Evaluation of the Efficacy of Photobiomodulation and Vitamin B12 for Burning Mouth Syndrome

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SUMMARY

This study aimed to evaluate the impact of low-level laser therapy (LLLT) and topical vitamin B12 treatment on patients with burning mouth syndrome (BMS). A total of 123 patients were enrolled and assigned randomly into three groups: LLLT, B12, or no-treatment. Patients completed the EuroQol Five-Dimension Health-Related Quality-of-Life (EQ-5D-5L HRQoL) questionnaire and a visual analog scale (VAS) both before and after treatment. The data were analyzed using R 4.4.2 statistical software to compare pre- and post-treatment differences. Significant differences in the post-treatment period were observed between the three groups for pain/discomfort, anxiety/depression, and VAS scores. Both the B12 and LLLT groups had significantly higher post-treatment scores compared to those in the no-treatment group. Although the differences between the B12 and LLLT groups were not statistically significant, the LLLT group had consistently higher scores. Significant improvements were observed in the LLLT group ($P < 0.001$). Similarly, pain/discomfort ($P < 0.001$) and anxiety/depression ($P < 0.001$) improved significantly after treatment ($P < 0.05$) in the B12 group. LLLT and topical vitamin B12 therapy both improved the overall systemic health status of patients with BMS, with LLLT being more effective than topical vitamin B12 treatment.

KEYWORDS

Burning mouth syndrome; *Low-level laser therapy*; *Vitamin B12*; *Systemic health assessment*; *Randomized controlled trial*

Introduction

Burning mouth syndrome (BMS) is a chronic, characteristic pain syndrome that predominantly affects the tongue and presents mainly as burning pain. Typically, the syndrome is not accompanied by obvious clinical lesions or specific histopathological changes[1,2]. Our current understanding of the syndrome suggests that the pathogenesis of BMS is multifaceted, including psychological, local, and other systemic contributors, such as endocrine, neurological, and immunological factors[3,4]. Patients with BMS experience symptoms that are not limited to oral discomfort alone, because as the condition progresses, they may also suffer from a decline in overall health status and quality of life (QoL), manifested as emotional fluctuations, alterations in dietary habits, the onset of depression, and reduced social engagement[5-8]. Various therapeutic approaches are currently available for BMS, such as photobiomodulation (PBM) and vitamin B12 treatment, both of which have demonstrated efficacy for treating the condition[6-8]. However, the therapeutic effects of these two modalities have not yet been compared.

Currently, the primary treatment modalities for patients with BMS include pharmacotherapy and physical therapy, with PBM being the representative physical therapeutic approach[9]. In recent years, multiple clinical trials have demonstrated that PBM effectively alleviates the symptoms of BMS[10,11]. According to research findings by Kim et al.[2,12,13], the levels of vitamin B1 (thiamine), B2 (riboflavin), B6 (pyridoxine), and B12 (cobalamin) are lower in BMS patients compared to those in healthy individuals. As a consequence, supplemental vitamin B12 can be used to treat BMS patients. Previous evaluations of the efficacy of PBM and vitamin B12 treatments for BMS have been limited to oral symptoms and manifestations, and did not use relevant scales to assess the patients' systemic condition.

The EuroQol Five-Dimension (EQ-5D) scale is a multidimensional health-related quality of life (HRQoL) assessment developed by the EuroQol Group[14]. The assessment includes the EuroQol Five-Dimension Five-Level (EQ-5D-5L) and EuroQol Five-Dimension Three-Level (EQ-5D-3L) scales. The EQ-5D-5L is an optimized version of the EQ-5D-3L developed to reduce the ceiling effect associated with EQ-5D-3L and to better detect subtle changes in health status. Due to its simplicity, strong applicability, and suitability for self-administration, EQ-5D-5L has become the primary tool used to evaluate QoL[15,16]. This assessment covers five dimensions of health: mobility, daily activities, self-care, anxiety/depression, and pain/discomfort, which together objectively describe the overall health status[17]. The visual analog scale (VAS) is a self-assessment measure used by patients to rate their own health status. Respondents record their self-perceived health status on a vertical visual analog scale, which combines individual self-assessment from a population-based perspective to quantitatively describe the respondents' perception of their overall health[18,19]. This study therefore used the EQ-5D-5L HRQoL questionnaire and the VAS scale to evaluate and compare the effects of PBM therapy, topical vitamin B12, and no treatment on pain and QoL in patients with BMS.

Materials and methods

Study subjects

Patients with BMS who attended the Department of Oral Mucosal Diseases at Tianjin Stomatological Hospital between January 1, 2024, and December 31, 2024, and who met the inclusion criteria were selected using a random number method. The study was approved by the Medical Ethics Committee of Tianjin Stomatological Hospital (No.: PH2021-B-009). All participants were required to sign an informed

consent form. All procedures in the study were conducted in accordance with the principles outlined in the Declaration of Helsinki.

(1) Diagnostic criteria

Patients were required to meet the following diagnostic criteria for BMS according to the International Classification of Headache Disorders, 3rd edition (ICHD-3), published by the International Headache Society in 2018[20]: oral pain lasting more than 3 months, with daily pain duration greater than 2 hours; pain characterized by a burning sensation limited to the superficial oral mucosa; clinical examinations of the oral mucosa, including a normal sensory test; and not fitting any other disease diagnoses specified in the ICHD-3 classification.

(2) Inclusion criteria

First-visit patients diagnosed with BMS according to the established diagnostic criteria; no sex-based restrictions; patients who consented to topical treatment with PBM or vitamin B12, volunteered to participate in the study and provided a signed informed consent.

(3) Exclusion criteria

Diseases of adjacent organs (e.g., temporomandibular joint, ear, nose, and throat); pain that corresponded to clearly identified residual roots, residual crowns, or ill-fitting dentures, which resolved after the removal of these factors; severe systemic diseases preventing cooperation; pregnant or lactating women; patients with poor compliance or an incomplete diagnosis; severe brain disorders affecting cognitive function and the ability to cooperate; conditions that may exacerbate BMS symptoms, such as depression, fibromyalgia, or smoking; or patients suspected of having drug-induced xerostomia[14].

