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Efficacy of photobiomodulation on oral lichen planus: a protocol study for a double-blind, randomised controlled clinical trial

Elza Padilha Ferri,[1] Camila de Barros Gallo,[2] Clery Saad Abboud,[1] Wellington Hideaki Yanaguizawa,[2] Anna Carolina Ratto Tempestini Horliana,[1] Daniela de Fatima Teixeira da Silva,[1] Christiane Pavani,[1] Sandra Kalil Bussadori,[1,3] Fabio Daumas Nunes,[4] Raquel Agnelli Mesquita-Ferrari,[1,3] Kristianne Porta Santos Fernandes,[1] Maria Fernanda Setúbal Destro Rodrigues[1]

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[1]Biophotonics Applied to Health Sciences, Nove de Julho University, São Paulo, Brazil
[2]Department of Stomatology, School of Dentistry, University of São Paulo, São Paulo, Brazil
[3]Rehabilitation Sciences, Nove de Julho University (UNINOVE), São Paulo, Brazil
[4]Department of Oral Pathology, School of Dntistry, University of São Paulo, São Paulo, Brazil

Correspondence to
Dr Maria Fernanda Setúbal Destro Rodrigues;
fernandarodrigues@usp.br

ABSTRACT

Introduction Oral lichen planus (OLP) is an idiopathic chronic mucocutaneous disease with a wide range of clinical manifestations, including white reticular patches, erosive/ulcerative and atrophic lesions, both associated with intense symptomatology. Topical corticosteroids are commonly used as standard therapy. However, patients frequently present relapses after the discontinuation of treatment as well as developing resistance to corticosteroid therapy. Photobiomodulation (PBM) has been shown to be a potential therapeutic tool to treat inflammatory disorders, including OLP. The aim of this study was to compare the efficacy of PBM (660 nm) with corticosteroid therapy with clobetasol propionate 0.05% for the treatment of OLP.

Methods and analysis Forty-four patients with symptomatic and histopathological diagnosis of OLP will be randomised into two experimental groups in a double-blind manner: control group (n=22): clobetasol propionate 0.05%+placebo PBM, and experimental group (n=22): PBM (λ=660 nm, power 100 mW, radiant exposure: 177 J/cm^2 and 0.5J per point)+placebo gel. Laser will be applied 2×/week for 1 month and clobetasol propionate three times a day for 30 days and the same for placebo treatments. The primary variable (pain) and the secondary variables (clinical score, evaluation of functional scores, clinical resolution, OLP recurrence, quality of life and anxiety and depression) will be evaluated at the baseline, once a week during treatment (depending on the variables) and after 30 days and 60 days of follow-up. Pain will be evaluated using visual analogue scale and clinical characteristics will be scored using the Thongprasom Index. The quality of life and anxiety and depression will be evaluated by Oral Health Impact Profile-14 questionnaire and by Hospital Anxiety and Depression Scale for anxiety scale, respectively. The serum and salivary levels of interleukin (IL)-6, IL-10, IL-1β, INF-γ and tumour necrosis factor-α will be evaluated by ELISA at baseline and at the end of treatment.

Ethics and dissemination This protocol was approved (#2.375.410) by the Nove de Julho University (UNINOVE) Research Ethics Committee. The data gathered using this protocol will be published in a peer-reviewed journal.

Trial registration number NCT03320460.

Strengths and limitations of this study

- Some studies in this area are not blinded because of the difficulty in masking the treatments. In this study, the treatments will be totally masked (with a placebo gel and laser turned off), and only the laser operator will know the which treatment is being given.
- Lesion size will be a limitation of the study. The number of photobiomodulation points will vary according to lesion size. Larger lesions will require greater total delivered energy and vice versa with smaller lesions. So we will consider radiant energy, which takes into account the total area of irradiated lesion.
- The sample size was calculated. We have a limited number of patients with the same clinical and histological characteristics in this population. Hence, we hope for a maximum dropout of 10%.

