Review

Efficacy of low level laser therapy in the treatment of burning mouth syndrome: A systematic review

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A B S T R A C T

\textit{Background:} Burning mouth syndrome (BMS) is a chronic pain condition with indefinite cure, predominantly affecting post-menopausal women. The aim of this study was to systematically review the efficacy of low level laser therapy in the treatment of burning mouth syndrome (BMS).

\textit{Methods:} PubMed, Embase and Scopus were searched from date of inception till and including October 2016 using various combinations of the following keywords: burning mouth syndrome, BMS, stomatodynia, laser therapy, laser treatment and phototherapy. The inclusion criteria were: Prospective, retrospective and case series studies. Letter to editors, reviews, experimental studies, studies that were not published in English, theses, monographs, and abstracts presented in scientific events were excluded. Due to heterogeneity of data no statistical analyses were performed.

\textit{Results:} Ten clinical studies fulfilled the eligibility criteria, five of which were randomized clinical trials. In these studies, the laser wavelengths, power output and duration of irradiation ranged between 630–980 nm, 20–300 mW, 10 s–15 min, respectively. Most of studies reported laser to be an effective therapy strategy for management of BMS.

\textit{Conclusion:} Majority of the studies showed that laser therapy seemed to be effective in reducing pain in BMS patients. However, due to the varied methodologies and substantial variations in laser parameters among these studies, more clinical trials are required to ascertain the efficacy of laser for treating BMS.

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1. Introduction

Burning mouth syndrome (BMS) (synonyms: glossodynia, glossopryosys, stomatopyrosis, stomatodynia, and dysesthesia [1]) is a chronic pain condition, which predominantly affects post-menopausal women in their 5th to 7th decade [2]. According to the International Headache Society, burning mouth syndrome (BMS) is defined as an intraoral burning sensation for which no medical or dental cause can be identified [3]. In addition to burning sensation in the mouth, patients with BMS usually complain of unrepairning mucosal pain, xerostomia and dysesthesia [1,4]. The anterior two thirds of the tongue is the most frequently affected site, although any site of oral mucosa can be affected [1,4]. BMS is a relatively common condition with an estimated prevalence rate of 2.6% in the general population, and up to 12–18% among postmenopausal women [1,4–7]. It is typically a disease of the middle-aged and elderly women, with a female-male ratio of 7:1 [1]. Although the exact etiopathogenesis remains unclear, recent evidence suggest that BMS is neuropathogenic in nature, and neuropsychophysical studies indicates the possibility of a dysfunction at the peripheral and central reflex arc path and the processing of cortical excitation [8,9]. There is no specific therapy for BMS as yet and the treatment is solely aimed to alleviate symptoms. Medications that have been used for treatment BMS include antidepressants, antipsychotics, antiepileptics, analgesics, and topical capsaicin [10,11]; vitamin B complex and dietary supplements (such as zinc and folic acid) hormonal replacement (conjugated estrogens), have also been proposed as potential therapeutic strategies [2,10]. Despite the large variety of medication and other approaches proposed for BMS management, the treatment has been unsatisfactory and as yet there is no a definite cure.

The use of Low-level laser therapy (LLLT), also known as photobiomodulation or cold laser therapy, in the treatment of pain induced by BMS has been of great interest in the recent years. LLLT is non-drug, non-invasive clinical application which has potential analgesics, anti-inflammatory and biostimulating effects, with minimum adverse effects [12,13]. Low-level energy laser showed several effects that can be helpful in reducing the burning sensation. These include increasing in synthesis and release of serotonin and β-endorphins, blocking the depolarization of c-fiber and decreasing bradykinin secretion [14–18]. A number of studies have assessed the efficacy of laser in treatment of BMS [8,14–22], Arbabi Kalati et al. [19] reported a significantly better improvement in BMS symptoms and quality of life among laser treated patients as compared to placebo group. Similarly, Spanenberg et al. [8] reported a significantly better improvement in BMS symptoms among infrared laser treated patients than control placebo group. On the other hand, Pezlj-Ribaric [21] did not find differences in the symptoms of BMS in laser treated patients when compared to placebo control. Additionally, Sugaya et al. [22] evaluate the efficiency of LLLT in treatment of BMS and reported that both laser as well as placebo showed similar effects on the symptoms, and that the laser group showed a statistically better improvement only at the fourth checkpoint.