Research methods

The patients were divided randomly into the following three groups using a random number method: PBM, B12, or no-treatment. The PBM group was treated with a nebulized Nd:YAG laser device with the parameters specifically set for BMS (irradiation mode: non-activated fiber, 100 mJ, 10 Hz; no water or air). The fiber tip was positioned vertically at a fixed distance of 6 mm above the mucosal treatment area, and provided non-contact irradiation that involved slow, repeated movements, with each point irradiated for 1 minute per session. Treatment was administered once per week, with the treatment course lasting three weeks. The B12 group underwent a topical rinse treatment that consisted of a solution prepared by mixing a 1 mL vitamin B12 injection (0.5 mg) with 10 mL sterile water for injection. A 1 mL aliquot of the mixture was applied as a topical rinse 3 times daily for a treatment course of 3 weeks. The no-treatment group did not receive any intervention. Oral mucosal discomfort symptoms and systemic medical histories were collected for each patient prior to treatment. After one treatment course, the patients completed the EQ-5D-5L HRQoL questionnaire and the VAS to evaluate and compare the therapeutic effects in the pre- and post-treatment periods.

Statistical methods

The statistical analyses were performed using R statistical software (version 4.4.2). Measurement data were expressed as the mean ± standard deviation. Intergroup comparisons were conducted using a one-way ANOVA, while pre- and post-treatment comparisons within groups were assessed by paired t-tests. Count data were expressed as frequencies (percentages), with differences between the three groups evaluated by Pearson's chi-square test or Fisher's exact test. A two-tailed test was applied, with $P < 0.05$ indicating statistical significance.

TABLE 1. The clinical characteristics of patients in the B12, PBM, and no-treatment groups.

		B12 group (n = 41)	PBM group (n = 41)	No-treatment group (n = 41)	F/c2	*P*
Burning discomfort	No	18 (43.90)	19 (46.34)	15 (36.59)	0.866	0.648
	Yes	23 (56.10)	22 (53.66)	26 (63.41)		
Pain	No	34 (82.93)	35 (85.37)	37 (90.24)	0.956	0.620
	Yes	7 (17.07)	6 (14.63)	4 (9.76)		
Taste abnormality	No	34 (82.93)	35 (85.37)	39 (95.12)	3.189	0.203
	Yes	7 (17.07)	6 (14.63)	2 (4.88)		
Foreign body sensation	No	39 (95.12)	36 (87.80)	35 (85.37)		0.429
	Yes	2 (4.88)	5 (12.20)	6 (14.63)		
Numbness	No	35 (85.37)	35 (85.37)	37 (90.24)	0.575	0.750
	Yes	6 (14.63)	6 (14.63)	4 (9.76)		
Hypertension	No	28 (68.29)	28 (68.29)	28 (68.29)	0.000	1.000
	Yes	13 (31.71)	13 (31.71)	13 (31.71)		
Diabetes mellitus	No	32 (78.05)	35 (85.37)	36 (87.80)	1.552	0.460
	Yes	9 (21.95)	6 (14.63)	5 (12.20)		
Coronary heart disease	No	38 (92.68)	33 (80.49)	36 (87.80)	2.730	0.255
	Yes	3 (7.32)	8 (19.51)	5 (12.20)		
Hyperlipidemia	No	37 (90.24)	38 (92.68)	37 (90.24)		1.000
	Yes	4 (9.76)	3 (7.32)	4 (9.76)		
Insomnia	No	34 (82.93)	37 (90.24)	38 (92.68)		0.456
	Yes	7 (17.07)	4 (9.76)	3 (7.32)		
Anxiety	No	40 (97.56)	41 (100.00)	38 (92.68)	0.322	0.322
	Yes	1 (2.44)	0 (0.00)	3 (7.32)		
Depression	No	38 (92.68)	41 (100.00)	41 (100.00)		0.106
	Yes	3 (7.32)	0 (0.00)	0 (0.00)		
Thyroid disease	No	39 (95.12)	40 (97.56)	41 (100.00)		0.772
	Yes	2 (4.88)	1 (2.44)	0 (0.00)		
Cancer	No	40 (97.56)	37 (90.24)	40 (97.56)		0.364
	Yes	1 (2.44)	4 (9.76)	1 (2.44)		
Sex	Male	8 (19.51)	5 (12.20)	6 (14.63)	0.871	0.647
	Female	33 (80.49)	36 (87.80)	35 (85.37)		
Age		62.54 ± 10.51	63.66 ± 9.88	62.54 ± 11.41	0.153	0.859

Results

The clinical characteristics of BMS patients

Initially, 130 patients were selected for the study using random sampling. Following screening using the inclusion and exclusion criteria, 123 patients were ultimately enrolled, comprising 19 men and 104 women. The patients were then assigned randomly into three groups: the PBM group (n = 41), the B12 group (n = 41), and the no-treatment group (n = 41) (Figure 1). The clinical data of these patients are summarized in Table 1 and Figure 2. The oral mucosa discomfort symptoms were categorized into five types: burning discomfort, pain, taste abnormalities, foreign body sensation, and numbness. Systemic diseases were classified into nine categories: hypertension, diabetes mellitus, coronary heart disease, hyperlipidemia, insomnia, anxiety, depression, thyroid diseases, and cancer. No statistically significant differences were observed between the PBM, B12, and no-treatment groups for age, sex, oral mucosa discomfort symptoms, and history of systemic diseases ($P > 0.05$). This indicated that the division of the patients into the three groups was homogeneous.

