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Efficacy of low-level laser therapy for the treatment of burning mouth syndrome: a randomized, controlled trial

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Abstract. The aim of the present study was to assess the effect of low-level laser therapy (LLLT) in the treatment of burning mouth syndrome (BMS). A diode laser was used in 78 BMS patients who were randomly assigned into four groups: IR1W, $n = 20$ (830 nm, 100 mW, 5 J, 176 J/cm^2, 50 s, LLLT weekly sessions, 10 sessions); IR3W, $n = 20$ (830 nm, 100 mW, 5 J, 176 J/cm^2, 50 s, three LLLT weekly sessions, 9 sessions); red laser, $n = 19$ (685 nm, 35 mW, 2 J, 72 J/cm^2, 58 s, three LLLT weekly sessions, 9 sessions); and control-group (CG), $n = 19$. Symptoms were assessed at the end of the treatment and eight weeks later; quality of life related to oral health was assessed using the Oral Health Impact Profile (OHIP-14). Statistical analysis was carried out using repeated measures analysis of variance followed by the posthoc Tukey test. There was significant reduction of the symptoms in all groups at the end of the treatment, which was maintained in the follow-up. The scores of the IR1W and IR3W laser groups differed significantly from those of the CG. There was also a decrease in the OHIP-14 scores in the four groups. The IR3W laser group scores differed significantly from those of the CG. LLLT reduces the symptoms of BMS and may be an alternative therapeutic strategy for the relief of symptoms in patients with BMS. [DOI: 10.1117/1.JBO.20.9.098001]

Keywords: burning mouth syndrome; oral pain; low-level laser therapy; laser phototherapy.

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1 Introduction

Burning mouth syndrome (BMS) is a complex disease characterized mainly by symptoms of burning, pain, or itching in the oral mucosa without apparent clinical alterations.[1] BMS shows a clear predisposition related to sex and age. The disorder rarely occurs before the age of 30[2], and women are 2.5 to 7 times more frequently affected than men. In addition, up to 90% of female patients with BMS are around menopause.[3] The burning symptoms affect one or more sites in the oral mucosa. The apex and sides of the tongue, and the lips are the most frequently affected sites.[4]

Although BMS is a disease of relatively high prevalence within the risk group of postmenopausal women, its etiology is still unknown. Among the possible causes of BMS are neuropathic[5–7] and hormonal[8,9] factors as well as psychological factors, such as stress, anxiety, and depression.[10–14] Neuropathy in BMS etiopathogenesis mechanism has been suggested, and the literature indicates the possibility of a dysfunction at the peripheral or central reflex arc path and the processing of cortical excitation.[3,15,16] Lauria et al.[5] described a trigeminal small-fiber sensory neuropathy in patients with BMS. Superficial biopsies of the lateral aspect of the anterior tongue were obtained, with the density of epithelial nervous fibers quantified; BMS patients showed a significantly lower density of epithelial nerve fibers than controls. Moreover, the epithelial and subpapillary nerve fibers exhibited diffuse morphological changes reflecting axonal degeneration. Albuquerque et al.[6] investigated brain activity, by functional magnetic resonance imaging, in patients with BMS following thermal stimulation of the trigeminal nerve. BMS patients had less volumetric activation throughout the entire brain compared to the control group, suggesting that brain hypoactivity can be an important feature in the pathophysiology of this syndrome. Guarneri et al.,[16] starting from the report of eight cases successfully treated with prazepam, examined the clinical features and the evidence from literature that support the possibility of the neuroinflammation role in BMS pathogenesis. They suggested that changes in the pain perception, neural transmission dysfunction, increases in excitability, or negative involvement of trigeminal vascular system can be mechanisms associated with the syndrome.

