Low-Level Laser Improves Quality of Life for Patients with Burning Mouth Syndrome. A Systematic Review and Meta-Analysis

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Abstract

Purpose: The aim of this systematic review is to evaluate if laser therapy produces an improvement in the values of quality of life related with oral health in patients affected by burning mouth syndrome.

Methods: An electronic searches was conducted in April 2020. Five Databases were searched inspected: Medline via Pubmed, Embase via Ovid, Cochrane Central, Scopus and Web of Science. Only Randomized clinical trials with placebo group were included.

Results: 324 article were identified and but only 6 were included. Five studies showed statistically significant differences between laser and placebo groups after treatment. The mean difference in studies between laser and placebo groups at the last session was from 3.5 to 15 points in favor of laser. The meta-analysis was carried out with five studies with data from baseline, last sessions and 4 weeks after. The results of the meta-analysis indicate statistically significant OHIP-14 scores for the laser versus placebo group both at the end of treatment and at 4 weeks, 5.05 (IC95% 7.02 - 3.08) and 2.98 (IC95% 4.31 - 1.64) respective respectively.

Conclusion: Low-Level Laser therapy produces an statistically significant improvement in OHrQoL scores. This non-invasive technique could be an option to treat the symptoms of BMS with fewer adverse effects than conventional drug treatments. More randomized clinical trials with longer follow-ups and larger samples and bigger sample sizes are needed.

Keywords: Low-Level Laser Therapy; LLLT; Photobiomodulation; Burning Mouth Syndrome; BMS; Oral Health Related with Quality of Life; OHrQoL; OHIP-14

Introduction

Burning mouth syndrome (BMS) is a complex disorder characterized by burning symptoms in the oral mucosa with a clinically healthy appearance and absence of other manifestations [1,2]. The condition usually affects the tongue, but it can also affect other areas, including the lips, the hard and soft palate, the buccal mucosa and the floor of the mouth. Symptoms vary from mild to severe in intensity. Patients complain of xerostomia and dysgeusia [3]. Prevalence of BMS is higher in patients over the age of 50 [4]. Male-female ratio ranges from 1:3 to 1:16 and prevalence varies between 0.7 and 4.6% [1,2,5]. Symptoms increase in severity during the day until afternoon. Despite many studies, its etiopathogenesis is uncertain. Causes could be neuropathic [6], hormonal [7] and stress or depression [8]. Treatment is predominantly symptomatic with medications such as clonazepam, amitriptyline, or imipramine [9-11]. They produce adverse secondary effects, such as xerostomia, that may aggravate the patients’ perception of the disorder [5].

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The lack of effective therapies has prompted new lines of research into the treatment of the BMS. Several studies have found a decrease in pain as a result of the application of low-level laser therapy (LLLT) [12-14]. In addition, the use of low-level laser radiation has been tested in several areas of medicine [15,16] due to its capacity to modulate metabolic and biochemical processes that generate energy in the cell. LLLT can be used to promote analgesia, cell biomodulation, fibroblast proliferation, collagen synthesis and tissue regeneration [17,18].

Oral health-related quality of life is defined as the impact of oral conditions on the day-to-day life of a patient with burning mouth syndrome, encompassing the physical, psychological and social dimensions. Therefore, it not only assesses the severity of the pain, but also how the burning mouth syndrome affects different aspects of the patient’s life. Several articles have found high values of affection in patients with burning mouth syndrome. Finding therapies that reduce this level of involvement may be useful for future research.

The oral health-related quality of life (OHRQoL) defines the impact of oral conditions in daily life [19] of a BMS patient in a physical, psychological and social dimensions [20]. Therefore, it evaluates not only the severity of the pain, but also how the BMS affects every aspect of the patients life. Several articles found high affectation values in patients with BMS [21-23]. Finding therapies that reduce this level of affection could be convenient in future research.

Aim of the Study

Therefore, the aim of this systematic review is to evaluate if laser therapy produces an improvement in the values of quality of life related with oral health in patients affected by burning mouth syndrome.

Materials and Methods

Protocol and registry

The present systematic review was performed according to the guidelines of the preferred reporting items for systematic reviews and meta-analyses (PRISMA) [24].

Eligibility criteria

Inclusion criteria

Types of studies

Randomized controlled trials.

Types of participants

Population with a diagnosis of BMS who presented symptoms in the oral cavity.