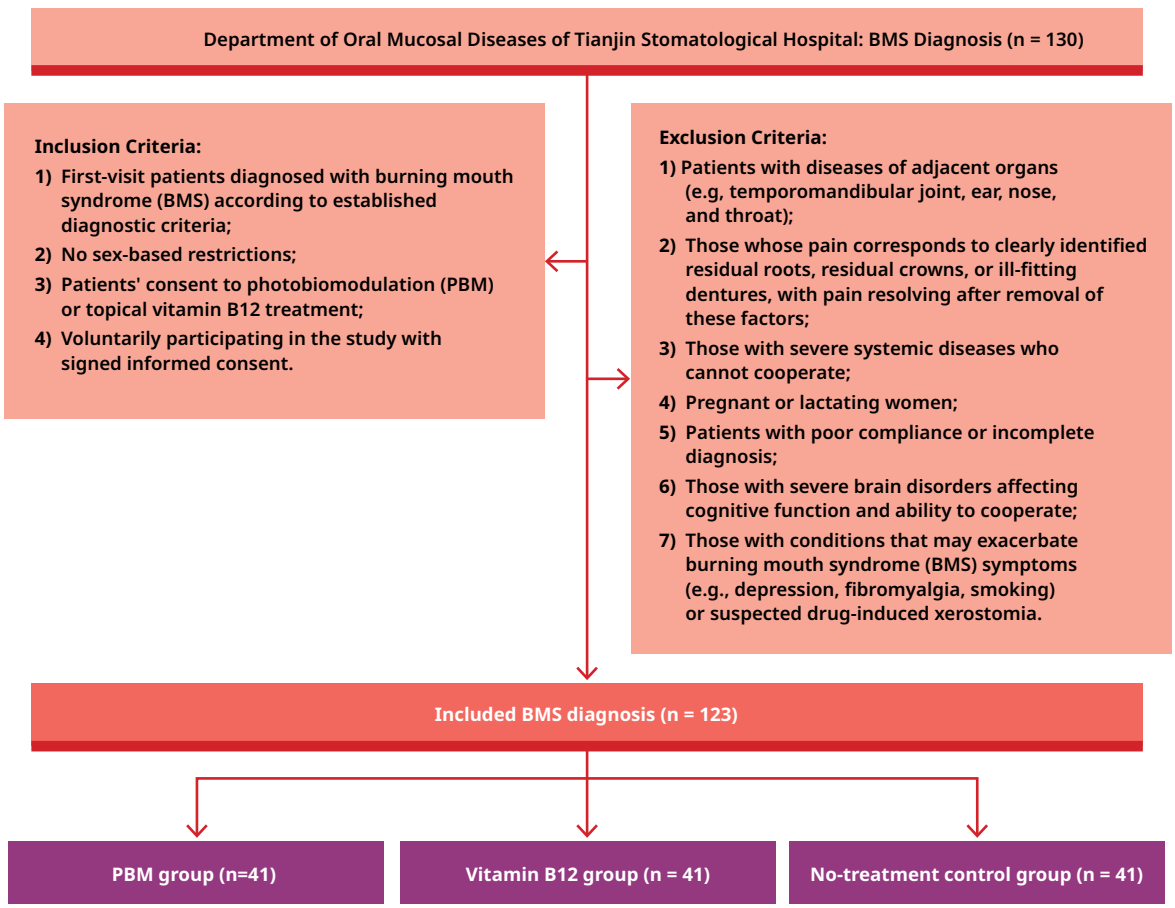

Fig. 1. A flowchart of patient screening and enrollment.

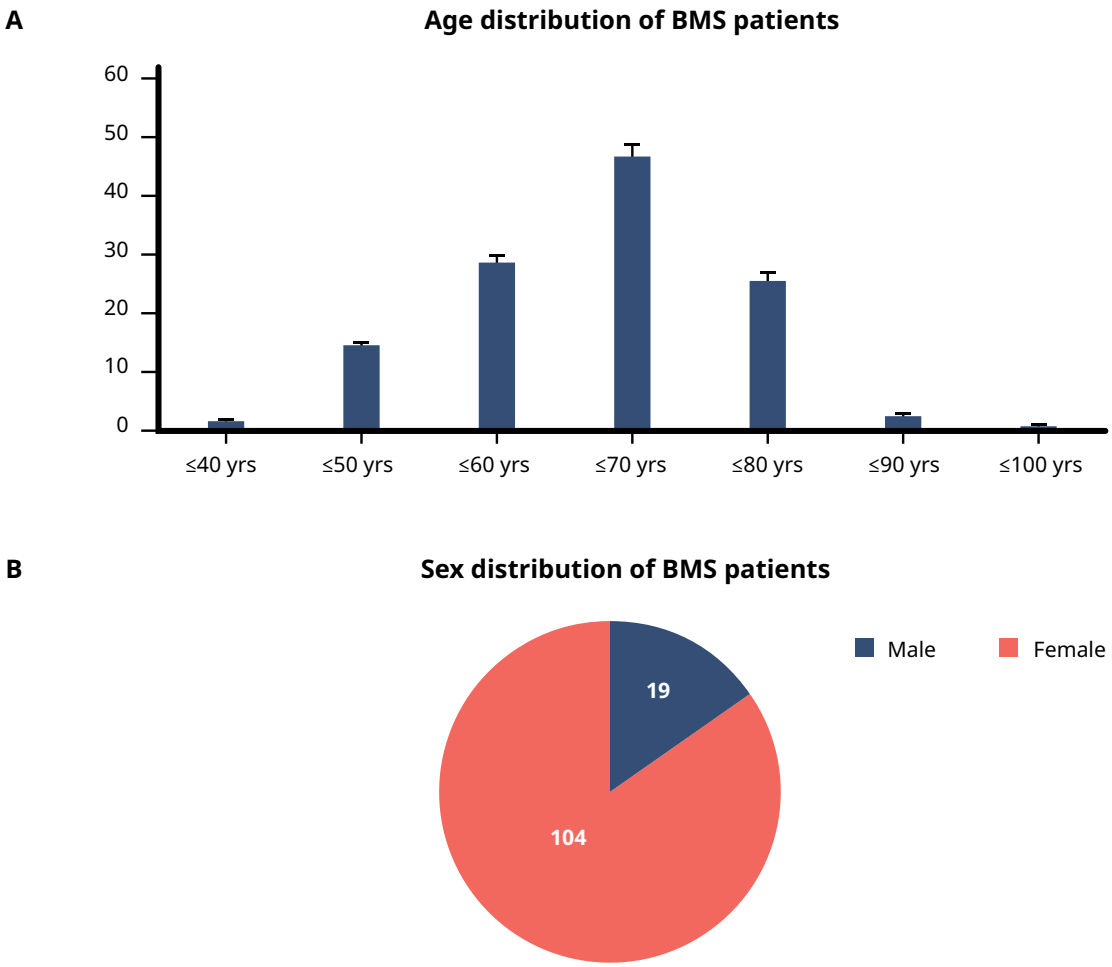

Fig. 2. Age and sex distribution of the BMS patients. A. A bar chart of the age distribution of the BMS patients; B. A pie chart of sex distribution of the BMS patients.

Table 2. The pre-treatment evaluation of BMS patients.