INTRODUCTION

Oral lichen planus (OLP) is a chronic inflammatory disease that commonly affects the skin and oral mucosa, although other mucous membranes such as conjunctiva, oesophagus and genitalia can also be affected.[1 2] OLP is observed in 1%–2% of the population, mainly in those older than 40 years, and shows a female predisposition.[1 3] The most typical involvement site for OLP is the buccal mucosa, but any other oral cavity site can be affected, including labial mucosa, tongue and gingiva.[4] Three main clinical forms of OLP have been described. The classical clinical presentation is reticular OLP, characterised by white lacy streaks, which are

referred to as Wickham striae, normally surrounded by an erythematous border.[5] The lesions are often asymptomatic. Atrophic and erosive/ulcerative OLP lesions are characterised by erythema associated with inflammation and/or epithelial thinning as well as mucosa ulceration, which is surrounded by keratotic striae on the periphery of the lesion.[5] Most importantly, these OLP presentations are associated with symptomatology ranging from a burning sensation to severe pain and rarely remit spontaneously.[1 4 5] The vast majority of patients with OLP have periods of relapses and remissions and, during periods of exacerbation, an increase in observable clinical signs and symptomatology, which can be associated with psychological disorders or stress.[4 6 7]

Although the aetiology and pathogenic mechanisms involved in OLP development are not completely understood, some aetiological factors, such as genetic predisposition, dental material, drugs, bacterial and viral infection, autoimmunity, immunodeficiency and allergies, among others, have been proposed as possibilities.[2 8]

Cellular immunity plays a major role in OLP development.[9 10] There is a dominant type 1 cellular-mediated immune response in which CD4+ cells are responsible for the production of Th1 factors and CD8+ cells are cytotoxic leading to the apoptosis of basal keratinocytes by tumour necrosis factor-α (TNF-α), perforin secretion as well as by Fas ligand expression.[2 7] In addition, Th1 and natural killer cells produce IFNγ, thus amplifying immune response and tissue damage.[10–12] Antigen-presenting cells and mast cell degranulation were also observed in OLP, being implicated in T cell activation and with the release of proinflammatory mediators such as TNF-α.[13 14]

Soluble factors secreted by the immune cells, such as the cytokines interleukin (IL)-12, TFNγ, IFNα, IL-17, IL-1β and the chemokines CXCL9 and CXCL10, have been previously identified in the lesions and peripheral blood of patients with OLP.[11 12 15 16] These factors contribute to the establishment of a proinflammatory environment that favours the attack of oral epithelium.

OLP diagnosis is based on criteria set by the WHO, which established a set of clinicopathological parameters in 1978.[17] These parameters were further modified by van der Meij and van der Waal in 2003 to improve said criteria for the clinical and histological diagnosis of OLP.[17 18] Thus, to confirm an OLP diagnosis and possibly exclude epithelial dysplasia and malignancy, an oral biopsy with histopathological parameters is strongly recommended.[4 19]

Completely curing OLP is very difficult, and many different therapeutic approaches have been tried.[20] The first line in treating OLP is based on high-potency topical steroids, such as clobetasol propionate, fluocinolone acetonide and fluocinonide.[21] In addition, the systemic corticosteroids cyclosporine and tacrolimus can be used in unresponsive patients with OLP in place of topical steroids.[22] Despite the potential for these drugs to control pain and the clinical appearance of OLP, they are associated with side effects including secondary candidiasis, mucosal atrophy and dryness, bad taste and delayed healing, due to the chronic nature of OLP and the long-term use of these drugs.[23] Most importantly, some patients may experience a refractory response. Thus, alternative therapeutic approaches are needed for the management of OLP.

