Review

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Effects of laser photobiomodulation in the management of oral lichen planus: a literature review

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Abstract

Objectives. This review aims to understand whether Photobiomodulation (PBM) therapy is a valid aid in the management of Oral Lichen Planus (OLP) and its symptoms. Moreover, an analysis to determine whether it is a valid replacement for conventional therapies and whether standardized protocols can be used in PBM sessions or whether these should be changed depending on the type of injury has been made. Finally, an evaluation to determine whether PBM may induce transformation of dysplastic oral keratinocytes into squamous cell carcinoma has been made.

Materials and Methods. Searches were conducted on two search databases for relevant publications released between 1992 and 2019. The databases used were: Pubmed "Medline", and Google Scholar. Forty-four articles complied with the inclusion criteria and were included for quality assessment and data extraction.

Results. All the studies reported positive effects of PBM; however, there was wide heterogeneity in the laser parameters used in the management of the OLP. The effective dose ranges from 2 to 3 J/cm^2, in order to see the desired biological effects.

Conclusions. PBM is useful in controlling algal sensation and can be used in cases of OLP lesions that are not responsive to conventional therapies or when corticosteroid doses are too high for the patient, resulting in possible side effects. Standardized biostimulation protocols with further scientific insights are therefore required. ***Clin Ter 2021; 172 (5):467-483. doi: 10.7417/CT.2021.2360***

Key words: *dentistry, laser, low-level laser therapy, oral lichen planus, photobiomodulation*

Introduction

Oral Lichen Planus (OLP) is a mucocutaneous chronic disease associated with the evolution of squamous cell carcinoma. To date, its etiology remains uncertain. It majorly affects the female sex and the lesions are visible in the mucous membranes and genitals, skin, nails, and scalp. In the mouth, it occurs as bilateral white lesions that are accompanied, in some cases, by ulcers. The world's OLP prevalence was estimated between 0.5% and 2% in 2015 (1), while the incidence was 2.2%. (2) The disease usually appears in people between the ages of 20 and 70, with few cases in young or pediatric subjects. (3,4) Although it is still not completely clear what triggers this disease, there is some agreement that the disease has an immune-mediated origin, which, from a macroscopic point of view, recalls a hypersensitivity reaction.

This condition is characterized by the presence of a rich lymphocyte T infiltrate present in the epithelial-connective interface. Other types of inflammation mediating cells are involved, such as macrophages, dendrocytes XIII+, and cells of Langerhans. (5) The pathogenetic mechanism is formed by several phases; these are summarized as follows: trigger event, localized release of immunoregulatory cytokines, activation of vascular adhesion molecules, and migration and localization of T lymphocytes with consequent cytotoxic response mediated by T lymphocytes, directed against keratinocytes located on the basal membrane. The determinant agent remains unknown.

However, it seems that the displacement of CD8+ T lymphocytes plays a key role in the pathogenic mechanism. The attraction of lymphocytes to a particular area requires the cytokines' activation of the adhesion molecules of the endothelial cells and the simultaneous expression of the spreading lymphocytes. More specifically, in Lichen Planus, an increased expression of many vascular adhesion molecules is observable, such as ELAM-1 (endothelial leukocyte adhesion molecule-1), ICAM-1 (intercellular adhesion molecule-1), and VCAM-1 (vascular cell adhesion molecule -1), and some lymphocytes expressing reciprocal receptors, such as L-selectine, LFA-1 (lymphocyte function-associated antigen-1), and VLA-4 (very late activation antigen-4), in favor of the hypothesis that a lymphocyte migration process is triggered in Lichen Planus.

The induction of TH1 cytokines appears to be a minor event in this mechanism. It is thought that among the cytokines considered responsible for the activation of adhesion molecules are Tumor Necrosis Factor-alpha (TNF-alpha),

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Interleukin 1, and Interferon Alpha. These cytokines originated from immunomodulatory cells present in the tissues, such as macrophages, dendrocytes XIII a+, and Langerhans cells, as well as from the lymphocytes themselves. Moreover, the keratinocytes of the basal lamina are protagonists in the pathogenesis of the disease, because they might release some of the inflammatory and chemotactic aforementioned cytokines; yet, they represent in the very first place the immunological objective of the lymphocyte reaction. This response also seems to be enhanced by the expression of the ICAM-1 adhesion molecule by the keratinocytes capable of attracting the lymphocytes of the corresponding receptor (LFA-1). This facilitates the cytotoxic reaction of T lymphocytes and keratinocytes. The cell death of keratinocytes seems, finally, to be conveyed by lymphocytes through a mechanism of apoptosis. (5)