	B12 group (n = 41)	PBM group (n = 41)	No-treatment group (n = 41)	F	*P*
Mobility	2.83 ± 0.38	2.88 ± 0.33	2.83 ± 0.38	0.244	0.784
Self-care	2.88 ± 0.33	2.93 ± 0.26	2.83 ± 0.38	0.902	0.408
Daily activities	2.83 ± 0.38	2.78 ± 0.42	2.83 ± 0.38	0.209	0.811
Pain/discomfort	2.29 ± 0.75	2.27 ± 0.74	2.24 ± 0.73	0.044	0.957
Anxiety/depression	2.41 ± 0.77	2.32 ± 0.72	2.29 ± 0.78	0.296	0.745
VAS score	77.85 ± 4.29	79.32 ± 5.66	80.00 ± 5.67	1.792	0.171

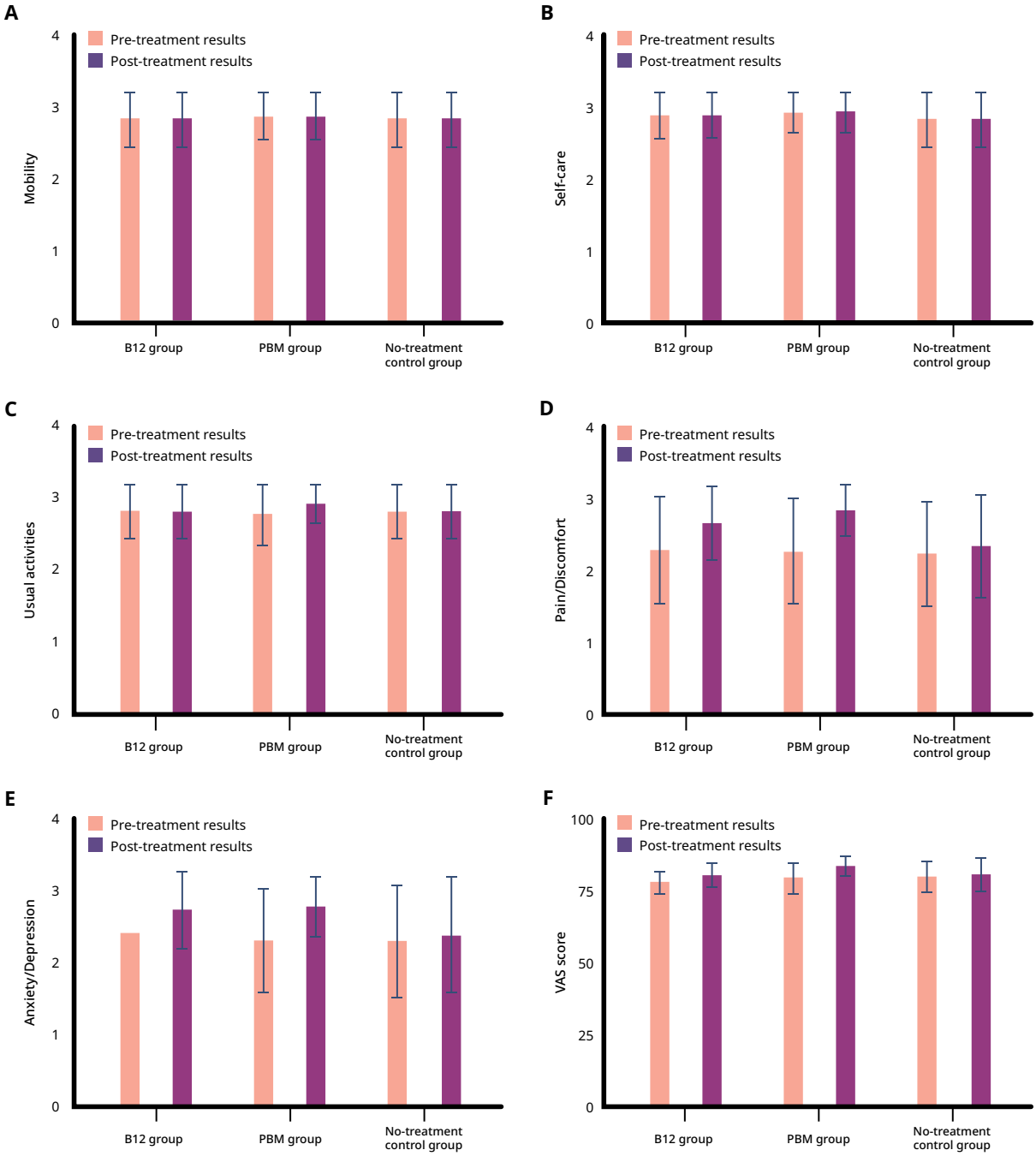

Fig. 3. A bar chart showing the analysis of the post-treatment status in BMS patients. The pre- and post-treatment bar charts of A) Mobility; B) Self-care; C) Daily activities; D) Pain/discomfort; E) Anxiety/depression; F) VAS score.

Pre-treatment evaluation of BMS patients

Pre-treatment evaluations of patients in the PBM, B12, and no-treatment groups are presented in Table 2. No statistically significant differences were observed between the three groups for mobility, self-care, daily activities, pain/discomfort, anxiety/depression, and VAS scores ($P > 0.05$).

Post-treatment evaluation of BMS patients

The post-treatment outcomes of the BMS patients are shown in Table 3 and Figure 3. Statistically significant differences were identified between the three groups for the pain/discomfort score ($F = 8.753$, $P < 0.001$), anxiety/depression score ($F = 4.962$, $P = 0.009$), and VAS score ($F = 5.722$, $P = 0.004$). Differences in mobility, self-care, and daily activities were not statistically significant ($P > 0.05$). A comparison of mean values showed that, compared with the no-treatment group, the B12 group had statistically significant differences in the pain/discomfort score ($P = 0.011$) and the anxiety/depression score ($P = 0.013$), while the difference in the post-treatment VAS score was not significant ($P = 0.981$). The PBM group showed statistically significant differences in the pain/discomfort score ($P < 0.001$), anxiety/depression score ($P = 0.005$), and VAS score ($P = 0.004$). Compared with the B12 group, the PBM group had a statistically significant difference in the VAS score ($P = 0.004$), whereas the differences in the pain/discomfort score ($P = 0.117$) and anxiety/depression score ($P = 0.719$) were not statistically significant. The pre-treatment differences in pain/discomfort, anxiety/depression, and VAS scores between the three groups were not statistically significant ($P > 0.05$). This indicated that the groups were comparable at baseline. Significant differences were observed in all three measures following treatment, with both the B12 and PBM groups having significantly higher scores than the no-treatment group. However, the differences between the B12 and PBM groups were not statistically significant.