In this context, photobiomodulation (PBM) has been proposed as a non-invasive clinical tool to treat OLP, with the advantage over current therapies of not being associated with any side effects.[24] The use of PBM in different inflammatory conditions has potential analgesic, biostimulatory and immunomodulatory effects, as well as for improving healing.[25–27] In OLP, PBM has been used to treat symptomatic lesions with controversial results. Dillenburg *et al* showed a significant improvement in signs, symptoms and reduced recurrence rates in patients treated with PBM in relation to standard treatment with clobetasol propionate.[24] In the study performed by Jajram *et al*, PBM showed comparable results with clobetasol propionate.[28] However, El-Shenawy *et al*, Othaman *et al* and Kazancioglu *et al* showed that corticosteroid therapy was associated with significant improvement of OLP when compared with PBM.[29–31] It is noteworthy that all of these studies used different PBM parameters, with wavelengths ranging between 630 nm and 970 nm, power density from 10 mW/cm^2 to 1000 mW/cm^2 and radiant exposure from 1.5 J/cm^2 to 120 J/cm^2. Treatment protocols also varied. These studies were recently included in two systematic reviews to access the efficacy of PBM in OLP.[32 33] However, with the exception of the study performed by Dillenburg *et al*,[24] the included studies were associated with a high risk of bias due to the lack of sample size calculation, methods of randomisation and treatment masking. In addition, a wide range of laser parameters and treatment outcomes were observed, and no effective dose or protocol could be established. Thus, both reviews have concluded that there is an urgent need for rigorous clinical studies to better understand the efficacy of PBM in OLP. Until now, due to the lack of well-designed randomised controlled trials evaluating the efficacy of PBM in OLP, it still remains unclear if PBM is a viable alternative option for treating this chronic disease. In this context, this double-blind, randomised controlled clinical trial aims to elucidate if the PBM is equivalent to topical corticosteroid therapy (gold standard) to treat the pain of patients with symptomatic OLP.

METHODS

This randomised (1:1), parallel-group, controlled, single-centre, 3-month clinical trial was designed according to the SPIRIT statement. It has been registered at www.clinicaltrial.gov (NCT03320460). All patients will sign the informed consent form after verbal (WHY) and written explanation of the methodology. This study was approved by Nove de Julho University's Research Ethics Committee (#2.375.410) (http://plataformabrasil.saude.gov.br). Forty-four patients currently in the care of the Stomatology Department, Nove de Julho University will receive treatment at the University of São Paulo's

School of Dentistry Dental Clinic from November 2018 to December 2020. Patients with both a clinical and histopathological diagnosis of OLP, as based on the WHO (1978) and modified by van der Meij and van der Waal (2003),[18] will be enrolled (WHY) for this study.

Sample size calculation

Sample size calculation was performed using G*Power Software (V.3.1.9.2, Dusseldorf, Germany), and the power analysis was determined by choosing ANOVA repeated measures, within–between interaction. The effect size was determined according to Idre/UCLA. The largest and the smallest mean values, as well as the SD, were taken from the study performed by Dillenburg *et al*.[24] The α error was set at 5%, and the β error was set at 95%. According to G*Power, a sample of 22 patients per group will be required for a power of 80%.

Patient and public involvement statement

Patients and/or the public were not involved in the design, recruitment to and conduct of the study. At the end of the study, the main results will be disseminated to participants by email.

Inclusion and exclusion criteria

The participants in this study will be male and female (over 18 years of age) diagnosed with symptomatic lesions of reticular, atrophic an erosive OLP, based on the clinical and histopathological criteria of the WHO (1978) and modified by van der Meij and van der Waal.[18] Patients with ongoing cancer, pregnant or breastfeeding women, patients with a history of corticosteroids or non-steroidal anti-inflammatory drugs treatment in the last 1 month, patients with uncontrolled systemic disease, consumption of illicit drugs, use of medication associated with oral lichenoid reactions such as methyldopa, IFNα, imatinib and/or infliximab[34]; amalgam restoration near to OLP lesions and/or epithelial dysplasia in the histopathological examination will be excluded from the study.

Randomisation

Randomisation will be performed (ACRTH) using the website www.randomization.com. Forty-four patients will be randomly allocated into the two groups. Randomisation will be blocked (1:1). Then, opaque envelopes, containing the information as to the corresponding group according to the performed random order, will be marked with sequential numbers (1–44). The envelopes will remain sealed until the time of treatment. Only the researcher responsible for the treatment (E.P.F) will open the envelope and perform the treatment written therein. These data will be revealed after statistical analysis.

