Original Article

Investigating the Effect of Capsaicin Oral Solution in the Treatment of Burning Mouth Syndrome in Female Patients: A Randomized Clinical Trial

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ABSTRACT

Background: Burning mouth syndrome (BMS) is a chronic oral pain disorder characterized by a persistent burning sensation in clinically normal oral mucosa. Its complex and unclear etiology has limited effective treatment options. Capsaicin has been proposed as a potential therapy; however, evidence regarding capsaicin oral solutions remains limited.

Purpose: To evaluate the effect of a novel capsaicin oral solution on burning mouth symptoms, salivary flow, xerostomia, and oral health-related quality of life in patients with BMS.

Materials and Method: This double-blind, parallel randomized controlled trial included 22 eligible female patients with BMS who were randomly assigned to capsaicin (n= 11) or placebo (n= 11). Both groups received vitamin B complex and zinc supplementation during the 30-day intervention. Participants in the capsaicin group used 10 drops of capsaicin oral solution diluted in one tablespoon of water as a mouth rinse twice daily for 1 minute, while the placebo group followed the same protocol using an identical placebo solution. Burning severity (visual analog scale), non-stimulated salivary flow (modified Schirmer's test), xerostomia symptoms, and oral health-related quality of life were assessed at baseline and day 30.

Results: Baseline demographic and clinical characteristics were comparable between groups (p Value > 0.05). At day 30, no statistically significant between-group differences were observed for burning severity, non-stimulated salivary flow, xerostomia symptoms, or oral health-related quality of life (all p> 0.05). Within-group analyses demonstrated significant improvements in burning severity, salivary flow, and selected xerostomia and quality-of-life measures in the capsaicin group (all p< 0.05); these findings were considered secondary and exploratory.

Conclusion: Capsaicin oral solution did not demonstrate statistically significant superiority over placebo in improving BMS-related outcomes. Larger multicenter randomized controlled trials with longer treatment duration and follow-up are warranted to clarify the potential role of capsaicin as an adjunctive therapy for BMS.

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Introduction

Burning mouth syndrome (BMS) is a chronic, idiopathic disorder characterized by persistent oral burning sensations, often involving the tongue, lips, palate, and other mucosal areas, in the absence of any discernible lesions. As per the World Health Organization (WHO), individuals with BMS report recurrent pain lasting for at least two hours per day over a period exceeding three months. The burning sensation is commonly described as a pricking, tingling, itching, or even numbness, typically localized and bilateral, and may fluctuate, improve, worsen, or remain constant over time [1-3].

The burning sensation in BMS is frequently accompanied by other symptoms such as dry mouth (xerostomia), altered taste perception (dysgeusia), and oral paresthesia. These symptoms are usually persistent but can vary in intensity [4-5]. Additionally, patients often report a significant reduction in their quality of life, with disturbances in sleep and emotional well-being [6]. Despite the lack of observable mucosal changes, objective findings in BMS patients reveal altered salivary function. In other words, studies have demonstrated a reduced flow rate and increased viscosity of non-stimulated whole saliva in individuals with BMS, which may exacerbate the sensation of dryness and contribute to the burning discomfort [7-8].

While BMS predominantly affects middle-aged and postmenopausal women with a prevalence of 0.7-15% of the general population, its precise etiology remains elusive. A multitude of potential factors, including both local and systemic conditions, have been implicated in its pathogenesis. Based on etiologic factors, BMS is broadly classified into primary (idiopathic) and secondary forms. Primary BMS is diagnosed when no identifiable local or systemic cause can be found and is considered a neuropathic pain disorder. In contrast, secondary BMS is associated with underlying local or systemic conditions, such as nutritional deficiencies, endocrine disorders, oral infections, medication use, or xerostomia, and management is directed toward treating the underlying cause [9-10].

Although various therapeutic approaches have been proposed, including hormone replacement therapy, systemic medications (e.g., antidepressants, clonazepam), topical agents, low laser therapy, acupuncture, herbal remedies, and stress management, none provide a definitive cure. Currently, the most effective strategy involves comprehensive pain assessment using the visual analog scale (VAS) followed by individualized supportive care [11-13].

Capsaicin is a natural protoalkaloid recognized as the primary component in chili peppers, which is now frequently used as a potential treatment for BMS. The main target of capsaicin in the body is the primary sensory neuron such as transient receptor potential vanilloid 1 (TRPV1); which is why this compound exhibits desensitizing, analgesic, and anti-inflammatory properties [14]. Capsaicin has been approved by food and drug administration (FDA) and administered topically at concentrations of 0.01% and 0.025%, applied three times per week, or as a 0.02% mouthwash, used three times daily for 30 seconds each time [15-17].

Subsequent to oral administration of topical capsaicin, some patients report side effects including mild to moderate burning sensations, stinging, itching, redness, and pain in the treated area. Although these symptoms are generally self-limiting, the need for repeated daily applications of topical capsaicin may lead to recurrent irritation from side effects, potentially reducing patient adherence to the treatment regimen [18-19]. On the other hand, capsaicin mouthwashes do not present the mentioned side effects observed using its topical form. However, the bitter taste and unpleasant texture of capsaicin mouthwashes have been noted to decrease compliance. Therefore, if the beneficial effects of capsaicin in reducing oral burning sensation is confirmed, the advantages of its mouthwash and oral solution form outweigh its topical form [15, 17].

Despite the availability of several therapeutic modalities, there is currently no universally accepted gold-standard treatment for BMS, as existing interventions demonstrate variable efficacy and primarily provide symptomatic relief rather than disease resolution. This has prompted continued investigation into alternative multimodal therapeutic strategies that target different aspects of the disorder [11-12]. Accordingly, the present randomized controlled trial aimed to evaluate the efficacy of capsaicin oral solution, administered alongside zinc and vitamin B complex supplementation, compared with placebo in patients with BMS.

Materials and Method

The study was conducted as a double-blind, parallel, ra-

ndomized controlled clinical trial with volunteers diagnosed with BMS who were referred to the School of Dentistry at Tehran Islamic Azad University of Medical Sciences and affiliated hospitals in 2022. Purpose-based sampling was used to select female volunteers, aged 30 to 80, who were literate and diagnosed with primary BMS. The inclusion of only female participants was based on the well-documented higher prevalence of BMS in women, particularly in the perimenopausal and postmenopausal age groups, with reported female-to-male ratios ranging from 3:1 to 7:1 [9-10]. Furthermore, the inclusion of male participants would have introduced significant heterogeneity related to sex-related differences in pain perception and hormonal profiles, which could not be adequately accounted for given the relatively small sample size of this single-center study. This approach is consistent with previous randomized clinical trials on BMS that have predominantly included female patients [16-17].