Pre- and post-treatment evaluation in the PBM group

The pre- and post-treatment results in the PBM group are shown in Table 4. Compared with pre-treatment results, there were statistically significant differences in the scores for daily activities

Table 3. Post-treatment evaluation of BMS patients.

	B12 group (n = 41)	PBM group (n = 41)	No-treatment group (n = 41)	F	*P*
Mobility	2.83 ± 0.38	2.88 ± 0.33	2.83 ± 0.38	0.244	0.784
Self-care	2.88 ± 0.33	2.93 ± 0.26	2.83 ± 0.38	0.902	0.408
Daily activities	2.83 ± 0.38	2.93 ± 0.26	2.83 ± 0.38	1.085	0.341
Pain/discomfort	2.66 ± 0.53a	2.85 ± 0.36a	2.34 ± 0.73b	8.753	< 0.001
Anxiety/depression	2.73 ± 0.55a	2.78 ± 0.42a	2.39 ± 0.80b	4.962	0.009
VAS score	80.41 ± 4.25b	83.37 ± 3.58a	80.39 ± 5.66b	5.722	0.004

Table 4. Pre- and post-treatment evaluation in the LLT group.

Variable	N	Pre-treatment	Post-treatment	Difference	t	*P*
Mobility	41	2.88 ± 0.33	2.88 ± 0.33	0.00 ± 0.00	0.000	1.000
Self-care	41	2.93 ± 0.26	2.93 ± 0.26	0.00 ± 0.00	0.000	1.000
Daily activities	41	2.78 ± 0.42	2.93 ± 0.26	0.15 ± 0.36	-2.619	0.012
Pain/discomfort	41	2.27 ± 0.74	2.85 ± 0.36	0.59 ± 0.71	-5.307	< 0.001
Anxiety/depression	41	2.32 ± 0.72	2.78 ± 0.42	0.46 ± 0.64	-4.663	< 0.001
VAS score	41	79.32 ± 5.66	83.37 ± 3.58	4.05 ± 3.83	-6.774	< 0.001

Table 5. Pre- and post-treatment evaluation in the B12 group.

Variable	N	Pre-treatment	Post-treatment	Difference	t	*P*
Mobility	41	2.83 ± 0.38	2.83 ± 0.38	0.00 ± 0.00	0.000	1.000
Self-care	41	2.88 ± 0.33	2.88 ± 0.33	0.00 ± 0.00	0.000	1.000
Daily activities	41	2.83 ± 0.38	2.83 ± 0.38	0.00 ± 0.00	0.000	1.000
Pain/discomfort	41	2.29 ± 0.75	2.66 ± 0.53	0.37 ± 0.54	- 4.367	< 0.001
Anxiety/depression	41	2.41 ± 0.77	2.73 ± 0.55	0.32 ± 0.57	-3.578	< 0.001
VAS score	41	77.85 ± 4.29	80.41 ± 4.25	2.56 ± 2.28	-7.189	< 0.001

(t = -2.619, $P = 0.012$), pain/discomfort, anxiety/depression, and VAS. Differences in the mobility and self-care scores were not statistically significant ($P > 0.05$). The mean pre-treatment score in the patients was lower than their post-treatment mean scores for daily activities (2.93 ± 0.26 vs 2.78 ± 0.42), pain/discomfort (2.85 ± 0.36 vs 2.27 ± 0.74), anxiety/depression (2.78 ± 0.42 vs 2.32 ± 0.72), and VAS (83.37 ± 3.58 vs 79.32 ± 5.66).

These results showed that PBM improved the patients' daily activity ability, substantially relieved pain and discomfort symptoms, and significantly reduced anxiety and depression. After receiving PBM, the patients reported an effective improvement in their overall health condition.

Pre- and post-treatment evaluation in the B12 group

The pre- and post-treatment results of the B12 group are shown in Table 5. The difference in the pain/discomfort score was statistically significant (t = -4.367, $P < 0.001$). A comparison of the mean values showed that the pre-treatment pain/discomfort score (2.29 ± 0.75) was significantly lower than the post-treatment score (2.66 ± 0.53). The difference in the anxiety/depression score was also statistically significant (t = -3.578, $P < 0.001$), with the pre-treatment score (2.41 ± 0.77) being significantly lower than the post-treatment score (2.73 ± 0.55). The VAS score showed a similar significant trend (t = -7.189, $P < 0.001$), with the pre-treatment score

(77.85 ± 4.29) being lower than the post-treatment score (80.41 ± 4.25). There were no statistically significant differences between the pre- and post-treatment scores for mobility, self-care, and daily activities ($P > 0.05$). Taken together, these results show that topical drug treatment relieved pain and discomfort symptoms, and reduced anxiety and depression. After receiving the topical drug treatment, the patients perceived an improvement in their overall health condition.

Pre- and post-treatment evaluation in the no-treatment group

The difference in the pain/discomfort score was statistically significant (t = -2.080, $P = 0.044$) in the no-treatment group. As shown in Table 6, a comparison of the mean values showed that the pre-treatment pain/discomfort score (2.24 ± 0.73) was lower than the post-treatment score (2.34 ± 0.73). The difference in the anxiety/depression score was also statistically significant (t = -2.080, $P = 0.044$), with the pre-treatment score (2.29 ± 0.78) being lower than the post-treatment score (2.39 ± 0.80). Similarly, the VAS score showed a statistically significant difference (t = -3.000, $P = 0.005$), with the pre-treatment score (80.00 ± 5.67) being significantly lower than the post-treatment score (80.39 ± 5.66).