The therapeutic measures used for the BMS patients aim mainly at eliminating local and systemic factors that might aggravate the symptoms. Due to its chronic nature, several treatments are described in the literature; however, there is no defined therapeutic protocol and, so far, no treatment to cure this disorder has been found.[17]

Low-level laser radiation is used due to its capacity to modulate several metabolic, biochemical, and photophysical processes that transform laser light into useful energy for the cell. This energy provokes reactions in the mitochondria, increasing

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ATP production, consumption of glucose by the cells, intracellular calcium levels, and the number of mitoses.[18] The analgesic, anti-inflammatory, and tissue repair action of this kind of radiation has been demonstrated.[19–21]

Some studies have verified that low-level laser therapy (LLLT) can be effective in reducing the burning mouth symptoms of patients with BMS.[22–25] Controlled trials investigating the effects of LLLT on BMS are still rare. Considering the evidences aforementioned, the present randomized, blind, placebo-controlled study aimed to clinically assess the effect of different LLLT protocols in the treatment of patients with BMS and investigate the impact of such therapy in the quality of life of those individuals.

2 Materials and Methods

2.1 *Patients and Treatment*

The present study has been approved by the Ethics in Research Committee of the Pontifical Catholic University of Rio Grande do Sul (PUCRS) (0038/12), and by local committees, based on the Declaration of Helsinki. Each of the participants in the study signed an informed consent form. The sample comprised 78 male and female patients diagnosed with BMS, who were randomly allocated into four groups. They were selected in the Oral Medicine Division of São Lucas Hospital of PUCRS.

The study included patients above 40 years who reported having had symptoms of burning or pain in the oral mucosa for at least six months and who presented a clinically normal mucosa. Individuals who were taking antidepressant, anxiolytic, or anticonvulsant drugs and those who had undergone chemo- and/or radiotherapy were excluded from the study. Patients who showed hyposalivation (salivary flow rate at rest ≤ 0.1 mL/min), as well as alterations in their blood count, glucose serum levels, iron, folic acid, and vitamin B12, were also excluded. All the patients received instructions regarding oral hygiene, mucosal hydration, and were advised to avoid spicy and citric foods, as well as alcoholic beverages and tobacco.