BMS was diagnosed according to the WHO diagnostic criteria, defined as recurrent oral burning pain lasting for at least two hours per day for more than three months, in the absence of any clinically detectable oral mucosal lesions or identifiable secondary causes [2, 20]. All participants underwent a comprehensive clinical examination by an oral medicine specialist (A.A) at the Department of Oral Medicine, School of Dentistry, Tehran Islamic Azad University. To exclude secondary etiologies, laboratory investigations including complete blood count, fasting blood sugar, and serum levels of vitamin B12 and folic acid were performed for all participants. Patients with abnormal laboratory findings suggestive of anemia, diabetes mellitus, or nutritional deficiencies were referred for appropriate management and were not included in the study. This diagnostic approach aligns with established clinical guidelines for BMS, which require the exclusion of local and systemic causes before establishing a diagnosis of primary BMS [2, 20, 25].

In addition, the exclusion criteria of the sampling were defined as (1) the presence of clinical lesions of the pharynx and nose, (2) the presence of systemic disease, (3) history of head and neck radiotherapy,(4) hypersensitivity reactions, (5) complete dental prosthesis wearier, (6) bad oral habits such as grinding (7) present diseases of the oral mucosa such as lichen planus, benign migratory glossitis and bacterial, fungal and viral infections, (8) neurological problems, (9) endocrine and digestive disorders, (10) anemia, (11) malnutrition, (12) present pregnancy or lactation, (13) allergic reaction to chili pepper and capsaicin, (14) current use of medications known to affect salivary secretion (including xerostomia-relieving agents and sialagogues), and (15) abnormal laboratory findings on complete blood count, fasting blood sugar, or serum vitamin B12 and folic acid levels [21].

The present study's protocol followed the *Declaration of Helsinki*. The Ethics Committee of the Islamic Azad University Faculty of Dentistry, Tehran, Iran (IR.IAU.DENTAL.REC.1400.155) also approved it on 01/10/2022, and it was subscribed to the Iranian Registry of Clinical Trials (IRCT20220117053748N1). After explaining the steps to the volunteers, all eligible patients were asked to complete and sign the informed consent form to participate in the study. The participants were subsequently asked to fill in the demographic information form, the burning mouth form, and the standard xerostomia [22] and quality of life questionnaire [23] and the level of non-stimulated saliva was measured. These steps were done to determine the individual's initial burning mouth and xerostomia severity, the level of non-stimulated saliva and their oral health related quality of life before the intervention [13, 17-18].

The sample size was calculated a priori using PASS version 15 software (NCSS, LLC, Kaysville, UT, USA) with the following parameters: α= 0.05 (two-sided) and β = 0.20 (80% statistical power). The primary outcome for power calculation was the change in burning mouth severity, as measured by the VAS from baseline to day 30. The expected effect size (Cohen's d = 1.0) was derived from the findings of the most comparable published randomized clinical trial evaluating capsaicin oral rinse in BMS, which reported a clinically meaningful reduction in VAS scores in the intervention group compared with baseline [17]. The standard deviation (SD = 1.25) was also estimated based on the variability reported in that study [17]. Using these assumptions, the minimum required sample size was calculated as 11 participants per group, for a total of 22 participants. This sample size was considered sufficient to detect a large effect size (Cohen's d= 1.0) in the primary outcome with 80% power.

Volunteer recruitment was conducted between April 2022 and September 2022. Subsequently, block randomization with a fixed block size of 4 was implemented to allocate 22 participants equally (11 treatment, 11 control) using Microsoft Excel's RAND function while maintaining allocation concealment. Within each block, treatment assignments (A = treatment, B = control) were randomly permuted (e.g., AABB, ABAB, BAAB, etc.) using a computer-generated sequence. Since 22 is not a multiple of 4, five complete blocks (20 participants) were generated, followed by a partial block of 2 (one A and one B in random order). Sequentially numbered, opaque, sealed envelopes (SNOSE) were prepared, each containing the pre-determined assignment based on the randomization sequence. As participants were enrolled, the envelopes were opened in sequential order to reveal their group allocation, ensuring concealment and minimizing selection bias. This process was done by A.A. The groups demonstrated near-homogeneity in terms of age, smoking habits, systemic condition, and educational background [17-18].

As illustrated in the CONSORT flow diagram (Figure 1), two distinct medicinal interventions were administered as follows:

1. Group A: 10 drops of capsaicin oral solution in one tablespoon of water, twice a day, and 1 pill of zinc and 1 pill of vitamin B complex daily,
2. Group B: 10 drops of placebo in one tablespoon of water, twice a day, and 1 pill of zinc and 1 pill of vitamin B complex daily.

Since capsaicin oral solution was not commercially available in the Iranian pharmaceutical market, it was formulated in the laboratory of the registered pharmaceutical institute named Yas Daru, Tehran, Iran. The oral solution was formulated to contain 0.025% standardized capsaicin as the active pharmaceutical ingredient in a hydroalcoholic base with liquid fructose and polyethylene glycol. Capsaicin was incorporated as a separate pharmaceutical ingredient during the formulation process and was not extracted from chili peppers. The capsaicin content of the final formulation was verified and standardized using high-performance liquid chromatography (HPLC) analysis to confirm the accuracy of the 0.025% concentration. HPLC analysis was performed using a validated method with a C18 reverse-phase column and UV detection at 280 nm, and the capsaicin concentration was determined against a standard calibration curve prepared from a capsaicin reference standard. This analytical procedure confirmed that the capsaicin concentration in the final oral solution was within the acceptable range of the target concentration.