Discussion

Data from the EQ-5D-5L HRQoL questionnaire and VAS were analyzed to assess the pre- and post-treatment status of patients in the PBM, B12, and no-treatment groups. The main findings of our study are: the pre-treatment status of the three groups was similar; laser and B12 treatments resulted in significantly higher pain/discomfort, anxiety/depression, and VAS scores; and the scores in the PBM group were consistently higher than those in the B12 group — although this difference was not statistically significant. Taken together, these findings demonstrate that PBM therapy and B12 topical treatment had a beneficial therapeutic effect by improving the condition of BMS patients. The data of the no-treatment group suggested that BMS caused a certain degree of self-limiting behavior resulting in some symptom improvement, although the degree of improvement was limited compared to that induced by laser or pharmacological intervention.

The majority of BMS patients in this study were aged 60 years or older. The results of a clinical trial performed by Jankovskis et al.[21] also reported that BMS mainly affected individuals over 55 years of age. The female–to–male ratio of the patients in the current clinical study was approximately 5.5:1. These findings are consistent with those of

Table 6. Pre- and post-treatment evaluation in the no-treatment group.

Variable	N	Pre-treatment	Post-treatment	Difference	t	*P*
Mobility	41	2.83 ± 0.38	2.83 ± 0.38	0.00 ± 0.00	0.000	1.000
Self-care	41	2.83 ± 0.38	2.83 ± 0.38	0.00 ± 0.00	0.000	1.000
Daily activities	41	2.83 ± 0.38	2.83 ± 0.38	0.00 ± 0.00	0.000	1.000
Pain/discomfort	41	2.24 ± 0.73	2.34 ± 0.73	0.10 ± 0.30	-2.080	0.044
Anxiety/depression	41	2.29 ± 0.78	2.39 ± 0.80	0.10 ± 0.30	-2.080	0.044
VAS score	41	80.00 ± 5.67	80.39 ± 5.66	0.39 ± 0.83	-3.000	0.005

a meta-analysis by Wu et al.[22], which demonstrated that the global prevalence of BMS showed significant variations and highlighted that the disorder was particularly common in postmenopausal women[23], with a female–to–male ratio of 3:1. Taken together, these findings indicate that middle-aged women account for the majority of BMS patients.

The results of our study showed that, in terms of treatment efficacy, the PBM group outperformed the B12 group, which in turn outperformed the no-treatment group. A randomized controlled trial conducted by Ardunio[20] also reported that the PBM group had significantly greater pain relief than the clonazepam group. This finding is consistent with our study. A clinical trial by de Abreu[14] also demonstrated that PBM improved the scores of BMS patients in four dimensions of the EQ-5D-5L questionnaire, including self-care, daily activities, pain/discomfort, and anxiety/depression. A study by Jankovskis[21] confirmed the effectiveness of pharmacological treatment for BMS, by showing that patients treated with vitamin B and zinc supplements had reduced symptoms of pain and a decreased burning sensation. The results of several clinical trials indicated that, although BMS symptoms are confined to the oral cavity[24,25], the disorder also has significant effects on a patient's ability to perform basic activities, such as eating, communication, and social interaction, as well as their overall perception of their health status.

Neurophysiological studies have shown that BMS has a neuropathic nature, involving dysfunction in both peripheral and central nervous system pathways[26,27]. Research findings have indicated that levels of vitamin B1 (thiamine), B2 (riboflavin), B6 (pyridoxine), and B12 (cobalamin) in BMS patients are lower than those in healthy individuals[7,12]. In addition, deficiencies in B1, B6, and B12 are considered to be etiological factors in neuropathies and other neurological disorders, making vitamin B12 a therapeutic option for BMS patients[2,13]. The mechanism by which vitamin B12 treats neuropathic pain primarily involves reducing damage to nerve fibers[28]. Another study reported that oral vitamin B12 supplements (1 to 2 mg per day) were as effective as parenteral administration for correcting anemia and alleviating neurological symptoms[29]. Vitamin B12 promotes the repair and regeneration of nerve myelin sheaths, regulates the synthesis and metabolism of neurotransmitters, and restores normal conduction function in damaged peripheral nerve fibers. This reduces the transmission of abnormal nerve impulses to the central nervous system, thereby alleviating pain and discomfort[30].

PBM is a non-invasive and painless laser treatment that has marked analgesic and anti-inflammatory effects[31]. PBM has been proven to be effective in the treatment of BMS, and has therefore been included as an initial or second-line intervention in clinical guidelines for the management of this disorder[6,10,11,32-35]. The therapeutic effects of PBM are based on the analgesic, anti-inflammatory, and biostimulatory properties induced by infrared irradiation[32-35]. The technique is applicable not only to patients with BMS, but also to those with other pain-related conditions, making it a treatment method with broad clinical applicability[10,35]. Although the precise mechanism of PBM remains unclear, current research has demonstrated that laser irradiation triggers intra- and extracellular responses, including an increased synthesis of adenosine triphosphate (ATP), the production of serotonin, the release of β-endorphins, a reduced discharge of C-fiber neurons, and a decreased secretion of bradykinin[6,34,36]. Mitochondria serve as the cellular powerhouses. When stimulated by laser energy, the activity of cytochrome c oxidase within mitochondria increases, promoting ATP synthesis and regulating reactive oxygen species. This reduces oxidative stress, accelerates the repair and regeneration of damaged cells, and consequently alleviates pain and discomfort caused by cellular injury[34,37]. Also, the secretion of vasopressin, a substance that induces vasodilation and pain, is reduced, effectively relieving local inflammation and pain symptoms[36,37]. C-fibers are the primary nerve fibers transmitting

pain signals. When the discharge of C-fiber neurons decreases, the brain receives weaker pain signals, and the patient perceives reduced pain intensity[36,37]. β-endorphins are an endogenous opioid substance with potent analgesic and mood-regulating effects. It binds to opioid receptors in the brain, producing morphine-like analgesia, while also improving the patient's emotional state and alleviating the symptoms of anxiety and depression[36,37].

Overall, vitamin B12 primarily alleviates BMS symptoms by repairing nerves and regulating neurotransmitters, while PBM therapy exerts effects across multiple levels, including cellular metabolism, inflammation regulation, and nerve conduction. Both approaches offer effective pathways for treating BMS.

Current studies on BMS still largely rely on outcome indicators with strong subjectivity, such as 'ineffective', 'effective', and 'cured'[9]. Therefore, we adopted more objective, reliable, and comprehensive assessment tools in our study, such as the EQ-5D-5L HRQoL questionnaire and the VAS scale. Our findings suggest that although BMS is an oral disease, its impact is not limited to the oral cavity. We therefore recommend that greater attention be paid to evaluating and addressing the overall systemic condition of patients with BMS.