Types of interventions

Low-level laser therapy (LLLT).

Types of outcome measure

Oral health-related quality of life (OHRQoL).

Only studies explicitly reporting on any subjective perception of OHRQoL by using any type of questionnaires or questions were included.

Exclusion criteria

RCTs without a placebo group were excluded.

Search strategy and bibliographic sources

Two independent reviewers (B.S and I.B) conducted the electronic searches independently in April 2020. Five Databases were searched: Medline via Pubmed, Embase via Ovid, Cochrane Central, Scopus, and Web of Science. The details of the Medline (via Ovid) search was shown in table 1. The strategies for the other databases were based on the search strategy developed for Medline but revised appropriately for each one. No restrictions were imposed regarding language or year of publication.

Table 1: Risk of bias summary.
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Other resources

We searched US National Institutes of Health Trials Registry (clinicaltrials.gov) for ongoing trials. Moreover, Open Gray (www.open-grey.eu) was used for the identification of the research of gray literature.

Data collection and analysis

Selection of studies

Two review authors independently carried out the selection of studies. They checked the titles and abstracts to screen out the irrelevant ones. According to inclusion criteria, full-text articles that could be relevant were obtained and read deeply. The two authors independently analyzed each article. Disagreements were resolved by consensus between the two authors. If supplemental information was required, these two reviewers would contact the corresponding author of the study. Articles were screened using the Rayyan app (Mourad Ouzzani, Hossam Hammady, Zbys Fedorowicz and Ahmed Elmagarmid). Rayyan - a web and mobile app for systematic reviews. Systematic Reviews (2016) 5:210, DOI: 10.1186/s13643-016-0384-4). Reasons for exclusion are listed in Annex XX.

Data extraction

The two authors (J.S and E.V) extracted and recorded the data independently. Disagreements were resolved by consensus between both authors. Data extracted were entered on a customized data collection form.

The collected information was:

- Citation details of the publication.
- Participants: (Sample size, age, inclusion and exclusion criteria).
- Intervention: Location of laser application, type of laser, dose, application time, frequency or number of sessions per week.
- Control: Type of control.
- Outcomes: Type of tool employed, frequency or number of applications, scores of OHRQoL.

Assessment of risk of bias in included studies

The risk of bias was evaluated by the same two independent reviewers using the Cochrane 'Risk of bias' tool. Following domains were assessed:

- Sequence generation (selection bias),
- Allocation sequence concealment (selection bias),
- Blinding of participants and personnel (performance bias),
- Blinding of outcome assessment (detection bias),
-Incomplete outcome data (attrition bias),
- Selective outcome reporting (reporting bias),
- Other potential sources of bias.
Statistical methods and data synthesis

For continuous results, the difference between the mean values were calculated. Only values \( p \leq .05 \) were considered statistically significant. When it was possible, a meta-analysis was carried out to integrate the results of different studies, using aleatory models. Studies that did not provide the information required to do the statistical analysis and to be included in the meta-analysis were subjected to a narrative description.

Meta-analysis was performed with RCTs with similar comparisons for the same measurements of results. Data was confined using an aleatory effects model. An analysis of the heterogeneity of results between the different studies was also performed by visual analysis of meta-analysis graphics and statistical heterogeneity \((I^2)\).

The number of participants for each comparison in cross-over studies will be divided equally between the groups. Calculations and graphics of meta-analysis were performed using Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014 (http://community.cochrane.org/tools/review-production-tools/revman-5).

Results

Description of studies results of the search

The electronic searches in June 2020 identified 324 articles. 107 of those were duplicates. After screening the remaining 217 by reading the titles and abstracts, 187 were discarded. On the remaining 30 articles, the full text was readed and 24 were excluded. Finally, 6 articles were included [25-29] (Figure 1).

![Figure 1: PRISMA flow diagram.](prisma_diagram.png)
One article was still ongoing. It is not published yet and the results were not available during the process of this review.

Characteristics of the trial settings and investigators

All studies were undertaken in university hospitals or Schools of Dentistry. There was one trial from Croatia [26], one from Brazil [28], two from Spain [27], one from Iran [25] and one from Italy [29].

Characteristics of the participants

There were between 20 [25] and 85 [29] participants in the 6 studies.

The studies were undertaken on adults. In five studies, the mean age of participants was between 60 and 70 years [26-29]. However, in one study the mean age was around 47 years [25]. In all studies, there were more females, the percentage ranges from 80% (de Pedro 2020) to 100% of female participants [25,29].