During the formulation process, 10% extracts of coriander fruit (*Coriandrum sativum* L.) and St. John's wort (*Hypericum perforatum* L.), prepared by the accelerated solvent extraction (ASE) method, were incorporated solely as pharmaceutical excipients to improve the

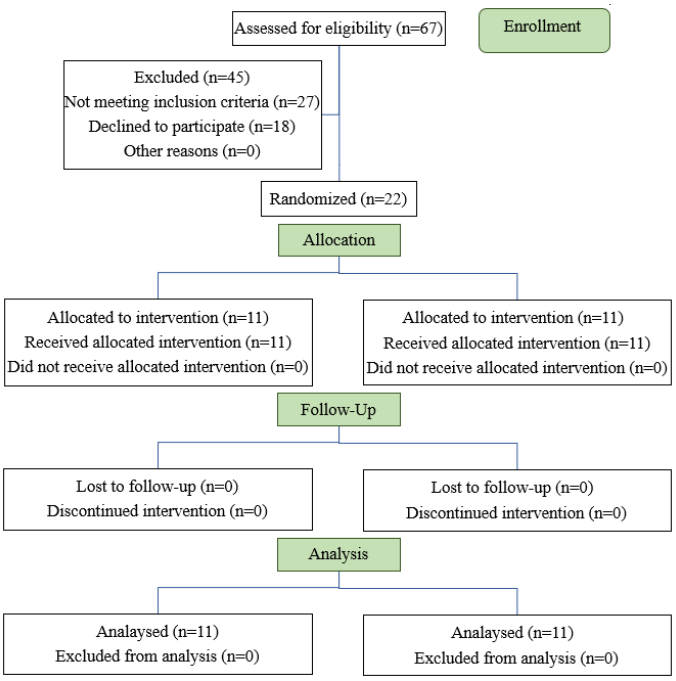


Figure 1: Consolidated Standards of Reporting Trials (CONSORT) diagram of participants' flow

taste, odor, and overall acceptability of the oral solution. In other words, these botanical extracts were included only as formulation aids and were not intended to provide additional therapeutic effects. ASE method is a type of solid-liquid extraction process that takes place at high temperatures, usually between 50 and 200 degrees Celsius, and pressures of about 10 to 15 MPa. At last, cardamom extract and sucralose were added to further enhance the flavor [17].

On the other hand, the placebo oral solution contained the same vehicle components as the active formulation, including the hydroalcoholic base, liquid fructose, and polyethylene glycol, and was matched in appearance using pharmaceutical-grade permitted food coloring. However, capsaicin was not included, and the botanical extracts (coriander fruit and St. John's wort), which were used as formulation excipients in the active solution, were also omitted.

The capsaicin and placebo oral solutions were prepared under good manufacturing practice (GMP)-compliant conditions at Yas Daru Institute, Tehran, Iran. Both formulations were filled into identical 35 mL amber glass bottles to protect the contents from light, sealed with tamper-evident caps, and labeled with randomly assigned codes by the pharmacologist (Gh.A.), who was not involved in participant assessment or data analysis.

Stability testing of the capsaicin oral solution was conducted under accelerated conditions (40°C±2°C/ 75% RH ±5% RH) for a period of 6 months, as well as under long-term storage conditions (25°C±2°C / 60% RH±5% RH) for 12 months, in accordance with ICH guidelines. The capsaicin content was monitored at predetermined time points using the validated HPLC method described above, and the formulation was considered stable if the capsaicin concentration remained within 90–110% of the initial labeled amount (0.025%). The results confirmed that the capsaicin oral solution remained stable throughout the study period.

Both active and placebo solutions were stored at controlled room temperature (20–25°C) and protected from light prior to dispensing. Participants were instructed to store the solution at room temperature and to avoid direct sunlight and excessive heat. Each bottle was labeled with a batch number, manufacturing date, and expiry date. The expiry date was determined based on the stability data and was set at 12 months from the date of manufacture. Quality control of the final formulations included assessment of organoleptic properties (appearance, color, odor, and taste), pH, density, and microbial contamination, all of which met the predefined specifications. Batch-to-batch consistency was ensured by analyzing three separate batches of the active formulation, all of which met the acceptance criteria for capsaicin content and physicochemical parameters.

To ensure the evaluation of capsaicin's effect on true BMS related to idiopathic oral dysesthesia rather than inter-individual variations in nutritional status, all participants received standardized supplementation with zinc (Abian Darou Co., Tehran, Iran) and B-complex vitamins (EuroVital, Germany) throughout the 30-day study period. This standardized co-intervention was not intended to correct deficiencies (as all participants had normal serum levels at baseline) but rather to control for potential confounding effects and to ensure comparability between groups. The zinc and vitamin B complex pills were taken as mentioned below [17]:

1) One 500mg zinc pill (15mg Zinc, 35mg Vitamin C, Glucose, Fructose, Magnesium Stearate (E470b))
2) One 370mg vitamin B complex pill (35 mg thiamine (vitamin B1), 35mg riboflavin (vitamin B2), 35mg niacin (vitamin B3), 35mg Pantothenic acid (vitamin B5), 25mg pyridoxine (vitamin B6), 10µg vitamins B12, 600µg Folic acid (vitamin B9), 150µg Biotin (vitamin B7))

The doses administered are within the daily recommended dietary allowances and are generally recognized as safe. This study design is consistent with the most comparable published randomized controlled trial on capsaicin in BMS [17]. Nevertheless, the study protocol, including the administration of zinc and vitamin B complex supplements, was reviewed and approved by the Ethics Committee of the Islamic Azad University Faculty of Dentistry, Tehran, Iran (IR.IAU.DENTAL.REC.1400.155).

In addition, the amount of non-stimulated saliva in participants was measured on day 0 before the intervention using the modified Schirmer's test. In order to do so, participants were instructed to refrain from eating, drinking, consuming coffee, smoking, and brushing their teeth for at least 2 hours prior to the measurement. They were also asked to rinse their mouths with 15 mL

of distilled water. Subsequently, in a quiet and well-ventilated room, participants rested for 1 minute and then sat upright in a dental chair. The researcher (K.Gh), adhering to strict sterilization protocols and wearing a mask and shield, conducted the measurement. Participants were first asked to swallow all the saliva in their mouths. Then, they were instructed to gently lift and pull their tongue upward and backward to avoid unintentional wetting of the Schirmer strip. The strip was held vertically using dental tweezers, with the end of the strip in contact with the floor of the mouth. During this process, the color of the strip changed due to contact with salivary moisture, and the length of the colored area on the strip was recorded in millimeters over a period of 3 minutes. It should be mentioned that all salivary measurements were carried out between 9 and 11 AM as saliva secretion may fluctuate during the day [24].

Following this step, participants in both groups were instructed to gently gargle 10 drops of their assigned oral solution diluted in 1 tablespoon of water for 1 minute twice a day (morning and evening) without swallowing any of it, then to completely expel the solution. Participants were also asked not to wash their mouth for 2 hours after using the oral solution. Additionally, participants were told to take 1 zinc and 1 vitamin B complex pill in the morning before gargling their mouth with the oral solution.

After complete instruction of participants, an 8-item burning mouth questionnaire, a 10-item xerostomia questionnaire based on the VAS, and a 12-item quality of life questionnaire was completed before the intervention on day 0 [13, 17, 25]. These questionnaires were again filled out, and non-stimulated saliva was also measured using the same technique on day 30 after the intervention for both groups.

