JULIANA CASSOL SPANEMBERG

EFEITO DA TERAPIA LASER DE BAIXA POTÊNCIA NO TRATAMENTO DA SÍNDROME DA ARDÊNCIA BUCAL: ENSAIO CLÍNICO, RANDOMIZADO, PLACEBO-CONTROLADO

Tese apresentada à Faculdade de Odontologia da Pontifícia Universidade Católica do Rio Grande do Sul como parte dos requisitos para a obtenção do título de DOUTOR EM ODONTOLOGIA, área de concentração em Estomatologia Clínica.

Orientadora: Profa. Dra. Fernanda Gonçalves Salum

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Dedico esse trabalho especialmente a Deus e à minha família.

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à minha vida. Em especial aos meus pais, Dirceu e Maria,

pelo incessante apoio, incentivo e compreensão – foram vocês

que me possibilitaram a alegria desta conquista.

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Não enumere jamais em sua imaginação o que lhe falta.

Pelo contrário, conte tudo o que possui.

Verá, em suma, que a vida foi esplêndida com você.

Amado Nervo

(1870-1919)

RESUMO

RESUMO

A síndrome da ardência bucal (SAB) é uma doença de etiopatogenia desconhecida, caracterizada pela sensação de queimação e ardência na mucosa bucal, que se apresenta clinicamente normal. No primeiro artigo desta tese foi realizada uma revisão da literatura com ênfase nas características da SAB, etiologia e terapêutica. Uma vez que a terapia laser de baixa potência (LLLT) tem sido amplamente utilizada em enfermidades bucais devido aos seus efeitos analgésicos, biomoduladores e antiinflamatórios, no segundo artigo foram revisados a aplicabilidade e os protocolos da LLLT no manejo do líquen plano, xerostomia, ulceração aftosa recorrente, herpes labial, mucosite e SAB. Ensaios clínicos controlados investigando o efeito da LLLT na SAB são ainda escassos; portanto, o presente estudo clínico randomizado e controlado teve como objetivos avaliar o efeito da LLLT nos sintomas da SAB, bem como, o impacto desta terapia na qualidade de vida relacionada à saúde bucal dos pacientes. A amostra foi constituída por 78 pacientes com SAB, distribuídos em três grupos laser e um grupo-controle (n=19), no qual foi empregada *sham* LLLT. Os seguintes protocolos de LLLT foram empregados nos grupos-laser: grupo IR1w, n=20 (830 nm, 100 mW, 5 J, 176 J/cm^2, 50 s, uma sessão semanal, total de 10 sessões); IR3w, n=20 (830 nm, 100 mW, 5 J, 176 J/cm^2, 50 s, três sessões por semana, total de nove sessões); laser vermelho, n=19 (685 nm, 35 mW, 2 J, 72 J/cm^2, 58 s, três sessões por semana, total de nove sessões). Os sintomas foram avaliados por meio de escala visual numérica e escala visual analógica no início e fim do tratamento, e oito semanas após. Para avaliação da qualidade de vida relacionada à saúde bucal foi usado o instrumento Oral Health Impact Profile (OHIP-14). Os dados foram analisados por meio do teste ANOVA de medidas repetidas,

seguido pelo teste de Tukey. Houve redução significativa dos sintomas ao final do tratamento em todos os grupos, o que se manteve no acompanhamento de oito semanas. Os escores dos grupos laser IR1w e IR3w foram significativamente inferiores aos do grupo-controle. Por outro lado, não houve diferença significativa entre o grupo laser vermelho e o grupo-controle. Houve também redução significativa nos escores do OHIP-14 nos quatro grupos, entretanto, somente o grupo laser IR3w apresentou diferença significativa em relação ao grupo-controle, mostrando que o tratamento teve impacto positivo na qualidade de vida relacionada à saúde bucal. Com base nos resultados, pode-se concluir que a LLLT no comprimento de onda infravermelho e nos parâmetros utilizados neste estudo, reduz os sintomas da SAB e pode ser uma alternativa terapêutica no tratamento desta doença.

Palavras-chave: Síndrome da Ardência Bucal. Terapia a Laser de Baixa Intensidade. Lasers.

ABSTRACT

ABSTRACT

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. The literature was reviewed in the first manuscript, emphasizing BMS characteristics, etiology and therapeutics. Low-level laser therapy (LLLT) has been widely used in oral disorders because of its analgesic, anti-inflammatory and tissue repair effects. Thereby, in the second manuscript we reviewed the applicability and protocols of LLLT in the management of lichen planus, xerostomia, recurrent aphthous stomatitis, herpes labialis, oral mucositis and BMS. Controlled trials investigating the effects of LLLT on BMS are still rare. The present randomized, placebo-controlled study aimed to clinically assess the effect of LLLT in the treatment of patients with BMS, and to investigate the impact of such therapy in the quality of life of these individuals. The sample consisted of 78 BMS patients who were randomly assigned into three laser groups and one control group (n=19), which was treated with sham LLLT. Laser groups were treated with the following parameters: IR1w group, n=20 (830 nm, 100 mW, 5 J, 176 J/cm^2, 50 s, weekly LLLT sessions, ten sessions); IR3w group, n=20 (830 nm, 100 mW, 5 J, 176 J/cm^2, 50 s, three weekly LLLT sessions, nine sessions); red laser group, n=19 (685 nm, 35 mW, 2 J, 72 J/cm^2, 58 s, three weekly LLLT sessions, nine sessions). Symptoms were assessed at initial, at the end of the treatment and eight weeks later using visual analogue scale and visual numeric scale. Quality of life related to oral health was assessed through the Oral Health Impact Profile (OHIP-14). Statistical analysis was carried out using repeated measures ANOVA followed by the Tukey test. There was a significant reduction in 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 were significantly lower in comparision to the control group. On the other hand, there was no significant difference between Red laser group and control group. There was also a decrease in the OHIP-14 scores in the four groups. The scores of the IR3w laser group differed significantly from those of the control group, showing that LLLT had a positive impact on the quality of life related to oral health. Based on the results of this study it is possible to conclude that infrared LLLT, in the parameters used, reduces the BMS symptoms and can be an alternative therapeutic for this disorder.

Keywords: Burning mouth syndrome. Low-level laser therapy. Lasers.

LISTA DE TABELAS

LISTA DE TABELAS

ARTIGO DE REVISÃO 1

ARTIGO DE REVISÃO 2

ARTIGO DE PESQUISA

LISTA DE FIGURAS

LISTA DE FIGURAS

ARTIGO DE PESQUISA

LISTA DE ABREVIATURAS, SIGLAS E SÍMBOLOS

LISTA DE ABREVIATURAS, SIGLAS E SÍMBOLOS

ALA	Alpha-lipoic Acid
ANOVA	Analysis Of Variance
ATP	Adenosina Triposfato/Adenosine Triphosphate
BMS	Burning Mouth Syndrome
CEP	Comitê de Ética em Pesquisa
COX-2	Cicloxigenase-2
DE	Densidade de Energia
EVA	Escala Visual Analógica
EVN	Escala Visual Numérica
GaAlAs	Arseneto de Gálio e Alumínio/ Aluminum-arsenide-gallium
GaAs	Arseneto de Gálio
InGaAlP	Fosfeto de Índio-Gálio-Alumínio/Aluminum-gallium-indium-phosphide
J	Joule
J/cm^2	Joule por centímetro quadrado
LASER	Light Amplification by Stimulated Emission of Radiation
LLLT	Low Level Laser Therapy
mW	Miliwatts
mW/cm^2	Miliwatts por centímetro quadrado
nm	Nanômetro
OHIP-14	Oral Health Impact Profile
SAB	Síndrome da Ardência Bucal
QLROH	Quality of Life Related to Oral Health
VAS	Visual Analogue Scale

VNS	Visual Numeric Scale
W	Watt

SUMÁRIO

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INTRODUÇÃO

1 INTRODUÇÃO

A Síndrome da Ardência Bucal (SAB) é uma doença de difícil manejo clínico e caracteriza-se, principalmente, pela sensação de queimação, ardência, dor ou prurido na mucosa bucal, que se apresenta normal ao exame físico[1-4]. Estudos apontam que sua prevalência na população mundial varia de 0,7% a 4,6%, podendo chegar a 15%[2,5,6]. A doença é mais freqüente em pacientes do sexo feminino, com média etária de 62 anos[5,6]. A sintomatologia manifesta-se espontaneamente e acomete com maior freqüência os dois terços anteriores da língua, o palato duro e a mucosa labial[7,8].

Para o estabelecimento do diagnóstico da síndrome, a mucosa bucal do paciente deve apresentar-se normal, sem alterações como candidíase, língua geográfica, ulcerações, dentre outras. Hábitos parafuncionais ou traumatismos por próteses necessitam ser descartados[3] e o paciente também deve ser submetido a exames laboratoriais incluindo hemograma, glicemia em jejum e dosagens séricas de ferro, ácido fólico e vitamina B_{12}[9]. Conforme Brailo et al.[10], realizada essa investigação e descartada a presença de lesões na mucosa bucal, de próteses desajustadas e de alterações sistêmicas como diabetes e deficiências nutricionais, o paciente pode ser diagnosticado como portador da Síndrome da Ardência Bucal.

Ainda que a SAB seja uma doença de prevalência relativamente elevada em determinados grupos populacionais, sua etiologia permanece desconhecida. Entre as possíveis causas da síndrome destacam-se fatores neuropáticos[11-16], psicológicos tais como estresse, ansiedade e depressão[17-24] e, hormonais[25-27].

Algumas evidências sugerem que desordens no balanço hormonal tenham relação com a SAB em mulheres, uma vez que a doença é mais frequente durante e após o climatério[6,25-27]. Segundo Wardrop et al.[25], Síndrome da Ardência Bucal,

depressão e ansiedade poderiam ser o produto de um fator comum, ou seja, desordens endócrinas seriam a causa da incidência destas alterações em mulheres no período pós-menopausa.

Alguns estudos têm demonstrado que o perfil psicológico da maioria dos pacientes com SAB segue um padrão semelhante[17-24]. Femiano et al.[17] demonstraram que pacientes com a síndrome exibem acentuada perda da auto-estima, ausência de personalidade sólida, e que o aparecimento da doença é geralmente precedido por perdas ou mudanças significativas na vida do indivíduo. Gao et al.[18] observaram que os pacientes com SAB apresentavam ao longo de sua vida inúmeros eventos adversos quando comparados a pacientes-controle. Além disso, Pokupec-Gruden et al.[19], Lee et al.[20] e Abetz e Savage[21] verificaram que os indivíduos portadores dessa doença apresentavam ansiedade e depressão. Adamo et al.[23], além de encontrarem diferenças significativas entre os escores de depressão e ansiedade entre pacientes com SAB e controles, evidenciaram maior grau de distúrbios do sono nesses indivíduos. Para Palacios-Sánchez et al.[24], existe uma clara associação entre alterações da vida afetiva dos pacientes e o estabelecimento da síndrome.

Além dos fatores anteriormente mencionados, uma condição neuropática mediada central e/ou perifericamente vem sendo aventada há algum tempo como possível causa da SAB[11-16]. Guarneri et al.[14] sugeriram que alterações na percepção da dor, distúrbios na transmissão neural, aumento da excitabilidade ou envolvimento negativo do sistema vascular trigeminal podem ser mecanismos associados à síndrome. Lauria et al.[11] observaram a ocorrência de neuropatia nas pequenas fibras do nervo trigêmeo em pacientes portadores da SAB. Segundo López-Jornet et al.[15], a hiperatividade das vias nociceptivas trigeminais é capaz de produzir uma intensa

resposta à ação de irritantes, levando à ocorrência dos sintomas característicos da SAB.

Levando-se em consideração os distúrbios neuropáticos, as alterações psicológicas comumente associadas e o curso crônico da doença, diversos tratamentos são descritos na tentativa de atenuar os sintomas de ardência e queimação bucal; entretanto, não há um protocolo terapêutico definido. Os fármacos antidepressivos tricíclicos, constituem as opções mais empregadas no tratamento da SAB, embora possam promover efeitos adversos tais como hipossalivação e xerostomia[28]. Essas drogas são amplamente utilizadas no tratamento da dor crônica e neuropática por bloquearem a recaptação de serotonina ou noradrenalina, podendo interagir com receptores opióides endógenos e inibir vias descendentes da dor[29].

A radiação laser de baixa potência é uma forma não ionizante de radiação e sem efeitos mutagênicos. A terapia laser de baixa potência (Low Level Laser Therapy - LLLT) é um tratamento não invasivo, que utiliza a energia da luz na forma de fótons, os quais são absorvidos pelos citocromos e porfirinas nas mitocôndrias[30-32]. Estudos têm demonstrado ação analgésica, anti-inflamatória e reparadora tecidual da LLLT[30,32-39]. Sua ação anti-inflamatória é exercida mediante aceleração da microcirculação, o que determina alterações na pressão hidrostática capilar, com reabsorção do edema e inativação de catabólitos intermediários. A LLLT também exerce estimulação seletiva das mitocôndrias, com aumento da produção de ATP, resultando em elevação na velocidade das mitoses, aumento no consumo de glicose pelas células e elevação dos níveis de cálcio intracelular[40]. Tais processos produzem elevação do metabolismo celular[41] e, como efeito indireto, há aumento do fluxo sanguíneo[42] e da drenagem linfática[43]. A ação analgésica da LLLT ocorre pela

inibição dos mediadores álgicos e liberação de substâncias analgésicas endógenas como endorfinas, dificultando a transmissão do estímulo doloroso[44]. A LLLT eleva o potencial de membrana celular, reduzindo a velocidade de condução do impulso nervoso[44].

Alguns estudos têm verificado que a LLLT pode ser eficaz para a redução dos sintomas de ardência e queimação bucal de pacientes com SAB[45-48]. Entretanto, são escassos os ensaios clínicos controlados utilizando a LLLT em pacientes com essa síndrome. O presente estudo randomizado, cego, placebo-controlado, teve como objetivos avaliar clinicamente o efeito de diferentes protocolos de LLLT no tratamento de pacientes com SAB e investigar o impacto desta terapia na qualidade de vida relacionada à saúde bucal. Além da pesquisa, foi realizada uma revisão da literatura com ênfase nas características da síndrome da ardência bucal, etiologia e abordagens terapêuticas, que gerou a publicação do primeiro artigo. No segundo artigo, foram revisadas a aplicabilidade e protocolos da LLLT no manejo de condições orais prevalentes na clínica estomatológica tais como líquen plano, xerostomia, ulceração aftosa recorrente, herpes labial, mucosite oral e síndrome da ardência bucal.

PROPOSIÇÃO

2 PROPOSIÇÃO

2.1 Objetivo Geral

Avaliar clinicamente o efeito da terapia laser de baixa potência (LLLT) no tratamento de pacientes com a Síndrome da Ardência Bucal (SAB).

2.2 Objetivos Específicos

- Revisar a literatura com ênfase nas características da SAB, etiologia e abordagens terapêuticas.
- Revisar a aplicabilidade e protocolos da LLLT no manejo de condições orais prevalentes na clínica estomatológica tais como líquen plano, ulceração aftosa recorrente, herpes labial, SAB, xerostomia e mucosite oral.
- Avaliar clinicamente o efeito de dois protocolos de LLLT, no comprimento de onda infravermelho (830 nm), no tratamento de pacientes com SAB.
- Avaliar clinicamente o efeito de um protocolo de LLLT, no comprimento de onda vermelho (685 nm), no tratamento de pacientes com SAB.
- Avaliar o impacto do tratamento com LLLT na qualidade de vida relacionada à saúde bucal destes pacientes.

ARTIGO DE REVISÃO 1

3 ARTIGO DE REVISÃO 1

BURNING MOUTH SYNDROME. UPDATE

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BURNING MOUTH SYNDROME. UPDATE

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ABSTRACT

Burning Mouth Syndrome (BMS) is a chronic disorder that predominately affects middle-aged women in the postmenopausal period. The condition is distinguished by burning symptoms of the oral mucosa and the absence of any clinical signs. The etiology of BMS is complex and it includes a variety of factors. Local, systemic and psychological factors such as stress, anxiety and depression are listed among the possible causes of BMS. BMS may sometimes be classified as BMS Type I, II or III. Although this syndrome is not accompanied by evident organic alterations and it does not present health risks, it can significantly reduce the patient's quality of life. This study analyzes the available literature related to BMS, and makes special reference to its therapeutic management. The pages that follow will also discuss the diagnostic criteria that should be respected, etiological factors, and clinical aspects. We used the PubMed database and searched it by using the keywords "burning mouth syndrome", "BMS and review", and "burning mouth and review", in the title or abstract of the publication. BMS treatment usually steers towards the management of the symptoms; however, the specific local factors that could play a significant role in worsening the oral burning sensation should be eradicated. The most widely accepted treatment options that show variable results include tricyclic antidepressants, benzodiazepines and antipsychotic drugs; nevertheless there are other therapies that can also be carried out. Professionals that work in the field of dentistry should formulate standardized symptomatic and diagnostic criteria in order to more easily identify the most effective and reliable strategies in BMS treatment through multidisciplinary research.

Keywords: Burning mouth syndrome. Etiology. Diagnosis. Treatment.

INTRODUCTION

Burning Mouth Syndrome (BMS) is distinguished by burning, pain, or symptoms of itching in oral mucosa, which arise without the presence of any changes in physical examinations, laboratory analysis, or salivary flow rates [1-5]. This condition tends to appear in middle-aged and elderly women [6-9]. The International Association for the Study of Pain defines BMS as a pain that lasts for at least 4-6 months of duration and which is located on tongue or in other mucosal membranes and that is presented in the absence of any clinical and/or laboratory findings. The terms “glossodynia” (painful tongue) and “glossopyrosis” (burning tongue), as well as “glossalgia”, describe the phenomenon present in this disorder with respect to the most affected area, the tongue (especially the tip and lateral borders). Other terms such as “stomatodynia”, “stomatopyrosis”, “oral dysesthesia”, and “burning mouth syndrome” are used to define this condition [10]. Although percentages in research findings may vary between .07% and 15%, we can state that this disease is highly prevalent [11].

The episodes of a burning sensation are described as being spontaneous and the symptoms that patients experience range in severity; some patients suffer from a moderate burn, while others experience intolerable pain [3,12]. Other changes in sensitivity are known to take place, besides oral stinging, which include: a feeling of dryness in the mouth [13-15] or gustative alterations, such as the perception of a bitter or metallic taste [16]. In certain instances dysesthesia in the mouth might also occur, which is characterized by the feeling of having sand in the mouth or swelling of the mouth [12,16,17].

The lack of unified criteria makes the diagnosis even more complicated, and consequently, epidemiological information can differ depending on the researcher who analyzes it [18,19]. Within the risk group of postmenopausal-women, the prevalence of this disorder ranges between 18% and 33% [20]. The majority of research conducted shows an evident predominance that women have over men, ranging between 3-1 and 9-1 for the female sex [21-24]. According to most of the authors, the typical average age of patients of BMS is from 50 to 60 years old, however, it can also arise in patients close to their thirties, but not in children or in teenagers.

The true cause BMS remains unknown. Although this syndrome is not accompanied by evident organic alterations and it does not present health risks, it can significantly reduce the patient's quality of life. BMS patients tend to have a history of frequent medical and dental visits with the objective of obtaining a cure that does not yet exist. Experts currently debate whether the psychological alterations that BMS patients experience are the cause or the consequence of such chronic pain [25-27]. The patient profile is rather specific and is comprised of the following personal characteristics: age range between 50 and 60, a history of prolonged suffering from chronic pain, and a history of having been treated by many different specialists without obtaining any solution to the problem. It is also often accompanied by a significant emotional profile and is usually related to cancerophobia [28].

Diligent clinical investigation fails to accurately identify the cause for the burning sensation in patients with true burning mouth syndrome. Specific criteria should be observed, since symptoms of oral burning are common and can be caused by either local or systemic factors, which do not describe true BMS [15-17,28]. The clinical or laboratorial conditions associated with burning mouth include candidiasis,

geographic tongue, hyposalivation, esophagic reflux, parafunctional habits, diabetes, nutritional deficiencies (iron, folate, B1, B2, B6, B12), and adverse effects of certain drugs. In such cases, if the cause of this disorder is eliminated, the patient will therefore experience symptom relief [29].

This study analyzes the available literature related to BMS, and makes special reference to its therapeutic management. Other important topics of discussion throughout this article also include the diagnostic criteria that should be followed, etiological factors, and clinical aspects of the disease.

A search in the PubMed database was performed in order to identify articles published in the last five years using the keywords: "burning mouth syndrome", "BMS and review", and "burning mouth and review". This search resulted in 259 articles. When we limited the search to articles published in the English language, we found 6 non-systematic reviews and one systematic review that we considered particularly relevant (Table 1).

Table 1. Most significant conclusions from the articles.

Article	Aspects from the review	Most relevant conclusions
Abetz and Savage [30]	No systematic review. This publication serves as a review of BMS' clinical presentation and focuses on contributing factors in the initial presentation of the condition, as well as its advancement.	A number of useful clinical indicators were proposed in this paper, these indicators or signs may prove to be helpful for both clinical assessment and subsequent patient discussions, seeing as they provide visible supportive evidence for the diagnosis. The main focal point of the article was the role of psychological disorders in the etiology of BMS, in addition to a presentation that highlighted the clinical management of patients.
Balasubramaniam et al. [26]	No systematic review. The article reviews different conditions and diseases that may be possible causes of oral burning.	The article provided knowledge about the local, systemic and psychosocial factors that can cause the onset of oral burning, which is associated with secondary BMS.
López-Jornet et al. [10]	No systematic review. The article reviews some recent studies related to BMS literature, especially those having to do with etiological factors that could be involved, clinical aspects, diagnostic criteria and therapeutic management.	The article included tables that helped to guide us through the clinical factors, diagnosis and treatment of burning mouth syndrome. It made the suggestion of the inclusion and exclusion protocols based on suggestions made throughout other literary sources.
Minguez-Sanz et al. [27]	No systematic review. This study describes different hypotheses relating to BMS etiology, as well as the psychological and anatomical data that serve as the basis for such hypotheses.	The study went in depth to describe the different theories that have been proposed as an explanation for the primary and idiopathic BMS etiology.
De Moraes et al. [32]	Systematic review. This study reviews several randomized clinical trials related to BMS treatment strategies.	The paper provided evidence in favor of the effectiveness of therapies and their main side effects with the objective of contributing to better therapeutic management of BMS.
Jääskeläinen [17]	No systematic review. This review recaps the recent neurophysiologic, psychophysical, neuropathological, and brain imaging evidence for neuropathic mechanisms in primary BMS.	The study set forth a thorough neurophysiological, psychophysical and neuropathological BMS approach.
Spanemberg et al. [33]	No systematic review. Different options for the management of BMS patients are proposed. These include etiological and therapeutical ones.	The article focused on BMS etiological and treatment options. In addition to this, it included a table summarizing the BMS placebo treatment.

PATHOGENESIS

The origin of BMS includes a variety of factors. We can divide the possible causes of BMS into local factors [26,30-36], systemic factors [26,37] and psychological factors such as: stress, anxiety and depression [2,12,30,31,37,38]. At times BMS can be directly related to a pathogenic factor that can act in either a local or systemic way. However, there are certain cases of idiopathic stomatodynia in which none of them are shown [39].

According to some authors, BMS is included within the group of diseases categorized by idiopathic orofacial pain [40]. Such disease share the common features that in all cases the pain is continuous, it is chronic for several months, and then it disappears while the patient is sleeping. It is known to be more common in women and it is closely related to psychosocial disorders [11,30].

Local allergic reactions may also have a possible influence on the etiology of BMS. Possible allergens include: allergens from dental materials or materials used in the manufacturing of prosthesis, especially in type III patients [41]. However, throughout the BMS literature there are some authors who do not pay special attention to such factors [42]. There are other agents and/or elements that must also be taken into account, these include: cosmetics, toothpastes and mouthwashes, all of which could provoke the sensation of oral burning and stinging [39].

Some authors consider xerostomia to be one of the most important coexisting causes and they directly relate it to the onset of BMS [43,44]. Systemic factors such as vitamin deficiencies, that can produce significant alterations on the tongue, may also play an important role in the development of burning mouth. Different types of glossitis can appear depending on the deficiencies of riboflavin, nicotinic acid, and

ascorbic acid, and as a result of the alteration in sensitive receptors and, in some degree, to the atrophy of the oral epithelium. Due to all of these factors, the mucosal sensitivity to external agents is increased [45,46]. Diabetes mellitus is frequently accompanied by stomatodynia, which can be produced by two mechanisms: peripheral neuropathy of the sensory nerves of oral mucosa and/or by the degree of xerostomia associated with fungal infection [47].