Experimental groups and study design

Forty-four patients with clinical and histopathological diagnosis of OLP according to the WHO criteria[17] and modified by van der Meij and van der Waal[18] and seen regularly by the Stomatology Department will be invited by phone (CAS) to participate in the study at the University of São Paulo's School of Dentistry Dental Clinic from November 2018 to November 2020. After verification of inclusion criteria, the anamnesis will be applied, and patients will be randomised into two groups: G1 (n=22) control group (topical corticosteroid therapy gold standard): patients will be treated (EPF) with topical clobetasol propionate gel 0.05% for 30 consecutive days and with placebo laser twice a week. Laser device will be positioned over the lesion but will be switched off to mask the treatment. Patients will be instructed to apply the clobetasol propionate gel 0.05% over the entire lesion three times/day. To prevent oral candidiasis, patients will use antimycotic solution (nystatin oral suspension 100 000 USP/mL) once a day for 4 weeks (figure 1). The patients will receive the medication free of charge from the researchers. G2 (n=22) experimental group: application of PBM: patients will be treated with localised low-level laser therapy with a continuous wave diode laser (Laser Therapy XT, DMC Equipment, São Carlos, SP, Brazil, λ=660±10 nm; power: 100 mW; energy density: 177 J/cm^2; 5 s exposure time per point and 0.5J of total energy per point) applied directly to the surrounding oral mucosa and to the centre of OLP, always by the same operator, twice a week for 4 weeks, totalling eight sessions. The number of points will vary according to lesion size. The output power of the laser equipment will be evaluated using a power metre (Laser Check; MMOptics LTDA, São Paulo, Brazil), before treatment, to confirm the effective mean power as well as the doses applied during the procedure. Patients will use antimycotic solution (nystatin oral suspension 100 000 USP/mL) once a day for 4 weeks. No antibiotics or oral antiseptics will be prescribed. Participants who discontinue or deviate from intervention protocols will be excluded from the study. For ethical reasons, these patients will continue to receive treatment according to their needs. The medications will be donated to the patients, and the transportation to and from the clinic will be paid for by the researchers.

The outcome assessor data analyst (DdFTdS) will be blinded during the statistical analyses of outcomes. All adverse effects will be evaluated and noted. Any important modifications to the study protocol will be communicated. We will add the adherence scale to treatment according to Nguyen *et al*[35] to access the adherence to treatment.

Primary outcome measures

Pain

Pain will be assessed by applying a visual analogue scale (VAS), consisting of a 100 mm line numbered in centimetres, with two closed ends. One end is labelled '0' and the other '100', meaning no pain and terrible pain, respectively. Each patient will be instructed to mark a vertical line according to the value, which best matches the intensity of pain during the evaluation. Participants will be evaluated at baseline, once a week during treatment and 30 days and 60 days after the end of treatment (follow-up).