Characteristics of the interventions

Five studies used in their control group the same laser but turned off [25-27,29]. In one study the control group consisted of using the laser with “a plastic tip with rubber interior that blocked radiation emission, checked by means of a power meter prior to the applications” [28].

In addition, two of the studies compared different doses and times for the laser application [27,28].

In three of the studies, laser irradiation was applied on the part of the mouth where the burning symptoms were presented [26,27,29]. In three studies the application areas were defined by clinicians previously [25,28].

Characteristics of the lasers

The characteristics of the lasers and the doses for each included study are explained below:

- The LLLT was performed by the Gallium. Aluminum and Arsenide (GaAlAs) laser in all 5 studies. In one study one group was treated with aluminum gallium indium phosphide laser (InGaAlP) [28].
- LLL irradiation at a wavelength of 630 nm, 30 mW of power for 10 seconds twice a week for 2 weeks. The laser dose for each area was 1 J/cm^2 [25].
- LLL irradiation at a wavelength of 810 nm, power of 0.6 W, power density of 1.2 W/cm^2, beam area of 0.5 cm^2 and energy of 6 J with an application time per point of 10 seconds in 56 points (de Pedro 2020).
- LLL irradiation at a wavelength of 830 nm. Laser parameters were set at: average power of 100 mW, chopped mode (switched on: 800 ms, switched off: 1 ms), fluence: 12 J/cm^2, duty factor of 80%, area: 1 cm^2 [26].
- LLL irradiation at wavelengths between 660 - 970 nm, medium power 3.2W (6.4W pulsed at 50%), treatment time 3’51”, frequency 1 - 20000 Hz, spot size 1 cm^2 [29].
- LLL irradiation at wavelengths 815 nm was applied Ten points spread over the area presenting symptoms were irradiated with a spot size of 0.03 cm^2. Group I (n = 16): GaAlAs laser. 815 nm wave-length. 1 W output power. continuous emissions. 4 seconds. 4 Joules and fluence rate is 133.3 joules/cm^2. Group II (n = 16): GaAlAs infrared laser. 815 nm wavelength. 1W output power: continuous emissions 6 seconds. 6 Joules and fluence rate of 200 joules/cm^2 [27].
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- Laser characteristics were different between the three groups. Group I: GaAlAs, 830 nm wavelength, 100 mW output power, continuous emissions, 3.57 W/cm², 5 J energy per point, 176 J/cm² radiant exposure, application time 50 s per point. Group III: GaAlAs, 830 nm wavelength, 100 mW output power, continuous emissions, 3.57 W/cm², 5 J energy per point, 176 J/cm² radiant exposure, application time 50 s per point. Patients underwent three LLLT weekly sessions for three weeks, total of nine sessions. Group III: InGaAlP, 685 nm wavelength, 35 mW output power, continuous emissions, 1.25 W/cm², 2 J energy per point, 72 J/cm² radiant exposure, application time 58 s per point. In all groups, the spot tip area of this tool is 0.028 cm² [28].

Characteristics of the outcomes

All included studies applied the 14-item Oral Health Impact Profile (OHIP-14) to measure the OHRQoL. The questionnaire has 14 items and 5 categories by item. All studies used the add system to sum the data.

All studies applied the OHIP-14 before the first laser or placebo application. In five studies the questionnaire was completed after the last intervention [25,26,28,29].

In three studies the questionnaire was filled at one month follow-up session [27,29].

In one study the Assessments were not performed during the last session, but after 2 and 4 weeks treatment [27]. Moreover, in one study, the OHIP-14 was completed after each session [29].

OHRQoL

In the laser group there was a decrease in the OHIP-14 scores at the end of the treatment. Five studies showed statistically significant differences between laser and placebo groups after treatment [25,27-29].

The mean difference in studies between laser and placebo groups at the last session was from 3.5 [29] to 15 [25] points in favor of laser.

Follow up scores obtained by the laser group at 4 weeks after the last intervention were significantly lower than the ones obtained by the placebo group [27,29].

One study showed no significant differences between the laser group before and after the treatment and between the control group before and after the treatment. However, it didn’t show the mean differences between laser and placebo groups at any time before or after treatment [26].

The meta-analysis was carried out with five studies with data from baseline, last sessions, and after 4 weeks. [25,27-29]. One study did not provide enough data, which made it not meta-analyzable [26].