Although no study has yet demonstrated their direct relationship with burning mouth syndrome [48], it is true that psychological factors play an important role in the onset of BMS [48]. According to some authors, stress is not considered to be a crucial factor in the appearance of BMS symptomatology [48], however the majority of these authors do agree that there is a significant relationship between the existence of psychogenic alterations (such as: anxiety, cancerphobia, and depression) and the manifestation of BMS.

Femiano et al. [2] have shown that patients who suffer from BMS exhibit a decrease in self-esteem, the absence of a solid and satisfactory personality, and they experience significant losses and important changes in their lives before being affected by the syndrome. Patients with BMS, as mentioned by Gao et al. [11], have suffered many unfavorable or negative events throughout their lives, when comparing them to the control-patients. Palacios-Sánchez [49] believes that there is an obvious link between the affective life alteration and the syndrome's onset. Patients who suffer from BMS have proved to have significantly higher levels of anxiety in their lives, as well as higher salivary cortisol levels than those of the control-patients [50].

Disorders of the hormone balance may be related to BMS in women as the disease is more frequent during and after menopause [23,37,51]. Tarkkila et al. [23] evaluated the relation between oral discomfort and menopause in 3173 patients,

verifying that 8% of these women exhibited burning sensations of the oral tissues. However, hormone replacement therapy did not prevent the occurrence of symptoms. In Forabosco et al. [37], symptoms of BMS were found in 46% of women at menopause and approximately 60% showed relief after hormone replacement. The authors attributed the relief of oral discomfort following hormone therapy, to the presence of oestrogen receptors on the oral mucosa.

CLINICAL SIGNS AND DIAGNOSIS

The clinical manifestation of BMS is described by a continual hot, burning and painful sensation that lasts throughout the day. It is a chronic disease that appears at different locations within the oral cavity, all of course in the absence of any type of lesion that could justify the symptoms, as well as any clinical or histological changes [39,52]. Patients tend to complain of a sensation of dry mouth and palate alterations, which include a metallic or bitter taste [24,35].

The tongue is the most common location of BMS manifestation (at the tip and at the lateral edges), together with lips, especially the lower lip [39]. The description of the symptomatology varies depending from patient to patient, although the majority of them describe the symptoms as unbearable and with prolonged evolution. The feeling of discomfort tends to be continuous, or it can be intermittent, and it often worsens throughout the day. Some patients, however, experience days without any symptoms.

It is important for us to consider that the burning sensation can worsen in the presence of specific foods, such as spicy food or acidic fruit, and it can even improve with intake of liquids, salivary stimulants or with certain foods. Many patients notice

an improvement when they consume sweets or chewing gum, since their mouth is normally dry and left with a bad taste, due to the fact that they are taking xerostomia causing drugs (antidepressants, anxiolytics or hypotensive drugs, among others). Additionally, very hot or very cold food can aggravate or improve the BMS related discomfort [39].

BMS is usually sometimes divided into three different types [53]. Both types I and II involve continual daily discomfort. For type III patients, those that experience asymptomatic periods, the main precipitating factor is emotional instability, although the onset of symptoms is also related to the exposure to a possible allergenic factor that triggers a contact allergy [54,55]. This classification can be useful in intuiting the prognosis and, at the same time, it allows us to guide the patients towards the need involve different specialists such as allergologist, psychiatrists and/or psychologists; although patient classification based on those three groups is not always an easy task.

The symptoms affect the patients' quality of life [9,31,52,56,57] and due to the significant emotional component that goes along with BMS, it is advisable that these patients' visits be quiet, one-on-one with the physician, and held in a relaxed environment so that he/she can explain his/her familiar and affective situation. These patients need time and dedication from their medical professional, seeing as they want to be heard and understood. Patient reassurance is paramount [31,57]. BMS patients tend to be characterized by a common profile; this profile is later summarized in Table 2.

Table 2. Profile of patients with burning mouth syndrome.

Most common in middle-aged or elderly women
Characterized by a burning, stinging and/or itching sensation
Patients usually experience a metallic or bitter taste
Oral discomfort is usually chronic and it lasts over time (months or years)
Patients usually experience dry mouth or a sensation of thick saliva
No clinical lesions related to the area of discomfort
Symptoms don't interfere with patients' ability to sleep, although most of them have trouble sleeping or take drugs in order to be able to sleep better
Oral discomfort can be continuous or intermittent and it tends to worsen throughout the day
Symptoms don't worsen while eating or drinking, they can even improve
Patients usually have a history of having visited different specialists and having taken numerous drugs without observing any improvement
They usually have a significant anxious or depressive factor, sometimes accompanied by cancerophobia
Clinical manifestations are usually triggered by psychological stress and they often appear after a dental treatment or a surgical intervention
Sometimes there is a clear beginning is marked, but with no clear trigger
Thanks to internet and social networking websites, many patients can self-diagnose

The sensation of xerostomia or dry mouth is something that the majority of BMS patients experience although, in most of them, it is not possible to demonstrate a significant reduction in salivary flow [39]. More often than not, patients report symptoms of thick and filamentous saliva. There are few unusual cases in which the oral dryness has made food intake difficult. On the other hand, the majority of BMS patients report improvements with respect to their overall discomfort and the burning sensation during food intake.

BMS diagnosis is fundamentally based on clinical signs. It is necessary to correctly examine the patient, discarding the existence of systemic and local factors that could cause such symptoms [39,52,55,57,58]. The administration of a blood test

is also highly recommended. In the case that any deficit should appear, replacement therapy will be initiated, and if in spite of this therapy the symptomatology persists, we at that point face idiopathic BMS, and therefore, we must begin with symptomatic treatment.

TREATMENT

BMS treatment is currently still posing serious problems, since the etiopathogenic factors that produce the onset of the disease, make it difficult to achieve advances in treatment. The main objective of the treatment is to control the various factors that are related to BMS, therefore decreasing the symptoms that are described by the patients.

As mentioned in some studies, topical capsaicin (*Capsicum frutescens L*) can be used to control neuropathic pain, since this drug has an effect on the sensory afferent neurons and also serves as an analgesic [51,59,60]. However, the use of capsaicin has been reduced since it has been proven to evoke an even worse burning sensation at the beginning of the treatment period [59]. It is important to note that there have not been any cases in which this BMS treatment drug has been investigated in placebo-controlled studies.

Medicine such as tricyclic antidepressants, benzodiazepines, and antipsychotic drugs have been researched and are considered to be the three most widely accepted options for the treatment of BMS, despite the fact that they produce hyposalivation and xerostomia. Treatment methods like psychotherapy and psychoactive drugs were prescribed for BMS patients once it was demonstrated that psychological factors play an important role in this disorder [61]. Bergdahl et al. [61] treated BMS patients by means of cognitive behavior therapy once a week for

between 12 and 15 weeks. They were able to observe a decrease in the intensity of the pain immediately after undergoing the therapy and at the six-month follow-up visit.

The use of topical clonazepam proved to be another treatment option for patients suffering from BMS [51,62-64]. Clonazepam is a benzodiazepine that acts as a GABA receptor agonist. Its main property includes the light inhibition of functions of the central nervous system, thus permitting anticonvulsant action, light sedation, muscular relaxation and a calming effect. Gremeau-Richard et al. [62] propose that the action of topical clonazepam has to do with the dysfunctions of the peripheral nervous system that are observed in patients with the syndrome, and the presence of GABA receptors in peripheral tissues. Another study was carried out in which 33 patients were treated with clonazepam tablets, while the other 33 patients were administered a placebo. The symptoms were then assessed after 1 month and 6 months of the treatment period had elapsed. After only 1 month of treatment, 23 of the 33 patients that were treated with clonazepam reported at least a 50% reduction in their symptoms [63]. This drug does not show the adverse effects of its systemic use when it is used topically.

In an uncontrolled study paroxetine, a tricyclic antidepressant, was administered to BMS patients throughout a period of 12 weeks [65]. Of these patients, approximately 80% reported a decrease in their symptoms, with little adverse effects, thus suggesting that paroxetine could be a plausible treatment option for this disorder. Ueda et al. [66] used the antipsychotic drug olanzapine and were therefore able to achieve symptom reduction in two patients that suffered from the syndrome. Olanzapine is classified as a potent antagonist of dopamine, norepinephrine and serotonin neuron receptors. However, in order to confirm the

effectiveness of this drug, and to explain its mechanisms of action, the realization of controlled studies is needed.

A drug that did not show suitable results in the relief of the symptoms of oral burning was trazodone, a drug that is typically used to treat depression. Trazodone is classified as an atypical antidepressant since it stimulates the presynaptic inhibition of serotonin recaptation, blockage of 5-HT2A and 5HT2C serotonin receptors on post-synapse neurons [58].

Hormonal treatments, or those that involve corticosteroids, phytotherapy, vitamins and trace elements, antifungal drugs and sialogogue drugs have also been described throughout the literature as an attempt to reduce the symptoms reported by the patients, although the studies are not always controlled and the patients' clinical symptoms do not always improve.

Because of alpha-lipoic acid's neuroprotective properties, it has been researched with respect to BMS treatment; however, studies involving this drug have presented controversial results. According to Femiano et al. [2], both patients treated with psychotherapy and those who received 200 mg of ALA three times a day throughout a period of two months, demonstrated significant improvement with respect to their symptoms of BMS. The group that was simultaneously treated with ALA and psychotherapy was the group that showed the most remarkable results. According to the researchers, it is necessary to combine psychotherapy with the drugs, the reason for this being that psychogenic alterations are known to have a strong relation to BMS [2]. Carbone et al. [67], López-Jornet et al. [68] and Cavalcanti and Silveira [29] were not able to demonstrate any significant improvement in BMS patients when utilizing alpha-lipoic acid. Both the placebo effect and the different

parameters that were used to calculate the intensity of the symptoms could be the source of possible explanations that account for such conflicting results.

In a controlled study that consisted of 60 patients, the phytotherapeutic drug Catuama®, which is composed of an association of four medicinal herbs, proved to be effective in reducing BMS symptoms in those who suffer from this disorder. The experimental group showed clinical improvement in week 4 and week 8 that was significant when compared to that of the placebo group. After 12 weeks of monitoring, the patients experienced a 51.3% reduction in their symptoms, whereas the reduction of symptoms in the control group was only about 18.8% [69]. There were no cases of toxicity with respect to the use of this medicine. In a previous study, Oliveira et al. [70] researched the chronic adminis tration of Catuama® 25ml, twice a day for 28 days in healthy humans volunteers of both sexes. There were no adverse reactions or relevant hematological and biochemical changes that were presented in the study.

Low power laser radiation therapy has proven to be useful in the reduction of BMS symptoms [71-74]. On the contrary, Vukoja et al. [74] were not able to confirm those results and therefore suggest that the therapeutic benefit of the laser in BMS patients was caused by placebo effect. Santos et al. [72] had 10 BMS patients undergo to a low power laser session (low-level laser therapy - LLLT) once a week over a 10-week span, utilizing the InGaAIP laser diode in continuous mode. A 660 nm wavelength, 40 mW, 20 J/cm2 of dosimetry and a 0.8 J per point in 10 seconds was used. Throughout all of the sessions the intensity of the symptoms was evaluated by using a visual analog scale. Patients reported an improvement after laser treatment, with a reduction of symptoms of up to 58% by the tenth session. On the other hand Kato et al. [71] used the LLLT in 11 patients with BMS at the specific

areas where the patients were experiencing symptoms. The affected areas were irradiated once a week, in a continuous mode, with a 790 wavelength and a dosimetry of 6 J/cm^2. The intensity of the symptoms was verified through VAS at each of the three sessions, as well as six weeks after the treatment was finished. At the end of the study the authors checked that the experimental group did in fact showed a significant improvement in their symptoms as compared to their state at the beginning of the treatment. The patients reported a decrease in the intensity of their symptoms after the laser radiation treatment. This decrease was approximately 80.4%, therefore suggesting that LLLT can be an alternative for BMS.

Low power laser therapy is a non-invasive treatment; it is well tolerated by patients and it is useful in treating sharp and chronic pain [40]. Different studies have investigated the possible adverse effects of laser but they were not significant [75,76].

BMS treatment is usually directed towards symptoms management, but local factors that may play a role in worsening the oral burning sensation should be eliminated [77]. These include: alcohol, spicy foods and acidic drinks due to their irritant effect on the oral mucosa. It is necessary to research if BMS symptoms are caused by parafunctional habits, galvanic currents, mechanical irritation, or a denture allergy [6]. With treatment or ridding of such factors, it has been demonstrated that the clinical symptoms improve [37,77-79]. This disease has a chronic clinical evolution seeing as patients experience alternating periods of exacerbation of the symptomatology, as well as periods of improvement. In some cases, those who suffer from BMS have also described spontaneous remission [77].

The typical BMS patient seeks diagnosis before undergoing any kind of special treatment. Therefore, the medical professional has the obligation of

explaining the nature of BMS and what that implies for the patient. Unfortunately, those who are affected by this disorder must accept that fact and learn to cope with it, and in turn, they must be conscious of that fact that the solution to this disorder may not be found in the short term [27].

CONCLUSIONS

BMS patient management is difficult, and more times than not, a frustrating task. However, it is essential to not only acknowledge the patient but also reassure him/her. The main objective of management is that of providing support to the patient and working towards symptom reduction, rather than total elimination of such symptoms. The complexity of this disease, as well as the ignorance of the mechanisms that cause its onset, are two key topics that need to be further researched. Such insight could enable us to establish effective treatment for this disorder. Finally, it is crucial for us to evaluate the quality of life of those BMS patients, trying to fully comprehend the impact that this condition has on all aspects of their lives.

REFERENCES

1. Danhauer SC, Miller CS, Rhodus NL, Carlson CR. Impact of criteria-based diagnosis of burning mouth syndrome on treatment outcome. *Journal of Orofacial Pain*. 2002; **16**: 305-311.

2. Femiano F, Gombos F, Scully C. Burning Mouth Syndrome: open trial of psychotherapy alone, medication with alpha-lipoic acid (thioctic acid), and combination therapy. *Medicina oral*. 2004; **9**: 8-13.
3. Cherubini K, Maidana JD, Weigert KL, Figueiredo MA. Síndrome da ardência bucal: revisão de cem casos. *Revista Odonto Ciência*. 2005; **20**: 109-113.
4. Brailo V, Vuéiaeeviae-Boras V, Alajbeg IZ, Alajbeg I, Lukenda J, et al. Oral burning symptoms and burning mouth syndrome-significance of different variables in 150 patients. *Medicina oral Patología Oral y Cirugía bucal*. 2006; **11**: E252-E255.
5. Salort-Llorca C, Mínguez-Serra MP, Silvestre FJ. Drug-induced burning mouth syndrome: a new etiological diagnosis. *Medicina oral Patología Oral y Cirugía bucal*. 2008; **13**: E167-E170.
6. Dutrée-Meulenberg RO, Kozel MM, Van Joost T. Burning mouth syndrome: a possible etiologic role for local contact hypersensitivity. *Journal of the American Academy of Dermatology*. 1992; **26**: 935-940.
7. Tourne LP, Fricton JR. Burning mouth syndrome. Critical review and proposed clinical management. *Oral Surgery, Oral Medicine, and Oral Pathology*. 1992; **74**: 158-167.
8. Bergdahl M, Bergdahl J. Burning mouth syndrome: prevalence and associated factors. *Journal of Oral Pathology & Medicine*. 1999; **28**: 350-354.
9. Thoppay JR, De Rossi SS, Ciarrocca KN. Burning mouth syndrome. *Dental Clinics of North America*. 2013; **57**: 497-512.
10. López-Jornet P, Camacho-Alonso F, Andujar-Mateos P, Sánchez-Siles M, Gómez-Garcia F. Burning mouth syndrome: an update. *Medicina oral, Patología Oral y Cirugía bucal*. 2010; **15**: e562-e568.

11. Gao J, Chen L, Zhou J, Peng J. A case-control study on etiological factors involved in patients with burning mouth syndrome. *Journal of Oral Pathology & Medicine*. 2009; **38**: 24-28.
12. Evans RW, Drage LA. Burning mouth syndrome. *Headache*. 2005; **45**: 1079-1081.
13. Beneyto YM, Jornet PL, Nicolás AV, García VJ. Letter to the Editor: Attitudes among Spanish general dentists in relation to burning mouth syndrome: results of a national survey. *Medicina oral*, *Patología Oral y Cirugía bucal*. 2008; **13**: e753-e754.
14. Bergdahl M, Bergdahl J. Low unstimulated salivary flow and subjective oral dryness: association with medication, anxiety, depression, and stress. *Journal of Dental Research*. 2000; **79**: 1652-1658.
15. Soares MS, Chimenos-Küstner E, Subirá-Pifarrè C, Rodríguez de Rivera-Campillo ME, López-López J. Association of burning mouth syndrome with xerostomia and medicines. *Medicina oral*, *Patología Oral y Cirugía bucal*. 2005; **10**: 301-308.
16. Ito M, Kurita K, Ito T, Arao M. Pain threshold and pain recovery after experimental stimulation in patients with burning mouth syndrome. *Psychiatry and Clinical Neurosciences*. 2002; **56**: 161–168.
17. Jääskeläinen SK. Pathophysiology of primary burning mouth syndrome. *Clinical Neurophysiology*. 2012; **123**: 71-77.
18. Sardella A, Carrassi A. BMS: S for syndrome or S for Symptom? A reappraisal of the burning mouth syndrome. *Minerva Stomatologica*. 2001; **50**: 241-246.

19. Lipton JA, Ship JA, Robinson DL. Estimated prevalence and distribution of reported orofacial pain in the United States. *Journal of the American Dental Association*. 1993; **124**: 115-121.

20. Rodrigo MA, Garcia JA. Síndrome de boca ardiente. *Gaceta Dental*. 2000; **104**: 86-88.

21. Silvestre FJ, Bagán JV, Rojo L. Síndrome de boca ardiente: Estudio clínico y biológico. *Rev Actual Odonto Estomatolol Esp*. 1991; **409**: 37-42.

22. Rojo L, Silvestre FJ, Bagán JV, De Vicente T. Prevalence of psychopathology in burning mouth syndrome. *Oral Surgery, Oral Medicine, and Oral Pathology*. 1994; **78**: 312-316.

23. Tarkkila L, Linna M, Tiitinen A, Lindqvist C, Meurman JH. Oral symptoms at menopause-the role of hormone replacement therapy. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics*. 2001; **92**: 276-280.

24. Grushka M, Sessle B. Taste dysfunction in burning mouth syndrome. *Gerodontics*. 1988; **4**: 254-258.

25. Carlson Cr, Miller CS, Reid KL. Psychosocial profiles of patients with burning mouth syndrome. *Journal of Orofacial Pain*. 2000; **14**: 59-64.

26. Balasubramaniam R, Klasser GD, Delcanho R. Separating oral burning from burning mouth syndrome: unravelling a diagnostic enigma. *Australian Dental Journal*. 2009; **54**: 293-299.

27. Minguez-Sanz MP, Salort-Llorca C, Silvestre-Donat FJ. Etiology of burning mouth syndrome: a review and update. *Medicina oral*, *Patología Oral y Cirugía bucal*. 2011; **16**: e144-e148.

28. El-Etr M. Critical commentary 3: steroid dysregulation and stomatodynia (burning mouth syndrome). *Journal of Orofacial Pain*. 2009; **23**: 216-218.

29. Cavalcanti DR, Silveira FRX. Alpha lipoic acid in burning mouth syndrome – a randomized double-blind placebo-controlled Trial. *Journal of Oral Pathology & Medicine*. 2009; **38**: 254–561.

30. Abetz LM, Savage NW. Burning mouth syndrome and psychological disorders. *Australian Dental Journal*. 2009; **54**: 84-93.

31. Mock D, Chugh D. Burning mouth syndrome. *International Journal Of Oral Science*. 2010; **2**: 1-4.

32. de Moraes M, do Amaral Bezerra BA, da Rocha Neto PC, de Oliveira Soares AC, Pinto LP, de Lisboa Lopes Costa A. Randomized trials for the treatment of burning mouth syndrome: an evidence-based review of the literature. *Journal of Oral Pathology & Medicine*. 2012; **41**: 281-287.

33. Spanemberg JC, Cherubini K, de Figueiredo MA, Yurgel LS, Salum FG. Aetiology and therapeutics of burning mouth syndrome: an update. *Gerodontology*. 2012; **29**: 84-89.

34. Klasser GD, Fischer DJ, Epstein JB. Burning mouth syndrome: recognition, understanding, and management. Oral and Maxillofacial Surgery Clinics of North America. 2008; **20**: 255-271.

35. Scala A, Checchi L, Montevecchi M, Marini I, Giamberardino MA. Update on burning mouth syndrome: overview and patient management. Critical Reviews in Oral Biology and Medicine. 2003; **14**: 275-291.

36. Dias Fernandes CS, Salum FG, Bandeira D, Pawlowski J, Luz C. Salivary dehydroepiandrosterone (DHEA) levels in patients with the complaint of

burning mouth: a case-control study. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics*. 2009; **108**: 537-543.

37. Forabosco A, Criscuol M, Coukos G, Uccelli E, Weinstein R, et al. Efficacy of hormone replacement therapy in postmenopausal women with oral discomfort. *Oral Surgery, Oral Medicine, and Oral Pathology*. 1992; **73**: 570-574.
38. Lauria G, Majorana A, Borgna M, Lombardi R, Penza P, et al. Trigeminal small-fiber sensory neuropathy causes burning mouth syndrome. Pain. 2005; **115**: 327-332.
39. Silvestre FJ, Serrano C. El syndrome de boca ardiente: revision de conceptos y puesta al día. *Medicina oral*. 1997; **2**: 30-38.
40. Riley JL, Gilbert GH. Orofacial pain symptoms: an interaction between age and sex. Pain. 2001; **90**: 245-256.
41. Lamey PJ, Lamb AB, Hughes A, Milligan KA, Forsyth A. Type 3 burning mouth syndrome: psychological and allergic aspects. *Journal of Oral Pathology & Medicine*. 1994; **23**: 216-219.
42. Helton J, Storrs F. The burning mouth syndrome: lack of a role for contact urticaria and contact dermatitis. *Journal of the American Academy of Dermatology*. 1994; **31**: 201-205.
43. Tammiala-Salonen T, Söderling E. Protein composition, adhesion, and agglutination properties of saliva in burning mouth syndrome. Scandinavian *Journal of Dental Research*. 1993; **101**: 215-218.
44. Gorsky M, Silverman S Jr, Chinn H. Burning mouth syndrome: a review of 98 cases. *Journal of Oral Medicine*. 1987; **42**: 7–9.

45. Main DM, Basker RM. Patients complaining of a burning mouth. Further experience in clinical assessment and management. *British Dental Journal*. 1983; **154**: 206-211.

46. Schmitt RJ, Sheridan PJ, Rogers RS. Pernicious anemia with associated glossodynia. *Journal of the American Dental Association*. 1988; **117**: 838-840.

47. López-Jornet P, Saura-Inglés A, Martínez-Mondéjar B, Bermejo-Fenoll A. Valoración de la tasa de flujo salival en pacientes con diabetes mellitus tipo 1 y tipo 2. *Archivos de Odontoestomatol*. 1996; **12**: 690-697.

48. Eli I, Kleinhauz M, Baht R, Littner M. Antecedents of burning mouth syndrome (glossodynia)--recent life events vs. psychopathologic aspects. *Journal of Dental Research*. 1994; **73**: 567-572.

49. Palacios-Sanchez MF, Jordana-Comín X, García-Sivoli CE. Burning Mouth Syndrome: A retrospective study of 140 cases in a sample of Catalan population. *Medicina oral*, *Patología Oral y Cirugía bucal*. 2005; **10**: 388-393.

50. Amenábar JM, Pawlowski J, Hilgert J, Hugo FN, Bandeira D, et al. Anxiety and salivary cortisol levels in patients with burning mouth syndrome: case-control study. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics*. 2008; **105**: 460-465.

51. Grushka M, Epstein JB, Gorsky M. Burning mouth syndrome. American Family Physician. 2002; **65**: 615-620.

52. Nasri-Heir C. Burning mouth syndrome. *The Alpha Omegan*. 2012; **105**: 76-81.

53. Lamey PJ, Lewis MAO. Oral medicine in practice: Burning mouth syndrome. *British Dental Journal*. 1989; **167**: 197-200.

54. Lamey PJ, Lamb AB. The usefulness of HAD scale in assesing anxiety and depression in patients with burning mouth syndrome. *Oral Surgery, Oral Medicine, and Oral Pathology*. 1989; **67**: 390-392.

55. Lamey PJ. Burning mouth syndrome. *Dermatologic Clinics*. 1996; **14**: 339-354.

56. Charleston L 4th. Burning mouth syndrome: a review of recent literature. *Current Pain and Headache* Reports. 2013; **17**: 336.

57. Chugh D, Mock D. How do I manage a patient with burning mouth syndrome? *Journal of Canadian Dental Association*. 2013; **79**: d41.

58. Tammiala-Salonen T, Forssell H. Trazodone in burning mouth pain: a placebo-controlled, double-blind study. *Journal of Orofacial Pain*. 1999; **13**: 83-88.