There seems to be some controversy on the efficacy of laser therapy in management of BMS. Therefore, the aim of this study was to systematically evaluate the evidence on the efficacy of laser therapy in the management of BMS.

2. Materials and methods

2.1. Focused question

According to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines, specific question was framed. The concerned focused question was “Is laser therapy effective in treatment of BMS?”

2.2. Eligibility criteria

The eligibility criteria for this systematic review were: Prospective, retrospective and case series studies, that assessed the efficacy of Laser in management of BMS. Additionally, studies were included only if they excluded patients with oral mucosal lesions or abnormal laboratory findings, such as anemia and vitamin deficiencies. Case reports, animal or in-vitro studies, letter to the editor, monographs, conference papers, reviews, unpublished data and studies published in a language other than English were excluded from the study.

2.3. Literature search

A literature search was conducted on Medline/PUBMED, Embase and Scopus to identify all relevant articles published in English from date of inception up to and including October 2016. Various keywords were used in different combinations: burning mouth syndrome, BMS, stomatodynia, Laser therapy, Laser treatment, phototherapy, low level laser therapy, low intensity laser therapy, infrared laser, low energy laser therapy.

Initially, titles and abstracts of all studies identified through the search strategies, described above, were screened by two authors (SA, NA), and irrelevant studies were excluded. Full-texts of all relevant studies (judged by title and abstract) were read and evaluated independently by the two authors for eligibility criteria. Additionally, Additionally, to locate any potential unidentified studies, we manually searched bibliographies and reference lists of the included studies. Moreover, a search in some journals highly likely to contain studies relevant to the review topic was done. These journals include the Journal of photomedicine Laser Surgery, journal of biomedical optics, Lasers Medical Sciences, Photomedical & photo-biological Sciences. The initial aim was to undergo meta-analysis but due to inconsistency of data and heterogeneity of the included studies, we did not perform statistical analysis [23].

2.4. Assessment of quality

The quality of Randomized Clinical trials was assessed by two independent authors following 5-point “Jadad” checklist [24], as illustrated in Table 1.

2.5. Data extraction

The following data were extracted by two independent authors using a standardized data collection form: authors and year of study, study design, gender, number of patients, age range, study protocol, site of laser application, methods of pain assessment, laser
Table 1
Quality assessment of the included RCT studies according to Jadad scale.

<table>
<thead>
<tr>
<th>Study</th>
<th>Randomized</th>
<th>Random described</th>
<th>Patient blind</th>
<th>Observer blind</th>
<th>Withdrawals handled</th>
<th>Total score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arbabi-Kalati et al. [19]</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Spannenberg et al. [8]</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Arduino et al. [14]</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Pezlj-Ribaric et al. [21]</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Sugaya et al. [22]</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>5</td>
</tr>
</tbody>
</table>

Fig. 1. Flow chart of methodology.

Type, dose, application time, frequency or number of sessions per week, follow up and pain outcomes.

3. Results

3.1. Study selection

The study search process is summarized Fig. 1. The initial search yielded a total of 25 studies, 10 of which did not fulfill the inclusion criteria and therefore excluded. Another 5 studies did not abide to eligibility criteria and were thus excluded. The remaining 10 studies [8,14–22] were reviewed and processed for data extraction.

3.2. General characteristics of included studies

Among the included studies, 5 were randomized clinical studies [8,14,19,21,22], 3 uncontrolled clinical studies [16,17,20] and 2 were case series [15,18]. Of the 5 RCT studies, 4 [8,19,21,22] compared the efficacy of laser with placebo, while one study [14] compared the efficacy of laser therapy to that of clonazepam.

Five studies were conducted in Brazil [8,15,16,20,22], two in Italy [14,17], one in Croatia [21], one in Taiwan [18] and one in Iran [19]. Study design, sample size, type of intervention and control of each study were analyzed and summarized according to the CONSORT protocol (Table 2). The total number of subjects involved in the intervention ranged between 10 and 78 patients. In all studies, more than two thirds of the subjects were females. Nine studies [8,14,15,18–22] reported the mean age of study participants, which was between 47.2 and 68.5 years with a range of 18–87 years.