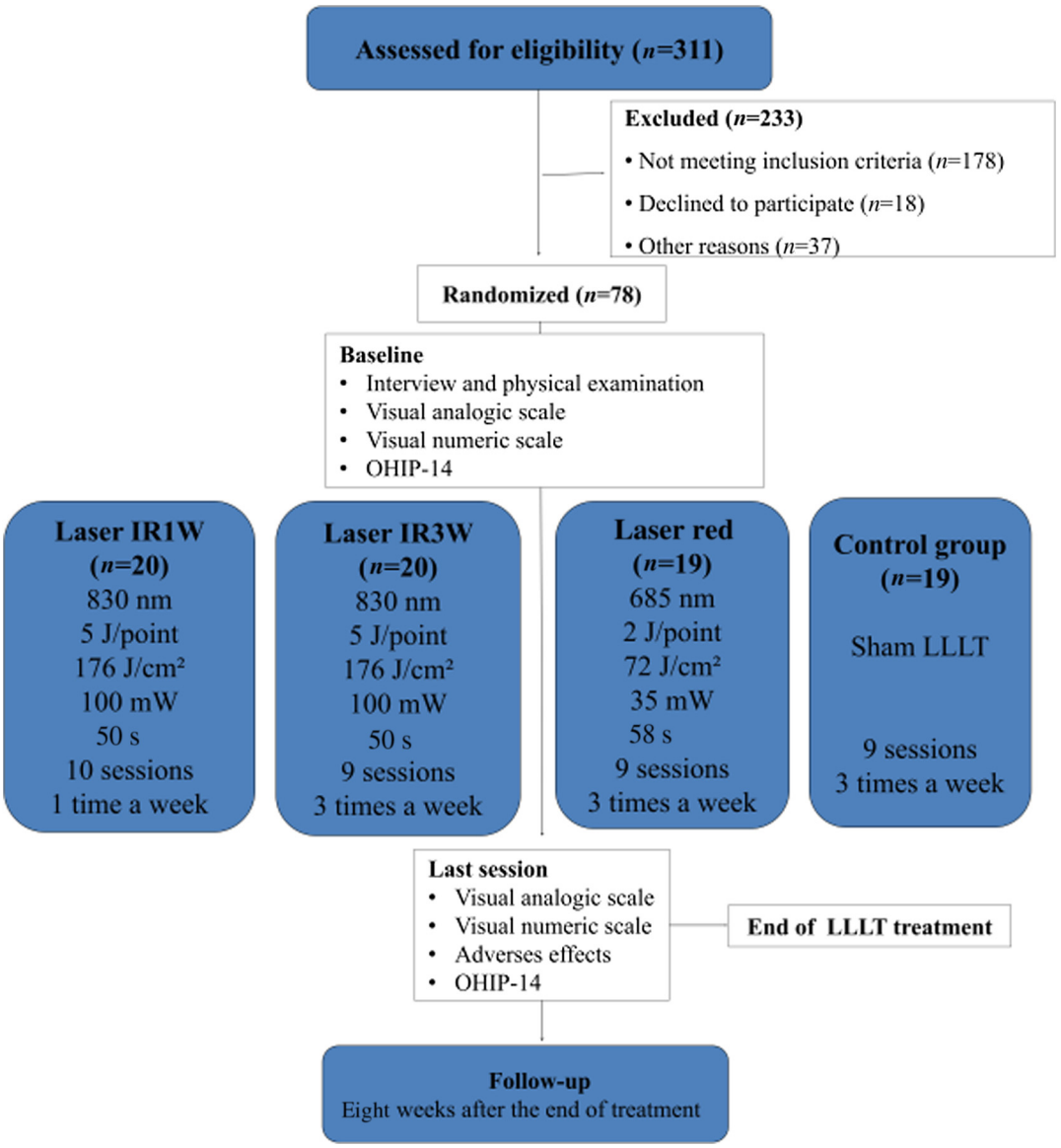

Fig. 1 Flow diagram of the trial phases.

2.2 *Low-Level Laser Therapy*

A diode laser was used (Thera Lase™, DMC Equipamentos LTDA., São Carlos, SP, Brazil); the spot tip area of this tool is 0.028 cm^2. LLLT was applied punctually on each of the sites with the symptom. For each of the anatomic sites, the points to be applied during the laser therapy were determined: apex of the tongue (3 points), side of the tongue (4 points), dorsum of the tongue (10 points), buccal mucosa (8 points), labial mucosa (5 points), hard palate (8 points), soft palate (3 points), and gums or alveolar ridge mucosa (3 points per sextant). The following LLLT parameters have been used:

1. Infrared laser weekly group (IR1W laser group, $n = 20$): GaAlAs, 830 nm wavelength, 100 mW output power, continuous emissions, 3.57 W/cm^2, 5 J energy per point, 176 J/cm^2 radiant exposure, application time 50 s per point. Patients underwent one LLLT weekly session for 10 weeks, total of 10 sessions.
2. Infrared laser three times a week group (IR3W laser group, $n = 20$): GaAlAs, 830 nm wavelength, 100 mW output power, continuous emissions, 3.57 W/cm^2, 5 J energy per point, 176 J/cm^2 radiant exposure, application time 50 s per point. Patients underwent three LLLT weekly sessions for three weeks, total of nine sessions.
3. Red laser group ($n = 19$): InGaAlP, 685 nm wavelength, 35 mW output power, continuous emissions, 1.25 W/cm^2, 2 J energy per point, 72 J/cm^2 radiant exposure, application time 58 s per point. Patients underwent three LLLT weekly sessions for three weeks, total of nine sessions.
4. Control group (Sham LLLT, $n = 19$): Nine sessions were carried out, searching for similarities to the IR3W and red laser groups; however, the tool received a plastic tip with rubber interior that blocked radiation emission, checked by means of a power meter prior to the applications.

The laser was calibrated before each LLLT session; the laser device had a system of calibration coupled to the equipment. Furthermore, after calibration, a power meter was used to check the power output. Protective glasses adequate for 830 and 685 nm wavelength were used by patients and professionals, as required for this laser class.