59. Espinosa LS, López JP, Frutos RR. Síndrome de boca ardiente. Eficacia de la aplicación tópica de capsaicina. Estudio Piloto. *Avances en Odontoestomatologia*. 2004; **20**: 297-304.

60. Epstein JB, Marcoe JH. Topical application of capsaicin for treatment of oral neuropathic pain and trigeminal neuralgia. *Oral Surgery, Oral Medicine, and Oral Pathology*. 1994; **77**: 135-140.

61. Bergdahl J, Anneroth G, Perris H. Personality characteristics of patients with resistant burning mouth syndrome. *Acta Odontologica Scandinavica*. 1995; **53**: 7-11.

62. Gremeau-Richard C, Woda A, Navez ML, Attal N, Bouhassira D, et al. Topical clonazepam in stomatodynia: a randomized placebo-controlled study. *Pain*. 2004; **108**: 51-57.

63. Rodríguez de Rivera-Campillo ME, López-López J, Chimenos-Küstner E. Tratamiento del síndrome de boca ardiente con clonacepam tópico. *Piel*. 2011; **26**: 263-268.

64. Rodriguez de Rivera Campillo E, López López J, Chimenos Küstner E. Response to topic Clonazepam in patients with burning mouth syndrome: a clinical study. *Bulletin du Groupèment International Pour la Recherche Scientifique en Stomatologie & Odontologie*. 2010; **49**: 19-29.

65. Yamazaki Y, Hata H, Kitamori S, Onodera M, Kitagawa Y. An open-label, noncomparative, dose escalation pilot study of the effect of paroxetine in treatment of burning mouth syndrome. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics*. 2009; **107**: e6-e11.

66. Ueda N, Kodama Y, Hori H, Umene W, Sugita A, Nakano H, Yoshimura R, Nakamura J. Two cases of burning mouth syndrome treated with olanzapine. *Psychiatry and Clinical Neurosciences*. 2008; 62: 359-361.

67. Carbone M, Pentenero M, Carrozzo M, Ippolito A, Gandolfo S. Lack of efficacy of alpha-lipoic acid in burning mouth syndrome: a double-blind, randomized, placebo-controlled study. *European Journal of Pain*. 2008; **13**: 492-496.

68. López-Jornet P, Camacho-Alonso F, Leon-Espinosa S. Efficacy of alpha lipoic acid in burning mouth syndrome: a randomized, placebo-treatment study. Journal of Oral Rehabilitation. 2009; **36**: 52-55.

69. Spanemberg JC, Cherubini K, de Figueiredo MA, Gomes AP, Campos MM, Salum FG. Effect of an herbal compound for treatment of burning mouth syndrome: randomized, controlled, double-blind clinical trial. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*. 2012; **113**: 373-377.

70. Oliveira CH, Moraes ME, Moraes MO, Bezerra FA, Abib E, De Nucci G. Clinical Toxicology Study of an Herbal Medicinal Extract of Paullinia cupana, Trichilia catigua, Ptychopetalum olacoides and Zingiber officinale (Catuama®) in Healthy Volunteers. *Phytotherapy Research*. 2005; **19**: 54-57.

71. Kato IT, Pellegrini VD, Prates RA, Ribeiro MS, Wetter NU, Sugaya NN. Low-level laser therapy in burning mouth syndrome patients: a pilot study. *Photomedicine and Laser Surgery*. 2010; **28**: 835-839.
72. Santos LF, Carvalho AA, Leão JC, Cruz Perez, Castro JF. Effect of low-level laser therapy in the treatment of burning mouth syndrome: a case series. *Photomedicine and Laser Surgery*. 2011; **29**: 793-796.
73. Yang HW, Huang YF. Treatment of burning mouth syndrome with a low-level energy diode laser. *Photomedicine and Laser Surgery*. 2011; **29**: 123-125.
74. Vukoja D, Alajbeg I, Vučićević Boras V, Brailo V, Alajbeg IZ, Andabak Rogulj A. Is effect of low-level laser therapy in patients with burning mouth syndrome result of a placebo? *Photomedicine and Laser Surgery*. 2011; **29**: 647-648.
75. Moore K. Lasers and pain treatment. *Laser Part Clinix.* 2004; **72**: 1-6.
76. Bjordal JM, Bensadoun RJ, Tunèr J, Frigo L, Gjerde K, Lopes-Martins RA. A systematic review with meta-analysis of the effect of low-level laser therapy (LLLT) in cancer therapy-induced oral mucositis. *Supportive Care in Cancer*. 2011; **19**: 1069-1077.
77. Sun A, Wu KM, Wang YP, Lin HP, Chen HM, Chiang CP. Burning mouth syndrome: a review and update. *Journal of Oral Pathology & Medicine*. 2013; **42**: 649-655.
78. Crow HC, Gonzalez Y. Burning mouth syndrome. *Oral and Maxillofacial Surgery Clinics of North America*. 2013; **25**: 67-76.
79. Rodríguez-de Rivera-Campillo E, López-López J. Evaluation of the res-ponse to treatment and clinical evolution in patients with burning mouth syndrome. *Medicina oral*, *Patología Oral y Cirugía bucal*. 2013; **18**: e403-e410.

ARTIGO DE REVISÃO 2

4 ARTIGO DE REVISÃO 2

LOW LEVEL LASER THERAPY: A REVIEW OF ITS APPLICATIONS IN THE MANAGEMENT OF ORAL MUCOSAL DISORDERS

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LOW LEVEL LASER THERAPY: A REVIEW OF ITS APPLICATIONS IN THE MANAGEMENT OF ORAL MUCOSAL DISORDERS

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ABSTRACT

Due to its analgesic, anti-inflammatory and biostimulating effects, low-level laser therapy (LLLT) has been widely used in oral disorders. The present study has reviewed the literature with emphasis on the applicability and LLLT clinical protocols in the management of oral disorders such as lichen planus, xerostomia, recurrent aphthous stomatitis, herpes labialis, burning mouth syndrome and oral mucositis. In lesions such as oral mucositis, recurrent aphthous stomatitis, herpes labialis and oral lichen planus, the course of wound healing and the pain are decreased, with a few, or most often, no adverse side effects. LLLT can also be effective in reducing the symptoms in patients with BMS. For the treatment of hyposalivation and xerostomia the use of LLLT has been described, but there is no consensus in the literature. There are very few controlled clinical studies with well established therapeutic protocols, except for oral mucositis, where LLLT has been widely researched. Although the use of laser in some lesions has already been consolidated, further research, especially randomized controlled clinical trials with long-term follow-up are needed. These studies will allow the use of LLLT with security, creating care protocols for the management of oral disorders.

Keywords: Oral Medicine. Laser Phototherapy. Low-Level Laser Therapy**.**

INTRODUCTION

Low-level laser radiation is a non-ionizing form of radiation with no mutagenic effects. Low-level laser therapy (LLLT) is a non-invasive treatment that uses light energy in the form of photons, absorbed by cytochromes and porphyrins in the mitochondria [1-3]. There is a temporary release of nitric oxide which increases respiratory rate and cell transcription [4], ATP synthesis stimulus [5] and the formation of oxygen reactive species, with cell activation as a consequence [6,7]. Thus, laser radiation triggers several intracellular ways, promoting regulation of protein and nucleic acid synthesis, modulation of cytokine levels, growth factors and inflammatory mediators, besides stimulus to cell proliferation and differentiation [8].

Some studies have shown analgesic, anti-inflammatory and on tissue repair action of LLLT [3,9-14]. Its anti-inflammatory action is obtained through microcirculation acceleration, which determines alterations in the capillary hydrostatic pressure, with edema absorption and inactivation of intermediary catabolites. LLLT also exerts selective stimulus of the mitochondria, with increased ATP production, resulting in mitosis speed increase, higher glucose consumption by the cells, and higher intracellular calcium levels [15]. Such processes produce cell metabolism increase [16] and, as an indirect effect, blood flow increase [17] and lymphatic drainage [18]. LLLT analgesic action occurs through inhibition of pain mediators and release (by the central nervous system) of endogenous analgesic substances, such as endorphins, making the transmission of the pain stimulus difficult. LLLT increases the cell membrane potential, reducing the speed of the nervous impulse [19].

LLLT has been widely used in oral disorders, such as recurrent aphthous stomatitis (RAS), herpes labialis, xerostomia, burning mouth syndrome (BMS), oral

lichen planus (OLP), oral mucositis (OM), among others [20-22]. Considering the above mentioned, in the present paper the literature has been reviewed in an attempt to investigate the effects of LLLT and clinical protocols used in the management of such oral disorders. Searches were carried out in the MEDLINE - PubMed databases by using the words *"oral lichen planus", "burning mouth syndrome", "recurrent aphthous stomatitis", "herpes labialis", "oral mucositis", "xerostomia"* and *"low-level laser therapy"* in the title and/or abstract. Controlled clinical trial articles published in English were selected. Suitable references from these articles have also been reviewed. In face of the great number of studies on LLLT being used in prevention and treatment of OM, we have opted for including just controlled clinical trials published in the last six years.

RECURRENT APHTHOUS STOMATITIS

The recurrent aphthous stomatitis is one of the most frequent disorders of the oral mucosa and is characterized by single or multiple and relapsing ulcerations [23,24]. The development of RAS involves deregulation in mechanisms of oral mucosal response against exogenous or endogenous antigens [25]. Several factors have been investigated in its etiology, but the mechanism that triggers the development of lesions remains unknown. The treatment consists basically in the suppression/decrease of the local immune response, pain relief, healing in a shorter period of time, as well as prevention of secondary infections [26,27].

According to the selection criteria used, the search for the terms *"recurrent aphthous stomatitis and low-level laser therapy"* yielded seven studies, among them three controlled clinical trials, investigating LLLT effect on RAS. De Souza et al. [28]

compared the effect of LLLT to corticotherapy in patients with RAS. An InGaAlP laser, 670 nm wavelength, 3 J/cm^2, 50 mW, was used in the laser group, in daily sessions on consecutive days. Both treatments were applied until the lesions had disappeared. There was no significant difference in RAS regression time among the groups. Although no statistically significant difference had been noted, 86.60% of the patients who underwent laser treatment reported a reduction in pain in the same session.

Albrektson et al. [29] investigated LLLT effect on the symptoms of patients with minor RAS. A GaAlAs laser was used with the following parameters: 809 nm wavelength, 6.3 J/cm^2, 60 mW, pulse frequency 1800 Hz and 80 seconds. After one session, VAS scores decreased (day 0 until day 3) from 84.7 to 31.5 in the LLLT group and from 81.7 to 76.1 in placebo. LLLT also alleviated the difficulty in drinking, eating, and brushing teeth compared with placebo.

Aggarwall et al. [30] also used LLLT to treat patients with RAS. Each patient presented two lesions, one of the ulcers was randomly allocated to be treated with LLLT and the other was treated with sham LLLT. A diode laser was applied with 810 nm wavelength, 0.5 W. The treatment consisted of one session with each sitting of four low-level laser applications, lasting about 45 seconds each with a gap of about 30-60 seconds between them. The laser beam was applied in a continuous sweeping, so as to cover the entire ulcer surface. Complete resolution of the ulcers in the experimental group was 3.05 ± 1.10 days as compared to 8.90 ± 2.45 days in the sham control group. Immediately, post the LLLT application, complete pain relief was observed in 28 out of the 30 patients in the laser group.

LLLT can decrease healing time, pain intensity, size, and recurrence of the lesion in patients with RAS, and hence can be considered an appropriate treatment modality for this disorder [31].

HERPES LABIALIS

After primary infection by herpes simplex virus (HSV), which can be a symptomatic or not, the individual becomes seropositive for that virus. Same factors, such as stress, anxiety, ultra-violet light exposition, immunosuppression, among others, can activate the virus. At this moment recurrent lesions may happen, developing specially in the edge of the lip vermilion and adjacent skin. The signs and symptoms are uncomfortable and, in many cases, the efficacy of treatment is unproven. Studies have demonstrated good results from the use of LLLT [32].

According to the selection criteria used in the present study, 21 articles with the words *"herpes labialis and low-level laser therapy"* were found, however, only three were controlled studies. Schindl and Neumann [33] observed that LLLT delayed the recurrence of herpetic lesion outbreaks. The effect of LLLT, 690 nm wavelength, 48 J/cm^2, 80 mW/cm^2 was investigated in 50 patients with recurrent perioral herpes simplex infection (at least once per month for 52 weeks) in a randomized, double-blind, placebo-controlled trial. Patients in the laser group received daily irradiations for 2 weeks (10 sessions), whereas patients in the placebo group were sham-irradiated. The median recurrence-free interval in the laser-treated group was 37.5 weeks and in the placebo group was three weeks.

In a randomized clinical trial, de Carvalho et al. [34] compared LLLT with topical acyclovir in prevention and reduction of severity of labial manifestations of

HSV. Seventy-one patients, divided into experimental and control groups were followed-up for 16 months. Patients in the control group were treated topically with acyclovir and patients in the experimental group were subjected to LLLT with diode laser GaAlAs, 780 nm wavelength, 60 mW, 3.0 J/cm^2 or 4.5 J/cm^2, one session per week during 10 weeks, on healthy (no HSV-1 infection) and affected (with HSV-1 infection) tissues, respectively. Patients in the laser group presented a significant decrease in size of herpes labialis lesions and inflammatory edema. The reduction in pain level and monthly recurrences did not differ between acyclovir and LLLT groups.

Muñoz-Sanchez et al. [35] treated 232 patients with HSV-1 using a GaAlAs laser. The patients were consecutively selected for either LLLT or conventional therapy, including acyclovir cream or tablets. Patients in the laser group received 670 nm laser irradiation, 2.04 J/cm^2, 1.6 J, 40 mW, 51 mW/cm^2 in the prodromal and blister stages and 4.8 J in the crust and secondarily infected stages, plus 1.2 J at the C2-C3 vertebrae. Out of 100% of the prodromal stages, 95% of the vesicular ones and 91% of crust stages were able to heal in the first 48 hours. Patients were monitored daily during the first week in order to control healing, and monthly for one year to check on recurrence. LLLT was more effective in reducing the frequency of recurrences when compared with acyclovir.

Donnarumma et al. [36] postulated that laser irradiation acts in the final stage of HSV-1 replication by limiting viral spread from cell to cell and also acts on the host immune response unblocking the suppression of pro-inflammatory mediators, induced by accumulation of progeny virus in infected epithelial cells. LLLT appears to strongly decrease pain and the interval between recurrences without causing any side effects, which make it a promising resource for use with this disorder [37].

LLLT can be used in association with conventional therapy. The treatment of perioral and oral lesions caused by HSV will depend on the stage the lesions are in [38]. The literature is unanimous in showing that the prodomic is the best stage for herpetic lesion treatment. In this initial stage, LLLT can inhibit lesion development [39]. In the pre-vesicular stage, when the region is erythematous and swollen, the intention is to reduce the edema and, consequently, pain. In this case, both infrared and red wavelength can be used. In the vesicular stage, clinicians must initially decontaminate lesions by rupturing the blisters. Only then the red laser can be applied punctually in order to trigger tissue reparation [38].

BURNING MOUTH SYNDROME

The Burning Mouth Syndrome is a complex disorder characterized by burning and itching symptoms in the oral mucosa with no evident clinical alterations [40-41]. Although BMS is a condition of relatively high prevalence in certain population groups, its cause remains unknown. BMS has a multifactorial origin and among the possible causes, local [42], systemic [43,44], neuropathic [45,46] and psychological factors as stress, anxiety and depression [47-49] have been suggested.

Studies have verified that LLLT can be effective in reducing the symptoms in BMS patients, who are able to report such effects soon after therapy [50-52]. However, controlled clinical studies investigating the effect of this kind of therapy in the BMS are still rare. Our research with the words *“burning mouth syndrome and low-level laser therapy”* yielded 18 articles, among which, only one controlled clinical trial.

Vukoja et al. [53] in a controlled study with 40 patients, did not find any improvement in the BMS clinical outcome, suggesting that the LLLT benefit in this disorder is caused by the placebo effect. The patients were irradiated with diode laser, 685 nm wavelength, 2 J/cm^2, 30 mW, frequency 4.56 Hz, five times a week during 2 weeks. Another 20 patients with BMS served as a control group and were treated with sham LLLT.

Studies have shown that BMS can have neuropathic origin [54,55]. López-Jornet et al. [46] suggest that hyperactivity of trigeminal nociceptive pathways can produce an intense response to the action of irritating factors, leading to the occurrence of BMS symptoms. Literature points out that LLLT increases the cell membrane potential, reducing the conduction speed of the nerve impulse and also promoting inhibition of pain mediators such as endorphins, and release of endogenous analgesic substances by the central nervous system [19]. Vukoja et al. [53] may not have found positive results in LLLT use in the management of BMS due to the irradiation parameters used.

ORAL LICHEN PLANUS

Oral lichen planus is a chronic immunologic inflammatory disease of the oral mucosa [56,57]. OLP etiology and pathogenesis have not been totally understood; however, some external and/or internal antigens have been suggested to trigger this disease, and different development mechanisms have also been hypothesized [58]. Since the OLP etiopathogenesis is idiopathic, treatment is usually symptomatic [57]. Topical corticosteroids are the most consistent and effective treatment for the erosive type of oral lichen planus, but there is even the possibility of adverse effects

by short term treatments [59]. In addition, some patients are unresponsive to even systemic corticosteroids.

LLLT has recently been investigated as an alternative or adjunctive treatment modality for OLP, although some researchers dispute its use in that disease. Sixty-seven articles have been found in the database containing the words *"oral lichen planus and low-level laser therapy".* Limiting the search to controlled studies, three articles were selected.

Jajarm et al. [60] evaluated the effect of LLLT on OLP erosive lesions. Thirty patients underwent corticosteroid or laser therapy. The parameters used were: 630 nm wavelength, 1.5 J/cm^2, 10 mW/cm^2, 10 mW, 1 cm² spot size, exposure time 2.5 min. Irradiation was done twice a week (once every third day) for a maximum of 10 sessions. LLLT has shown to be as effective in reducing pain and in clinical improvement as the topical use of dexamethasone.

Dillemburg et al. [61], in a randomized controlled trial, compared the efficacy of LLLT with topical clobetasol propionate 0.05% for the treatment of atrophic and erosive OLP. LLLT was administered with 660 nm, 6 J/cm^2, 0.24 J per point, 40 mW, 1000 mW/cm^2 and 6 seconds exposure time. The irradiation was performed in punctual contact mode with a spot size of 0.04 cm^2. At the end of the treatment (day 30), significant reduction in the symptoms, clinical signs, functional scores and Beck anxiety inventory (BAI) were found in both groups. The LLLT group had a higher percentage of complete lesion resolution. At follow-up periods (days 60 and 90), the LLLT group maintained the clinical pattern seen at day 30, with no recurrence of the lesions, whereas the clobetasol group exhibited worsening for all variables analyzed. LLLT proved more effective than topical clobetasol 0.05% for the treatment of OLP and in preventing its recurrence.

A comparative evaluation of LLLT and CO_2 laser for the treatment of OLP was performed for Agha-Hosseini et al. [62]. In a randomized open clinical trial, 28 patients with 57 lesions were randomly assigned into two groups. One group received CO_2 laser surgical therapy, the other received LLLT with diode laser GaAs, 890 nm wavelength, 0.3-0.5 J/cm^2 for 5 sessions every other day. Improvements in size of lesions, in pain and clinical response scores were achieved in both groups. After 3 months, clinical response showed 100% and 85% improvement in LLLT and CO_2 laser surgery groups, respectively.

The effects of LLLT in pain relief and clinical solution of the erosive and atrophic OLP have been demonstrated in the studies therein described. However, it is important to point out that only cases that fulfil all histopathological criteria for OLP can be treated with LLLT.

HYPOSALIVATION AND XEROSTOMIA

Xerostomia and hyposalivation are salivary dysfunctions, which predispose patients to disorders such as dysgeusia, pain and burning mouth, dysphagia, dysphonia, caries and other oral infectious diseases. Those dysfunctions have a negative impact on quality of life, and can be caused by a number of local and systemic conditions. The use of LLLT for the treatment of hyposalivation and xerostomia has been described in clinical and pre-clinical studies [63-65]. Eighty-seven articles have been found with the words *“hyposalivation, xerostomia and low-level laser therapy”. As* the research was restricted to controlled clinical studies published in English, six articles have been selected.

Loncar et al. [64] verified that LLLT triggered an increase in salivary flow in patients with xerostomia. A pulsed GaAs laser operating at 904 nm, 29.5 J/cm^2, 246 mW/cm^2, 120 seconds, was applied bilaterally on each salivary gland area: extra-orally on the parotid and submandibular gland and intra-orally on the sublingual gland per daily treatment during 10 consecutive days.

Lopes et al. [15] evaluated the effect of LLLT in preserving salivary flow in patients undergoing radiotherapy in the head and neck region. InGaGIP laser was used, 685 nm wavelength, 2J/cm^2, 35 mW, 58 seconds per point. Salivary flow speed was maintained significantly higher in patients who had received LLLT in comparison with controls. Simões et al. [66] have also observed that LLLT was effective in reducing xerostomia and increasing salivary flow, when used in prevention and treatment of OM in patients undergoing radiotherapy in the neck and head. AlGaIP diode laser, 660 nm wavelength, 6 J/cm^2, 40 mW, was used in three weekly sessions.

Oton-Leite et al. [65], in a randomized clinical trial investigated the effect of LLLT on reducing the occurrence and severity of oral complications in 60 patients with head and neck cancer undergoing radiotherapy. The laser group was treated with an InGaAlP laser diode operating at 685 nm, 35 mW, 30 J/cm^2, 0.8 J per point, 25 seconds. Better outcomes were observed in the laser group when compared with the control, indicating lower degrees of oral mucositis, pain and higher salivary flow. Arbabi-Kalati et al. [67] in a randomized double-blind controlled study used LLLT in patients who were undergoing chemotherapy. The application consisted of irradiation with 630 nm, 30 mW, 5 J/cm^2 in 10 spots in the oral mucosa. The results showed that LLLT could decrease the effect of chemotherapy on oral mucositis, xerostomia and pain.

However, when used post head and neck radiotherapy in patients with presence of intense hyposalivation, LLLT did not cause any increase in salivary flow. Saleh et al. [68] evaluated 23 patients with a history of head and neck malignancy. LLLT was applied at least 6 months after radiotherapy, when patients were already showing morphological and functional alterations in the salivary glands. A GaAlAs laser, 830 nm, 71 J/cm^2, 2.0 J,100 mW, 3.57 W/cm^2, 20 seconds, illuminated area 0.028 cm^2 was used punctually in the major salivary glands, twice a week for 6 weeks, with a 12 session total.

There is no consensus in the literature, neither an LLLT established protocol for the management of salivary dysfunctions. Use of high doses of infra-red laser should be considered, due to its greater penetration into the tissues [69].

ORAL MUCOSITIS

Oral mucositis is one of the most frequent and early side effects due to anticancer therapy. Several ulcerations, distribute all over the oral cavity, with bleeding, pain and edema are characteristics of mucositis. There is usually intense pain, swallowing and feeding are compromised, which affects the quality of life of the patient [70].

Most of the studies in LLLT area on oral lesions have been done for preventing and treating oral mucositis. LLLT has shown to be efficient in the management of OM, due to the fact that it accelerates the lesion healing process, and has anti-inflammatory and analgesic action [9-11].

The search for *“oral mucositis and low-level laser therapy”* resulted in 254 articles. When we limited the search to the last 6 years and selected articles only in

English, that number was reduced to 97 studies, out of which, 14 controlled and randomized clinical trials. Table 1 describes the controlled studies that used LLLT in the prevention or treatment of oral mucositis.

LLLT has well defined and documented indications in the literature both in prevention and treatment of that disorder. Regarding OM prevention, studies have shown the effectiveness of daily applications before starting oncological therapy [71,72]. When the lesions are already present, both the infrared wavelength, trying to obtain analgesic effect, and the red wavelength, to speed healing in these lesions, can be used.

Table 1: Controlled trials using LLLT in the prevention or treatment of oral mucositis.