The results of the meta-analysis indicate statistically significant OHIP-14 scores for the laser versus placebo group both at the end of treatment and at 4 weeks, 5.05 (IC95% 7.02 - 3.08) and 2.98 (IC95% 4.31 - 1.64) respectively. The heterogeneity was in all cases less than 60% and not statistically significant. At the beginning of the treatment no statistically significant difference was detected between the laser and the placebo groups (Figure 2-4).

Risk of bias in included studies

All included studies were considered to have a low risk of bias except for Spanemberg [28] which had an unclear risk of bias in three areas because of the lack of knowledge about the impact on blinding of participants and evaluators of the placebo system used (Figure 5).
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Discussion

The results of the RCTs included in this review indicate that laser achieves statistically significant improvements in oral health-related quality of life compared to placebo for patients with burning mouth syndrome. In the same line are the results of the meta-analysis with a mean difference compared to the control of 5.05 points in the last session.

The results of the RCTs included in this review indicate that laser achieves statistically significant improvements in oral health-related quality of life compared to placebo for patients with burning mouth syndrome. In the same line are the results of the meta-analysis with a mean difference compared to the control of 5.05 points in the last session.

In one study, positive differences between before and after were detected for the patients included in the control groups that consisted of the application of the off laser [28]. This could be indicative of a placebo effect by the laser, which is not surprising given the possible psychological component of the BMS. However, this pattern was not detected in the rest of the included studies.

In one study, positive differences were detected between the before and after for the patients included in the control groups that received the laser application with the laser turned off [28]. This could be indicative of a placebo effect, which is not surprising given the possible psychological component of BMS. However, this pattern was not detected in the rest of the included studies.

In a previous review, the reduction of pain with the use of laser was evaluated, but not the OHrQoL. An improvement in the values was found, but the heterogeneity in the data reporting forces, according to the authors, to take the conclusions with caution (Al-Maweri 2016). Although the use of the VAS scales to assess the reduction of pain in RCTs is a transcendent measure, in recent years the evaluation of OHrQoL has become popular as an outcome measure within RCTs in dentistry [30,31]. The OHIP-14 is the most widely used questionnaire for this purpose and with adequate psychometric characteristics [32].

Only three studies carried out follow-up of the patients once the treatment was finished and the results could be meta-analyzed at one month, being statistically significant in favor of the laser although with a reduction in deference with respect to the data obtained in the last session of the intervention [27,29]. The longest follow-up period was 4 months, finding a mean difference of 11.6 points between the groups (p ≤ 0.01) (From Pedro 2020).

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None of the included studies performed a sample size calculation, choosing an arbitrary size [27] or for another outcome measure (From Pedro 2020). Failure to perform a sample size calculation could cause larger samples to change the results of independent studies, so performing the meta-analysis is essential to increase the sample.

None of the included studies carried out sample size calculations, choosing an arbitrary size [27] or for another outcome measure (de Pedro 2020). Not performing a sample size calculation could cause larger samples to change the results of the independent studies, so performing the meta-analysis is essential to increase the sample.

It must be taken into account that each study uses a specific laser mark, with parameters that, although in some cases are similar, do not coincide. Therefore, this factor could explain part of the variability between studies. In the same way, there was heterogeneity in the number of sessions and the distance between them, which could be another factor that generated variability in the data.

The value of 4 points has been considered as the least important difference for the OHIP-14 questionnaire for patients undergoing prosthetic restorations [33]. However, none of the included studies asked anchor questions (anchor bases) to determine a value on the OHIP-14 scale that could be considered as a different important minimum for patients with burning mouth syndrome, from which it can be said that patients perceive this improvement in OHrQoL [34].

The value of 4 points has been considered the minimum important difference for the OHIP-14 questionnaire for patients who were undergoing prosthetic rehabilitations (Masood 2014). However, none of the included studies ask anchorage questions to determine a value on the OHIP-14 scale that could be considered as a different minimum important for patients with burning mouth syndrome, from which it can be said that patients perceive that improvement in the OHrQoL [34].

Conclusion

The results of the present systematic review show that LLLT produces an statistically significant improvement in OHrQoL scores. This non-invasive technique could be an option to treat the symptoms of BMS with fewer adverse effects than conventional drug treatments. More randomized clinical trials with longer follow-ups and bigger sample sizes are needed.

Bibliography

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