2.3 *Measurement of Symptoms*

Symptoms were measured using a visual analogue scale (VAS) and a visual numeric scale (VNS) at baseline, after each visit, and at the eight-week follow-up (Fig. 1). Both scales were applied to check whether patients would be consistent in their responses. VAS and VNS are internationally validated instruments and are widely used in clinical research.[26–29]

2.4 *Quality of Life Related to Oral Health*

The quality of life related to oral health (QLROH) was assessed through the Oral Health Impact Profile (OHIP-14) questionnaire (Table 1), Portuguese language version.[30] This questionnaire indicates the quality of life aspects that are more affected by the oral health condition and helps in establishing better approaches for an integral patient care. This tool can show the extent to which the quality of life is affected by oral health.[31] OHIP-14 was applied at baseline and at the end of the treatment.

Table 1 Questions for the Oral Health Impact Profile (OHIP-14).

In the past six months, because of problems with your teeth or your mouth:
1. Have you had trouble pronouncing any word?
2. Have you felt that your sense of taste has worsened?
3. Have you had painful aching in your mouth?
4. Have you found it uncomfortable to eat any foods?
5. Have you been self-conscious?
6. Have you felt tense?
7. Has your diet been unsatisfactory?
8. Have you had to interrupt meals?
9. Have you found it difficult to relax?
10. Have you been a bit embarrassed?
11. Have you been a bit irritable with other people?
12. Have you had difficulty doing your usual jobs?
13. Have you felt that life in general was less satisfying?
14. Have you been totally unable to function?

Table 2 Demographic distribution of patients within the groups studied.

	IR1W laser $n = 20$	IR3W laser $n = 20$	Red laser $n = 19$	Control group $n = 19$
Mean age (±SD)	63.6 ± 9.61	60.5 ± 6.42	63.2 ± 6.91	61.5 ± 8.76
Age range	45 to 79	51 to 72	48 to 78	45 to 75
Males	3 (15%)	2 (10%)	1 (5.2%)	5 (26.3%)
Females	17 (85%)	18 (90%)	18 (94.8%)	14 (73.7%)
Sites of burning				
Apex of tongue	18 (90%)	16 (80%)	16 (84.2%)	15 (78.9%)
Dorsum of tongue	15 (75%)	16 (80%)	14 (73.6%)	15 (78.9%)
Sides of tongue	12 (60%)	13 (65%)	13 (68.4%)	10 (52.6%)
Lips	8 (40%)	10 (50%)	5 (26.3%)	7 (36.8%)
Palate	2 (10%)	5 (25%)	8 (42.1%)	3 (15.7%)
Other sites	2 (10%)	4 (20%)	1 (5.2%)	2 (10.5%)

2.5 *Statistical Analysis*

The data were initially analyzed through descriptive statistics. For the statistical analysis, the VNS and VAS scores, obtained at baseline, immediately after the end of the treatment, and eight-week follow-up, were considered. The VNS, VAS, and OHIP-14 scores were compared among the four groups using repeated measure analysis of variance (ANOVA) followed by the posthoc Tukey test. The value established for rejecting the null hypothesis was $p \leq 0.05$.

3 Results

All the patients in the sample ($n = 78$) completed the study. Sixty-seven patients (85.9%) were females and 11 (14.1%) males; the average age was 62.82 (±7.54) years. The duration of the symptoms ranged from 6 months to 30 years; 33.3% of the patients had been presenting the disorder for one to three years. The demographic characteristics and clinical data of the subjects are presented in Table 2.

The scores for VNS obtained at baseline, end of treatment, and eight-week follow-up are presented in Tables 3 and 4. The scores for VAS are presented in Tables 5 and 6. In both scales, the patients were consistent in their responses, presenting

Table 3 Comparison of the visual numeric scale (VNS) scores among groups (mean ±SD) obtained at baseline, end of treatment, and eight-week follow-up.