Authors	Laser / Number of patients (n)	LLLT Parameters (reported in the study)	Frequency	Number of sesions	Results
Chor et al., [71]	Diode laser (AsGaAl) n= 34	660 nm, 50 mW, 11 points	Daily	D-7 to D0	The cumulative probability to develop OM and median number of days with OM grade zero (primary endpoint) was minor in the laser group.
Khouri et al., [72]	Diode laser (InGaAlP and AsGaAl) n= 22	660 nm and 780 nm, 25 mW, 6.3 J/cm^2, 10s	Daily. Each day, a type of laser.	Applications performed up to D+15	Laser reduced the frequency and severity of OM, suggesting that LLLT can be used both as a form of prevention and treatment of OM.
Kuhn et al., [14]	Diode laser (AsGaAl) n = 21	830 nm, 100 mW, 4 J/cm^2	Daily	5 sessions	In the laser group, the mean of OM duration was 5.8±2 days and in the placebo was 8.9±2.4 days. LLLT in addition to oral care can decrease the duration of chemotherapy induced OM.
Simões et al., [73]	Diode laser (InGaAlP and AsGaAl) n = 39	G1 and G3: 660 nm, 40 mW, 6 J/cm^2, 6s, 0.24 J, 72 points G2: 808nm, 1 W, 10 J/cm^2, 10s, 1 W/cm², scanning. 0.036 cm^2 for all groups.	G1 3 times a week G2 3 times a week G3 once a week	D 21 after the first RT session to OM became extinct.	There were no differences between the grades of mucositis in function of LLLT protocols. Independently of the protocol employed the grade of OM at the time of the last radiotherapy (RT) session was similar to that recorded at the first LLLT session.
Zanin et al., [74]	Diode laser (InGaAlP) n= 72	660 nm, 30 mW, 2 J, 21 points, 2 mm	Twice a week before or after radiotherapy sessions.	14 sessions	There was an improvement in the quality of life of patients with cancer receiving LLLT in association with radiotherapy and chemotherapy. OM, pain, dysphonia, and dysphagia were minimized with laser therapy.
Carvalho et al, [75]	Diode laser (InGaAlP) n= 70	G1: 660 nm, 15 mW, 3.8 J/cm^2 G2: 660 nm, 5 mW, 1.3 J/cm^2 10s, 0,4 cm^2 for both groups.	Daily (5 times a week)	Starting on the first day of RT until the last day.	The patients in Group 1 reported lower pain levels. LLLT during radiotherapy was found to be effective in controlling the intensity of OM and pain.

Hodgson et al, [76]	LED laser n = 80	670 nm, 50 mW/cm^2, 4 J/cm^2, 80s, 3 extra-oral points, 75 cm^2	Daily	14 sessions	The extra-oral application of led was shown to have a statistically significant reduction in pain, but not for other mucositis scoring scales such as the National Cancer Institute and oral mucositis assessment scales.
Silva et al., [77]	Diode laser (InGaAlP) n= 42	660 nm, 40 mW, 4 J/cm^2, 4s, 0.16J, 12.8J total dose, 10 points, 0.04cm^2	Daily	9 sessions	The results show that laser application reduced the occurrence and intensity of OM when LLLT was performed preventively.
Lima et al., [78]	Diode Laser (AsGaAl) n= 74	660 nm, 10 mW, 2.5 J/cm^2, 10s, 9 points, 0.1 J, 0,4 cm^2	Daily (5 times a week)	30 sessions	No difference was detected between the treatment arms in the incidence of severe pain.
Cunha et al., [79]	Diode laser (InGaAlP and AsGaAl) n = 62	G1: 660 nm, 30 mW, 7,5 J/cm^2 G2: 780 nm + 660 nm, 15 mW, 3.8 J/cm^2 10s, 6 points, 0.04cm^2 for 2 groups	Daily	5 sessions	The association of RT with LLLT in the red region with infrared for the treatment of OM was efficacious in reducing the severity of these lesions and led to improvement in the eating pattern of patients.
Gautam et al, [80]	He-Ne laser n= 121	632.8 nm, 24 mW, 3.5 J/cm^2, 145 s, 0,19 cm^2	Daily (5 times a week)	32 sesions	Incidence of severe OM and its associated pain, opioid analgesic use and total parenteral nutrition was significantly less in LLLT than placebo group patients.
Gautam et al, [81]	He-Ne laser n= 221	632.8 nm, 24 mW, 3 J/cm^2, 3 J point, 36-40 J total dose, 1 cm^2	Daily	45 sessions	There was significant reduction in incidence of severe OM and its associated pain, dysphagia and opioid analgesics use in LLLT than placebo group patients.
Gautam et al, [70]	He–Ne laser n = 220	632.8 nm, 24 mW/cm^2, 145 s, 3J, 36-40 J total dose, 9 points, 1 cm^2	Daily (5 times a week)	32 sessions	Patients reported better well-being and oral functions in the LLLT than the control group. There was a significant difference for the incidence of severe OM. In LLLT group performed fairly well in all the domains of quality of life.
Antunes et al., [82]	Diode laser (InGaAlP) n = 94	660 nm, 100 mW, 4 J/cm^2, 1 J, 10 s, 0,24 cm^2, 9 points	Daily (5 times a week)	15 sessions	A six-fold decrease in the incidence of grades 3-4 OM was detected in the LLLT group. Physical, emotional functioning, fatigue, pain, swallowing, and trouble with social eating showed improvements after treatment.

FINAL CONSIDERATIONS

LLLT has shown to be an excellent option in the prevention and treatment of many oral disorders, which can be used alone or in association with conventional therapy. In lesions such as oral mucositis, recurrent aphthous stomatitis, herpes labialis and oral lichen planus, the course of wound healing and the pain are decreased, with most often, no adverse side effects. Except for oral mucositis OM, there are few randomized and controlled clinical studies available for the other disorders studied. Furthermore, any of these studies do not describe all the irradiation protocols or parameters, this being an important limitation to the advances in the knowledge about LLLT. Thus there is no consensus in the literature regarding the parameters related to the use of LLLT in the oral disorders investigated in this study. Further research, especially randomized controlled clinical trials with long-term follow-up, are needed to give any solid recommendation on the use of laser therapy. These studies will permit the creation of care protocols for the management of various oral disorders.

REFERENCES

1. Karu T (1999) Primary and secondary mechanisms of action of visible to near-IR radiation on cells. J Photochem Photobiol 49(1):1-17.
2. Sutherland JC (2002) Biological effects of polychromatic light. Photochem Photobiol 76(2):164-170.
3. Karu T (1989) Laser biostimulation: a photobiological phenomenon. J Photochem Photobiol 3(4):638-640.

4. Karu TI, Pyatibrat LV, Afanasyeva NI (2005) Cellular effects of low power laser therapy can be mediated by nitric oxide. Lasers Surg Med 36(4):307-314.
5. Borutaite V, Budriunaite A, Brown GC (2000) Reversal of nitric oxide, peroxynitrite- and S-nitrosothiol induced inhibition of mitochondrial respiration or complex I activity by light and thiols. Biochim Biophys 1459(2-3):405-412.
6. Yu W, Naim JO, McGowan M, Ippolito K, Lanzafame RJ (1997) Photomodulation of oxidative metabolism and electron chain enzymes in rat liver mitochondria. Photochem Photobiol 66(6):866-871.
7. Passarella S (1989) He-Ne laser irradiation of isolated mitochondria. J Photochem Photobiol 3(4):642-643.
8. Lubart R, Eichler M, Lavi R, Friedman H, Shainberg A (2005) Low-energy laser irradiation promotes cellular redox activity. Photomed Laser Surg 23(1):3-9.
9. Catão MHCV (2004) The benefits of low intensity laser in oral diseases practice. Rev Bras Patol Oral 3(4):214-218.
10. Sandoval RL, Koga DH, Buloto LS, Suzuki R, Dib LL (2003) Management of chemo- and radiotherapy induced oral mucositis with low-energy laser: initial results of A.C. Camargo Hospital. J Appl Oral Sci 11(4):337-341.
11. Bensadoun RJ, Franquin JC, Cias G, Darcourt V, Schubert MM, Viot M (1999) Low energy He-Ne laser in the prevention of radiationinduced mucositis. A multicenter phase III randomized study in patiens with head and neck cancer. Sup Care Canc 7(4):244-252.
12. Pesevska S, Nakova M, Pejcic A, Ivanovski K, Angelov N, Mindova S (2006) Biostimulative laser therapy: base for favorized and accented results in Dentistry. Acta Fac Med Naiss 23(1):75-78.

13. Abramoff MM, Lopes NN, Lopes LA, Dib LL, Guilherme A, Caran EM, Barreto AD, Lee ML, Petrilli AS (2008) Low-level laser therapy in the prevention and treatment of chemotherapy-induced oral mucositis in young patients. Photomed Laser Surg 26(4):393-400.
14. Kuhn A, Porto FA, Miraglia P, Brunetto AL (2009). low-level infrared laser therapy in chemotherapy-induced oral mucositis. A randomized placebo-controlled trial in children. J Pediatr Hematol Oncol 31(1):33-37.
15. Lopes CO, Mas JR, Zângaro RA (2006) Low-level laser therapy in the prevention of radiotherapy-induced xerostomia and oral mucositis. Radiol Bras 39(2):131-136.
16. Bolton P, Young S, Dyson M (1995) The direct effect of 860 nm light on cell proliferation and on succinic deshydrogenase activity of human fibroblasts in vitro. Laser Ther 7(1):55-60.
17. Kubota J, Ohsiro T (1989) The effects of diode laser low reactive level laser therapy (LLLT) on flap survival in a rat model. Laser Ther 1(3):127.
18. Lievens PC (1991) The effect of I.R. laser irradiation on the vasomotricity of the lymphatic system. Laser Med Sci 6(1):189-191.
19. Pozza DH, Neto NR, Sobrinho JBM, Oliveira MG, Marzola C (2009) Analgesic effect analysis of the laser therapy red laser (660nm) and infrared laser irradiation (830nm) in healthy tissues of the mice. Rev Acad Tirad Odontol 9(5):466-490.
20. Catão MH, Gerby ME, Gonçalves RC (2003) The laser therapy in the treatment of Radiomucositis in patients with squamous cell carcinoma of the soft palate: case report. Laser Dental Show 3(4):8-9.

21. Henriques ACG, Maia AMA, Cimões R, de Castro JFL (2008) The lasertherapy in Dentistry: properties, indications and current aspects. Odontologia Clín Científ 7(3):197-200.
22. Azevedo LR, Magalhães AC, Dias A (2003) The use of lasers in the treatment of oral lesions. JBC 7(42):496-498.
23. Chattopadhyay A, Shetty KV (2011) Recurrent aphthous stomatitis. Otolaryngol Clin North Am 44(1):79-88.
24. Chavan M, Jain H, Diwan N, Khedkar S, Shete A, Durkar S (2012) Recurrent aphthous stomatitis: a review. J Oral Pathol Med 41(8) 577-583.
25. Jurge S, Kuffer R, Scully C, Porter SR (2006) Mucosal disease series. Number VI. Recurrent aphthous stomatitis. Oral Dis 12(1):1-21.
26. Femiano F, Lanza A, Buonaiuto C, Gombos F, Nunziata M, Piccolo S, Cirillo N (2007) Guidelines for diagnosis and management of aphthous stomatitis. Pediat Infect Dis J 26(8):728-732.
27. Scully C, Porter S (2008). Oral mucosal disease: recurrent aphthous stomatitis. Br J Oral Maxillofac Surg 46(3):198-206.
28. De Souza TO, Martins MA, Bussadori SK, Fernandes KP, Tanji EY, Mesquita-Ferrari RA (2010) Clinical evaluation of low-level laser treatment for recurring aphthous stomatitis. Photomed Laser Surg 28(2):S85-88.
29. Albrektson M, Hedström L, Bergh H (2014) Recurren aphthous stomatitis and pain management with low-level laser therapy: a randomized controlled trial. Oral Surg Oral Med Oral Pathol Oral Radiol 117(5):590-594.
30. Aggarwal H, Singh MP, Nahar P, Mathur H, Gv S (2014) Efficacy of low-level laser therapy in treatment of recurrent aphthous ulcers - a sham controlled, split mouth follow up study. J Clin Diagn Res 8(2):218-221.

31. Khademi H, Shirani AM, Nikegbal F (2009) Evaluation of low level laser therapy in recurrent aphthous stomatitis. Shiraz Univ Dent J 10(2):160-162.
32. De Paula Eduardo C, Aranha AC, Simões A, Bello-Silva MS, Ramalho KM, Esteves-Oliveira M, de Freitas PM, Marotti J, Tunér J (2014) Laser treatment of recurrent herpes labialis: a literature review. Lasers Med Sci 29(4):1517-1529.
33. Schindl A, Neuman R (1999) Low-intensity laser therapy is an effective treatment for recurrent herpes simplex infection. Results from a randomized double-blind placebo-controlled study. J Invest Dermatol 113(2): 221-223.
34. De Carvalho RR, de Paula Eduardo F, Ramalho KM, Antunes JL, Bezinelli LM, de Magalhães MH, Pegoretti T, de Freitas PM, de Paula Eduardo C (2010) Effect of laser phototherapy on recurring herpes labialis prevention: an in vivo study. Lasers Med Sci 25(3):397-402.
35. Muñoz-Sanchez PJ, Capote-Femenías JL, Díaz-Tejeda A, Tunér J (2012) The Effect of 670-nm low laser therapy on herpes simplex type 1. Photomed Laser Surg 30(1):37-40.
36. Donnarumma G, De Gregorio V, Fusco A, Farina E, Baroni A, Esposito V, Contaldo M, Petruzzi M, Pannone G, Serpico R (2010) Inhibition of HSV-1 replication of laser diode-irradiation: possible mechanism of action. Int J Immunopathol Pharmacol 23(4);1167-1176.
37. Stona P, da Silva Viana E, Dos Santos Pires L, Blessmann Weber JB, Floriani Kramer P (2014) Recurrent labial herpes simplex in pediatric dentistry: low-level laser therapy as a treatment option. Int J Clin Pediatr Dent 7(2):140-143.
38. Lizarelli RFZ (1996) Low level laser therapy - treatment for herpes labialis. Rev Gaúcha de Odontol 44(5):12-13.

39. Marotti J (2008) Treatment of herpes labialis by photodynamic therapy. Rev Assoc Paul Cir Dent 62(5): 370-373.

40. Komiyama O, Nishimura H, Makiyama Y, Iida T, Obara R, Shinoda M, Kobayashi M, Noma N, Abe O, De Laat A, Kawara M (2013) Group cognitive-behavioral intervention for patients with burning mouth syndrome. J Oral Sci 55(1):17-22.

41. Coculescu EC, Ţovaru Ş, Coculescu BI (2014) Epidemiological and etiological aspects of burning mouth syndrome. J Med Life 7(3):305-309.

42. Scala A, Checchi L, Montevecchi M, Marini I, Giamberardino MA (2003) Update on burning mouth syndrome: overview and patient management. Crit Rev Oral Biol Med 14(4): 275-291.

43. Souza FT, Santos TP, Bernardes VF, Teixeira AL, Kummer AM, Silva TA, Abreu MH (2011) The impact of burning mouth syndrome on health-related quality of life. Health Qual Life Outcomes 9(1):57.

44. Minor JS, Epstein JB (2011) Burning mouth syndrome and secondary oral burning. Otolaryngol Clin North Am 44(1):205-219.

45. Sardella A, Lodi G, Tarozzi M, Varoni E, Franchini RDDS, Carrassi A (2013) Acupuncture and burning mouth syndrome: a pilot study. Pain Pract 13(8):627-632.

46. López-Jornet P, Camacho-Alonso F, Andujar-Mateos P, Sánchez-Siles M, Gómez-Garcia F (2010) Burning mouth syndrome: an update. Med Oral Patol Oral Cir Bucal 15(4):e562-568.

47. Abetz LM, Savage NW (2009) Burning mouth syndrome and psychological disorders. Aust Dent J 54(2): 84-93.

48. Gao J, Chen L, Zhou J, Peng J (2009) A case-control study on etiological factors involved in patients with burning mouth syndrome. J Oral Pathol Med 38(1):24-28.

49. Mínguez-Sanz MP, Salort-Llorca C, Silvestre-Donat FJ (2011) Etiology of burning mouth syndrome: a review and update. Med Oral Patol Oral Cir Bucal 16(2):E144-148.

50. Kato IT, Pellegrini VD, Prates RA, Ribeiro MS, Wetter NU, Sugaya NN (2010) Low-level laser therapy in burning mouth syndrome patients: a pilot study. Photomed Laser Surg 28(6):835-839.

51. Santos LF, Carvalho AA, Leão JC, Cruz Perez, Castro JF (2011) Effect of low-level laser therapy in the treatment of burning mouth syndrome: a case series. Photomed Laser Surg 29(12):793-796.

52. Yang HW, Huang YF (2011) Treatment of burning mouth syndrome with a low-level energy diode laser. Photomed Laser Surg 29(2):123-125.

53. Vukoja D, Alajbeg I, Vučićević Boras V, Brailo V, Alajbeg IZ, Andabak Rogulj A (2011) Is effect of low-level laser therapy in patients with burning mouth syndrome result of a placebo? Photomed Laser Surg 29(9):647-648.

54. Lauria G, Majorana A, Borgna M, Lombardi R, Penza P, Padovani A, Sapelli P (2005) Trigeminal small-fiber sensory neuropathy causes burning mouth syndrome. Pain 115(3): 327-332.

55. Albuquerque RJ, de Leeuw R, Carlson CR, Okeson JP, Miller CS, Anderesen AH (2006) Cerebral activation during thermal stimulation of patients who have burning mouth disorder: An fMRI study. Pain 122(3):223-234.

56. Carbone, M., Arduino, P.G., Carrozzo M., Gandolfo S, Argiolas MR, Bertolusso G, Conrotto D, Pentenero M, Broccoletti R (2009) Course of

oral lichen planus: a retrospective study of 808 northern Italian patients. Oral Dis 15(3):235-243.

57. Cafaro A, Albanese G, Arduino PG, Mario C, Massolin I G, Mozzati M, Broccoletti R (2010) Effect of low-level laser irradiation on unresponsive oral lichen planus: early preliminary results in 13 patients. Photomed Laser Surg 28(2):99-103.

58. Payeras MR, Cherubini K, Figueiredo MA, Salum FG (2013) Oral lichen planus: focus on etiopathogenesis. Arch Oral Biol 58(9):1057-1069.

59. Basirat M (2012) The Effects of the low power lasers in the healing of the oral ulcers. J Lasers Med Sci 3(2):79-83.

60. Jajarm HH, Falaki F, Mahdavi O (2011) A comparative pilot study of low intensity laser versus topical corticosteroids in the treatment of erosive-atrophic oral lichen planus. Photomed Laser Surg 29(6):421-425.

61. Dillenburg CS, Martins MA, Munerato MC, Marques MM, Carrard VC, Sant'Ana Filho M, Castilho RM, Martins MD (2014) Efficacy of laser phototherapy in comparison to topical clobetasol for the treatment of oral lichen planus: a randomized controlled trial. J Biomed Opt 19(6):068002-09. doi: 10.1117/1.JBO.19.6.068002.

62. Agha-Hosseini F, Moslemi E, Mirzaii-Dizgah I (2012) Comparative evaluation of low-level laser and CO2 laser in treatment of patients with oral lichen planus. Int J Oral Maxillofac Surg 41(10):1265-1269.

63. Simões A, Nicolau J, de Souza DN, Ferreira LS, de Paula Eduardo C, Apel C, Gutknecht N (2008) Effect of defocused infrared diode laser on salivary flow rate and some salivary parameters of rats. Clin Oral Invest 12(1):25-30.

64. Lončar B, Stipetić MM, Baričević M, Risović D (2011) The effect of low-level laser therapy on salivary glands in patients with xerostomia. Photomed Laser Surg 29(3):171-175

65. Oton-Leite AF, Elias LS, Morais MO, Pinezi JC, Leles CR, Silva MA, Mendonça EF (2013) Effect of low level laser therapy in the reduction of oral complications in patients with cancer of the head and neck submitted to radiotherapy. Spec Care Dentist 33(6):294-300.

66. Simões A, de Campos L, de Souza DN, de Matos JA, Freitas PM, Nicolau J (2010) Laser phototherapy as topical prophylaxis against radiation-induced xerostomia. Photomed and Laser Surg, 28(3):357-363.

67. Arbabi-Kalati F, Arbabi-Kalati F, Moridi T (2013) Evaluation of the effect of low level laser on prevention of chemotherapy-induced mucositis. Acta Med Iran 51(3): 157-162.

68. Saleh J, Figueiredo MA, Cherubini K, Braga-Filho A, Salum FG (2014) Effect of low-level laser therapy on radiotherapy induced hyposalivation and xerostomia: a pilot study. Photomed Laser Surg 32(10):546-552.

69. Prockt AP, Takahashi A, Pagnoncelli RM (2008) Low level laser therapy use in oral and maxillofacial surgery. Rev Port Estomatol Cir Maxilofac 49(4):247-255.

70. Gautam AP, Fernandes DJ, Vidyasagar MS, Maiya AG, Nigudgi S (2013) Effect of low-level laser therapy on patient reported measures of oral mucositis and quality of life in head and neck cancer patients receiving chemoradiotherapy-a randomized controlled trial. Support Care Cancer 21(5):1421-1428.

71. Chor A, Torres SR, Maiolino A, Nucci M (2010) Low-power laser to prevent oral mucositis in autologous hematopoietic stem cell transplantation. Eur J Haematol 84(2):178-179.

72. Khouri VY, Stracieri ABPL, Rodrigues MC, Moraes DA, Pieroni F, Simões BP, Voltarelli JC (2009) Use of therapeutic laser for prevention and treatment of oral mucositis. Braz Dent J 20(3): 215-220.

73. Simões A, Eduardo FP, Luiz AC, Campos L, Sá PHRN, Faro MC, Marques M, Eduardo CP (2009) Laser phototherapy as topical prophylaxis against head and neck cancer radiotherapy-induced oral mucositis: comparison between low and high/low power lasers. Lasers Surg Med 41(4):264-270.

74. Zanin T, Zanin F, Carvalhosa AA, Castro PH, Pacheco MT, Zanin IC, Brugnera A Jr (2010) Use of 660-nm diode laser in the prevention and treatment of human oral mucositis inducedby radiotherapy and chemotherapy. Photomed Laser Surg 28(2):233-237.

75. Carvalho PA, Jaguar GC, Pellizzon AC, Prado JD, Lopes RN, Alves FA (2011) Evaluation of low-level laser therapy in the prevention and treatment of radiation-induced mucositis: a double-blind randomized study in head and neck cancer patients. Oral Oncol 47(12): 1176-1181

76. Hodgson BD, Margolis DM, Salzman DE, Eastwood D, Tarima S, Williams LD, Sande JE, Vaughan WP, Whelan HT (2012) Amelioration of oral mucositis pain by NASA near-infrared light-emitting diodes in bone marrow transplant patients. Support Care Cancer 20(7):1405-1415.

77. Silva GB, Mendonça EF, Bariani C, Antunes HS, Silva MA (2011) The prevention of induced oral mucositis with low-level laser therapy in bone

marrow transplantation patients: a randomized clinical trial. Photomed Laser Surg 29(1):27-31.

78. Lima AG, Villar RC, de Castro G Jr, Antequera R, Gil E, Rosalmeida MC, Federico MH, Snitcovsky IM. (2012) Oral mucositis prevention by low-level laser therapy in head-and- neck cancer patients undergoing concurrent chemoradiotherapy: a phase III randomized study. Int J Radiat Oncol Biol Phys 82(1):270-275.

79. Cunha CB, Eduardo FP, Zezell DM, Bezinelli LM, Shitara PP, Correa L (2012) Effect of irradiation with red and infrared laser in the treatment of oral mucositis: a pilot study with patients undergoing chemotherapy with 5-FU. Lasers Med Sci 27(6):1233-1240.

80. Gautam AP, Fernandes DJ, Vidyasagar MS, Maiya GA (2012) Low level helium neon laser therapy for chemoradiotherapy induced oral mucositis in oral cancer patients - a randomized controlled trial. Oral Oncol 48(9):893-897.

81. Gautam AP, Fernandes DJ, Vidyasagar MS, Maiya AG, Vadhiraja BM (2012) Low level laser therapy for concurrent chemoradiotherapy induced oral mucositis in head and neck cancer patients - a triple blinded randomized controlled trial. Radiother Oncol 104(3):349-354.

82. Antunes HS, Herchenhorn D, Small IA, Araújo CM, Viégas CM, Cabral E, Rampini MP, Rodrigues PC, Silva TG, Ferreira EM, Dias FL, Ferreira CG (2013) Phase III trial of low-level laser therapy to prevent oral mucositis in head and neck cancer patients treated with concurrent chemoradiation. Radiother Oncol 109(2):297-302.

ARTIGO DE PESQUISA

5 ARTIGO DE PESQUISA

EFFICACY OF LOW-LEVEL LASER THERAPY FOR THE TREATMENT OF BURNING MOUTH SYNDROME: A RANDOMIZED, CONTROLLED TRIAL

Artigo submetido para avaliação (Anexo F)

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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 present study aimed 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 (830nm, 100mW, 5J, 176J/cm^2, 50s, LLLT weekly sessions, 10 sessions); IR3w, n=20 (830nm, 100mW, 5J, 176J/cm^2, 50s, three LLLT weekly sessions, 9 sessions); Red laser, n=19 (685nm, 35mW, 2J, 72J/cm^2, 58s, three LLLT weekly sessions, 9 sessions) and control-group (CG) (Sham LLLT), 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 ANOVA followed by the Tukey test. There was a 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 scores of the IR3w laser group differed significantly from those of the CG. LLLT reduces the symptoms of BMS and may be an alternative therapeutic strategy for this disorder.