This study had several limitations. First, the sample size was relatively small. In the future, multicenter studies should be conducted to expand the sample size. Second, the evaluation of the therapeutic effects of PBM and vitamin B12 treatment for BMS was based on subjective assessment scales and lacked objective supporting data. This may have introduced a certain degree of bias in the efficacy of the evaluations. Future studies should therefore incorporate additional experimental analyses. The last issue was the current lack of standardized protocols regarding the dosage and administration of PBM and vitamin B12. Different doses or intensities may lead to different outcomes, which require further research to determine their potential effectiveness.

Conclusions

Both PBM and topical vitamin B12 treatment improve the overall systemic condition of patients with BMS. This study confirmed that PBM was more effective than topical vitamin B12 treatment, and it also improved the daily activity performance of patients. BMS is associated with a certain degree of self-limiting behavior, with patients possibly experiencing only mild symptom improvement without treatment. However, such improvements are less significant compared to those achieved with laser or pharmacological intervention. This study also showed that although BMS is an oral disorder, its impact is not limited to the oral cavity. Greater attention should therefore be given to evaluating the overall systemic condition of BMS patients.

ETHICS AND CONSENT TO PARTICIPATE DECLARATIONS The study was approved by the Medical Ethics Committee of the authors' institution (No.: PH2021-B-009), with strict adherence to the principles of the Declaration of Helsinki. Informed consent was obtained from all patients.

CONSENT FOR PUBLICATION Not applicable.

AVAILABILITY OF DATA AND MATERIALS The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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References

1. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia. 2013;33(9):629-808. doi: 10.1177/0333102413485658
2. Klasser GD, Grushka M, Su N. Burning Mouth Syndrome. Oral Maxillofac Surg Clin North Am. 2016;28(3):381-396. doi: 10.1016/j.coms.2016.03.005
3. Tu TT, Watanabe M, Suga T, et al. Personality traits in burning mouth syndrome patients with and without a history of depression. Front Psychiatry. 2021;12:659245. doi: 10.3389/fpsyt.2021.659245
4. Tu TT, Takenoshita M, Matsuoka H, et al. Current management strategies for the pain of elderly patients with burning mouth syndrome: a critical review. Biopsychosoc Med. 2019;13:1. doi: 10.1186/s13030-019-0142-7
5. Adamo D, Spagnuolo G. Burning Mouth Syndrome: An Overview and Future Perspectives. Int J Environ Res Public Health. 2022;20(1):682. doi: 10.3390/ijerph20010682
6. De Pedro M, López-Pintor R, De La Hoz-Aizpurua J, et al. Efficacy of Low-Level Laser Therapy for the Therapeutic Management of Neuropathic Orofacial Pain: A Systematic Review. J Oral Facial Pain Headache. 2020;34(1):13-30. doi: 10.11607/ofph.2310
7. Tan HL, Renton T. Burning Mouth Syndrome: An Update. Cephalalgia Rep. 2020;3:251581632097014. doi: 10.1177/2515816320970143
8. Russo M, Crafa P, Guglielmetti S, et al. Burning Mouth Syndrome Etiology: A Narrative Review. J Gastrointestin Liver Dis. 2022;31(2):223-228. doi: 10.15403/jgld-4245
9. Ślebioda Z, Lukaszewska-Kuska M, Dorocka-Bobkowska B. Evaluation of the efficacy of treatment modalities in burning mouth syndrome—A systematic review. J Oral Rehabil. 2020;47(11):1435-1447. doi: 10.1111/joor.13102
10. Camolesi GCV, Marichalar-Mendía X, Padín-Iruegas ME, et al. Efficacy of Photobiomodulation in Reducing Pain and Improving the Quality of Life in Patients with Idiopathic Burning Mouth Syndrome: A Systematic Review and Meta-Analysis. Lasers Med Sci. 2022;37:2123-2133. doi: 10.1007/s10103-022-03518-y
11. Matos AL, Silva PU, Paranhos LR, et al. Efficacy of the Laser at Low Intensity on Primary Burning Oral Syndrome: A Systematic Review. Med Oral Patol Oral Cir Bucal. 2021;26(2):e216-e225. doi: 10.4317/medoral.24144
12. Kim J, Kim MJ, Kho HS. Oral manifestations in vitamin B12 deficiency patients with or without history of gastrectomy. BMC Oral Health. 2016;16(1):60. doi: 10.1186/s12903-016-0215-y
13. Morr Verenzuela CS, Davis MDP, Bruce AJ, et al. Burning mouth syndrome: Results of screening tests for vitamin and mineral deficiencies, thyroid hormone, and glucose levels—experience at Mayo Clinic over a decade. Int J Dermatol. 2017;56(9):952-956. doi: 10.1111/ijd.13634
14. de Abreu JM, Nunes T, Almiro PA, et al. Long-Term Benefits of Photobiomodulation Therapy on Health-Related Quality of Life in Burning Mouth Syndrome Patients: A Prospective Study. J Clin Med. 2024;13(14):4272. doi: 10.3390/jcm13144272
15. Devlin N, Pickard S, Busschbach J. The Development of the EQ-5D-5L and its Value Sets. Springer. 2022;24:1-12. doi: 10.1007/978-3-030-89289-0_1
16. Roudijk B, Ludwig K, Devlin N. EQ-5D-5L Value Set Summaries. Springer. 2022;24:55-212. doi: 10.1007/978-3-030-89289-0_4
17. Zhou T, Guan H, Wang L, et al. Health-Related Quality of Life in Patients With Different Diseases Measured With the EQ-5D-5L: A Systematic Review. Front Pub Health. 2021;9:675523. doi: 10.3389/fpubh.2021.675523
18. Åström M, Thet Lwin ZM, Teni FS, et al. Use of the visual analogue scale for health state valuation: a scoping review. Qual Life Res. 2023;32(10):2719-2729. doi: 10.1007/s11136-023-03411-3
19. Haapiainen H, Valli J, Murtola T, et al. Visual Analogue Scale (VAS) in the Evaluation of Functional Outcomes After Three-dimensional Laparoscopic Prostatectomy. Urol. 2023;172:121-125. doi: 10.1016/j.urology.2022.12.003
20. Arnold M. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018;38(1):1-211. doi: 10.1177/0333102417738202