All 10 studies [8,14–22] evaluated the effect of laser therapy in reducing pain in BMS patients. Three studies evaluated both pain and quality of life related to oral health among BMS patients [8,14,19] using Oral Health Impact Profile (OHIP), one study [14] assessed levels of anxiety and depression, and one study evaluated levels of saliva pro-inflammatory cytokines [21]. Nine studies (8, 14–16, 18–22) assessed pain by Visual Analogue Scale (VAS) while one study [17] assessed pain by Numerical Rating Scale (NRS) and in one study [14] present pain intensity (PPI) was also used. Six studies reported post-operative follow up period, which ranged from 6 weeks up to 12 months [8,14–16,18,22].
### General characteristics of the included studies

<table>
<thead>
<tr>
<th>Author/year of publication</th>
<th>Type of study</th>
<th>No. of subjects</th>
<th>Gender</th>
<th>No. of follow-up</th>
<th>Evaluation methods</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arabi Kalati et al. 2015 [19]</td>
<td>RCT</td>
<td>12</td>
<td>M:F</td>
<td>4:8</td>
<td>VAS</td>
<td>58% improvement (VAS)</td>
</tr>
<tr>
<td>Spanemberg et al. 2015 [8]</td>
<td>RCT</td>
<td>78</td>
<td>M:F</td>
<td>8:20</td>
<td>VAS, NA</td>
<td>68% improvement (VAS)</td>
</tr>
<tr>
<td>Kim et al. 2010 [16]</td>
<td>CT</td>
<td>11</td>
<td>M:F</td>
<td>3:7</td>
<td>VAS</td>
<td>56.6</td>
</tr>
<tr>
<td>No. Santos et al. 2015 [15,20]</td>
<td>Case series</td>
<td>25</td>
<td>M:F</td>
<td>10</td>
<td>VAS, NA</td>
<td>65.8</td>
</tr>
<tr>
<td>Vran and Huang 2011 [18]</td>
<td>CT</td>
<td>17</td>
<td>M:F</td>
<td>43</td>
<td>VAS</td>
<td>56.6</td>
</tr>
</tbody>
</table>

### 3.3 Laser related characteristics of included studies

In all 10 studies [8,14–22] diode laser was used with wavelengths ranging from 630 to 980 nanometer (nm) and power output ranging from 20 to 300 MW (Table 3). Six studies [8,15,16,19,20,22] reported the dose of radiation which ranged between 0.4–6 Joule (J). In nine studies [8,14–18,20–22] fluence energy of laser was reported that ranged from 0.53 up to 176 Joul per square centimeter (J/cm²). The power density was reported by 5 studies which ranged between 1 and 4 watt per square centimeter (W/cm²). The reported exposure time was between 10 s to 15 min. Seven studies [14–16,18,20–22] reported the surface area exposed to laser that ranged between 0.04 millimeter (mm) to 1 cm. Number of laser sessions ranged from one to 20 sessions and frequency of radiation ranged from one to 5 sessions per week.

### 3.4 Main outcome of the studies

In all uncontrolled studies [15–18,20] a significant improvement of BMS symptoms that ranged from 47% to 80.4% was reported. In one controlled study, Arabi Kalati et al. [19] reported a significant improvement of BMS symptoms among laser treated patients compared with placebo group.

Spanemberg et al. [8] has evaluated the efficacy of Laser therapy in treatment of BMS. A diode laser was used in 78 patients, randomly divided into 4 groups. one group (IR3W) received infrared laser (wavelength 830 nm, weekly session, 10 sessions); one group (IR3W) received infrared laser (wavelength 830 nm, 1 session/week, 9 sessions); one group received red laser (685 nm, 35 MW, 2J/cm², 3 session/week, 9 sessions), and control group (placebo). The authors found that all groups have shown a significant reduction in symptoms. Compared to the baseline scores, the decrease in symptoms at the end of treatment was 67% in IR3W group, 59.9% in the IR1W, 49% in the red laser group, and only 26.3% in the placebo group. The results showed significant differences between infrared laser groups and control group. Yet there was no significant difference between the red laser group versus the control group. The authors suggested a beneficial effect of laser therapy when the appropriate wavelength is applied.