Group	Baseline	Final	Eight-week follow-up
Control	9.00 ± 1.00	6.05 ± 1.7	6.47 ± 2.31
IR1W laser	8.20 ± 1.57	3.20 ± 2.52	3.75 ± 2.40
p	0.989	**0.002**	**0.005**
Control	9.00 ± 1.00	6.05 ± 1.7	6.47 ± 2.31
IR3W laser	8.00 ± 1.33	3.00 ± 2.31	2.90 ± 2.10
P	0.943	**<0.001**	**<0.0001**
Control	9.00 ± 1.00	6.05 ± 1.7	6.47 ± 2.31
Red laser	8.16 ± 1.74	4.32 ± 2.68	4.42 ± 2.69
P	0.986	0.323	0.118
IR1W laser	8.20 ± 1.57	3.20 ± 2.52	3.75 ± 2.40
IR3W laser	8.00 ± 1.33	3.00 ± 2.31	2.90 ± 2.10
P	1.000	1.000	0.981
IR1W laser	8.20 ± 1.57	3.20 ± 2.52	3.75 ± 2.40
Red laser	8.16 ± 1.74	4.32 ± 2.68	4.42 ± 2.69
P	1.000	0.886	0.998
IR3W laser	8.00 ± 1.33	3.00 ± 2.31	2.90 ± 2.10
Red laser	8.16 ± 1.74	4.32 ± 2.68	4.42 ± 2.69
p	1.000	0.726	0.514

Repeated measures analysis of variance (ANOVA) followed by Tukey posthoc test at 5% significance level (bold values).

Table 4 Comparison of the VNS scores among the experimental times (mean ± SD) of the laser groups and control group.

Time	Control	IR1W laser	IR3W laser	Red laser
Baseline	9.00 ± 1.00	8.20 ± 1.57	8.00 ± 1.33	8.16 ± 1.74
Final	6.05 ± 1.7	3.20 ± 2.52	3.00 ± 2.31	4.32 ± 2.68
P	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Baseline	9.00 ± 1.00	8.20 ± 1.57	8.00 ± 1.33	8.16 ± 1.74
Eight-week follow-up	6.47 ± 2.31	3.75 ± 2.40	2.90 ± 2.10	4.42 ± 2.69
P	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Final	6.05 ± 1.7	3.20 ± 2.52	3.00 ± 2.31	4.32 ± 2.68
Eight-week follow-up	6.47 ± 2.31	3.75 ± 2.40	2.90 ± 2.10	4.42 ± 2.69
P	0.999	0.991	1.000	1.000

Repeated measures analysis of variance (ANOVA) followed by Tukey posthoc test at 5% significance level (bold values).

Table 5 Comparison of the VAS scores among groups (mean ± SD) obtained at baseline, end of treatment, and eight-week follow-up.

Group	Baseline	Final	Eight-week follow-up
Control	85.26 ± 14.25	66.37 ± 19.81	62.84 ± 26.30
IR1W laser	82.15 ± 14.47	28.20 ± 27.24	32.95 ± 28.92
P	1.000	**<0.0001**	**0.004**
Control	85.26 ± 14.25	66.37 ± 19.81	62.84 ± 26.30
IR3W laser	78.90 ± 15.25	30.85 ± 24.08	25.90 ± 19.48
P	0.999	**<0.0001**	**<0.0001**
Control	85.26 ± 14.25	66.37 ± 19.81	62.84 ± 26.30
Red laser	80.68 ± 18.63	44.87 ± 28.32	41.11 ± 27.14
P	1.000	0.125	0.131
IR1W laser	82.15 ± 14.47	28.20 ± 27.24	32.95 ± 28.92
IR3W laser	78.90 ± 15.25	30.85 ± 24.08	25.90 ± 19.48
P	1.000	1.000	0.998
IR1W laser	82.15 ± 14.47	28.20 ± 27.24	32.95 ± 28.92
Red laser	80.68 ± 18.63	44.87 ± 28.32	41.11 ± 27.14
P	1.000	0.521	0.993
IR3W laser	78.90 ± 15.25	30.85 ± 24.08	25.90 ± 19.48
Red laser	80.68 ± 18.63	44.87 ± 28.32	41.11 ± 27.14
p	1.000	0.770	0.626

Repeated measures analysis of variance (ANOVA) followed by Tukey posthoc test at 5% significance level (bold values).