21. Jankovskis V, Selga G. Vitamin B and Zinc Supplements and Capsaicin Oral Rinse Treatment Options for Burning Mouth Syndrome. Medicina. 2021;57(4):391. doi: 10.3390/medicina57040391
22. Wu S, Zhang W, Yan J, et al. Worldwide prevalence estimates of burning mouth syndrome: A systematic review and meta-analysis. Oral Dis. 2022;28(6):1431-1440. doi: 10.1111/odi.13868
23. Adamo D, Calabria E, Canfora F, et al. Burning mouth syndrome: Analysis of diagnostic delay in 500 patients. Oral Dis. 2023;30(3):1543-1554. doi: 10.1111/odi.14553
24. Kohorst JJ, Bruce AJ, Torgerson RR, et al. A Population-Based Study of the Incidence of Burning Mouth Syndrome. Mayo Clin Proc. 2014;89(11):1545-1552. doi: 10.1016/j.mayocp.2014.05.018
25. Klein B, Thoppay JR, De Rossi SS, et al. Burning Mouth Syndrome. Dermatol Clin. 2020;38(4):477-483. doi: 10.1016/j.det.2020.05.008
26. Hanna R, Bensadoun RJ, Beken SV, et al. Outpatient Oral Neuropathic Pain Management with Photobiomodulation Therapy: A Prospective Analgesic Pharmacotherapy-Paralleled Feasibility Trial. Antioxidants. 2022;11(3):533. doi: 10.3390/antiox11030533
27. Vicencio SD, Reyes SG, Alvo VA, et al. Síndrome de la boca ardiente: Revisión de la literatura. Rev Otorrinolaringol Cir Cabeza Cuello. 2022;82(1):86-94. doi: 10.4067/s0718-48162022000100086
28. Alvarado AM, Navarro SA. Complex B vitamins: Physiology and Therapeutic Effect on Pain. Am J Pharmacol Sci. 2016;4(2):20-27.
29. Vidal-Alaball J, Butler CC, Cannings-John R, et al. Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency. Cochrane Database Syst Rev. 2005;(3):CD004655. doi: 10.1002/14651858.CD004655.pub2
30. Julian T, Syeed R, Glascow N, et al. B12 as a Treatment for Peripheral Neuropathic Pain: A Systematic Review. Nutrients. 2020;12(8):2221. doi: 10.3390/nu12082221
31. Pandeshwar P, Roa MD, Das R, et al. Photobiomodulation in oral medicine: a review. J Invest Clin Dent. 2016;7(2):114-126. doi: 10.1111/jicd.12148
32. Tan HL, Smith JG, Hoffmann J, et al. A Systematic Review of Treatment for Patients with Burning Mouth Syndrome. Cephalalgia. 2022;42(2):128-161. doi: 10.1177/03331024211036152
33. Zhang W, Hu L, Zhao W, et al. Effectiveness of Photobiomodulation in the Treatment of Primary Burning Mouth Syndrome—A Systematic Review and Meta-Analysis. Lasers Med Sci. 2021;36(2):239-248. doi: 10.1007/s10103-020-03109-9
34. Spadari F, Pulicari F, Ghizzoni M, et al. Photobiomodulation as a Therapeutic Strategy in Burning Mouth Syndrome: A Scoping Review. Appl Sci. 2023;13(15):8880. doi: 10.3390/app13158880
35. Lu C, Yang C, Li X, et al. Effects of Low-Level Laser Therapy on Burning Pain and Quality of Life in Patients with Burning Mouth Syndrome: A Systematic Review and Meta-Analysis. BMC Oral Health. 2023;23(1):734. doi: 10.1186/s12903-023-03441-w
36. Al-Maweri SA, Javed F, Kalakonda B, et al. Efficacy of Low Level Laser Therapy in the Treatment of Burning Mouth Syndrome: A Systematic Review. Photodiagn Photodyn Ther. 2017;17:188-193. doi: 10.1016/j.pdpdt.2016.11.017
37. Khemiss M, Dammak N, Lajili O, et al. Efficacy of laser therapy on primary burning mouth syndrome: a systematic review. J Oral Facial Pain Headache. 2024;38(1):17-31. doi: 10.22514/jofph.2024.003

SAŽETAK

Procjena učinkovitosti fotobiomodulacije i vitamina B12 kod sindroma pekućih usta

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Cilj ove studije bio je procijeniti utjecaj tretmana laserom niske snage (LLLT) i liječenja lokalnom primjenom vitamina B12 na pacijente sa sindromom pekućih usta. Ukupno su uključena 123 pacijenta, nasumično raspoređena u tri skupine: LLLT, B12 ili bez liječenja. Pacijenti su ispunili upitnik *EuroQol Five-Dimension Health-Related Quality-of-Life* (EQ-5D-5L HRQoL) i vizualnu analognu skalu (VAS) prije i nakon liječenja. Podaci su analizirani pomoću statističkog softvera R 4.4.2 radi usporedbe razlika prije i nakon liječenja. U poslijeterapijskom razdoblju uočene su značajne razlike između triju skupina u pogledu bolova/nelagode, anksioznosti/depresije i VAS bodova. I B12 skupina i LLLT skupina imale su značajno više poslijeterapijske bodove u usporedbi sa skupinom bez liječenja. Iako razlike između B12 i LLLT skupina nisu bile statistički značajne, LLLT skupina imala je dosljedno više bodove i u njoj su zabilježena značajna poboljšanja ($P < 0,001$). Slično tome, bol/nelagoda ($P < 0,001$) i anksioznost/depresija ($P < 0,001$) značajno su se poboljšali nakon liječenja ($P < 0,05$) u B12 skupini. Terapija laserom niske snage (LLLT) i lokalna terapija vitaminom B12 poboljšale su cjelokupno sistemsko zdravstveno stanje pacijenata sa sindromom pekućih usta, pri čemu je LLLT bio učinkovitiji od lokalne terapije vitaminom B12.

KLJUČNE RIJEČI

Sindrom pekućih usta; *Terapija laserom niske snage*; *Vitamin B12*; *Procjena sistemskog zdravstvenog stanja*; *Randomizirano kontrolirano ispitivanje*