The burning mouth questionnaire assessed five parameters: occurrence time, change in burning level during the day, change in burning when eating or drinking, interference with sleep, and severity of burning sensation. Burning mouth severity was evaluated using a VAS, a 10-cm horizontal line ranging from 0 (no pain) to 10 (worst possible pain) [25]. To score the variable of the occurrence time of burning mouth, a score of 1 was given for a response in the morning (4 a.m. to 12 p.m.), a score of 2 for a response in the afternoon (12p.m. to 8p.m.), a score of 3 for a response at night (8p.m. to 4a.m.), a score of 4 for a response throughout the entire day, and a score of 5 for a response throughout the entire night. Additionally, to score the variables of the change in the level of burning mouth sensation during the day and mouth burning interference with sleep patterns, a score of 1 was given for a "Yes" response and a score of 0 for a "No" response. Finally, to score the variable of the change in burning mouth sensation when eating food or drinking water, a score of 1 was given for a "Better" response, a score of 2 for a "No effect" response, and a score of 3 for a "Worse" response.

Xerostomia was assessed using a 10-item questionnaire based on the VAS, adapted from the validated xerostomia inventory developed by Fox *et al.* [22]. Each item was scored on a VAS ranging from 0 to 10, with higher scores indicating greater severity of dry mouth symptoms. This questionnaire has been validated in Persian populations in previous studies conducted in Iran, with reported Cronbach's alpha coefficients exceeding 0.85, indicating excellent internal consistency [22, 25].

Oral health-related quality of life was assessed using the validated Persian version of the oral health impact profile (OHIP-14), a 12-item questionnaire that evaluates the impact of oral conditions on daily functioning and well-being [23]. Each item is scored on a 5-point Likert scale, the response “Never” is given a score of 0, the response “Rarely” is given a score of 1, the response “Sometimes” is given a score of 2, the response “Often” is given a score of 3, and the response “Always” is given a score of 4. The Persian version of the OHIP-14 has been validated in Iranian populations, with demonstrated reliability (Cronbach's alpha > 0.80) and construct validity [23].

All questionnaires were administered in Persian, and participants were instructed by a trained researcher (K. Gh) on how to complete each instrument. The questionnaires were self-administered, with the researcher available to clarify any questions. The minimum clinically important difference (MCID) for the VAS in oral pain conditions has been reported as 1.5 cm on the 10-cm VAS [25]. For the OHIP-14 and xerostomia questionnaire, a reduction of 2 points was considered clinically meaningful based on previous studies in similar populations [23]. The scoring procedures for each questionnaire were standardized and applied consistently across

all participants at both assessment time points (day 0 and day 30).

At the final visit on day 30, participants were asked to return their study medication bottles. The returned bottles were checked by the research team to assess the remaining volume of the oral solution, which served as an objective measure of adherence to the prescribed regimen. The percentage of adherence was calculated as the ratio of the volume of solution used to the expected volume based on the prescribed twice-daily regimen over 30 days. Participants were considered adherent if they used at least 80% of the prescribed solution volume.

Throughout the 30-day study period, participants were contacted by telephone every 5 days by a member of the research team (K. Gh). These scheduled calls were used to monitor adherence to the intervention protocol, reinforce compliance with the prescribed regimen, address participants' questions or concerns, and document any difficulties or adverse events reported during the study. At each scheduled telephone contact and during the final visit on day 30, participants were systematically questioned about the occurrence of any adverse events. Participants were specifically asked about local oral symptoms (burning or stinging sensation following solution use, mucosal irritation, redness, swelling, altered taste sensation) as well as any systemic symptoms (nausea, gastrointestinal discomfort, or any other unusual symptoms). Participants were also instructed to report any adverse effects or discomfort experienced during the study immediately to the research team outside of the scheduled calls.

The severity of adverse events was graded by the researcher (K. Gh) as mild (transient, well-tolerated, requiring no intervention), moderate (causing discomfort but not interfering with daily activities), or severe (interfering with daily activities or requiring medical attention). All adverse events were recorded and documented in the study records. Participants were also informed that they could withdraw from the study at any time without providing a reason. Additionally, the research team reserved the right to discontinue a participant from the study in the event of a severe adverse event (grade 3) that was definitely, probably, or possibly related to the study intervention; a participant's request to withdraw at any time; pregnancy during the study period; development of any exclusion criteria, such as systemic disease or oral mucosal lesions; use of prohibited medications or interventions; or poor adherence to the study protocol, defined as using less than 80% of the prescribed solution volume.

In addition to adverse event monitoring, safety was assessed by evaluating local tolerance of the oral solution at each follow-up contact. Participants were specifically questioned about the tolerability of the solution, including any burning or stinging sensation immediately after use, persistence of discomfort, or any mucosal changes they may have noticed. Any participant experiencing severe or persistent local irritation was to be evaluated by the oral medicine specialist. Serious adverse events were to be reported to the Ethics Committee within 24 hours; however, no serious adverse events occurred during the study. Moreover, participants were instructed to avoid using any medications that alleviate burning mouth during the study. However, they were permitted to consume medications which relieve dry mouth or increase saliva, water, chew gum, and use topical local anesthesia without restrictions.

Statistical Analysis

Statistical analyses were performed using SPSS version 26 (IBM Corp., Armonk, NY, USA). Data distribution was assessed using the Shapiro–Wilk test, which is recommended for small sample sizes. For continuous variables (age, non-stimulated salivary flow, VAS for burning mouth severity, and VAS-based xerostomia items), baseline characteristics and between-group comparisons were analyzed using independent-samples *t*-tests or Mann–Whitney *U* tests according to data distribution. For ordinal variables (burning mouth occurrence time, change in burning level during the day, change in burning when eating or drinking, and burning interference with sleep), non-parametric tests (Mann–Whitney *U* test for between-group comparisons and Wilcoxon signed-rank test for within-group comparisons) were used exclusively, as these variables do not represent equal intervals and parametric assumptions are not met.