Keywords: Burning mouth syndrome. Oral pain. Low-level laser therapy. Laser phototherapy.

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 has a clear predisposition related to sex and age. The disorder rarely occurs before the age of 30 and women are 2.5 to 7 times more frequently affected than men[2]. 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. Apex and sides of the tongue, and 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[10-13]. 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[3,14-16].

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 trying to alleviate the mouth burning symptoms; 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 mitochondrias increasing 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 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 burning mouth syndrome, and investigate the impact of such therapy in the quality of life of these individuals.

MATERIALS AND METHODS

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 patients of both sexes with BMS diagnosis, 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 over 40 years old who reported symptoms of burning or pain in the oral mucosa for at least 6 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 hemogram, serum levels of

glucose, 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.

Low-level Laser Therapy (LLLT)

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 where there was a symptom of BMS. 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:

- *Infrared laser weekly group (IR1w laser group, n=20):* GaAlAs, 830 nm wavelength, 100 mW output power, continuous emissions, 3.57 W/cm², 5 J energy per point, 176 J/cm^2 radiant exposure, application time 50 seconds per point. Patients underwent one LLLT weekly session for ten weeks, total of 10 sessions.
- *Infrared laser 3 times a week group (IR3w laser group, n=20):* GaAlAs, 830 nm wavelength, 100 mW output power, continuous emissions, 3.57 W/cm², 5 J energy per point, 176 J/cm^2 radiant exposure, application time 50 seconds per point. Patients underwent three LLLT weekly sessions for three weeks, total of 9 sessions.
- *Red laser group (n=19):* InGaAlP, 685 nm wavelength, 35 mW output power, continuous emissions, 1.25 W/cm², 2 J energy per point, 72 J/cm^2 radiant

exposure, application time 58 seconds per point. Patients underwent three LLLT weekly sessions for three weeks, total of 9 sessions.

- *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 nm and 685 nm wavelength were used by patient and professional, as required for this laser class.

Measurement of Symptoms

Symptoms were measured using a visual analogue scale (VAS) and a visual numeric scale (VNS) at the initial, after each visit, and 8-week follow-up (Figure 1).

Quality of Life Related to Oral Health (QLROH)

The QLROH was assessed through the Oral Health Impact Profile (OHIP-14) questionnaire, Portuguese language version[26]. This questionnaire indicates the quality of life aspects that are more affected by the oral health state, 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 conditions[27]. OHIP-14 was applied at the initial and at the end of the treatment.

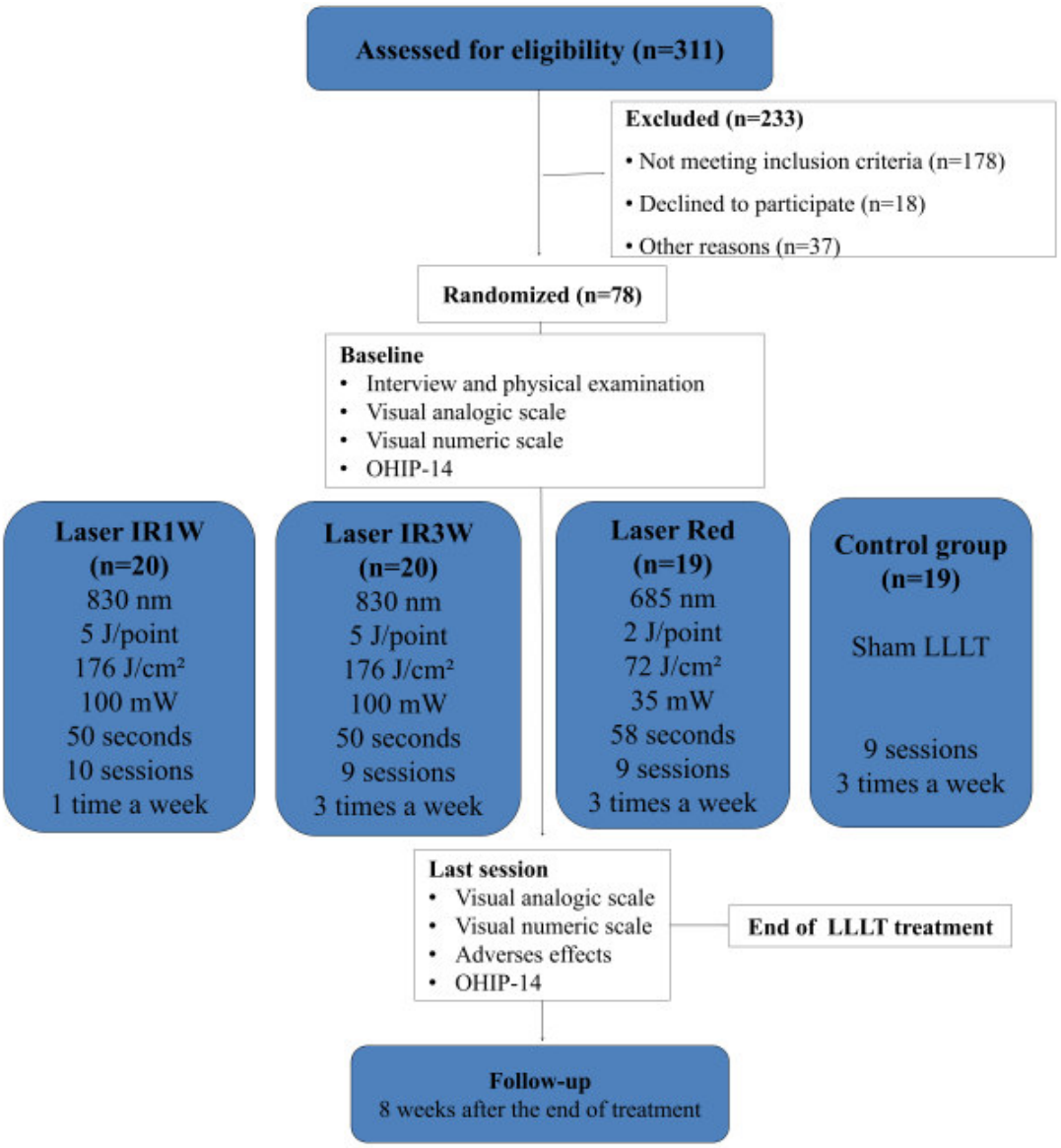

Fig. 1. Flow diagram of phases of the trial.

Statistical Analysis

The data were initially analyzed through descriptive statistics. For the statistical analysis, the VNS and VAS scores, obtained at the initial, immediately after the end of the treatment and 8-week follow-up, were considered. The VNS, VAS and OHIP-14 scores were compared among the four groups using repeated measures analysis

of variance (ANOVA) followed by the Tukey test. The value established for rejecting the null hypothesis was P≤0.05.

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 1 to 3 years. The demographic characteristics and clinical data of the subjects are presented in Table 1.

Table 1. 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	45-79	51-72	48-78	45-75
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%)

The mean scores for VNS and VAS, obtained at initial, at the end of treatment and 8-week follow-up, are presented in Tables 2 and 3, respectively. All the groups have shown significant decrease in symptoms at the end of the treatment, and maintained in the 8-week follow-up. When the initial and 8-week follow-up scores, obtained through VAS, were compared, 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 symptoms 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.

Table 2. Scores of the visual numeric scale (VNS; mean ±SD) of the laser groups and control group obtained at the initial, end of treatment and 8-week follow-up.

Group	Initial	Final	8-week follow-up
Control	$9.00^{Aa} \pm 1.00$	$6.05^{Ab} \pm 1.7$	$6.47^{Ab} \pm 2.31$
IR1w laser	$8.20^{Aa} \pm 1.57$	$3.20^{Bb} \pm 2.52$	$3.75^{Bb} \pm 2.40$
IR3w laser	$8.00^{Aa} \pm 1.33$	$3.00^{Bb} \pm 2.31$	$2.90^{Bb} \pm 2.10$
Red laser	$8.16^{Aa} \pm 1.74$	$4.32^{ABb} \pm 2.68$	$4.42^{ABb} \pm 2.69$

Means followed by different upper-case letters in the columns and means followed by different lower-case letters within the rows differ significantly through the repeated measures ANOVA followed by Tukey test at 5% significance level.

Table 3. Scores of the visual analogic scale (VAS; mean ±SD) of the laser group and control group obtained at the initial, end of treatment and 8-week follow-up.

Group	Initial	Final	8-week follow-up
Control	$85.26^{Aa} \pm 14.25$	$66.37^{Ab} \pm 19.81$	$62.84^{Ab} \pm 26.30$
IR1w laser	$82.15^{Aa} \pm 14.47$	$28.20^{Bb} \pm 27.24$	$32.95^{Bb} \pm 28.92$
IR3w laser	$78.90^{Aa} \pm 15.25$	$30.85^{Bb} \pm 24.08$	$25.90^{Bb} \pm 19.48$
Red laser	$80.68^{Aa} \pm 18.63$	$44.87^{ABb} \pm 28.32$	$41.11^{ABb} \pm 27.14$

Means followed by different upper-case letters in the columns and means followed by different lower-case letters within the rows differ significantly through the repeated measures ANOVA followed by Tukey test at 5% significance level.

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 the initial (Table 4). 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.

Table 4. Oral health impact profile (OHIP-14; mean ±SD) scores for quality of life related to oral health in laser groups and control group in initial and after the end of LLLT sessions.

Group	Initial	Final
Control	17.80 ± 5.37^{Aa}	13.39 ± 3.62^{Ab}
IR1w laser	13.77 ± 7.46^{Aa}	8.54 ± 5.10^{ABb}
IR3w laser	12.87 ± 7.78^{Aa}	6.89 ± 4.05^{Bb}
Red laser	14.46 ± 7.21^{Aa}	9.77 ± 4.92^{ABb}

Means followed by different upper-case letters in the columns and means followed by different lower-case letters within the rows differ significantly through the repeated measures ANOVA followed by Tukey test at 5% significance level.

DISCUSSION

The present study has clinically assessed LLLT effects in the treatment of patients with burning mouth syndrome. Early in the study, the scores of patients had reached about 80% in both pain scales used, showing that those individuals had significant complaints regarding BMS symptoms. Although all the groups had presented reduction in the symptoms in relation to the initial values, the scores of the infrared laser groups (IR1w and IR3w) were significantly lower to 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.

Non-controlled 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.[28], used diode laser, pulse mode, 685 nm emission, five times a week for 2 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 the protocols were different from those used by Vukoja et al.[28], we have not found any significant difference, 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.[28], and observed in control group of the present study. Many BMS patients mention 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 increased cell membrane potential, reducing the nerve impulse conduction velocity[21,29], which could justify the analgesic action of that kind of therapy evidenced in this study. As infrared laser have higher wavelength, it penetrates more deeply into the tissues when compared with red laser, being able to reach the nervous fibers[30-31]. 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 the feeling of burning mouth, characteristic of BMS. Lauria et al.[5], Forssell et al.[32], Albuquerque et al.[6] and Khan et al.[7] also showed that BMS can have neuropathic implications.

Studies have pointed out that BMS can negatively affect the quality of life of the patients[4,33] thus, in this study, the LLLT impact on quality of life related to oral

health has also been assessed. All groups have shown significant decrease in the OHIP-14 scores. This, a decrease in BMS symptoms had a positive impact on the QLROL 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 QLROL.

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, 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 three to ten sessions[22-25,28]. The protocols used in our study aimed at the analgesic effect, once neuropathic factors have been suggested as the cause of BMS. 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 quality of life related to oral health. 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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Conflicts of Interest

The funders had no role in the study design, data collection, data analysis, decision to publish or preparation of the manuscript. There was no industrial funding for the study.

REFERENCES

1. E. C. Coculescu, Ş. Țovaru and B. I. Coculescu, “Epidemiological and etiological aspects of burning mouth syndrome,” *J Med Life*. **7**(3), 305-9 (2014).
2. G. D. Klasser and J. B. Epstein, “Oral burning and burning mouth syndrome,*” J Am Dent Assoc.* **143**(12), 1317-9 (2012).
3. G. E. Gurvits and A. Tan, “Burning mouth syndrome,*” J Gastroenterol.* **19**(5), 665-72 (2013).
4. J. C. Spanemberg et al., “Aetiology and therapeutics of burning mouth syndrome: an update,” *Gerodontology.* **29**(2), 84-9 (2012).
5. G. Lauria et al., “Trigeminal small-fiber sensory neuropathy causes burning mouth syndrome,” *Pain* **115**(3), 327-32 (2005).
6. R. J. Albuquerque et al., “Cerebral activation during thermal stimulation of patients who have burning mouth disorder: An fMRI study,” *Pain* **122**(3), 223-34 (2006).

7. S. A. Khan et al., “Altered structure and function in the hippocampus and medial prefrontal cortex in patients with burning mouth syndrome,” *Pain* **155**(8), 1472-80 (2013).
8. J. H. Meurman, L. Tarkkila and A. Tiitinen, “The menopause and oral health,” *Maturitas* **63**(1), 56–62 (2009).
9. L. Tarkkila et al., “Oral symptoms at menopause-the role of hormone replacement therapy,” *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* **92**(3), 276-80 (2001).
10. J. Gao et al., “A case-control study on etiological factors involved in patients with burning mouth syndrome,” *J Oral Pathol Med*. **38**(1), 24-8 (2009).
11. L. M. Abetz and N. W. Savage, “Burning mouth syndrome and psychological disorders,” *Aust Dent J*. **54**(2), 84-93 (2009).
12. M. Takenoshita et al., “Psychiatric diagnoses in patients with burning mouth syndrome and atypical odontalgia referred from psychiatric to dental facilities,” *Neuropsychiatr Dis Treat*. **13**(6), 699-705 (2010).
13. Y. T. Lee, L. Y. Chen and H. C. Lee., “Psychosomatic consideration to the burning mouth syndrome,” *Psychiatry Clin Neurosci.* **69**(2), 125-6 (2015).
14. P. López-Jornet et al. “*Burning mouth syndrome: an update,” Med Oral Patol Oral Cir Bucal.* **15**(4), 562-8 (2010).
15. Z. Yilmaz et al., “Burning mouth syndrome as a trigeminal small fibre neuropathy: Increased heat and capsaicin receptor TRPV1 in nerve fibres correlates with pain score,” *J Clin Neurosci.* **14**(9), 864-71 (2007).
16. F. Guarneri, C. Guarneri and Marini H., “Contribution of neuroinflammation in burning mouth syndrome: indications from benzodiazepine use,” *Dermatol Ther*. **21**(2), 21-4 (2008).

17. J. C. Spanemberg et al., “Burning Mouth Syndrome: update,” *Oral Health Dent Manag*. **13**(2), 418-24 (2014).

18. C. O. Lopes, J. R. Mas and R. A. Zângaro, “Low-level laser therapy in the prevention of radiotherapy-induced xerostomia and oral mucositis,” *Radiol Bras*. **39**(2), 131-136 (2006).

19. M. M. Abramoff et al., “Low-level laser therapy in the prevention and treatment of chemotherapy-induced oral mucositis in young patients,” *Photomed Laser Surg*. **26**(4), 393-400 (2008).

20. A. Kuhn et al., “Low-level infrared laser therapy in chemotherapy-induced oral mucositis: a randomized placebo-controlled trial in children,” *J Pediatr Hematol Oncol*. **31**(1), 33-7 (2009).

21. D. H. Pozza et al., “Analgesic effect analysis of the laser therapy red laser (660nm) and infrared laser irradiation (830nm) in healthy tissues of the mice,” *Rev Acad Tirad Odontol*. **9**(5), 466-90 (2009).

22. U. Romeo et al., “The low level laser therapy in the management of neurological burning mouth syndrome. A pilot study,” *Ann Stomatol*. **1(**1), 14-8 (2010).

23. I. T. Kato et al., “Low-level laser therapy in burning mouth syndrome patients: a pilot study,” *Photomed Laser Surg*. **28**(6), 835-9 (2010).

24. L. F. Santos et al., “Effect of low-level laser therapy in the treatment of burning mouth syndrome: a case series,” *Photomed Laser Surg.* **29**(12), 793-6 (2011).

25. H. W. Yang and Y. F. Huang., “Treatment of burning mouth syndrome with a low-level energy diode laser,” *Photomed Laser Surg.* **29**(2), 123-5 (2011).

26. B. H. Oliveira and P. Nadanovsky., “Psychometric properties of the Brazilian version of the Oral Health Impact Profile-short form,” *Community Dent. Oral Epidemiol.* **33**(4), 307-14 (2005).

27. K. K. Soe, S. Gelbier and P. G. Robinson., “Reliability and validity of two oral health related quality of life measures in Myanmar adolescents,” *Community Dent Health.* **21**(4), 306-11 (2004).

28. D. Vukoja et al., “Is effect of low-level laser therapy in patients with burning mouth syndrome result of a placebo?” *Photomed Laser Surg.* **29**(9), 647-8 (2011).

29. K. Moore., “Lasers and pain treatment,” *Laser Part Clinix.* **72**, 1-6 (2004).

30. R. C. Patriota., “Laser in dermatology,” *Rev Medic.* **86**(2):64-70 (2007).

31. A. P. Prockt, A. Takahashi and R. M. Pagnoncelli., “Using Laser Therapy Low Level in Oral and Maxillofacial Surgery,” *Rev Port Estomatol Cir Maxilofac* **49**(4), 247-55 (2008).

32. H. Forssell et al., “Sensory dysfunction in burning mouth syndrome,” *Pain*. **99**(1-2), 41-7 (2002).

33. P. López-Jornet, F. Camacho-Alonso and M. Lucero-Berdugo., “Quality of life in patients with burning mouth syndrome,” *J Oral Pathol Med*. **37**(7), 389-94 (2008).

DISCUSSÃO COMPLEMENTAR

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A Síndrome da Ardência Bucal caracteriza-se, principalmente, por sintomas de queimação e ardência na mucosa bucal, na ausência de alterações evidentes ao exame físico[1,2,3,4]. Apesar de ser uma doença cada vez mais frequente em determinados grupos populacionais, sua causa permanece desconhecida e uma etiologia multifatorial com envolvimento de alterações neurológicas, psicológicas e hormonais tem sido proposta[11,21,23,27]. A síndrome pode exercer influência negativa na qualidade de vida dos pacientes[23,28,49], portanto, seu diagnóstico correto e a exclusão de possíveis fatores locais ou sistêmicos que possam estar associados aos sintomas são fundamentais, bem como a busca por novas alternativas terapêuticas.

A LLLT tem se mostrado efetiva para o tratamento de diversas enfermidades da mucosa bucal e objeto de investigação de muitos pesquisadores. No presente estudo, randomizado e controlado, foi investigada a ação de três protocolos de LLLT na sintomatologia de pacientes com SAB. São poucos os relatos na literatura investigando o efeito da LLLT no tratamento da SAB e a maioria destes são séries de casos e estudos não controlados. Os resultados deste estudo demonstraram que todos os grupos laser obtiveram redução significativa dos sintomas ao final do tratamento. Entretanto, somente nos grupos laser em que foi empregado o laser diodo GaAlAs, em um comprimento de onda na faixa de 830 nm, com energia de 5J, a redução dos sintomas foi significativamente superior à observada no grupo-controle. Há evidências científicas, em estudos pré-clínicos e clínicos, da ação analgésica da terapia laser de baixa potência[30-34,36,37,40-44], que ocorre pela inibição dos mediadores álgicos e elevação do potencial de membrana celular, reduzindo a

velocidade de condução do impulso nervoso[44]. Esses efeitos da LLLT justificam a redução dos sintomas observada em pacientes com SAB.

Os lasers de emissão infravermelha possuem maior profundidade de penetração nos tecidos devido a sua baixa absorção na água ou nos pigmentos da pele[50,51]. Esta propriedade permite que a radiação laser alcance estruturas mais profundas como as fibras nervosas, podendo exercer sua ação analgésica e bioestimuladora. Tais evidências justificam a maior efetividade dos protocolos de LLLT no comprimento de onda infravermelho (830 nm) e vão ao encontro de estudos que afirmam que alterações neuropáticas estão fortemente envolvidas na etiologia da SAB[11-16]. Por outro lado, devemos também considerar que o grupo tratado com o laser no comprimento de onda vermelho (685 nm) recebeu dosimetria e energia inferiores e por isso pode não ter apresentado resultados satisfatórios na redução dos sintomas.

O grupo controle, que recebeu *sham* LLLT, tanto ao final do tratamento, quanto no *follow-up* de oito semanas apresentou redução significativa dos sintomas em relação aos escores iniciais. Este efeito placebo promovido pela LLLT foi relatado previamente por Vukoja et al.[52]. Considerando-se a natureza psicológica da SAB, esse efeito placebo já era esperado em função dos pacientes estarem recebendo atendimento e orientações.

Foram contatados 311 pacientes com diagnóstico de SAB, provenientes do Serviço de Estomatologia do Hospital São Lucas PUCRS. Após a seleção inicial, observando-se os fatores de exclusão, setenta e oito indivíduos iniciaram o experimento e não houve desistências durante a terapia. Destes, 85,9% eram do sexo feminino e 14,1% do masculino, com média de idade de 62,82 (±7,54) anos. As características da amostra do presente estudo corroboram os dados da literatura,

que demonstram maior prevalência da doença em pacientes do sexo feminino nas sexta e sétima décadas de vida[4,7,53-56]. A estrutura anatômica acometida com maior frequência foi a língua, sendo o ápice a área mais afetada, indo também ao encontro dos achados de outros autores[5,53,55,57-59]. Os sintomas de xerostomia e de disgeusia são frequentes em pacientes com SAB e podem estar associados às mesmas anormalidades sensoriais que promovem a queimação bucal[59,60]. Neste estudo também foram observados relatos de disgeusia e xerostomia, salientando que nenhum dos pacientes da amostra apresentou hipossalivação.

As escalas visual analógica e visual numérica são escalas de mensuração de sintomas validadas internacionalmente e amplamente utilizadas em pesquisas clínicas[61]. Neste estudo foram utilizados os dois instrumentos de mensuração para verificar se os pacientes seriam coerentes em suas respostas, conferindo maior credibilidade aos resultados. Como a SAB pode afetar a qualidade de vida dos pacientes[49,62], optamos por avaliar também a qualidade de vida relacionada à saúde oral antes e após o tratamento com LLLT. Para tal, utilizamos o instrumento OHIP-14[63] (Anexo G). Em relação aos escores do OHIP-14, o único grupo que diferiu significativamente do controle foi o do laser infravermelho aplicado três vezes por semana. Considerando este dado, podemos sugerir que este protocolo promoveu os melhores resultados no tratamento da SAB.

Uma vez que são escassos os protocolos referidos na literatura para o uso da LLLT na síndrome da ardência bucal, nos baseamos em estudos anteriores[45-48,52] para definir o número e periodicidade de sessões, buscando melhores resultados com essa modalidade de tratamento. Em relação aos efeitos colaterais, o uso do laser de baixa potência é comumente considerado de baixo risco, uma vez observados os cuidados quanto ao manejo dos aparelhos[64-66]. No presente ensaio

clínico, nenhuma reação adversa foi observada nos pacientes durante as sessões de LLLT, corroborando os dados obtidos por Romeo et al.[45], Kato et al.[46], Santos et al.[47] e Yang e Huang[48].

Embora os resultados do presente estudo sejam motivadores, mais pesquisas são necessárias no intuito de buscar novos parâmetros e duração do tratamento com LLLT no manejo da SAB, possibilitando assim protocolos mais eficazes. Nossos resultados demonstram que a LLLT reduz os sintomas da SAB, podendo ser uma alternativa terapêutica sem efeitos adversos, quando comparada às drogas comumente utilizadas no tratamento dessa doença.

CONCLUSÕES

7 CONCLUSÕES

Com base nos resultados obtidos e na metodologia empregada neste estudo, pode-se concluir que:

- Os dois protocolos que aplicaram a LLLT no comprimento de onda infravermelho (830 nm) reduziram os sintomas da SAB, podendo ser uma alternativa para o tratamento dessa doença.
- O protocolo que aplicou a LLLT no comprimento de onda vermelho (685 nm) foi menos efetivo em reduzir a sintomatologia dos pacientes com SAB.
- O protocolo que aplicou a LLLT no comprimento de onda infravermelho (830 nm), três vezes por semana, exerceu impacto positivo na qualidade de vida relacionada à saúde bucal dos pacientes.