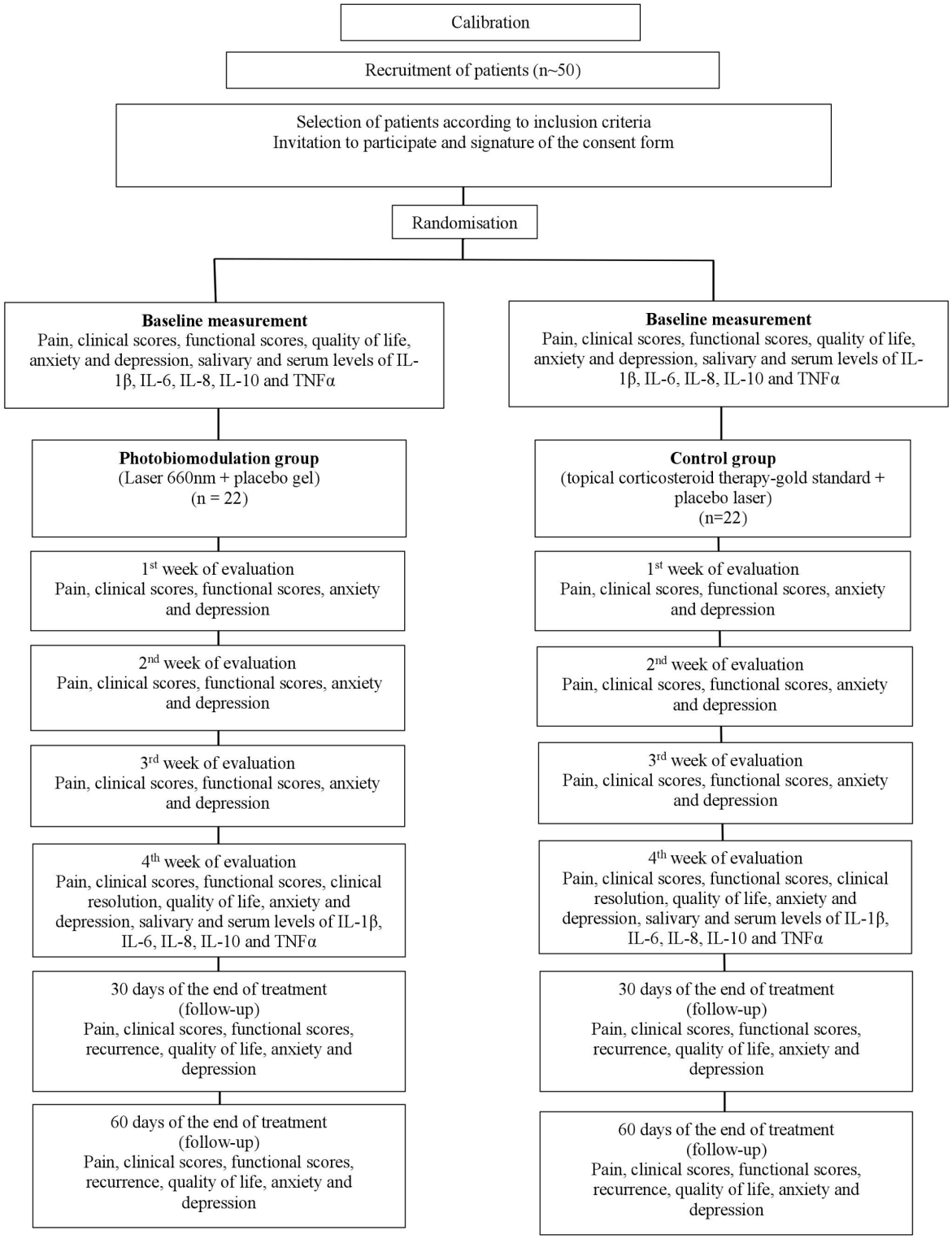

Figure 1 Flow chart of the study. IL, interleukin; TNF-α, tumour necrosis factor-α.

Secondary outcome measures

Assessment of clinical presentation of OLP

Clinical data will be evaluated by photos and scores according to Thongprasom *et al*[36] and the OLP lesions will receive a score of 0 (no lesions), 1 (hyperkeratotic lesions), 2 (atrophic area ≤1 cm^2), 3 (atrophic area >1 cm^2), 4 (erosive area ≤1 cm^2) and 5 (erosive area >1 cm^2). All patients will be evaluated at baseline (day 0), once a week during treatment, as well as 30 days and 60 days after the discontinuation of treatment (follow-up period). Clinical scores will be performed at seven points: at baseline, once a week during treatment and 30 days and 60 days after the discontinuation of treatment (follow-up period). Photographs will be taken during all periods of evaluation.

Function

Functional scores will be applied to evaluate chewing function, swallowing, fluid intake and altered sense of taste, according to Libelly *et al*.[37] Each function evaluated will receive one of the following scores: 0 (no difficulty), 1 (mild difficulty), 2 (moderate difficulty), 3 (severe difficulty) and 4 (impossible to perform specific function). Participants will be evaluated at baseline, once a week during treatment and 30 days and 60 days after the end of treatment (follow-up).

Clinical resolution

Clinical resolution will be evaluated at the end of treatment (day 30) according to Corozzo *et al*.[38] Complete resolution will be considered when patients present absence of symptoms and remission of atrophic/erosive lesions regardless of the presence of any persisting hyperkeratotic lesions. Partial resolution will be considered when a decrease, but not a complete remission of atrophic/erosive areas and symptoms, is observed. No response to treatment will be considered when OLP lesions present the same clinical, or worse, presentation in relation to the baseline condition.

Recurrence rate

The recurrence rate will be evaluated 30 days and 60 days after discontinuation of treatment (follow-up) in comparison with the patient's clinical conditions at the end of treatment. No recurrence will be considered when the patient's lesion presents the same clinical aspect as presented at the end of treatment and recurrence when the patient presents a new atrophic/erosive lesion at the same site during the follow-up period.

Quality of life

Quality of life will be measured by means of the Oral Health Impact Profile (OHIP-14).[39] Each patient will complete the questionnaire at baseline, at the end of treatment and 30 days and 60 days after the end of treatment (follow-up).