The primary analysis consisted of between-group comparisons of all study outcomes at day 30, as well as comparisons of change scores (day 30 minus day 0) between the two groups. Within-group comparisons from baseline to day 30 were considered secondary analyses. Given the exploratory nature of the within-group secondary analyses and the multiple outcomes evaluated,

Table 1: Demographic characteristics of the examined groups

Characteristics	Capsaicin Oral Solution	Placebo Oral Solution	Total	*p* Value
Age (year)	55.64±4.03	59.82±5.67	57.72±5.25	0.059
Educational Level (high school degree)	11 (100%)	8 (72.7%)	19 (86.4%)	0.06
Marital Status (married)	9 (81.8%)	9 (81.8%)	18 (81.8%)	1

no adjustment for multiple testing (e.g., Bonferroni correction) was applied to the primary between-group comparisons, as these were prespecified and limited in number. Categorical variables were compared using the Chi-square test or Fisher's exact test, where applicable. Statistical significance was set at p Value < 0.05.

Results

In the present study, adherence rates were high and comparable between the two groups (capsaicin group: 96.4%±2.1%; placebo group: 95.8%±2.3%), with no participants excluded due to poor adherence. The demographic characteristics along with variables of burning mouth sensation, non-stimulated saliva, xerostomia, and quality of life were evaluated in each capsaicin and placebo group consisting of 11 participants. As shown in Table 1, there was no significant difference between the studied groups in age, educational level, and marital status (p> 0.05), confirming successful randomization.

The burning mouth sensation

No subjects were lost to follow-up during the study. The effects of the intervention on burning mouth sensation parameters are summarized in Table 2. No significant between-group differences were observed in any burning mouth sensation parameter at day 30 (all p> 0.05), indicating no superiority of capsaicin over placebo. Within-group analyses showed a significant reduction in burning mouth severity in the capsaicin group only (p< 0.05), whereas no significant within-group changes were observed in the placebo group. These within-group findings should be interpreted as secondary analyses.

The non-stimulated saliva

Changes in non-stimulated salivary flow are presented in Table 3. No significant between-group difference in non-stimulated salivary flow was observed at day 30 (p> 0.05), indicating no superiority of capsaicin over placebo. Although significant within-group increases in salivary flow were observed in both groups (p< 0.05), these findings represent secondary analyses and do not indicate a treatment effect.

The xerostomia

None of the assessed xerostomia variables showed significant between-group differences (Table 4). No significant between-group differences were observed at day 30 (all p> 0.05), indicating that capsaicin did not provide greater improvement than placebo. Within-group analyses demonstrated significant improvements in several xerostomia items only in the capsaicin group, whereas no significant within-group changes were observed in the placebo group. These within-group findings should be interpreted as secondary outcomes.

The quality of life

Quality-of-life outcomes are summarized in Table 5. No significant between-group differences were observed in quality-of-life outcomes at day 30 (all p> 0.05). Within group analyses demonstrated significant improvements in several quality-of-life items in the capsaicin group only, whereas no significant within-group changes were

Table 2: Burning mouth sensation parameters before and after the intervention

Assessment time	Burning mouth sensation variables	Capsaicin group	Placebo group	*p* Value
Day 0	Occurrence time*	1.0 [1.0–2.0]	1.0 [1.0–2.0]	0.944
	Change in burning during the day*	1.0 [0.0–1.0]	0.0 [0.0–1.0]	0.655
	Change in burning with eating/drinking*	2.0 [1.0–3.0]	2.0 [1.0–3.0]	0.522
	Burning interference with sleep*	0.0 [0.0–1.0]	0.0 [0.0–1.0]	0.619
	Severity of burning (VAS)**	7.0 ± 1.55	6.18 ± 0.60	0.185
Day 30	Occurrence time*	1.0 [1.0–2.0]	1.0 [1.0–2.0]	0.789
	Change in burning during the day*	1.0 [0.0–1.0]	1.0 [0.0–1.0]	1.000
	Change in burning with eating/drinking*	2.0 [1.0–2.0]	2.0 [1.0–3.0]	0.347
	Burning interference with sleep*	0.0 [0.0–1.0]	0.0 [0.0–1.0]	1.000
	Severity of burning (VAS)**	5.64 ± 1.29	6.45 ± 1.04	0.116

*Ordinal variables are presented as median [interquartile range, IQR] and were analyzed using non-parametric tests (Mann–Whitney U for between-group comparisons; Wilcoxon signed-rank for within-group comparisons).
**VAS-based severity is a continuous variable and is presented as mean ± SD; analyzed using independent-samples t-test or Mann–Whitney U test as appropriate.

Table 3: Non-stimulated salivary flow measured using the modified Schirmer's test before and after the intervention

Assessment time	Capsaicin group	Placebo group	*p* Value
Day 0	23.36±3.107	24.45±2.979	0.409
Day 30	24.55±2.162	24.09±2.663	0.685
p Value	0.03	0.037	

observed in the placebo group. These within-group findings should be interpreted with caution because they do not establish treatment efficacy in a randomized controlled trial.

Summary of Between-Group Comparisons (Change Scores)

For the primary outcome of burning mouth severity (VAS), the mean change from baseline to day 30 was -1.286±1.549 in the capsaicin group and -1.036±0.603 in the placebo group. The mean difference in change between groups was -0.25 (95% CI: -0.89 to 0.39; Cohen's d= 0.21), indicating a small effect size that was not statistically significant (p= 0.116).

For non-stimulated salivary flow (Schirmer's test, mm), the mean change was +1.18±2.162 in the capsaicin group and -0.36±2.663 in the placebo group. The mean difference in change between groups was +1.54 (95% CI: -0.65 to 3.73; Cohen's d= 0.64), indicating a moderate effect size that was not statistically significant (p= 0.685).

For xerostomia symptoms (mean of 10 VAS items), the mean change was -0.52±0.98 in the capsaicin group and -0.11±0.76 in the placebo group. The mean difference in change between groups was -0.41 (95% CI: -1.21 to 0.39; Cohen's d= 0.47), indicating a moderate effect size that was not statistically significant (all individual items p> 0.05).

For oral health-related quality of life (OHIP-14 total score), the mean change was -1.02±1.06 in the capsaicin group and -0.44±0.82 in the placebo group. The mean difference in change between groups was -0.58 (95% CI: -1.59 to 0.43; Cohen's d= 0.61), indicating a moderate effect size that was not statistically significant (all individual items p> 0.05).

It is important to note that while the effect sizes for several outcomes were small to moderate (Cohen's d ranging from 0.21 to 0.64), none reached statistical significance due to the limited sample size. The 95% confidence intervals for all between-group differences crossed zero, confirming the absence of statistically significant superiority of capsaicin over placebo for all outcomes.

