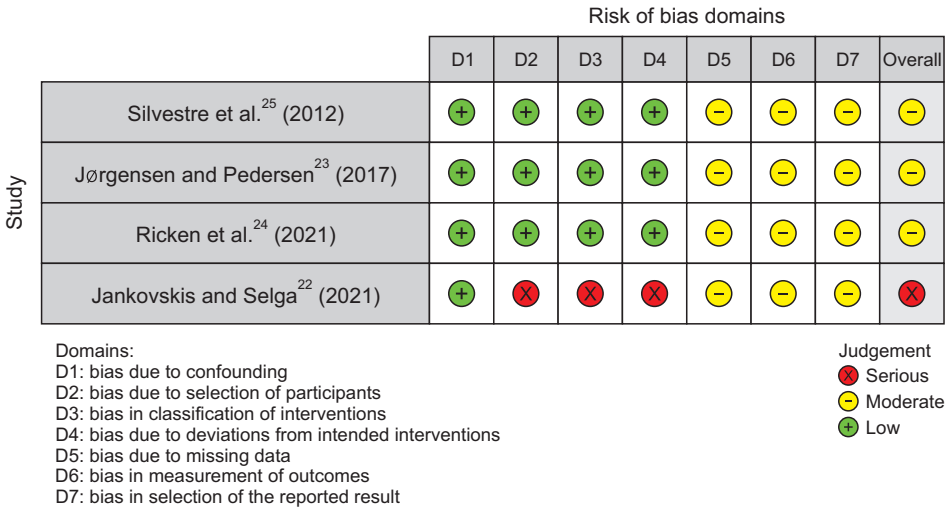

Fig. 2. Risk of bias graph.
Sunny Priyatham Tirupathi et al: Burning measure for burning mouth syndrome: a systematic review. J Korean Assoc Oral Maxillofac Surg 2024

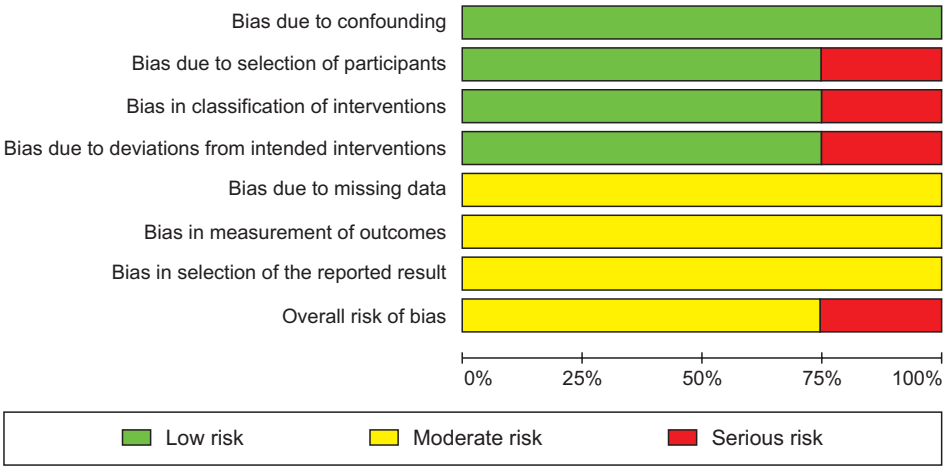

Fig. 3. Risk of bias summary.
Sunny Priyatham Tirupathi et al: Burning measure for burning mouth syndrome: a systematic review. J Korean Assoc Oral Maxillofac Surg 2024

in three studies[23-25], but was used in conjunction with other agents such as zinc and vitamin B_{12} supplements in the study by Jankovskis and Selga[22].

1. Application and duration of capsaicin

Capsaicin application varied by study, with topical gel applied on the BMS-affected tongue by Jørgensen and Pedersen[23]. Topical capsaicin was applied for a period of 28 days (excluding the washout period of 14 days) in the study by Jørgensen and Pedersen[23]. The capsaicin application duration was the longest at 180 days in the study by Ricken et al.[24]. Three weeks continuous capsaicin topical application as mouthwash three times a day was used in the study by Jankovskis and Selga[22].

2. Remission of symptoms of BMS

Remission of the symptoms of BMS was observed as early as 28 days in the study by Jørgensen and Pedersen[23]. The study by Ricken et al.[24] reported remission of symptoms in 50% of the patients and significant improvement in 40% in the first 30 days. Ricken et al.[24] also performed evaluation after 180 days and after medication withdrawal, and 60% of the patients reported total absence of BMS symptoms. In 40% of patients, the score of BMS decreased, while 10% showed a smaller decrease but still below baseline. Topical capsaicin used as a mouthwash three times a day for three weeks reduced the symptoms of BMS in cases where adequate remission was not achieved using vitamin B and zinc supplementation[22].

3. Adverse effects

An unpleasant taste with strong burning sensation was observed in all the participants in the study and were resolved within 30 minutes of capsaicin application[23]. Reversible gastrointestinal side effects such as nausea and itching and soreness of the throat were observed in 18% of the participants in the study by Jørgensen and Pedersen[23]. More frequent side effects were reported with the higher concentration of 0.025% as opposed to 0.01%[23]. Burning was observed in 30% of the population in the study by Silvestre et al.[25].

4. Summary of evidence

This systematic review aimed to investigate the effect of topical application of capsaicin in reducing the symptoms of BMS. All included studies reported significant reduction in the self-reported pain scores in the patients affected by BMS.

5. Strengths and limitations of the study

The current systematic review aimed to include only studies that used topical capsaicin in well-established BMS patients. To improve the quality of analysis, exclusion of studies was performed[8]. The study by Marino et al.[8] was excluded as the concentration of capsaicin was not standardized. A limitation of the current systematic review is the data related to VAS not mentioned in the studies included for quantitative pooling of data, for which meta-analysis was not performed.

6. Directions for future research

Capsaicin can be compared with an active agent (alpha-lipoic acid) in a split mouth fashion to evaluate the remission of symptoms.

V. Conclusion

Based on the available results, the following conclusions can be made.

1. Capsaicin as a mouthwash has potential for application in the treatment of symptoms related to burning mouth.
2. The quality of available studies is moderate to low, and a well-designed randomized multicentric study comparing capsaicin with other active agents should be planned to obtain more definitive conclusions.

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Authors' Contributions

S.P.T. has conceived the idea and has done data collection, performed statistical analysis and wrote manuscript. S.M., U.A., S.V., L.A., S.B., and M.S. participated in data collection and study design. L.A. participated in drafting of the manuscript. All authors read and approved the final manuscript.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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