REFERÊNCIAS COMPLEMENTARES

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1. Coculescu EC, Ţovaru Ş, Coculescu BI. Epidemiological and etiological aspects of burning mouth syndrome. J Med Life. 2014;7(3):305-9.
2. Maltsman-Tseikhin A, Moricca P, Niv D. Burning mouth syndrome: will better understanding yield better management? Pain Pract. 2007;7(2):151-62.
3. Evans RW, Drage LA. Burning mouth syndrome. Headache. 2005;45(8):1079-81.
4. Soares MS, Chimenos-Küstner E, Subirá-Pifarrè C, Rodríguez de Rivera-Campillo ME, López-López J. Association of burning mouth syndrome with xerostomia and medicines. Med Oral Patol Oral Cir Bucal. 2005;10(4):301-8.
5. Bergdahl M, Bergdahl J. Burning mouth syndrome: prevalence and associated factors. J Oral Pathol Med. 1999; 28(8):350-4.
6. Grushka M, Epstein JB, Gorsky M. Burning mouth syndrome. Am Fam Physician. 2002; 65(4):615-20.
7. Bergdahl M, Bergdahl J. Low unstimulated salivary flow and subjective oral dryness: association with medication, anxiety, depression, and stress. J Dent Res. 2000; 79(9):1652-8.
8. Spanemberg JC, Rodríguez de Rivera Campillo E, Salas EJ, López López J. Burning Mouth Syndrome: update. Oral Health Dent Manag. 2014; 13(2):418-24.
9. Scully C, Felix DH. Oral medicine-update for the dental practitioner orofacial pain. Br Dent J. 2006; 200(2):75-83.
10. Brailo V, Vuéiaeeviae-Boras V, Alajbeg IZ, Alajbeg I, Lukenda J, Aeurkoviae M. Oral burning symptoms and burning mouth syndrome-significance of different variables in 150 patients. Med Oral Patol Oral Cir Bucal. 2006; 11(3):252-5.

11. Lauria G, Majorana A, Borgna M, Lombardi R, Penza P, Padovani A, et al.Trigeminal small-fiber sensory neuropathy causes burning mouth syndrome. Pain. 2005; 115(3): 327-32.
12. Albuquerque RJ, de Leeuw R, Carlson CR, Okeson JP, Miller CS, Anderesen AH. Cerebral activation during thermal stimulation of patients who have burning mouth disorder: An fMRI study. Pain. 2006; 122(3):223–34.
13. Khan SA, Keaser ML, Meiller TF, Seminowicz DA. Altered structure and function in the hippocampus and medial prefrontal cortex in patients with burning mouth syndrome. Pain. 2014 Aug; 155(8):1472-80.
14. Guarneri F, Guarneri C, Marini H. Contribution of neuroinflammation in burning mouth syndrome: indications from benzodiazepine use. Dermatol Ther. 2008; 21(2):21-4.
15. López-Jornet P, Camacho-Alonso F, Andujar-Mateos P, Sánchez-Siles M, Gómez-Garcia F. Burning mouth syndrome: an update. Med Oral Patol Oral Cir Bucal. 2010; 15:e562-8.
16. Yilmaz Z, Renton T, Yiangou Y, Zakrzewska J, Chessell IP, Bountra C et al. Burning mouth syndrome as a trigeminal small fibre neuropathy: Increased heat and capsaicin receptor TRPV1 in nerve fibres correlates with pain score. J Clin Neurosci. 2007; 14(9):864-71.
17. Femiano F, Gombos F, Scully C. Burning Mouth Syndrome: open trial of psychotherapy alone, medication with alpha-lipoic acid (thioctic acid), and combination therapy. Med Oral. 2004; 9(1):8-13.
18. Gao J, Chen L, Zhou J, Peng J. A case-control study on etiological factors involved in patients with burning mouth syndrome. J Oral Pathol Med. 2009; 38(1):24-8.

19. Pokupec-Gruden JS, Cekic-Arambasin A, Gruden V. Psychogenic factors in the aetiology of stomatopyrosis. Coll Antropol. 2000; 24 (1):119-26.
20. Lee YT, Chen LY, Lee HC. Psychosomatic consideration to the burning mouth syndrome. Psychiatry Clin Neurosci. 2015; 69(2):125-6.
21. Abetz LM, Savage NW. Burning mouth syndrome and psychological disorders. Aust Dent J 2009; 54(2):84-93.
22. Takenoshita M, Sato T, Kato Y, Katagiri A, Yoshikawa T, Sato Y, et al. Psychiatric diagnoses in patients with burning mouth syndrome and atypical odontalgia referred from psychiatric to dental facilities. Neuropsychiatr Dis Treat. 2010; 13(6):699-705.
23. Adamo D, Schiavone V, Aria M, Leuci S, Ruoppo E, Dell'Aversana G, et al. Sleep disturbance in patients with burning mouth syndrome: a case-control study. J Orofac Pain. 2013; 27(4):304-13.
24. Palacios-Sanchez MF, Jordana-Comín X, García-Sivoli CE. Burning Mouth Syndrome: A retrospective study of 140 cases in a sample of Catalan population. Med Oral Patol Oral Cir Bucal. 2005; 10(5):388-93.
25. Wardrop RW, Hailes J, Burger H, Reade PC. Oral discomfort at menopause. Oral Surg Oral Med Oral Pathol. 1989; 67(5):535-40.
26. Forabosco A, Criscuolo M, Coukos G, Uccelli E, Weinstein R., Spintato S et al. Efficacy of hormone replacement therapy in postmenopausal women with oral discomfort. Oral Surg Oral Med Oral Pathol. 1992; 73(5):570-81.
27. Meurman JH, Tarkkila L, Tiitinen A. The menopause and oral health. Maturitas. 2009; 63(1): 56-62.

28. Spanemberg JC, Cherubini K, de Figueiredo MA, Yurgel LS, Salum FG. Aetiology and therapeutics of burning mouth syndrome: an update. Gerodontology. 2012; 29(2):84-9.

29. Mínguez-Serra MP, Salort-Llorca C, Silvestre-Donat FJ. Pharmacological treatment of burning mouth syndrome: a review and update. Med Oral Patol Oral Cir Bucal. 2007;12(4):E299-304.

30. Karu T. Laser biostimulation: a photobiological phenomenon. J. Photochem. Photobiol. 1989;3:638-40.

31. Karu T. Primary and secondary mechanisms of action of visible to near-IR radiation on cells. J Photochem Photobiol. 1999; 49:1-17.

32. Sutherland JC. Biological effects of polychromatic light. Photochem Photobiol. 2002; 76:164-70.

33. Sandoval RL, Koga DH, Buloto LS, Suzuki R, Dib LL. Management of chemo- and radiotherapy induced oral mucositis with low-energy laser: initial results of A.C. Camargo Hospital. J Appl Oral Sci. 2003; 11(4):337-41.

34. Bensadoun RJ, Franquin JC, Cias G, Darcourt V, Schubert MM, Viot M et al. Low energy He-Ne laser in the prevention of radiationinduced mucositis. A multicenter phase III randomized study in patiens with head and neck cancer. Sup Care Canc. 1999; 7(4):244-52.

35. Pesevska S, Nakova M, Pejcic A, Ivanovski K, Angelov N, Mindova S. Biostimulative Laser Therapy: base for favorized and accented results in Dentistry. Acta Fac Med Naiss. 2006; 23(1):75-8.

36. Abramoff MM, Lopes NN, Lopes LA, Dib LL, Guilherme A, Caran EM et al. Low-level laser therapy in the prevention and treatment of chemotherapy-induced oral mucositis in young patients. Photomed Laser Surg. 2008; 26(4):393-400.

37. Kuhn A, Porto FA, Miraglia P, Brunetto AL. Low-level Infrared Laser Therapy in Chemotherapy-induced Oral Mucositis A Randomized Placebo-controlled Trial in Children. J Pediatr Hematol Oncol. 2009; 31:33-7.
38. Catão MH, Gerby ME, Gonçalves RC. The laser therapy in the treatment of Radiomucositis in patients with squamous cell carcinoma of the soft palate: case report. Laser Dental Show. 2003; 8-9.
39. Catão MHCV. The benefits of low intensity laser in oral diseases practice. Rev Bras Patol Oral. 2004; 3:214-8.
40. Lopes CO, Mas JR, Zângaro RA. Low-level laser therapy in the prevention of radiotherapy-induced xerostomia and oral mucositis. Radiol Bras. 2006; 39(2):131-6.
41. Bolton P, Young S, Dyson M. The direct effect of 860 nm light on cell proliferation and on succinic deshydrogenase activity of human fibroblasts in vitro. Laser Ther. 1995: 7:55-60.
42. Kubota J, Ohsiro T. The effects of diode Laser low reactive level Laser therapy (LLLT) on flap survival in a rat model. Laser Ther. 1989; 1(3):127.
43. Lievens PC. The effect of I.R. Laser irradiation on the vasomotricity of the lymphatic system. Laser Med. Sci 1991; 6:189-91.
44. Pozza DH, Neto NR, Sobrinho JBM, Oliveira MG, Marzola C. Analgesic effect analysis of the laser therapy red laser (660nm) and infrared laser irradiation (830nm) in healthy tissues of the mice. Rev Acad Tirad Odontol. 2009; 9(5):466-90.
45. Romeo U, Del Vecchio A, Capocci M, Maggiore C, Ripari M. The low-level laser therapy in the management of neurologica burning mouth syndrome. A pilot study. Ann Stomatol (Roma). 2010; 1(1):14-8.

46. Kato IT, Pellegrini VD, Prates RA, Ribeiro MS, Wetter NU, Sugaya NN. Low-level laser therapy in burning mouth syndrome patients: a pilot study. Photomed Laser Surg. 2010; 28(6):835-9.
47. Santos LF, Carvalho AA, Leão JC, Cruz Perez, Castro JF. Effect of low-level laser therapy in the treatment of burning mouth syndrome: a case series. Photomed Laser Surg. 2011; 29(12):793-6.
48. Yang HW, Huang YF. Treatment of burning mouth syndrome with a low-level energy diode laser. Photomed Laser Surg. 2011; 29(2):123-5.
49. Spanemberg JC, Dias AP, Barreiro BOB, Cherubini K, Figueiredo MAZ, Salum FG. Impact of burning mouth syndrome on quality of life. Rev Odonto Cienc. 2012; 27(3):191-95.
50. Basford JR. Low intensity laser therapy: still not an established clinical tool. Lasers Surg Med. 1995; 16:331-42.
51. Kolavora H, Ditrichova D, Wagner J. Penetration of the laser light into the skin in vitro. Lasers Surg Med. 1999; 24(3):231-5.
52. Vukoja D, Alajbeg I, Vučićević Boras V, Brailo V, Alajbeg IZ, Andabak Rogulj A. Is effect of low-level laser therapy in patients with burning mouth syndrome result of a placebo? Photomed Laser Surg. 2011; 29(9):647-8.
53. Eguia-del-valle A, Aguirre-Urizar JM, Martinez-Conde R, Echebarria-Goikouria MA, Sagasta-Pujana OA. Burning mouth syndrome in the Basque country: a preliminary study of 30 cases. Med Oral. 2003; 8(2):84-90.
54. Soto-Araya M, Rojas-Alcayaga G, Esguep A. Association between psychological disorders and the presence of oral lichen planus, burning mouth syndrome and recurrent aphthous stomatitis. Med Oral. 2004; 9(1):1-7.

55. Fernandes CS, Salum FG, Bandeira D, Pawlowski J, Luz C, Cherubini K. Salivary dehydroepiandrosterone (DHEA) levels in patients with the complaint of burning mouth: a case-control study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2009; 108(4):537-43.

56. Neto OG, Diniz IM, Grossmann SM, Abreu MH, do Carmo MA, Aguiar MC. Risk factors in burning mouth syndrome: a case-control study based on patients records. Clin Oral Invest. 2010; 15(4):571-5.

57. Spanemberg JC, Cherubini K, de Figueiredo MA, Gomes AP, Campos MM, Salum FG. Effect of an herbal compound for treatment of burning mouth syndrome: randomized, controlled, double-blind clinical trial. Oral Surg Oral Med Oral Pathol Oral Radiol. 2012; 113(3):373-7.

58. Nasri C, Teixeira MJ, Siqueira JT. Burning mouth: evaluation of a clinical sample. Rev Simbidor. 2000; 1(2):75-82.

59. Rodriguez de Rivera Campillo E, López López J, Chimenos Küstner E. Response to topic Clonazepam in patients with burning mouth syndrome: a clinical study. Bull Group Int Rech Sci Stomatol Odontol. 2010; 49:19-29.

60. White TL, Kent PF, Kurtz DB, Emko P. Effectiveness of gabapentin for treatment of burning mouth syndrome. Arch Otolaryngol Head Neck Surg. 2004; 130(6):786-8.

61. Miguel JP. Pain as the 5th vital sign: systematic recording of pain intensity. Circular Normative 09/DGCG of 6.14. General Ministry of Health 2003. Lisbon.

62. López-Jornet P, Camacho-Alonso F, Lucero-Berdugo M. Quality of life in patients with burning mouth syndrome. J Oral Pathol Med. 2008; 37(7): 389-94.

63. Soe KK, Gelbier S, Robinson PG. Reliability and validity of two oral health related quality of life measures in Myanmar adolescents. Community Dent Health 2004; 21(4):306-11.

64. Garcez AS, Ribeiro MS, Núñez SC. Laser de Baixa Potência. Princípios básicos e aplicações clínicas na Odontologia. Rio de Janeiro: Elsevier, 2012.

65. Brugnera Junior A., Santos AECG, Bologna ED, Ladalardo TCCGP. Atlas de Laserterapia aplicada à clínica odontológica. São Paulo: Santos, 2003.

66. Pansini M. Avaliação de requisitos de segurança em lasers terapêuticos de baixa intensidade. São Paulo. Dissertação [Mestrado em Lasers em Odontologia] - Universidade de São Paulo; 2001.

APÊNDICES

APÊNDICE A

FICHA DE EXAME DOS PACIENTES

DADOS DE IDENTIFICAÇÃO:

Nome:_____
RG:_____
Raça: _____Sexo:_____
Telefone:_____ Celular:_____
Data de nascimento: __ __/__ __/19__ __.

ANAMNESE:

1.História Médica:

_____
_____
_____

2. Medicamentos que faz uso continuamente:

_____
_____
_____

3. Tabagista ( ) Sim ( ) Não
4. Etilista ( ) Sim ( ) Não
5. Climatério ( ) Sim ( ) Não

EXAME FÍSICO:

1. Alterações na Mucosa Bucal:

_____
_____
_____

2. Uso de próteses:
( ) Parcial ( )superior ( ) Inferior
( ) Total ( )superior ( ) Inferior

APÊNDICE B

FICHA DE AVALIAÇÃO DOS SINTOMAS

Nome do paciente:_____

Exame: ( ) Inicial

( ) 1ª sessão ( ) 2ª sessão ( ) 3ª sessão ( ) 4ª sessão ( ) 5ª sessão ( ) 6ª sessão

( ) 7ª sessão ( ) 8ª sessão ( ) 9ª sessão ( ) 10ª sessão ( ) Reavaliação – 2 meses

Data:_____

SINTOMAS

1. Sente a boca seca? ( ) sim ( ) não
2. Sofre de alteração no paladar? ( ) sim ( ) não
3. Quais sintomas apresenta? Há quanto tempo?_____
4. Localização:

( ) Ponta da língua ( ) Dorso da língua ( ) Borda da língua - ( ) E ( ) D

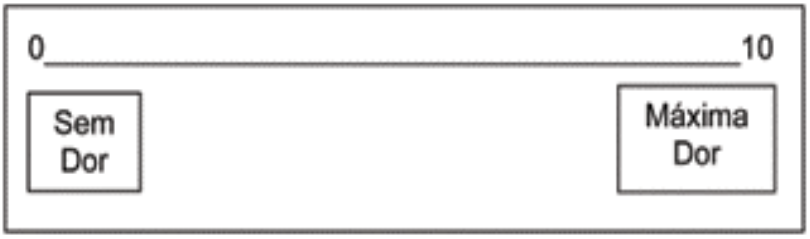
( ) Lábios – ( ) S ( ) I ( ) Mucosa bucal ( ) Palato ( ) Outro:_____

5. Horários de Manifestação:

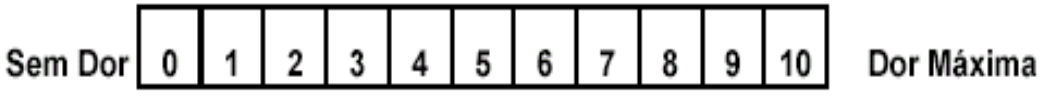
( ) Manhã ( ) Meio-dia ( ) Tarde ( ) Noite

6. Apresenta os sintomas todos os dias? ( ) sim ( ) não
7. Tipo de SAB: ( )Tipo I ( )Tipo II ( )Tipo III

ESCALA VISUAL ANALÓGICA



ESCALA VISUAL NUMÉRICA



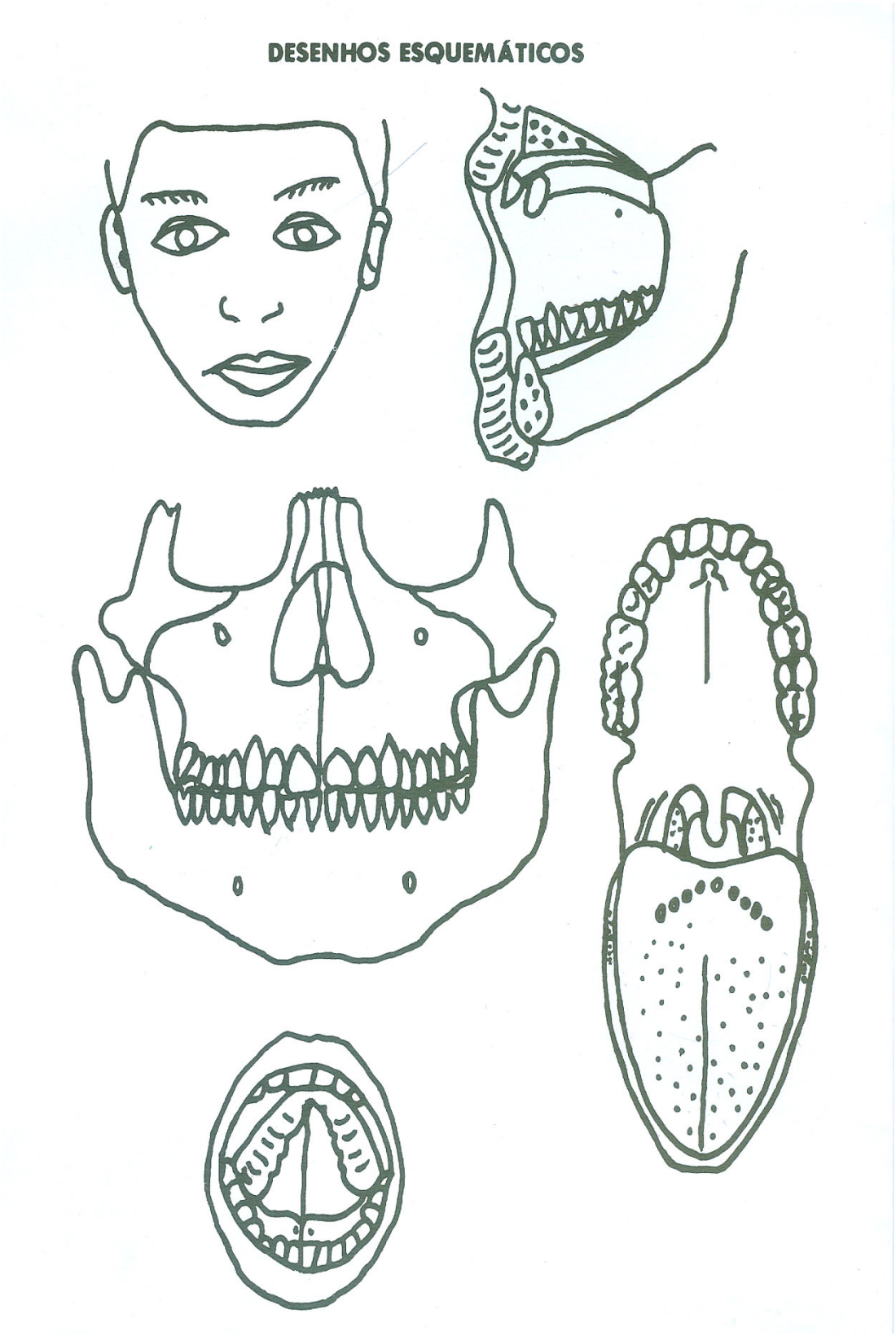
Após o início do tratamento:
Tolerou bem a terapia a laser? ( ) sim ( ) não

Alguma alteração foi observada após a aplicação do laser?

_____
_____

APÊNDICE C

FICHA DE AVALIAÇÃO DOS SINTOMAS (verso)



ANEXOS

ANEXO A

APROVAÇÃO DO PROJETO NA COMISSÃO CIENTÍFICA E DE ÉTICA DA FO-PUCRS

Comissão Científica e de Ética
Faculdade da Odontologia da PUCRS

Porto Alegre 08 de agosto de 2012

O Projeto de: Tese

Protocolado sob nº:	0038/12
Intitulado:	Efeito da radiação laser de baixa potência no tratamento da síndrome da ardência bucal: ensaio clínico, randomizado, duplo-cego, placebo-controlado.
Pesquisador Responsável:	Profa. Dra. Fernanda Gonçalves Salum
Pesquisadores Associados:	Juliana Cassol Spanemberg
Nível:	Tese / Doutorado

Foi ***aprovado*** pela Comissão Científica e de Ética da Faculdade de Odontologia da PUCRS em *08 de agosto de 2012.*

Este projeto deverá ser imediatamente encaminhado ao CEP/PUCRS.

Profa. Dra. Ana Maria Spohr
Coordenadora da Comissão Científica e de Ética da
Faculdade de Odontologia da PUCRS

Av. Ipiranga, 6681, Prédio 06 sala 210
Porto Alegre /RS – Brasil – Cx. Postal: 1429
90619-900
Fone/Fax: (51) 3320-3538
e-mail: odontologia-pg@pucrs.br

ANEXO B

APROVAÇÃO DO PROJETO NO

COMITÊ DE ÉTICA EM PESQUISA DA PUCRS

PONTIFÍCIA UNIVERSIDADE CATÓLICA DO RIO GRANDE DO SUL - PUC/RS

Plataforma Brasil

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: EFEITO DA RADIAÇÃO LASER DE BAIXA POTÊNCIA NO TRATAMENTO DA SÍNDROME DA ARDÊNCIA BUCAL: ENSAIO CLÍNICO, RANDOMIZADO, DUPLO-CEGO, PLACEBO-CONTROLADO

Pesquisador: Fernanda Gonçalves Salum

Área Temática: Área 3. Fármacos, medicamentos, vacinas e testes diagnósticos novos (fases I, II e III) ou não registrados no país (ainda que fase IV), ou quando a pesquisa for referente a seu uso com modalidades, indicações, doses ou vias de administração diferentes daquelas estabelecidas, incluindo seu emprego em combinações.

Versão: 2

CAAE: 06948012.0.0000.5336

Instituição Proponente: Pontifícia Universidade Católica do Rio Grande do Sul - PUC/RS

DADOS DO PARECER

Número do Parecer: 147.581

Data da Relatoria: 09/10/2012

Apresentação do Projeto:

A Síndrome da Ardência Bucal é uma doença complexa que se caracteriza por sintomas de ardência e queimação na mucosa bucal sem alterações clínicas evidentes durante o exame físico do paciente. Essa doença pode ter um impacto negativo sobre o bem-estar geral dos pacientes e afetar a qualidade de vida dos mesmos. Como a etiologia da SAB ainda é desconhecida, não há um protocolo terapêutico definido na literatura e a cura desta doença inexiste. A conduta nesses casos é o esclarecimento dos pacientes a fim de tranquilizá-los de que não se trata de uma doença grave e de que não há riscos a sua saúde física. Todos os

pacientes receberão este esclarecimento. Dessa forma, o uso do placebo no estudo não os prejudicará em nenhum momento e não haverá negligência no tratamento dos mesmos. Caso, através desta pesquisa, haja confirmação da eficácia da laserterapia no tratamento dos pacientes com SAB, os indivíduos que fizeram parte do grupo placebo serão chamados para nova avaliação e laserterapia.

Objetivo da Pesquisa:

O presente estudo, randomizado, duplo-cego, placebo-controlado, tem como objetivo avaliar clinicamente o efeito do uso da radiação laser de diodo de baixa potência no tratamento da

Endereço: Av.Ipiranga, 6681
Bairro: **CEP:** 90.619-900
UF: RS **Município:** PORTO ALEGRE
Telefone: (513)320--3345 **Fax:** (513)320--3345 **E-mail:** cep@pucrs.br

PONTIFÍCIA UNIVERSIDADE CATÓLICA DO RIO GRANDE DO SUL - PUC/RS

sintomatologia de pacientes com a Síndrome da Ardência Bucal e avaliar se essa terapia promove variação na qualidade de vida dos pacientes.