Adverse Events and Safety

No serious adverse events were reported during the study. The most commonly reported adverse event was a mild, transient burning sensation immediately after using the oral solution, which was reported by 4 participants (36.4%) in the capsaicin group and 2 participants (18.2%) in the placebo group. These sensations were self-limiting and resolved within 5-10 minutes without intervention. No participants reported moderate or severe

Table 4: Xerostomia parameters (mean ± SD) before and after the intervention

Assessment time	Xerostomia variables (VAS)	Capsaicin group	Placebo group	*p* Value
Day 0	Dry mouth feeling	5.45 ± 1.97	5.09 ± 1.92	0.69
	Difficulty during swallowing	5.36 ± 2.20	5.00 ± 2.10	0.641
	Need for drinking water when eating dry foods	6.55 ± 2.30	5.91 ± 1.81	0.387
	Dryness during eating	5.55 ± 2.54	5.18 ± 2.23	0.716
	Low salivation during most hours	4.64 ± 2.46	4.91 ± 2.07	0.713
	Dry mouth at the moment	4.64 ± 2.16	4.82 ± 2.32	0.947
	Waking up due to dry mouth	3.82 ± 2.96	3.82 ± 2.75	0.973
	Drinking a lot of water due to dry mouth	6.09 ± 2.63	5.91 ± 2.77	0.842
	Difficulty speaking due to dry mouth	5.73 ± 2.49	5.73 ± 3.17	0.974
	Need for chocolate/candy to alleviate dry mouth	3.27 ± 2.69	1.45 ± 1.70	0.08
Day 30	Dry mouth feeling	4.82 ± 1.78	4.91 ± 1.64	0.92
	Difficulty during swallowing	4.82 ± 1.83	5.36 ± 1.86	0.463
	Need for drinking water when eating dry foods	5.64 ± 1.96	6.27 ± 1.95	0.462
	Dryness during eating	4.82 ± 2.14	5.36 ± 1.80	0.571
	Low salivation during most hours	4.27 ± 1.74	5.18 ± 1.94	0.302
	Dry mouth at the moment	4.27 ± 1.95	5.27 ± 1.90	0.244
	Waking up due to dry mouth	3.09 ± 2.30	3.55 ± 2.84	0.841
	Drinking a lot of water due to dry mouth	5.36 ± 2.42	6.18 ± 2.75	0.421
	Difficulty speaking due to dry mouth	5.00 ± 2.32	6.09 ± 2.47	0.245
	Need for chocolate/candy to alleviate dry mouth	0.73 ± 2.49	1.00 ± 1.79	0.072

Table 5: Oral health related-quality of life parameters (mean ± SD) before and after the intervention

Assessment time	Quality of life variables	Capsaicin group	Placebo group	*p* Value
Day 0	Difficulty in chewing food	2.00 ± 1.41	1.55 ± 0.93	0.416
	Limiting the type or amount of food	1.27 ± 1.10	1.45 ± 1.13	0.684
	Difficulty in speaking	2.00 ± 1.10	1.82 ± 1.25	0.675
	Uncomfortable during eating	2.09 ± 1.14	1.91 ± 1.04	0.726
	Sensitivity to heat, cold, sweets	1.36 ± 1.43	1.09 ± 1.04	0.705
	Using medications to alleviate pain	0.36 ± 0.67	0.82 ± 0.98	0.265
	Difficulty in swallowing	2.00 ± 1.10	2.27 ± 1.01	0.628
	Anxiety regarding poor oral condition	1.82 ± 1.47	1.73 ± 1.01	0.838
	Limiting connections due to poor oral condition	1.55 ± 1.29	1.82 ± 1.08	0.61
	Uncomfortable eating in public	2.00 ± 1.18	2.36 ± 0.81	0.448
	Frustration due to poor oral condition	1.36 ± 1.21	1.82 ± 1.08	0.45
	Satisfaction with oral condition	1.82 ± 1.17	1.55 ± 0.69	0.699
Day 30	Difficulty in chewing food	1.36 ± 1.03	1.73 ± 1.19	0.435
	Limiting the type or amount of food	1.00 ± 1.10	1.36 ± 1.03	0.406
	Difficulty in speaking	1.55 ± 0.82	1.91 ± 0.94	0.423
	Uncomfortable during eating	1.64 ± 0.67	2.09 ± 1.04	0.31
	Sensitivity to heat, cold, sweets	0.73 ± 0.91	1.27 ± 1.10	0.226
	Using medications to alleviate pain	0.45 ± 0.69	0.82 ± 1.17	0.55
	Difficulty in swallowing	2.64 ± 0.92	2.36 ± 1.12	0.539
	Anxiety regarding poor oral condition	1.55 ± 1.29	1.91 ± 0.83	0.584
	Limiting connections due to poor oral condition	1.27 ± 1.10	1.73 ± 0.91	0.375
	Uncomfortable eating in public	1.82 ± 0.98	2.27 ± 0.79	0.321
	Frustration due to poor oral condition	1.09 ± 0.94	1.73 ± 1.01	0.171
	Satisfaction with oral condition	2.27 ± 0.79	1.64 ± 0.67	0.054

adverse events, and no participant discontinued the study due to adverse effects. The oral solution was generally well-tolerated in both groups. No mucosal irritation, ulceration, or other oral mucosal changes were observed during the study.

Discussion

The primary findings of this randomized controlled trial indicate that capsaicin oral solution, administered in combination with zinc and vitamin B complex for 30 days, did not produce statistically significant improvements in burning mouth severity, non-stimulated salivary flow, xerostomia symptoms, or oral health-related quality of life compared with placebo. However, within-group analyses demonstrated significant improvements from baseline to day 30 in the capsaicin group for several parameters. These within-group improvements should be interpreted with caution, as they may reflect placebo effects, regression to the mean, or natural fluctuations in symptoms rather than a true therapeutic effect of capsaicin. Since this study was designed as a randomized controlled trial, the primary evidence for treatment efficacy is derived from between-group comparisons rather than within-group changes. Therefore, the absence of statistically significant between-group differences indicates that the observed within-group improvements cannot be attributed specifically to capsaicin and should instead be regarded as exploratory secondary findings.

In the present study, capsaicin oral solution did not demonstrate statistically significant superiority over placebo in improving burning mouth symptoms. Although some within-group improvements were observed in the capsaicin group, these findings cannot be attributed specifically to the intervention in the absence of significant between-group differences. Several factors may have contributed to these findings, including the relatively low capsaicin dose, the 30-day treatment duration, the placebo response commonly reported in BMS trials, and the limited sample size despite achieving the predetermined sample size based on the a priori power analysis. In addition, recruitment was restricted to patients with primary BMS who met strict eligibility criteria, which limited the number of eligible participants. In addition, recruitment was restricted to patients with primary BMS who met strict eligibility criteria, which limited the number of eligible participants [17,20].