Table 6 Comparison of the VAS scores among experimental times (mean ± SD) of the laser groups and control group.

Time	Control	IR1W laser	IR3W laser	Red laser
Baseline	85.26 ± 14.25	82.15 ± 14.47	78.90 ± 15.25	80.68 ± 18.63
Final	66.37 ± 19.81	28.20 ± 27.24	30.85 ± 24.08	44.87 ± 28.32
P	**0.036**	**<0.001**	**<0.001**	**<0.001**
Baseline	85.26 ± 14.25	82.15 ± 14.47	78.90 ± 15.25	80.68 ± 18.63
Eight-week follow-up	62.84 ± 26.30	32.95 ± 28.92	25.90 ± 19.48	41.11 ± 27.14
P	**0.004**	**<0.001**	**<0.001**	**<0.001**
Final	66.37 ± 19.81	28.20 ± 27.24	30.85 ± 24.08	44.87 ± 28.32
Eight-week follow-up	62.84 ± 26.30	32.95 ± 28.92	25.90 ± 19.48	41.11 ± 27.14
P	1.000	0.999	0.999	1.000

Repeated measures analysis of variance (ANOVA) followed by Tukey posthoc test at 5% significance level (bold values).

Table 7 Comparison among groups of OHIP-14 (mean ± SD) scores for quality of life related to oral health obtained at baseline and end of treatment.

Group	Baseline	Final
Control	17.80 ± 5.37	13.39 ± 3.62
IR1W laser	13.77 ± 7.46	8.54 ± 5.10
P	0.404	0.186
Control	17.80 ± 5.37	13.39 ± 3.62
IR3W laser	12.87 ± 7.78	6.89 ± 4.05
P	0.169	**0.021**
Control	17.80 ± 5.37	13.39 ± 3.62
Red laser	14.46 ± 7.21	9.77 ± 4.92
P	0.659	0.563
IR1W laser	13.77 ± 7.46	8.54 ± 5.10
IR3W laser	12.87 ± 7.78	6.89 ± 4.05
P	1.000	0.986
IR1W laser	13.77 ± 7.46	8.54 ± 5.10
Red laser	14.46 ± 7.21	9.77 ± 4.92
P	1.000	0.998
IR3W laser	12.87 ± 7.78	6.89 ± 4.05
Red laser	14.46 ± 7.21	9.77 ± 4.92
P	0.999	0.791

Repeated measures analysis of variance (ANOVA) followed by Tukey posthoc test at 5% significance level (bold values).

Pearson correlation coefficient >0.9. All the groups have shown a significant decrease in symptoms at the end of the treatment which was maintained in the eight-week follow-up. When the baseline and eight-week follow-up scores, obtained through VAS, were compared, the decrease in symptoms was 67.1% in the IR3W laser group, 59.9% in the IR1W laser group, and 49% in the red laser group. In the control group, the decrease in symptoms was 26.3%. In both symptom scales, scores of IR1W laser and IR3W laser groups differed significantly compared to the control group. On the other hand, there was no significant difference between red laser and control groups.

Both in the laser and in the control groups, there was a decrease in the OHIP-14 scores at the end of the treatment when compared to the assessment carried out at baseline. A significant difference was observed between the IR3W laser group and the control group. IR1W laser and red laser groups did not differ significantly in relation to the control group (Tables 7 and 8).

4 Discussion

The present study has clinically assessed LLLT effects in the treatment of patients with BMS. Early in the study, patient scores had reached ~80% in both pain scales used, showing that those individuals had significant complaints regarding

Table 8 Comparison between experimental times of OHIP-14 (mean ± SD) scores for quality of life related to oral health in laser groups and control group.