Anxiety and depression

The Hospital Anxiety and Depression Scale, which has 14 items, 7 to evaluate anxiety and 7 for depression, will be applied at baseline, during treatment and 30 days and 60 days after the end of treatment (follow-up).[40]

Salivary levels of IL-1β, IL-6, IL-8, IL-10 and TNF-α

Saliva will be collected at baseline and at the end of treatment (day 30). Five millilitres of unstimulated salivary samples will be collected in the morning at baseline and at the end of treatment using the spitting technique. Immediately after, samples will be centrifuged at 400× *g* for 10 min at 4°C, aliquoted and stored at −80°C for later analysis of IL-1β, IL-6, IL-8, IL-10 and TNF-α via ELISA, according to manufacturer's instructions (R&D).

Serum levels of IL-1β, IL-6, IL-8, IL-10 and TNF-α

Blood sample collection will be performed by a trained technician using venous puncture at baseline and and at the end of treatment (day 30). Peripheral blood will be centrifuged at 400× *g* for 10 min at 4°C. Serum will be collected and stored at −80°C. Serum levels of IL-1β, IL-6, IL-8, IL-10 and TNF-α will be evaluated via ELISA, according to manufacturer's instructions (R&D).

Statistical analysis

The statistical distribution of the data will be analysed, and if the data follow a Gaussian curve, parametric tests will be applied. If we notice that the adherence is different from the expected, we will consider intention-to-treat analysis instead of excluding the participants who discontinue or deviate from intervention protocols. Transformation methods or non-parametric tests will be used if the data are unsuitable for a normal distribution. To present the data, box-type and quartile graphs will be constructed according to the median values. The level of significance of 5% will be considered ($p<0.05$). All dada analysis will be performed using GraphPad Prism Software (V.7.0, La Jolla, California, USA).

DISCUSSION

There are few controlled randomised clinical studies in the literature that have evaluated the efficacy of PBM for the treatment of OLP. These few studies have demonstrated, by using the VAS scale, that PBM is effective in reducing OLP patient pain as well as for promoting clinical improvement of OLP lesions during treatment and during the follow-up period.[24 28 30 33] However, these studies present several limitations, including reduced number of patients, inadequate methods of randomisation and absence of treatment masking. In addition, there is no consensus regarding the optimal dosimetric parameters for the treatment of OLP, nor the number of sessions, duration of treatment or length of follow-up period for patients with OLP treated with PBM. For these reasons, it is still debatable if PBM is more effective when compared with the standard corticosteroid treatment when treating OLP, as the scientific evidence is weak.

Thus, it is necessary to determine the efficacy and safety of PBM in OLP, analysing the symptoms, quality of life, clinical presentation and recurrence time in patients with OLP as well as the effects of PBM on the modulation of cytokines involved in the pathogenesis of OLP to better understand the biological mechanism by which this therapeutic tool acts.

Placebo treatment is based on the use of an inert substance. The placebo response is the effect; thereafter, the administration of the placebo and many psychological and neurobiological placebo effects have been described.[41] In this study, to test if PBM as a new treatment modality is as effective as clobetasol propionate 0.05% in the treatment of OLP, the placebo treatment will be used in addition to both standard and PBM treatment. This will facilitate blinding and also control for the placebo effect. Patients allocated to the control group will receive placebo PBM treatment with the device turned off, but

the equipment sound will be prerecorded and played back during treatment to mimic a turned on laser. In the PBM group, patients will be treated with placebo gel for 30 consecutive days.

The laser wavelength of 660 nm selected in this study was based on the controlled randomised trial performed by Dillenburg *et al*[24] in which the authors observed improvement in OLP pain, clinical aspect and recurrence rate in patients treated three times a week with PBM in relation to clobetasol propionate. The dosimetric parameters used in this protocol were based on the equipment available for treatment (Laser Therapy XT, DMC), which has a power output of 100 mW. The rest of the parameters were adjusted for this potency, with the exception of total energy used, which was adjusted to 0.5 J per point so the patients could be treated only twice a week.