Another factor that may have influenced treatment outcomes is the formulation of capsaicin. Although an oral solution was investigated in the present study, previous studies have reported inconsistent findings regarding capsaicin-based treatments for BMS, highlighting

the need for further clinical evidence [15,17]. Furthermore, capsaicin administered as a mouthwash or oral solution may become diluted by saliva, potentially reducing mucosal exposure; however, this possibility was not directly investigated in the present study and therefore remains speculative [17,20]. Additionally, in the present study, pain intensity was assessed using the VAS, a widely validated and reliable instrument for pain assessment in clinical research, with established test–retest reliability (intraclass correlation coefficient> 0.80) and demonstrated validity in oral pain conditions [25].

A recent randomized controlled trial involving 89 patients with BMS evaluated a 0.02% capsaicin rinse administered three times daily for three weeks in combination with zinc and vitamin B complex supplementation. Similar to the present study, participants receiving capsaicin reported improvement in burning symptoms, but no statistically significant differences were observed between the capsaicin and placebo groups [17]. These findings are consistent with our results and suggest that additional well-powered randomized controlled trials are needed to determine whether capsaicin provides a clinically meaningful benefit beyond placebo.

In contrast, some studies have suggested that topical capsaicin gel may provide greater symptomatic relief than oral solution formulations, possibly because the gel allows prolonged contact with the affected mucosal area [16,26]. For example, Ricken *et al.* [26] reported a significant reduction in burning pain after treatment with 0.025% capsaicin gel applied three times daily for one month. However, this study did not include a placebo control group, limiting the ability to attribute the observed improvements specifically to capsaicin. Similarly, Jørgensen *et al.* [16] reported improvements in burning symptoms following treatment with both 0.01% and 0.025% capsaicin gels in a randomized double-blind crossover study. However, no statistically significant difference was observed between the two gel concentrations, and the study was not designed to compare capsaicin with placebo. Therefore, although these studies suggest that topical gel formulations may be beneficial, the available evidence remains limited and should be interpreted cautiously. Together with the findings of the present study and previous placebo-controlled trials that did not demonstrate significant superiority of capsaicin over placebo [17], the current evidence regarding the efficacy of capsaicin for BMS remains inconclusive.

Capsaicin's effectiveness in treating burning mouth sensation may not vary based on BMS underlying etiologies. In other words, capsaicin reduces neuropathic pain through activation and subsequent desensitization of TRPV1 receptors on sensory nerve fibers, resulting in reduced substance P-mediated nociceptive signaling. Based on this mechanism, capsaicin was selected as the therapeutic agent in the present study. Nevertheless, formulation and dosage may influence therapeutic efficacy more than BMS etiology [27]. In line with this possibility, Jankovskis et al. [17] reported findings similar to those of the present study, despite including 89 patients with BMS without restrictions based on systemic health status, whereas the present study included only otherwise healthy patients.

Furthermore, BMS is commonly observed in older individuals who often have one or more systemic conditions. As a result, the use of multiple medications in these patients may restrict the administration of capsaicin due to potential drug interactions [17]. In the present study, the extensive exclusion criteria prevented the inclusion of participants with underlying systemic diseases, narrowing the causes of burning mouth sensation in our study population to factors such as hormonal changes, mental stress, and idiopathic causes [21]. Therefore, future research should focus on conducting trials involving individuals who experience a burning mouth sensation as a result of systemic diseases.

Participants in this study were asked to take vitamin B complex pills. It is said that vitamin B supplements may offer benefits in managing neuropathic pain as vitamin B12 helps protect nerve fibers from damage, whereas vitamins B1 and B6 provide antinociceptive and antihyperalgesic benefits [28]. Subsequently, recent studies on patients with BMS who had deficiencies in vitamin B showed positive results in improving symptoms after vitamin B therapy in contrast to the present study [29-30]. In a study by Lončar-Brzak *et al.* [29], patients received vitamin B injections (solution contained 100 mg of vitamin B1 and B6 and 1 mg of vitamin B12 in 3 mL of aqueous solution) every other day into the gluteal muscle for three weeks, excluding weekends. The results of this study manifested a remarkable improvement of quality of life and burning sensation in the mouth [29]. Furthermore, the consump-

tion of a caplet of 250 mg of vitamin B_6 daily for 60 days in 28 female patients suffering from BMS, in a study by Aouididi *et al.* [30], showed a significant reduction in VAS scores [30]. Due to the contrasting results between the studies, more research is required in the future to assess the impact of vitamin B level on burning mouth sensation.

Zinc pills were also taken by the participants in this study. Since it is believed that zinc plays a critical role in growth and immune system function, zinc deficiency and lower serum zinc levels may contribute to the development of oral mucosal diseases and a burning sensation [31]. In contrast to the present study in which the administration of zinc did not effectively reduce the burning sensation in the mouth, a not-so-recent study by Cho *et al.* [32] on 276 patients with BMS demonstrated that the administration of a zinc supplement (14.1 mg/day) for 6 months can significantly reduce the burning mouth pain [32]. Hence, more detailed research is needed to investigate this subject.

Non-stimulated salivary flow was another outcome that did not demonstrate statistically significant improvement in the capsaicin group compared with the placebo group after the 30-day intervention. Although a small within-group increase in non-stimulated salivary flow was observed in the capsaicin group, this finding cannot be attributed specifically to the intervention since no significant between-group difference was detected. In addition, the participants had normal baseline non-stimulated salivary flow, which may have limited the potential for clinically meaningful improvement. The mechanism underlying the observed changes in salivary flow remains uncertain [17]. Although psychological factors such as anxiety, depression, and stress have been reported to influence salivary flow, these variables were not assessed in the present study; therefore, no conclusions can be drawn regarding their potential contribution to the observed findings. Furthermore, differences in the methods used to assess non-stimulated salivary flow make direct comparisons across studies challenging. Nevertheless, our findings obtained using the modified Schirmer's test are consistent with those of another study that used the whole saliva collection method and likewise found no statistically significant difference between the capsaicin and placebo groups [17].

No significant differences were observed in the volunteers' statements regarding xerostomia before and after the treatment. Since the atrophic and dry changes in the mouth are usually caused by saliva deficiency, the slight improvement in a few parameters of the xerostomia questionnaire does not define the true improvement of the problem. In other words, the little changes in dry mouth observed in participants after 30 days of using capsaicin oral solution could quickly reverse with the end of the period of application. Therefore, xerostomia-specific medications such as pilocarpine are required to manage this issue appropriately [19].