Pezlj-Ribaric et al. [21] evaluated the effect of laser on saliva proinflammatory cytokines among 40 BMS patients. The subjects were randomly allocated into two groups, Laser group and placebo controls. The authors did not find significant differences in symptoms of BMS between the two groups. However, the authors found a significant decrease in the level of saliva proinflammatory cytokines in favor of the laser group.

Arduini et al. [14] treated 33 BMS patients, randomly assigned into two groups: One group received laser (two sessions weekly for 5 weeks) while the other received a topical clonazepam therapy for three weeks, (1 mg, three times a day). The Laser group showed a significant improvement in all pain parameters compared to the clonazepam group. The authors concluded that LLL is superior to Clonazepam in reducing BMS symptoms.

Sugaya et al. [22] evaluated the efficiency of LLI in treatment of BMS in 23 patients randomly allocated into two groups (Laser and placebo). The results showed that the laser group as well as the placebo group showed a significant improvement in the symptoms, and that the laser group showed a statistically better improvement only at the fourth checkpoint. The authors concluded that laser therapy is as effective as placebo in treatment of BMS, suggesting an emotional involvement in the symptomology of BMS.
4. Discussion

LLLT has generated interest as an alternative treatment option in BMS as it is a non-invasive treatment with anti-inflammatory and biostimulatory properties that accelerate wound healing. Hence, this systematic review was envisioned to address a focused research question related to the efficacy of LLLT in the treatment of BMS. Analysis of the limited evidence available confirms that LLLT was shown to be an effective treatment strategy for the management of BMS. However, the outcome of this systematic review should be considered with caution owing to the varied methodologies and substantial variations in laser dosimetry among these studies.

A key area of concern in LLLT is the lack of consensus related to the laser parameters used by various researchers in their studies. The therapeutic effects of LLLT on the tissues are governed by various factors such as wavelength of the laser, power output, spot size, energy dose, application interval and irradiation output. One among the key parameters is related to the laser dose. Despite the various recommendations put forward by researchers, the ideal dose remains a topic of controversy. Dosage guidelines for LLLT from analysis of the literature suggest that an energy dose in the range of 0.5–8 J/cm² is ideal to reduce inflammation and accelerate wound healing [25]. The studies included in the scope of this review displayed a wide variation in the dose, with energy dose per treatment point ranging from 0.4 J to 6 J reflecting a lack of uniformity in the ideal dose of LLLT in the treatment of BMS. Furthermore, the studies, which were included as part of this review displayed substantial heterogeneity regarding the overall laser parameters, with widespread variations in the wavelength (630–980 nm), power output (20–300 mW), energy dose per treatment point (0.4–6 J), energy density of laser (0.53–176 J/cm²), exposure time (10 s to 15 min) and frequency of laser sessions varying from 1 to 20. Hence, a meta-analysis of these studies could not have been conducted due to the diverse methodologies and absence of uniformity in laser parameters. Though these studies [8,14–20] differed in the laser parameters, they collectively showcased the efficacy of laser to relieve symptoms associated with BMS. However, a lack of consensus on the ideal laser parameters creates a barrier in establishment of an ideal laser-based treatment protocol for BMS.

As per most research guidelines, it is mandatory to consider a credible study methodology in order to investigate the efficacy of any treatment approach. Therefore, it is imperative that the superior efficacy of LLLT in reducing pain associated with BMS can be assessed accurately only through the inclusion of a properly designed randomized trial with a placebo. Among the studies included in the present systematic review, only a few studies [8,19,21,22] complied and had a placebo arm in the study design. The majority of the studies failed to include a placebo which would have established the relative supremacy of LLLT and minimized the risk of bias in the interpretation of the results.

The desired outcomes of LLLT in BMS were to reduce the symptoms of pain and burning sensation. Of these two, reduction in pain was chosen as the key outcome of LLLT. Among the various scales, VAS is recognized as the most common sensitive scale for quantitative evaluation of a subject’s pain and is accurate in assessment of the effects of a treatment.