Avaliação dos Riscos e Benefícios:

Nenhum risco.

Uma alternativa de tratamento pode ser oferecida para o manejo de pacientes com a Síndrome da Ardência Bucal.

Comentários e Considerações sobre a Pesquisa:

Se a eficácia da terapia com laser de baixa potência no tratamento da Síndrome da Ardência Bucal for comprovada será possível melhorar a qualidade de vida do pacientes.

Considerações sobre os Termos de apresentação obrigatória:

O protocolo apresentou adequadamente a documentação.

Recomendações:

O projeto está bem estruturado e a pesquisa é relevante.

Para evitar vies na pesquisa deve ser realizado um rigoso controle das fontes de variabilidade entre os dois grupos, embora haja randomização do processo. Uma alternativa pode ser o uso da ANOVA fatorial supondo como covariaveis as condições basais das variáveis investigadas.

Conclusões ou Pendências e Lista de Inadequações:

Protocolo já aprovado anteriormente.

A emenda apresentada está adequada.

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

Considerações Finais a critério do CEP:

PORTO ALEGRE, 16 de Novembro de 2012

Assinador por:
Rodolfo Herberto Schneider
(Coordenador)

Endereço: Av.Ipiranga, 6681
Bairro: **CEP:** 90.619-900
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ANEXO C

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

AOS VOLUNTÁRIOS DA PESQUISA

(Resolução CNS/MS 196/96)

Projeto

EFEITO DO LASER DE BAIXA POTÊNCIA

NO TRATAMENTO DA SÍNDROME DA ARDÊNCIA BUCAL:

ENSAIO CLÍNICO, RANDOMIZADO, PLACEBO-CONTROLADO

O senhor(a) está sendo convidado(a) a participar deste estudo por apresentar os sintomas da Síndrome da Ardência Bucal (SAB). Esta doença caracteriza-se por sintomas de queimação e ardência bucal, sem que alterações sejam observadas em sua mucosa quando lhe examinamos. É importante que leia estas informações sobre o estudo e o seu papel nesta pesquisa. **Deixamos claro que a sua participação não é obrigatória.** A qualquer momento você pode desistir de participar e retirar seu consentimento sem qualquer restrição.

O presente estudo tem como objetivo avaliar clinicamente o efeito do uso do laser diodo de baixa potência (Thera Lase, DMC Equipamentos Ltda. São Carlos, São Paulo, Brasil) no tratamento de indivíduos com a Síndrome da Ardência Bucal.

Se o senhor(a) concordar em participar deste estudo, será submetido a um exame clínico e nos descreverá a intensidade dos seus sintomas. Também será convidado a realizar um exame de coleta de saliva para verificarmos a quantidade de saliva produzida. Antes do início do tratamento, o senhor(a) necessitará realizar exames de sangue: hemograma, contagem de plaquetas, concentrações séricas de glicose, ferro, ácido fólico e vitamina $B_{12,}$ propostos como protocolo de diagnóstico para esta doença.

A participação no estudo inclui uma série de atendimentos ambulatoriais para avaliação e aplicação do laser de baixa potência nos locais em que o senhor (a) apresenta sintomatologia (ardência, queimação, dor) durante 10 semanas (uma sessão por semana). Todos os pacientes serão examinados antes do início do experimento e 8 semanas após. Qualquer efeito colateral observado pelo senhor(a) deve ser imediatamente informado aos pesquisadores pelos telefones aqui referidos.

O senhor (a) deve manter a mucosa hidratada por meio da ingestão de líquidos e evitar o uso de alimentos condimentados e bebidas com teor ácido que atuam como irritantes da mucosa bucal. Além disso, deve evitar fumar e ingerir bebidas alcoólicas.

Pelo presente Termo de Consentimento, declaro que fui esclarecido, de forma detalhada, livre de qualquer constrangimento e obrigação, dos procedimentos a que serei submetido, eventuais desconfortos e benefícios do presente projeto de pesquisa, todos acima citados.

Fui igualmente informado:

- da garantia de receber resposta a qualquer pergunta ou esclarecimento a qualquer dúvida acerca dos procedimentos, benefícios e outros assuntos relacionados com a pesquisa;
- da liberdade de retirar meu consentimento a qualquer momento, e deixar de participar do estudo, sem que isto traga prejuízo à continuação do meu acompanhamento e tratamento;
- da segurança que não serei identificado, e que se manterá o caráter confidencial das informações relacionadas com a minha privacidade;
- do compromisso de fornecer informação atualizada durante o estudo;

Eu, _____, declaro que, após ler as informações acima e estar suficientemente esclarecido(a) estou plenamente de acordo com a realização do estudo. Assim, autorizo minha participação neste estudo.

ASSINATURA: _____.
Data:_____.
R.G:_____.
FONE:_____.

O pesquisador responsável por esse projeto é a Profª. Drª. Fernanda Gonçalves Salum, tendo este documento sido revisado e aprovado pelo Comitê de Ética em Pesquisa da Faculdade de Odontologia e da Pontifícia Universidade Católica do Rio Grande do Sul em __/__ /__ .

Para qualquer esclarecimento ou dúvidas, antes e durante a pesquisa, entre em contato com a pesquisadora responsável Profª. Drª. Fernanda Gonçalves Salum (51) 8182-9945 ou com a Doutoranda Juliana Cassol Spanemberg (51) 8498-8370. Comitê de Ética em Pesquisa (51) 3320-3345.

Pesquisador: _____.

Testemunha: _____.

ANEXO D

ARTIGO PUBLICADO NO PERIÓDICO
ORAL HEALTH AND DENTAL MANAGEMENT

Burning Mouth Syndrome: Update

Juliana Cassol Spanemberg[1], Eugenia Rodríguez de Rivera Cámpillo[2], Enric Jané Salas[2], José López López[3]

[1]PhD Student, Stomatology and Bucomaxilofacial Cancer Prevention Division, São Lucas Hospital, Pontifical Catholical University of Rio Grande do Sul (PUCRS), Porto Alegre, Brazil. [2]Professor of Oral Pathology, School of Dentistry, University of Barcelona, Spain. [3]Department of Odontoestomatology - School of Dentistry, Pabellón de Gobierno, C/Feixa LLarga s/n 08907 L'Hospitalet de Llobregat. Barcelona, Spain.

Abstract

Burning Mouth Syndrome (BMS) is a chronic disorder that predominately affects middle-aged women in the postmenopausal period. The condition is distinguished by burning symptoms of the oral mucosa and the absence of any clinical signs. The etiology of BMS is complex and it includes a variety of factors. Local, systemic and psychological factors such as stress, anxiety and depression are listed among the possible causes of BMS. BMS may sometimes be classified as BMS Type I, II or III. Although this syndrome is not accompanied by evident organic alterations and it does not present health risks, it can significantly reduce the patient's quality of life. This study analyzes the available literature related to BMS, and makes special reference to its therapeutic management. The pages that follow will also discuss the diagnostic criteria that should be respected, etiological factors, and clinical aspects. We used the PubMed database and searched it by using the keywords "burning mouth syndrome", "BMS and review", and "burning mouth and review", in the title or abstract of the publication. BMS treatment usually steers towards the management of the symptoms; however, the specific local factors that could play a significant role in worsening the oral burning sensation should be eradicated. The most widely accepted treatment options that show variable results include tricyclic antidepressants, benzodiazepines and antipsychotic drugs; nevertheless there are other therapies that can also be carried out. Professionals that work in the field of dentistry should formulate standardized symptomatic and diagnostic criteria in order to more easily identify the most effective and reliable strategies in BMS treatment through multidisciplinary research.

Key Words: Burning mouth syndrome, Etiology, Diagnosis, Treatment

Introduction

Burning Mouth Syndrome (BMS) is distinguished by burning, pain, or symptoms of itching in oral mucosa, which arise without the presence of any changes in physical examinations, laboratory analysis, or salivary flow rates [1-5]. This condition tends to appear in middle-aged and elderly women [6-9]. The International Association for the Study of Pain defines BMS as a pain that lasts for at least 4-6 months of duration and which is located on tongue or in other mucosal membranes and that is presented in the absence of any clinical and/or laboratory findings. The terms "glossodynia" (painful tongue) and "glossopyrosis" (burning tongue), as well as "glossalgia", describe the phenomenon present in this disorder with respect to the most affected area, the tongue (especially the tip and lateral borders). Other terms such as "stomatodynia", "stomatopyrosis", "oral dysesthesia", and "burning mouth syndrome" are used to define this condition [10]. Although percentages in research findings may vary between .07% and 15%, we can state that this disease is highly prevalent [11].

The episodes of a burning sensation are described as being spontaneous and the symptoms that patients experience range in severity; some patients suffer from a moderate burn, while others experience intolerable pain [3,12]. Other changes in sensitivity are known to take place, besides oral stinging, which include: a feeling of dryness in the mouth [13-15] or gustative alterations, such as the perception of a bitter or metallic taste [16]. In certain instances dysesthesia in the mouth might also occur, which is characterized by the feeling of having sand in the mouth or swelling of the mouth [12,16,17].

The lack of unified criteria makes the diagnosis even more complicated, and consequently, epidemiological information can differ depending on the researcher who analyzes it [18,19]. Within the risk group of postmenopausal-women, the prevalence of this disorder ranges between 18% and 33% [20]. The majority of research conducted shows an evident predominance that women have over men, ranging between 3-1 and 9-1 for the female sex [21-24]. According to most of the authors, the typical average age of patients of BMS is from 50 to 60 years old, however, it can also arise in patients close to their thirties, but not in children or in teenagers.

The true cause BMS remains unknown. Although this syndrome is not accompanied by evident organic alterations and it does not present health risks, it can significantly reduce the patient's quality of life. BMS patients tend to have a history of frequent medical and dental visits with the objective of obtaining a cure that does not yet exist. Experts currently debate whether the psychological alterations that BMS patients experience are the cause or the consequence of such chronic pain [25-27]. The patient profile is rather specific and is comprised of the following personal characteristics: age range between 50 and 60, a history of prolonged suffering from chronic pain, and a history of having been treated by many different specialists without obtaining any solution to the problem. It is also often accompanied by a significant emotional profile and is usually related to cancerophobia [28].

Diligent clinical investigation fails to accurately identify the cause for the burning sensation in patients with true burning mouth syndrome. Specific criteria should be observed, since

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symptoms of oral burning are common and can be caused by either local or systemic factors, which do not describe true BMS [15-17,28]. The clinical or laboratorial conditions associated with burning mouth include candidiasis, geographic tongue, hyposalivation, esophagic reflux, parafunctional habits, diabetes, nutritional deficiencies (iron, folate, B_1, B_2, B_6, B_{12}), and adverse effects of certain drugs. In such cases, if the cause of this disorder is eliminated, the patient will therefore experience symptom relief [29].

This study analyzes the available literature related to BMS, and makes special reference to its therapeutic management. Other important topics of discussion throughout this article also include the diagnostic criteria that should be followed, etiological factors, and clinical aspects of the disease.

A search in the PubMed database was performed in order to identify articles published in the last five years using the key words: "burning mouth syndrome", "BMS and review", and "burning mouth and review". This search resulted in 259 articles. When we limited the search to articles published in the English language, we found 6 non-systematic reviews and one systematic review that we considered particularly relevant (*Table 1*)".

The objective of this article was to perform a literature review on BMS based on three main sections: pathogenesis, diagnosis, and treatment, with a special focus on the latter.

Pathogenesis

The origin of BMS includes a variety of factors. We can divide the possible causes of BMS into local factors [26,30-36], systemic factors [26,37] and psychological factors such as: stress, anxiety and depression [2,12,30,31,37,38]. At times BMS can be directly related to a pathogenic factor that can act in either a local or systemic way. However, there are certain cases of idiopathic stomatodynia in which none of them are shown [39].

According to some authors, BMS is included within the group of diseases categorized by idiopathic orofacial pain [40]. Such disease share the common features that in all cases the pain is continuous, it is chronic for several months, and then it disappears while the patient is sleeping. It is known to be more common in women and it is closely related to psychosocial disorders [11,30].

Local allergic reactions may also have a possible influence on the etiology of BMS. Possible allergens include: allergens from dental materials or materials used in the manufacturing of prosthesis, especially in type III patients [41]. However, throughout the BMS literature there are some authors who do not pay special attention to such factors [42]. There are other agents and/or elements that must also be taken into account, these include: cosmetics, toothpastes and mouthwashes, all of which could provoke the sensation of oral burning and stinging [39].

Table 1. *Most significant conclusions from the articles.*

Article	Aspects from the review	Most relevant conclusions
Abetz and Savage [32]	No systematic review. This publication serves as a review of BMS' clinical presentation and focuses on contributing factors in the initial presentation of the condition, as well as its advancement.	A number of useful clinical indicators were proposed in this paper, these indicators or signs may prove to be helpful for both clinical assessment and subsequent patient discussions, seeing as they provide visible supportive evidence for the diagnosis. The main focal point of the article was the role of psychological disorders in the etiology of BMS, in addition to a presentation that highlighted the clinical management of patients.
Balasubramaniam et al. [16]	No systematic review. The article reviews different conditions and diseases that may be possible causes of oral burning.	The article provided knowledge about the local, systemic and psychosocial factors that can cause the onset of oral burning, which is associated with secondary BMS.
López-Jornet et al. [9]	No systematic review. The article reviews some recent studies related to BMS literature, especially those having to do with etiological factors that could be involved, clinical aspects, diagnostic criteria and therapeutic management.	The article included tables that helped to guide us through the clinical factors, diagnosis and treatment of burning mouth syndrome. It made the suggestion of the inclusion and exclusion protocols based on suggestions made throughout other literary sources.
Minguez-Sanz et al. [29]	No systematic review. The article describes different hypotheses relating to BMS etiology, as well as the psychological and anatomical data that serve as the basis for such hypotheses.	The study went in depth to describe the different theories that have been proposed as an explanation for the primary and idiopathic BMS etiology.
De Moraes et al. [34]	Systematic review. This study reviews several randomized clinical trials related to BMS treatment strategies.	The paper provided evidence in favor of the effectiveness of therapies and their main side effects with the objective of contributing to better therapeutic management of BMS.
Jääskeläinen [28]	No systematic review. This review recaps the recent neurophysiologic, psychophysical, neuropathological, and brain imaging evidence for neuropathic mechanisms in primary BMS.	The study set forth a thorough neurophysiological, psychophysical and neuropathological BMS approach.
Spanemberg et al. [35]	No systematic review. Different options for the management of BMS patients are proposed. These include etiological and therapeutical ones.	The article focused on BMS etiological and treatment options. In addition to this, it included a table summarizing the BMS placebo treatment.

Some authors consider xerostomia to be one of the most important coexisting causes and they directly relate it to the onset of BMS [43,44].

Systemic factors such as vitamin deficiencies, that can produce significant alterations on the tongue, may also play an important role in the development of burning mouth. Different types of glossitis can appear depending on the deficiencies of riboflavin, nicotinic acid, and ascorbic acid, and as a result of the alteration in sensitive receptors and, in some degree, to the atrophy of the oral epithelium. Due to all of these factors, the mucosal sensitivity to external agents is increased [45,46]. Diabetes mellitus is frequently accompanied by stomatodynia, which can be produced by two mechanisms: peripheral neuropathy of the sensory nerves of oral mucosa and/or by the degree of xerostomia associated with fungal infection [47].

Although no study has yet demonstrated their direct relationship with burning mouth syndrome [48], it is true that psychological factors play an important role in the onset of BMS [48]. According to some authors, stress is not considered to be a crucial factor in the appearance of BMS symptomatology [48], however the majority of these authors do agree that there is a significant relationship between the existence of psychogenic alterations (such as: anxiety, cancerphobia, and depression) and the manifestation of BMS.

Femiano et al. [2] have shown that patients who suffer from BMS exhibit a decrease in self-esteem, the absence of a solid and satisfactory personality, and they experience significant losses and important changes in their lives before being affected by the syndrome. Patients with BMS, as mentioned by Gao et al. [11], have suffered many unfavorable or negative events throughout their lives, when comparing them to the control-patients. Palacios-Sánchez [49] believes that there is an obvious link between the affective life alteration and the syndrome's onset. Patients who suffer from BMS have proved to have significantly higher levels of anxiety in their lives, as well as higher salivary cortisol levels than those of the control-patients [50].

Disorders of the hormone balance may be related to BMS in women as the disease is more frequent during and after menopause [23,37,51]. Tarkkila et al. [23] evaluated the relation between oral discomfort and menopause in 3173 patients, verifying that 8% of these women exhibited burning sensations of the oral tissues. However, hormone replacement therapy did not prevent the occurrence of symptoms. In Forabosco et al. [37] symptoms of BMS were found in 46% of women at menopause and approximately 60% showed relief after hormone replacement. The authors attributed the relief of oral discomfort following hormone therapy, to the presence of oestrogen receptors on the oral mucosa.

Clinical Signs and Diagnosis

The clinical manifestation of BMS is described by a continual hot, burning and painful sensation that lasts throughout the day. It is a chronic disease that appears at different locations within the oral cavity, all of course in the absence of any type of lesion that could justify the symptoms, as well as any clinical or histological changes [39,52]. Patients tend to complain of a sensation of dry mouth and palate alterations, which include a metallic or bitter taste [24,35].

The tongue is the most common location of BMS manifestation (at the tip and at the lateral edges), together with lips, especially the lower lip [39]. The description of the symptomatology varies depending from patient to patient, although the majority of them describe the symptoms as unbearable and with prolonged evolution. The feeling of discomfort tends to be continuous, or it can be intermittent, and it often worsens throughout the day. Some patients, however, experience days without any symptoms.

It is important for us to consider that the burning sensation can worsen in the presence of specific foods, such as spicy food or acidic fruit, and it can even improve with intake of liquids, salivary stimulants or with certain foods. Many patients notice an improvement when they consume sweets or chewing gum, since their mouth is normally dry and left with a bad taste, due to the fact that they are taking xerostomia causing drugs (antidepressants, anxiolytics or hypotensive drugs, among others). Additionally, very hot or very cold food can aggravate or improve the BMS related discomfort [39].

BMS is usually sometimes divided into three different types [53]. Both types I and II involve continual daily discomfort. For type III patients, those that experience asymptomatic periods, the main precipitating factor is emotional instability, although the onset of symptoms is also related to the exposure to a possible allergenic factor that triggers a contact allergy [54,55]. This classification can be useful in intuiting the prognosis and, at the same time, it allows us to guide the patients towards the need involve different specialists such as allergologist, psychiatrists and/or psychologists; although patient classification based on those three groups is not always an easy task.

The symptoms affect the patients' quality of life [9,31,52,56,57] and due to the significant emotional component that goes along with BMS, it is advisable that these patients' visits be quiet, one-on-one with the physician, and held in a relaxed environment so that he/she can explain his/her familiar and affective situation. These patients need time and dedication from their medical professional, seeing as they want to be heard and understood. Patient reassurance is paramount [31,57]. BMS patients tend to be characterized by a common profile; this profile is later summarized in *Table 2*.

The sensation of xerostomia or dry mouth is something that the majority of BMS patients experience although, in most of them, it is not possible to demonstrate a significant reduction in salivary flow [39]. More often than not, patients report symptoms of thick and filamentous saliva. There are few unusual cases in which the oral dryness has made food intake difficult. On the other hand, the majority of BMS patients report improvements with respect to their overall discomfort and the burning sensation during food intake.

BMS diagnosis is fundamentally based on clinical signs. It is necessary to correctly examine the patient, discarding the existence of systemic and local factors that could cause such symptoms [39,52,55,57,58]. The administration of a blood test is also highly recommended. In the case that any deficit should appear, replacement therapy will be initiated, and if in spite of this therapy the symptomatology persists, we at that point face idiopathic BMS, and therefore, we must begin with symptomatic treatment.

Table 2. Profile of patients with burning mouth syndrome.

Most common in middle-aged or elderly women
Characterized by a burning, stinging and/or itching sensation
Patients usually experience a metallic or bitter taste
Oral discomfort is usually chronic and it lasts over time (months or years)
Patients usually experience dry mouth or a sensation of thick saliva
No clinical lesions related to the area of discomfort
Symptoms don't interfere with patients' ability to sleep, although most of them have trouble sleeping or take drugs in order to be able to sleep better
Oral discomfort can be continuous or intermittent and it tends to worsen throughout the day
Symptoms don't worsen while eating or drinking, they can even improve
Patients usually have a history of having visited different specialists and having taken numerous drugs without observing any improvement
They usually have a significant anxious or depressive factor, sometimes accompanied by cancerophobia
Clinical manifestations are usually triggered by psychological stress and they often appear after a dental treatment or a surgical intervention
Sometimes there is a clear beginning is marked, but with no clear trigger
Thanks to internet and social networking websites, many patients can self-diagnose

Treatment

BMS treatment is currently still posing serious problems, since the etiopathogenic factors that produce the onset of the disease, make it difficult to achieve advances in treatment. The main objective of the treatment is to control the various factors that are related to BMS, therefore decreasing the symptoms that are described by the patients.

As mentioned in some studies, topical capsaicin (*Capsicum frutescens L*) can be used to control neuropathic pain, since this drug has an effect on the sensory afferent neurons and also serves as an analgesic [51,59,60]. However, the use of capsaicin has been reduced since it has been proven to evoke an even worse burning sensation at the beginning of the treatment period [59]. It is important to note that there have not been any cases in which this BMS treatment drug has been investigated in placebo-controlled studies.

Medicine such as tricyclic antidepressants, benzodiazepines, and antipsychotic drugs have been researched and are considered to be the three most widely accepted options for the treatment of BMS, despite the fact that they produce hyposalivation and xerostomia. Treatment methods like psychotherapy and psychoactive drugs were prescribed for BMS patients once it was demonstrated that psychological factors play an important role in this disorder [61]. Bergdahl et al. [61] treated BMS patients by means of cognitive behavior therapy once a week for between 12 and 15 weeks. They were able to observe a decrease in the intensity of the pain immediately after undergoing the therapy and at the six-month follow-up visit.

The use of topical clonazepam proved to be another treatment option for patients suffering from BMS [51,62-64]. Clonazepam is a benzodiazepine that acts as a GABA receptor agonist. Its main property includes the light inhibition of functions of the central nervous system, thus permitting anticonvulsant action, light sedation, muscular relaxation and a calming effect. Gremeau-Richard et al. [62] propose that the action of topical clonazepam has to do with the dysfunctions of the peripheral nervous system that are observed in patients with the syndrome, and the presence of GABA receptors in peripheral tissues. Another study was carried out in which 33 patients were treated with clonazepam tablets, while the other 33 patients were administered a placebo. The symptoms were then assessed after 1 month and 6 months of the treatment period had elapsed. After only 1 month of treatment, 23 of the 33 patients that were treated with clonazepam reported at least a 50% reduction in their symptoms [63]. This drug does not show the adverse effects of its systemic use when it is used topically.

In an uncontrolled study paroxetine, a tricyclic antidepressant, was administered to BMS patients throughout a period of 12 weeks [65]. Of these patients, approximately 80% reported a decrease in their symptoms, with little adverse effects, thus suggesting that paroxetine could be a plausible treatment option for this disorder. Ueda [66] used the antipsychotic drug olanzapine and were therefore able to achieve symptom reduction in two patients that suffered from the syndrome. Olanzapine is classified as a potent antagonist of dopamine, norepinephrine and serotonin neuron receptors. However, in order to confirm the effectiveness of this drug, and to explain its mechanisms of action, the realization of controlled studies is needed.

A drug that did not show suitable results in the relief of the symptoms of oral burning was trazodone, a drug that is typically used to treat depression. Trazodone is classified as an atypical antidepressant since it stimulates the presynaptic inhibition of serotonin recaptation, blockage of 5-HT2A and 5HT2C serotonin receptors on post-synapse neurons [58].

Hormonal treatments, or those that involve corticosteroids, phytotherapy, vitamins and trace elements, antifungal drugs and sialogogue drugs have also been described throughout the literature as an attempt to reduce the symptoms reported by the patients, although the studies are not always controlled and the patients' clinical symptoms do not always improve.

Because of alpha-lipoic acid's neuroprotective properties, it has been researched with respect to BMS treatment; however, studies involving this drug have presented controversial results. According to Femiano et al. [2], both patients treated with psychotherapy and those who received 200 mg of ALA three times a day throughout a period of two months, demonstrated significant improvement with respect to their symptoms of BMS. The group that was simultaneously treated with ALA and psychotherapy was the group that showed the most remarkable results. According to the researchers, it is necessary to combine psychotherapy with the drugs, the reason for this being that psychogenic alterations are known to have a strong relation to BMS [2]. Carbone et al. [67], López-Jornet et al. [68] and Cavalcanti and Silveira [29] were not able to demonstrate any significant improvement in BMS patients when utilizing alpha-lipoic acid. Both the placebo effect and the different parameters that were used to calculate the intensity of the symptoms could be the source of possible explanations that account for such conflicting results.