The assessment of oral health-related quality of life showed no statistically significant difference between the capsaicin and placebo groups after the 30-day intervention. Although a modest within-group improvement was observed in the capsaicin group, this finding cannot be attributed specifically to the intervention in the absence of significant between-group differences. Since BMS can adversely affect oral health-related quality of life, reducing symptom severity may contribute to improvements in this outcome; however, no significant superiority of capsaicin over placebo was demonstrated in the present study. In contrast, Ricken *et al.* [26] reported a significant improvement in oral health-related quality of life using the OHIP-14 questionnaire. Differences between the findings of the two studies may be related to variations in study design, treatment duration, formulation, or other methodological factors; however, the present study was not designed to evaluate these factors, and no definitive conclusions can be drawn.

It should be note that the secondary within-group analyses and the multiple xerostomia and quality-of-life items should be interpreted with caution, as the risk of Type I error (false-positive findings) is increased due to multiple testing. Therefore, the within-group significant findings reported in this study should be considered exploratory and hypothesis-generating rather than confirmatory.

Unfortunately, capsaicin oral solutions and gels are currently unavailable in the Iranian pharmaceutical market, leaving BMS patients with limited treatment options. Aside from other supportive treatments, the only alternative is the use of capsaicin mouthwashes, whose bitter taste often reduces patient compliance. To address the bitter taste of capsaicin in our study, we used extracts of cardamom and sucralose as they help mask

the unpleasant flavor. We are confident that with a bit more modification in the formulation of the presented capsaicin oral solution and conducting more clinical trial studies, we can achieve a desirable product which can be used for alleviating BMS symptoms in Iran and other countries facing similar shortages.

The primary limitation of this study was the relatively small sample size (11 participants per group), which may have limited the statistical power to detect modest but clinically meaningful between-group differences. Although the sample size was calculated a priori to detect a large effect size (Cohen's d = 1.0) with 80% power for the primary outcome (change in VAS score), the study was not adequately powered to detect smaller effects or differences in secondary outcomes, which should therefore be interpreted as exploratory. Although some outcomes showed small-to-moderate effect sizes (Cohen's d = 0.21–0.64), none of the between-group differences reached statistical significance, and all 95% confidence intervals crossed zero. Therefore, the absence of statistically significant differences should be interpreted cautiously and does not necessarily exclude the possibility of smaller treatment effects. Furthermore, the strict eligibility criteria, single-center design, and challenges in recruiting patients with primary BMS, owing to the need to exclude secondary causes, limited the feasibility of recruiting a larger sample within the study timeframe and available resources.

Another important limitation is the short intervention period of 30 days, which may have been insufficient to observe the full therapeutic potential of capsaicin. Previous studies have reported that the desensitizing effect of capsaicin on TRPV1 receptors may require longer periods of administration to achieve maximum clinical benefit [17,20]. Furthermore, the absence of post-treatment follow-up means that the durability of any observed improvements and the potential for symptom recurrence after treatment cessation could not be assessed. The transient nature of the observed changes, particularly the slight improvements in xerostomia and quality of life parameters, raises the possibility that these effects might not persist beyond the intervention period. Future studies should include extended treatment periods and post-intervention follow-up assessments to evaluate the long-term efficacy and sustainability of any treatment effects.

Furthermore, no adjustment was made for multiple testing in the secondary within-group analyses. Given that multiple outcome measures and questionnaire items were evaluated, the significant within-group findings observed in this study may be attributable to Type I error (false-positive findings) rather than true treatment effects. Therefore, these secondary findings should be considered exploratory and hypothesis-generating, and confirmation in adequately powered future studies is required. Overall, the findings should be interpreted with caution. Larger multicenter randomized controlled trials with longer treatment durations, extended follow-up, and larger sample sizes are required to confirm these findings.

Another limitation was the potential difficulty in maintaining complete participant blinding due to the characteristic burning sensation induced by capsaicin. Although efforts were made to minimize this issue by using a placebo solution with a similar appearance, consistency, and flavoring components to the capsaicin formulation, some participants may have speculated about their treatment allocation despite the use of a matched placebo formulation. Hence, future studies should consider objective assessment of blinding effectiveness and improved placebo formulations.

One other prominent limitation of the study is the use of topical local anesthetics for symptomatic relief during the intervention period for ethical reasons. Although this approach prevented unnecessary discomfort, it may have influenced pain-related outcome measures independently of the study intervention and should be considered when interpreting the findings. Other limitations included a shortage of volunteers caused by the coronavirus pandemic, challenges in sourcing capsaicin drops from the pharmaceutical market, and difficulties in maintaining follow-up with study participants.

Conclusion

In this randomized clinical trial, capsaicin oral solution administered for 30 days in combination with zinc and vitamin B complex did not demonstrate statistically significant superiority over placebo in improving burning mouth severity, non-stimulated salivary flow, xerostomia symptoms, or oral health-related quality of life. Although within-group improvements were observed in the capsaicin group, these findings cannot be attributed

specifically to capsaicin in the absence of significant between-group differences. The study was limited by its small sample size and short follow-up period. Larger multicenter randomized controlled trials with longer follow-up are warranted to determine whether capsaicin oral solution provides any clinical benefit beyond placebo in the management of BMS.

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Authors' contributions

Ghods: Conducting the experiments, performing measurements, contacting the patients, statistical analysis.

Alaee & Azizi: Study design.

Amin: Preparing oral solutions and placebo, blinding the solutions.

Karamatishahri: Writing the manuscript.

The authors read and approved the final manuscript.

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Availability of data and materials

The data supporting this study's findings are available from the corresponding author (Arezoo Alaee) upon your request.

Ethics approval and consent to participate

The study's protocol followed the Declaration of Helsinki and was approved by the ethics committee of the Islamic Azad University Faculty of Dentistry, Tehran, Iran (IR.IAU.DENTAL.REC.1400.155), and it was subscribed to the Iranian registry of clinical trials (IRCT20220117053748N1). After explaining the steps to the patients, all eligible volunteers were asked to complete and sign the informed consent form to participate in the study. The protocol of the study is available on: https://irct.behdasht.gov.ir/trial/61360.

Consent for publication

Not applicable.

Availability of the preprint

A preprint version of this manuscript has been previously deposited on Research Square and is publicly available online. The preprint has not been peer reviewed and can be accessed at: https://doi.org/10.21203/rs.3.rs-619-7107/v1.

Conflict of Interests

The authors declare they have no conflicts of interest in the matter of the study.

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