The majority of included studies [8,14–16,18–22] used VAS for subjective assessment of pain. Some studies used different pain scales, such as the Visual Numeric Scale [8], McGill pain questionnaire [14] and Numeric Rating scale [17]. Though most of the studies applied VAS to evaluate pain bringing homogeneity and reliability, comparison of the outcomes was not possible owing to the wide disparities in the data reporting practices for VAS scores across these studies, as summarized in Table 2. The reduction of VAS scores and pain relief by LLLT in our review has been corrob-

### Table 3: Laser parameters of the included studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Source</th>
<th>Wave-length (nm)</th>
<th>Spot size (cm²)</th>
<th>Duration of irradiation (s)</th>
<th>Power output (W/cm²)</th>
<th>Power density (W/cm²)</th>
<th>Laser schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sugaya et al. [21]</td>
<td>Diode laser</td>
<td>630</td>
<td>6 mm²</td>
<td>10</td>
<td>50</td>
<td>10</td>
<td>G1:3 sessions/week once 2 weeks</td>
</tr>
<tr>
<td>Arbabi-Kalati et</td>
<td>Diode laser</td>
<td>630</td>
<td>6 mm²</td>
<td>10</td>
<td>50</td>
<td>10</td>
<td>G1:3 sessions/week once 2 weeks</td>
</tr>
<tr>
<td>Spamerberg et al.</td>
<td>Diode laser</td>
<td>630</td>
<td>6 mm²</td>
<td>10</td>
<td>50</td>
<td>10</td>
<td>G1:3 sessions/week once 2 weeks</td>
</tr>
<tr>
<td>Aradini et al. [14]</td>
<td>Diode laser</td>
<td>630</td>
<td>6 mm²</td>
<td>10</td>
<td>50</td>
<td>10</td>
<td>G1:3 sessions/week once 2 weeks</td>
</tr>
<tr>
<td>Ribic et al.</td>
<td>Diode laser</td>
<td>630</td>
<td>6 mm²</td>
<td>10</td>
<td>50</td>
<td>10</td>
<td>G1:3 sessions/week once 2 weeks</td>
</tr>
<tr>
<td>Kahr et al. [16]</td>
<td>Diode laser</td>
<td>630</td>
<td>6 mm²</td>
<td>10</td>
<td>50</td>
<td>10</td>
<td>G1:3 sessions/week once 2 weeks</td>
</tr>
<tr>
<td>Romeo et al. [17]</td>
<td>Diode laser</td>
<td>630</td>
<td>6 mm²</td>
<td>10</td>
<td>50</td>
<td>10</td>
<td>G1:3 sessions/week once 2 weeks</td>
</tr>
<tr>
<td>Deo et al.</td>
<td>Diode laser</td>
<td>630</td>
<td>6 mm²</td>
<td>10</td>
<td>50</td>
<td>10</td>
<td>G1:3 sessions/week once 2 weeks</td>
</tr>
<tr>
<td>Yang and Huang</td>
<td>Diode laser</td>
<td>630</td>
<td>6 mm²</td>
<td>10</td>
<td>50</td>
<td>10</td>
<td>G1:3 sessions/week once 2 weeks</td>
</tr>
</tbody>
</table>
orated by successful use of LLLT in various applications; recurrent aphthous stomatitis [26], temporomandibular joint disorders [12], oral mucositis induced by cancer therapy [27]. The reduction in pain and burning sensation by LLLT has been attributed to various mechanisms. The analgesic effect of LLLT is primarily due to release of β-endorphins and enkephalins, which are natural pain killers in our body and through decreased secretion of pain mediators like bradykinin and histamine. Pain relief is also attributed to a decrease in the activity of C fibers and enhanced ATP synthesis thereby leading to reduction in pain stimuli conductance [14,19,28].

The present systematic review has certain limitations. Most of the studies included in this review had a small sample size, certain a shortcoming when a new treatment modality is assessed. Also, there was inconsistency in data reporting ofVAS scores among all the studies. Furthermore, a major limitation was a substantial heterogeneity of the laser parameters among all the studies. Further well designed randomized, double-blinded, placebo controlled trial with adequate sample size are warranted to assess the role of LLLT in the treatment of BMS. It is recommended that ideal laser parameters based on the analysis of the best available evidence should be considered. Adequate measures should be taken to control bias while reporting the outcome assessment.

References