Group	Baseline	Final	*p*
Control	17.80 ± 5.37	13.39 ± 3.62	**0.002**
IR1W laser	13.77 ± 7.46	8.54 ± 5.10	**<0.001**
IR3W laser	12.87 ± 7.78	6.89 ± 4.05	**<0.001**
Red laser	14.46 ± 7.21	9.77 ± 4.92	**0.001**

Repeated measures ANOVA followed by Tukey posthoc test at 5% significance level.

BMS symptoms. Although all the groups had presented reduction in the symptoms in relation to the baseline values, the scores of the infrared laser groups (IR1W and IR3W) were significantly lower than the control group, showing the beneficial effect of LLLT in patients with BMS when used in that wavelength. A reason for our results with the red laser group could have been that the dosage, energy, and output power used in this group were lower in comparison with the ones in the infrared laser groups.

Noncontrolled clinical studies, using both red and infrared wavelengths, have shown LLLT benefits in patients with BMS.[22–25] On the other hand, in a controlled study, Vukoja et al.[32] used diode laser, pulse mode, 685 nm emission, five times a week for two weeks and did not find any improvement in the clinical picture of the BMS patients, suggesting that the LLLT therapeutic benefit in that disorder had been caused by the placebo effect. Although we have not used pulsed laser, and protocols were different from those used by Vukoja et al.,[32] we have not found any significant difference either, regarding the control group, when LLLT was used in the red wavelength. It must be taken into consideration that many patients improve due to the placebo effect as mentioned by Vukoja et al.,[32] and observed in the present study control group. Many BMS patients mention a decrease in symptoms and psychological improvement due to the fact that they have been receiving medical attention and advice.

The literature shows that LLLT can promote inhibition of the pain mediators and increase cell membrane potential, reducing the nerve impulse conduction velocity,[21,33] which could justify the analgesic action of that kind of therapy evidenced in this study. As infrared laser has a longer wavelength, it penetrates more deeply into the tissues when compared with red laser, being able to reach the nervous fibers.[34,35] López-Jornet et al.[14] suggest that hyperactivity of trigeminal nociceptive pathways can produce an intense response to the action of irritating factors, leading to the occurrence of burning mouth feeling, characteristic of BMS. Lauria et al.,[5] Forssell et al.,[36] Albuquerque et al.,[6] and Khan et al.[7] have also shown that BMS can have neuropathic implications.

Studies have pointed out that BMS can negatively affect the quality of life of the patients;[4,37] thus, the LLLT impact on QLROH has also been assessed in this study. All groups have shown a significant decrease in the OHIP-14 scores; in other words, a decrease in BMS symptoms had a positive impact on the QLROH of patients. However, just the infrared laser group, where the therapy was applied three times per week (IR3W), differed significantly from the control group regarding QLROH.

Almost all studies that have used laser therapy as a treatment option in patients with BMS were not controlled and differed considerably with respect to the LLLT parameters, such as wavelength, power, dosimetry, and energy, among others. In addition, the frequency of the sessions in these studies varied from one to five times per week, and the total number from 3 to 10 sessions.[22–25,32] The protocols used in the present study aimed at the analgesic effect, once neuropathic factors have been suggested as the cause of BMS. As the spot tip of the laser device is 0.028 cm^2, it is interesting to mention that 176 J/cm^2 (infrared laser groups) and 72 J/cm^2 (red laser group) dosimetry were not particularly meaningful and were equivalent to 5 and 2 J energy, respectively. Due to the variability of options regarding LLLT parameters, we believe that several protocols, besides the ones applied in the present study, could bring beneficial results to the BMS patients.

The management of BMS patients is difficult and many times frustrating. The correct diagnosis of the syndrome and the exclusion of local or systemic factors that could be associated with mouth burning symptoms are fundamental, as well as the search for new therapeutic alternatives. The results of the present study show that the protocols that used infrared laser were effective in reducing BMS symptoms. Furthermore, when LLLT was carried out in a three times per week frequency, there was a significant effect on the QLROH. This modality of treatment guarantees a remarkable analgesic effect and could be a therapeutic alternative in the management of BMS patients.

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