In this study, we will include only patients with symptomatic OLP despite the clinical appearance of the lesions. The symptoms of OLP can range from a discrete burning sensation to severe pain; due to the chronic nature of this disease, patient quality of life can be significantly decreased. The VAS will be used to evaluate pain as the vast majority of the studies have used this scale to access OLP symptoms.[42] In addition, the assessment of OLP patients' quality of life, which is important for better understanding the patient's perception of the disease in a psychological, physical and social context, will be evaluated using the OHIP-14 questionnaire. Although this instrument was developed without input from patients with OLP, it is the most frequently used, patient-reported outcome measure used in the literature.[42]

OLP is characterised by an imbalance of Th1 and Th2 immune response and the cytokines produced by immune cells have an important role in the pathogenesis of this disease.[7] There are innumerous inflammatory cytokines characteristic of OLP such as IL-1β, IL-6, IL-8, IL-10 and TNF-α, identified in immunohistochemical studies as well as in the serum and saliva of patients with this disease.[7 43]

TNF-α, a proinflammatory cytokine, plays a very important role in the innate and adaptive immune response, performing several types of functions, including migration and phagocytosis.[44] This cytokine represents one of the most frequent cytokines involved in the OLP pathogenesis.[44] Rhodus *et al* evaluated the levels of TNF-α in the saliva of patients with OLP and observed a significant increase in this cytokine in patients with the disease in relation to healthy patients.[45] The authors point out that it has the potential to be used for prognosis as well as for disease monitoring and response to therapy.

Studies have shown that IL-6 is highly correlated with OLP, being produced at high levels by patients with the disease, exacerbating the local inflammatory response and patient discomfort.[46] Abdel-Haq *et al* demonstrated that patients with OLP have high salivary and plasma concentrations of IL-6 in relation to healthy individuals.[47]

IL-10 is an important cytokine that regulates Th1/Th2 balance and suppresses proinflammatory cytokine production as well as T lymphocyte proliferation.[47] This cytokine is involved in the differentiation and function of T regulatory cells, which control immune response and tolerance. In OLP, high IL-10 levels in both serum and saliva have been observed, and this may be associated with a host-defense response to prevent additional tissue damage by immune cells.[48 49]

In this study, salivary and serum levels of IL-1β, IL-6, IL-8, IL-10 and TNF-α will be evaluated in patients with OLP treated with PBM and clobetasol propionate to evaluate the local and systemic effects of both treatments. In relation to the standard treatment, it has been previously demonstrated that saliva concentrations of the inflammatory cytokines TNF-α, IL1α, IL-6 and IL-8 in patients with OLP showed a significant reduction after treatment with dexamethasone, and the levels of IL-1α and IL-8 were correlated with decreased pain.[45] Regarding PBM, there are no studies in the literature that have investigated the effect of this therapy on the production of inflammatory cytokines in both saliva and blood. However, it is known that PBM has a positive effect on the oral mucosa healing process as it can activate cellular signalling pathways that lead to cell proliferation and migration, modulate the cytokine and chemokine production and control leucocyte influx and oxidative stress.[25] The study of these cytokines will help increase our knowledge of the biological mechanisms triggered by PBM.

The expectation with the protocol presented here is that PBM is as effective as the gold standard therapy with corticosteroid. Moreover, this therapeutic tool has the advantage of not causing adverse effects.

ETHICS AND DISSEMINATION

Results gathered from this protocol will be presented at national and international conferences and will be published in a peer-reviewed journal. All confidential patient data will be protected. Patient identity will not be disclosed.

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Contributors EPF has made contributions to the acquisition of data, analysis and interpretation of data; CdBG has made contributions to acquisition of data or analysis and interpretation of data and has been involved in drafting the manuscript or revising it critically for important intellectual content. CSA has made contributions to acquisition of data; WHY has been involved in drafting the manuscript or revising it critically for important intellectual content. ACRTH has been involved in drafting the manuscript or revising it critically for important intellectual content; DdFTdS has been involved in drafting the manuscript or revising it critically for important intellectual content; CP, SKB and FDN have given final approval of the version to be published. RAM-F and KPSF have given final approval of the version to be published. MFSDR has made contributions to acquisition of data, or analysis and interpretation of data, has been involved in drafting the manuscript or revising it critically for important intellectual content and has given final approval of the version to be published.

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Competing interests None declared.

Patient consent Not required.

Ethics approval Research Ethics Committee of Nove de Julho University.

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