In a controlled study that consisted of 60 patients, the phytotherapeutic drug Catuama®, which is composed of an association of four medicinal herbs, proved to be effective in reducing BMS symptoms in those who suffer from this disorder. The experimental group showed clinical improvement in week 4 and week 8 that was significant when compared to that of the placebo group. After 12 weeks of monitoring, the patients experienced a 51.3% reduction in their symptoms, whereas the reduction of symptoms in the control group was only about 18.8% [69]. There were no cases of toxicity with respect to the use of this medicine. In a previous study, Oliveira et al. [70] researched the chronic administration of Catuama® 25ml, twice a day for 28 days in healthy humans volunteers of both sexes. There were no adverse reactions or relevant hematological and biochemical changes that were presented in the study.

Low power laser radiation therapy has proven to be useful in the reduction of BMS symptoms [71-74]. On the contrary, Vukoja et al. [74] were not able to confirm those results and therefore suggest that the therapeutic benefit of the laser BMS patients was caused by placebo effect. Santos et al. [72] had 10 BMS patients undergo to a low power laser session (low-level laser therapy - LLLT) once a week over a 10-week span, utilizing the InGaAIP laser diode in continuous mode. A 660 nm wavelength, 40 nW, 20 J/cm^2 of dosimetry and a 0.8 J per point in 10 seconds was used. Throughout all of the sessions the intensity of the symptoms was evaluated by using a visual analog scale. Patients reported an improvement after laser treatment, with a reduction of symptoms of up to 58% by the tenth session. On the other hand Kato et al. [71] used the LLLT in 11 patients with BMS at the specific areas where the patients were experiencing symptoms. The affected areas were irradiated once a week, in a continuous mode, with a 790 wavelength and a dosimetry of 6 J/cm^2. The intensity of the symptoms was verified through a VAS at each of the three sessions, as well as six weeks after the treatment was finished. At the end of the study the authors checked that the experimental group did in fact show a significant improvement in their symptoms as compared to their state at the beginning of the treatment. The patients reported a decrease in the intensity of their symptoms after the laser radiation treatment. This decrease was approximately 80.4%, therefore suggesting that LLLT can be an alternative for BMS.

Low power laser therapy is a non-invasive treatment; it is well tolerated by patients and it is useful in treating sharp and chronic pain [40]. Different studies have investigated the possible adverse effects of laser but they were not significant [75,76].

BMS treatment is usually directed towards symptoms management, but local factors they may play a role in worsening the oral burning sensation should be eliminated [77]. These include: alcohol, spicy foods and acidic drinks due to their irritant effect on the oral mucosa. It is necessary to research if BMS symptoms are caused by parafunctional habits, galvanic currents, mechanical irritation, or a denture allergy [6]. With treatment or ridding of such factors, it has been demonstrated that the clinical symptoms improve [37,77-79]. This disease has a chronic clinical evolution seeing as patients experience alternating periods of exacerbation of the symptomatology, as well as periods of improvement. In some cases, those who suffer from BMS have also described spontaneous remission [77].

The typical BMS patient seeks diagnosis before undergoing any kind of special treatment. Therefore, the medical professional has the obligation of explaining the nature of BMS and what that implies for the patient. Unfortunately, those who are affected by this disorder must accept that fact and learn to cope with it, and in turn, they must be conscious of that fact that the solution to this disorder may not be found in the short term [27].

Conclusions

BMS patient management is difficult, and more times than not, a frustrating task. However, it is essential to not only acknowledge the patient but also reassure him/her. The main objective of management is that of providing support to the patient and working towards symptom reduction, rather than total elimination of such symptoms. The complexity of this disease, as well as the ignorance of the mechanisms that cause its onset, are two key topics that need to be further researched. Such insight could enable us to establish effective treatment for this disorder. Finally, it is crucial for us to evaluate the quality of life of those BMS patients, trying to fully comprehend the impact that this condition has on all aspects of their lives.

References

1. Danhauer SC, Miller CS, Rhodus NL, Carlson CR. Impact of criteria-based diagnosis of burning mouth syndrome on treatment outcome. *Journal of Orofacial Pain*. 2002; **16**: 305-311.

2. Femiano F, Gombos F, Scully C. Burning Mouth Syndrome: open trial of psychotherapy alone, medication with alpha-lipoic acid (thioctic acid), and combination therapy. *Medicina oral*. 2004; **9**: 8-13.

3. Cherubini K, Maidana JD, Weigert KL, Figueiredo MA. Síndrome da ardência bucal: revisão de cem casos. *Revista Odonto Ciência*. 2005; **20**: 109-113.

4. Brailo V, Vuéiaeeviae-Boras V, Alajbeg IZ, Alajbeg I, Lukenda J, et al. Oral burning symptoms and burning mouth syndrome-significance of different variables in 150 patients. *Medicina oral Patología Oral y Cirugía bucal*. 2006; **11**: E252-E255.

5. Salort-Llorca C, Mínguez-Serra MP, Silvestre FJ. Drug-induced burning mouth syndrome: a new etiological diagnosis. *Medicina oral Patología Oral y Cirugía bucal*. 2008; **13**: E167-E170.

6. Dutrée-Meulenberg RO, Kozel MM, Van Joost T. Burning mouth syndrome: a possible etiologic role for local contact hypersensitivity. *Journal of the American Academy of Dermatology*. 1992; **26**: 935-940.

7. Tourne LP, Fricton JR. Burning mouth syndrome. Critical review and proposed clinical management. *Oral Surgery, Oral Medicine, and Oral Pathology*. 1992; **74**: 158-167.

8. Bergdahl M, Bergdahl J. Burning mouth syndrome: prevalence and associated factors. *Journal of Oral Pathology & Medicine*. 1999; **28**: 350-354.

9. Thoppay JR, De Rossi SS, Ciarrocca KN. Burning mouth syndrome. *Dental Clinics of North America*. 2013; **57**: 497-512.

10. López-Jornet P, Camacho-Alonso F, Andujar-Mateos P, Sánchez-Siles M, Gómez-Garcia F. Burning mouth syndrome: an

update. *Medicina oral, Patología Oral y Cirugía bucal*. 2010; **15**: e562-e568.

11. Gao J, Chen L, Zhou J, Peng J. A case-control study on etiological factors involved in patients with burning mouth syndrome. *Journal of Oral Pathology & Medicine*. 2009; **38**: 24-28.

12. Evans RW, Drage LA. Burning mouth syndrome. *Headache*. 2005; **45**: 1079-1081.

13. Beneyto YM, Jornet PL, Nicolás AV, García VJ. Letter to the Editor: Attitudes among Spanish general dentists in relation to burning mouth syndrome: results of a national survey. *Medicina oral, Patología Oral y Cirugía bucal*. 2008; **13**: e753-e754.

14. Bergdahl M, Bergdahl J. Low unstimulated salivary flow and subjective oral dryness: association with medication, anxiety, depression, and stress. *Journal of Dental Research*. 2000; **79**: 1652-1658.

15. Soares MS, Chimenos-Küstner E, Subirá-Pifarrè C, Rodríguez de Rivera-Campillo ME, López-López J. Association of burning mouth syndrome with xerostomia and medicines. *Medicina oral, Patología Oral y Cirugía bucal*. 2005; **10**: 301-308.

16. Ito M, Kurita K, Ito T, Arao M. Pain threshold and pain recovery after experimental stimulation in patients with burning mouth syndrome. *Psychiatry and Clinical Neurosciences*. 2002; **56**: 161–168.

17. Jääskeläinen SK. Pathophysiology of primary burning mouth syndrome. *Clinical Neurophysiology*. 2012; **123**: 71-77.

18. Sardella A, Carrassi A. BMS: S for syndrome or S for Symptom? A reappraisal of the burning mouth syndrome. *Minerva Stomatologica*. 2001; **50**: 241-246.

19. Lipton JA, Ship JA, Robinson DL. Estimated prevalence and distribution of reported orofacial pain in the United States. *Journal of the American Dental Association*. 1993; **124**: 115-121.

20. Rodrigo MA, Garcia JA. Síndrome de boca ardiente. *Gaceta Dental*. 2000; **104**: 86-88.

21. Silvestre FJ, Bagán JV, Rojo L. Síndrome de boca ardiente: Estudio clínico y biológico. *Rev Actual Odonto Estomatolol Esp*. 1991; **409**: 37-42.

22. Rojo L, Silvestre FJ, Bagán JV, De Vicente T. Prevalence of psychopathology in burning mouth syndrome. *Oral Surgery, Oral Medicine, and Oral Pathology*. 1994; **78**: 312-316.

23. Tarkkila L, Linna M, Tiitinen A, Lindqvist C, Meurman JH. Oral symptoms at menopause-the role of hormone replacement therapy. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics*. 2001; **92**: 276-280.

24. Grushka M, Sessle B. Taste dysfunction in burning mouth syndrome. *Gerodontics*. 1988; **4**: 254-258.

25. Carlson Cr, Miller CS, Reid KL. Psychosocial profiles of patients with burning mouth syndrome. *Journal of Orofacial Pain*. 2000; **14**: 59-64.

26. Balasubramaniam R, Klasser GD, Delcanho R. Separating oral burning from burning mouth syndrome: unravelling a diagnostic enigma. *Australian Dental Journal*. 2009; **54**: 293-299.

27. Minguez-Sanz MP, Salort-Llorca C, Silvestre-Donat FJ. Etiology of burning mouth syndrome: a review and update. *Medicina oral, Patología Oral y Cirugía bucal*. 2011; **16**: e144-e148.

28. El-Etr M. Critical commentary 3: steroid dysregulation and stomatodynia (burning mouth syndrome). *Journal of Orofacial Pain*. 2009; **23**: 216-218.

29. Cavalcanti DR, Silveira FRX. Alpha lipoic acid in burning mouth syndrome – a randomized double-blind placebo-controlled Trial. *Journal of Oral Pathology & Medicine*. 2009; 38: 254–561.

30. Abetz LM, Savage NW. Burning mouth syndrome and psychological disorders. *Australian Dental Journal*. 2009; **54**: 84-93.

31. Mock D, Chugh D. Burning mouth syndrome. *International Journal Of Oral Science*. 2010; **2**: 1-4.

32. de Moraes M, do Amaral Bezerra BA, da Rocha Neto PC, de Oliveira Soares AC, Pinto LP, de Lisboa Lopes Costa A. Randomized trials for the treatment of burning mouth syndrome: an evidence-based review of the literature. *Journal of Oral Pathology & Medicine*. 2012; **41**: 281-287.

33. Spanemberg JC, Cherubini K, de Figueiredo MA, Yurgel LS, Salum FG. Aetiology and therapeutics of burning mouth syndrome: an update. *Gerodontology*. 2012; **29**: 84-89.

34. Klasser GD, Fischer DJ, Epstein JB. Burning mouth syndrome: recognition, understanding, and management. Oral and Maxillofacial Surgery Clinics of North America. 2008; **20**: 255-271.

35. Scala A, Checchi L, Montevecchi M, Marini I, Giamberardino MA. Update on burning mouth syndrome: overview and patient management. Critical Reviews in Oral Biology and Medicine. 2003; **14**: 275-291.

36. Dias Fernandes CS, Salum FG, Bandeira D, Pawlowski J, Luz C. Salivary dehydroepiandrosterone (DHEA) levels in patients with the complaint of burning mouth: a case-control study. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics*. 2009; **108**: 537-543.

37. Forabosco A, Criscuol M, Coukos G, Uccelli E, Weinstein R, et al. Efficacy of hormone replacement therapy in postmenopausal women with oral discomfort. *Oral Surgery, Oral Medicine, and Oral Pathology*. 1992; **73**: 570-574.

38. Lauria G, Majorana A, Borgna M, Lombardi R, Penza P, et al. Trigeminal small-fiber sensory neuropathy causes burning mouth syndrome. Pain. 2005; **115**: 327-332.

39. Silvestre FJ, Serrano C. El syndrome de boca ardiente: revision de conceptos y puesta al día. *Medicina oral*. 1997; **2**: 30-38.

40. Riley JL, Gilbert GH. Orofacial pain symptoms: an interaction between age and sex. Pain. 2001; **90**: 245-256.

41. Lamey PJ, Lamb AB, Hughes A, Milligan KA, Forsyth A. Type 3 burning mouth syndrome: psychological and allergic aspects. *Journal of Oral Pathology & Medicine*. 1994; **23**: 216-219.

42. Helton J, Storrs F. The burning mouth syndrome: lack of a role for contact urticaria and contact dermatitis. *Journal of the American Academy of Dermatology*. 1994; **31**: 201-205.

43. Tammiala-Salonen T, Söderling E. Protein composition, adhesion, and agglutination properties of saliva in burning mouth syndrome. Scandinavian *Journal of Dental Research*. 1993; **101**: 215-218.

44. Gorsky M, Silverman S Jr, Chinn H. Burning mouth syndrome: a review of 98 cases. *Journal of Oral Medicine*. 1987; **42**: 7–9.

45. Main DM, Basker RM. Patients complaining of a burning mouth. Further experience in clinical assessment and management. *British Dental Journal*. 1983; **154**: 206-211.

46. Schmitt RJ, Sheridan PJ, Rogers RS. Pernicious anemia with associated glossodynia. *Journal of the American Dental Association*. 1988; **117**: 838-840.

47. López-Jornet P, Saura-Inglés A, Martínez-Mondéjar B, Bermejo-Fenoll A. Valoración de la tasa de flujo salival en pacientes con diabetes mellitus tipo 1 y tipo 2. *Archivos de Odontoestomatol*. 1996; **12**: 690-697.

48. Eli I, Kleinhauz M, Baht R, Littner M. Antecedents of burning mouth syndrome (glossodynia)--recent life events vs. psychopathologic aspects. *Journal of Dental Research*. 1994; **73**: 567-572.

49. Palacios-Sanchez MF, Jordana-Comín X, García-Sivoli CE. Burning Mouth Syndrome: A retrospective study of 140 cases in a sample of Catalan population. *Medicina oral, Patología Oral y Cirugía bucal*. 2005; **10**: 388-393.

50. Amenábar JM, Pawlowski J, Hilgert J, Hugo FN, Bandeira D, et al. Anxiety and salivary cortisol levels in patients with burning mouth syndrome: case-control study. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics*. 2008; **105**: 460-465.

51. Grushka M, Epstein JB, Gorsky M. Burning mouth syndrome. American Family Physician. 2002; **65**: 615-620.

52. Nasri-Heir C. Burning mouth syndrome. *The Alpha Omegan*. 2012; **105**: 76-81.

53. Lamey PJ, Lewis MAO. Oral medicine in practice: Burning mouth syndrome. *British Dental Journal*. 1989; **167**: 197-200.

54. Lamey PJ, Lamb AB. The usefulness of HAD scale in assesing anxiety and depression in patients with burning mouth

syndrome. *Oral Surgery, Oral Medicine, and Oral Pathology*. 1989; **67**: 390-392.

55. Lamey PJ. Burning mouth syndrome. *Dermatologic Clinics*. 1996; **14**: 339-354.

56. Charleston L 4th. Burning mouth syndrome: a review of recent literature. *Current Pain and Headache* Reports. 2013; **17**: 336.

57. Chugh D, Mock D. How do I manage a patient with burning mouth syndrome? *Journal of Canadian Dental Association*. 2013; **79**: d41.

58. Tammiala-Salonen T, Forssell H. Trazodone in burning mouth pain: a placebo-controlled, double-blind study. *Journal of Orofacial Pain*. 1999; **13**: 83-88.

59. Espinosa LS, López JP, Frutos RR. Síndrome de boca ardiente. Eficacia de la aplicación tópica de capsaicina. Estudio Piloto. *Avances en Odontoestomatologia*. 2004; **20**: 297-304.

60. Epstein JB, Marcoe JH. Topical application of capsaicin for treatment of oral neuropathic pain and trigeminal neuralgia. *Oral Surgery, Oral Medicine, and Oral Pathology*. 1994; **77**: 135-140.

61. Bergdahl J, Anneroth G, Perris H. Personality characteristics of patients with resistant burning mouth syndrome. *Acta Odontologica Scandinavica*. 1995; **53**: 7-11.

62. Gremeau-Richard C, Woda A, Navez ML, Attal N, Bouhassira D, et al. Topical clonazepam in stomatodynia: a randomized placebo-controlled study. *Pain*. 2004; **108**: 51-57.

63. Rodríguez de Rivera-Campillo ME, López-López J, Chimenos-Küstner E. Tratamiento del síndrome de boca ardiente con clonacepam tópico. *Piel*. 2011; **26**: 263-268.

64. Rodriguez de Rivera Campillo E, López López J, Chimenos Küstner E. Response to topic Clonazepam in patients with burning mouth syndrome: a clinical study. *Bulletin du Groupèment International Pour la Recherche Scientifique en Stomatologie & Odontologie*. 2010; **49**: 19-29.

65. Yamazaki Y, Hata H, Kitamori S, Onodera M, Kitagawa Y. An open-label, noncomparative, dose escalation pilot study of the effect of paroxetine in treatment of burning mouth syndrome. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics*. 2009; **107**: e6-e11.

66. Ueda N, Kodama Y, Hori H, Umene W, Sugita A, Nakano H, Yoshimura R, Nakamura J. Two cases of burning mouth syndrome treated with olanzapine. *Psychiatry and Clinical Neurosciences*. 2008; 62: 359-361.

67. Carbone M, Pentenero M, Carrozzo M, Ippolito A, Gandolfo S. Lack of efficacy of alpha-lipoic acid in burning mouth syndrome: a double-blind, randomized, placebo-controlled study. *European Journal of Pain*. 2008; **13**: 492-496.

68. López-Jornet P, Camacho-Alonso F, Leon-Espinosa S. Efficacy of alpha lipoic acid in burning mouth syndrome: a randomized, placebo-treatment study. Journal of Oral Rehabilitation. 2009; **36**: 52-55.

69. Spanemberg JC, Cherubini K, de Figueiredo MA, Gomes AP, Campos MM, Salum FG. Effect of an herbal compound for treatment of burning mouth syndrome: randomized, controlled, double-blind clinical trial. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*. 2012; **113**: 373-377.

70. Oliveira CH, Moraes ME, Moraes MO, Bezerra FA, Abib E, De Nucci G. Clinical Toxicology Study of an Herbal Medicinal Extract of Paullinia cupana, Trichilia catigua, Ptychopetalum olacoides and Zingiber officinale (Catuama®) in Healthy Volunteers. *Phytotherapy Research*. 2005; **19**: 54-57.

71. Kato IT, Pellegrini VD, Prates RA, Ribeiro MS, Wetter NU, Sugaya NN. Low-level laser therapy in burning mouth syndrome patients: a pilot study. *Photomedicine and Laser Surgery*. 2010; **28**: 835-839.

72. Santos LF, Carvalho AA, Leão JC, Cruz Perez, Castro JF. Effect of low-level laser therapy in the treatment of burning mouth syndrome: a case series. *Photomedicine and Laser Surgery*. 2011; **29**: 793-796.

73. Yang HW, Huang YF. Treatment of burning mouth syndrome with a low-level energy diode laser. *Photomedicine and Laser Surgery*. 2011; **29**: 123-125.

74. Vukoja D, Alajbeg I, Vučićević Boras V, Brailo V, Alajbeg IZ, Andabak Rogulj A. Is effect of low-level laser therapy in patients with burning mouth syndrome result of a placebo? *Photomedicine and Laser Surgery*. 2011; **29**: 647-648.

75. Moore K. Lasers and pain treatment. *Laser Part Clinix*. 2004; **72**: 1-6.

76. Bjordal JM, Bensadoun RJ, Tunèr J, Frigo L, Gjerde K, Lopes-Martins RA. A systematic review with meta-analysis of the effect of low-level laser therapy (LLLT) in cancer therapy-induced oral mucositis. *Supportive Care in Cancer*. 2011; **19**: 1069-1077.

77. Sun A, Wu KM, Wang YP, Lin HP, Chen HM, Chiang CP. Burning mouth syndrome: a review and update. *Journal of Oral Pathology & Medicine*. 2013; **42**: 649-655.

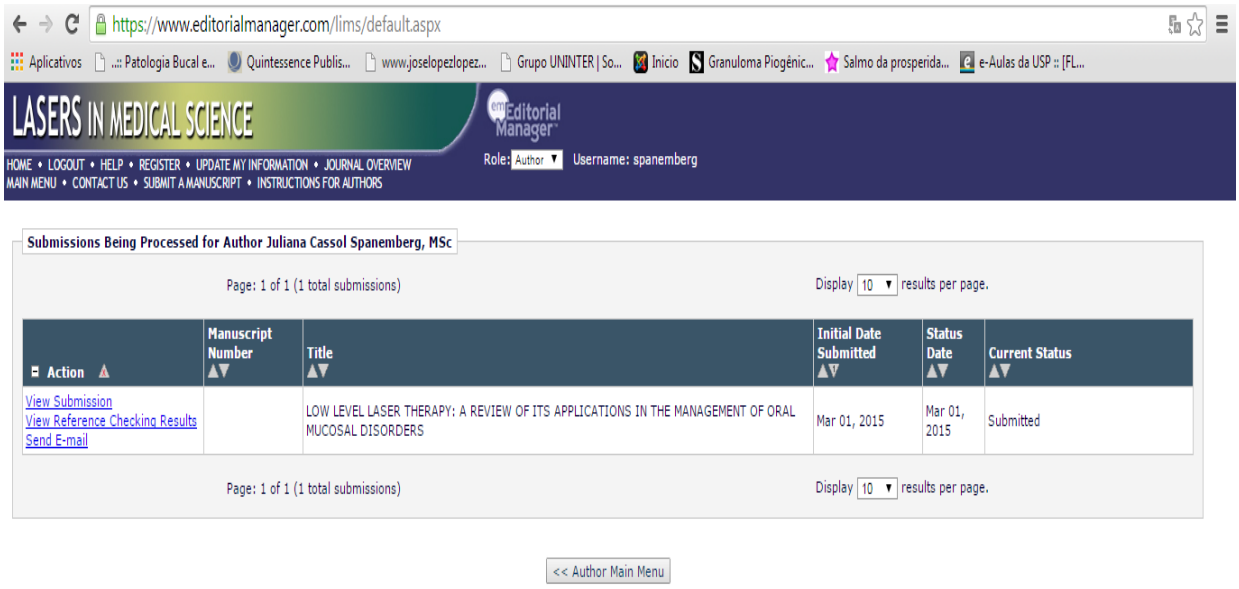
78. Crow HC, Gonzalez Y. Burning mouth syndrome. *Oral and Maxillofacial Surgery Clinics of North America*. 2013; **25**: 67-76.

79. Rodríguez-de Rivera-Campillo E, López-López J. Evaluation of the res-ponse to treatment and clinical evolution in patients with burning mouth syndrome. *Medicina oral, Patología Oral y Cirugía bucal*. 2013; **18**: e403-e410.

ANEXO E

SUBMISSÃO DO 2º ARTIGO DE REVISÃO DA LITERATURA NO PERIÓDICO

LASERS IN MEDICAL SCIENCE



ANEXO F

SUBMISSÃO DO ARTIGO DE PESQUISA NO PERIÓDICO

JOURNAL OF BIOMEDICAL OPTICS

Dear Mrs. Spanemberg,

This is an automated email from the Journal of Biomedical Optics (JBO) to notify you that the following manuscript submission has been received by our system:

Manuscript Title: EFFICACY OF LOW-LEVEL LASER THERAPY FOR THE TREATMENT OF BURNING MOUTH SYNDROME: A RANDOMIZED, CONTROLLED TRIAL
Authors: Juliana Spanemberg, José López-López, Maria Antonia Figueiredo, Karen Cherubini, and Fernanda Salum
Paper Number: JBO 150110

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ANEXO G

QUESTIONÁRIO OHIP-14 (Oral Health Impact Profile)

REPRODUÇÃO DO "PERFIL DE IMPACTO NA SAÚDE ORAL" (OHIP14)[26]

Nos últimos seis meses, por causa de problemas com seus dentes ou sua boca:	Nunca	Raramente	Às vezes	Repetidamente	Sempre
1. Você teve problemas para falar alguma palavra?					
2. Você sentiu que o sabor dos alimentos tem piorado?					
3. Você sentiu dores em sua boca ou nos seus dentes?					
4. Você se sentiu incomodado(a) ao comer algum alimento?					
5. Você ficou preocupado(a)?					
6. Você se sentiu estressado(a)?					
7. Sua alimentação ficou prejudicada?					
8. Você teve que parar suas refeições?					
9. Você encontrou dificuldade para relaxar?					
10. Você se sentiu envergonhado(a)?					
11. Você ficou irritado(a) com outras pessoas?					
12. Você teve dificuldade para realizar suas atividades diárias?					
13. Você sentiu que a vida, em geral, ficou pior?					
14. Você ficou totalmente incapaz de fazer suas atividades diárias?					