There are different OLP clinical forms: reticular, plaque, erosive, erythematous, and bullous. The assessment and diagnosis of this disease forms resulted important because some of them have been associated with the evolution in Oral Squamous Cell Carcinoma (OSCC). (5) Malignancy transformation into OSCC is considered one of the most serious complications of the disease. However, the dispute about OLP malignant transformation still persists. Several factors appear to be involved in the progression of malignant transformation. Molecular changes in OLP samples may be useful biomarkers for predicting and monitoring malignant progression. (6)

Photobiomodulation (PBM), formerly known as Low-Level Laser Therapy (LLLT), is the application of laser or LED to beneficially influence cellular metabolism. It is a non-thermal and safe treatment. The energy and power levels associated with this therapeutic regimen don't cause adverse heating effects or mechanical cellular damage. Since its anti-inflammatory and regenerating properties, PBM was proposed by many authors in the management of OLP.

The aim of this systematic review is to evaluate all studies performed with PBM and OLP, analysing the effects, the action of the technique, the improvement of the algic symptomatology, the stimulation of wound healing and the anti-inflammatory effects. All the physical parameters of laser technology used in the various studies will also be evaluated. A comparison between PBM and other therapies used in OLP treatment has also been proposed in order to understand the various differences among the treatments, including the use of corticosteroids and Photodynamic Therapies (PDT) and the consequent effects on OLP lesions. Finally, the effects of PBM on histologically dysplastic lesions were also analysed. This study examined case series, case reports, not randomized controlled trials, randomized clinical trials, in vitro, in vivo and in ex vivo studies, systematic reviews, and narrative reviews.

Materials and Methods

Clinical Question (PICO)

The elements taken into consideration for the selection of the studies to be included in the systematic review were determined according to the reference methodology "P.I.C.O." (Patient and problem; Intervention; Comparison; Outcome):

- P: A population of participants diagnosed with OLP older than 18 years
- I: Analysis of the efficacy of PBM in patients with OLP
- C: Comparison of the positive and negative effects of PBM on affected subjects
- O: Prevalence of positive effects of PBM in patients with OLP and their response to define when and what are the most appropriate parameters for the treatment of lesions with PBM

Protocol and Registration

The inclusion methods and criteria have been selected on the basis of the PRISMA declaration, which provides a protocol for the reference items that have been included in this systematic review.

Eligibility Criteria: Inclusion and Exclusion Criteria

This systematic review included all articles concerning PBM on lesions from OLP that met the following requirements:

- Participants must have been diagnosed with lichen planus.
- PBM should have been applied to participants.
- Participants must have been over 18 years old.
- In vitro studies

The exclusion criteria were:

- Participants aged under 18 years old
- Lichenoid lesions
- Articles not in the English language

Search

Electronic research was carried out to identify the relevant studies that had been published by 2019, without imposing restrictions on the language of primary studies or methodology, provided that they at least had an English translation. Database Pubmed "Medline" and Google Scholar were used. The keywords used were the same for all two databases and they were all combined with the Boolean term "AND": "low level laser therapy", "photobiomodulation", "oral lichen planus", and "dentistry". The research was completed in November 2019.

Study Selection

The researchers independently analysed the title, abstract, and full text of each article in English to identify which articles could be included and excluded. The disagreements between the auditors were resolved by consensus. Articles that have been published in other languages have not been taken into account, as have studies where lichenoid lesions, or diagnosis of OLP concerned subjects under 18 years of age, and, finally, studies involving the use of laser only for surgical purposes were also excluded.

Data Selection Process

The Authors extracted the data and collected the following information: study design (case series; case control studies; in vivo, ex vivo, and in vitro studies; systematic reviews; narrative reviews; randomized clinical trials; non-randomized controlled trials), participants' characteristics (such as OLP diagnosis), need for treatment with PBM and quantitative data on participants undergoing PBM including treatment response.

Quality assessment

The Newcastle-Ottawa scale (NOS) was used to assess the quality of studies.

Results

At first, 200 studies published between 1992 and 2019 were selected from the databases. After evaluating abstracts, titles, and their full texts, only 44 studies met the inclusion criteria and were included for quality assessment and data extraction. All studies were evaluated using the Newcastle-Ottawa scale. Figure 1 shows a flowchart of the evaluation of publications.

Study Selection and Characteristics

The detailed characteristics of the studies included are presented in Tables 1-9 with reference to the type of study, the author, and the year of publication. This review included five systematic reviews, three case reports, four in vitro studies, four in vivo studies, four non-randomized control trials (CTs), eight randomized control trials (RCTs), 12 case series, one ex vivo study, and three narrative reviews. All included articles were in written in or translated in English.

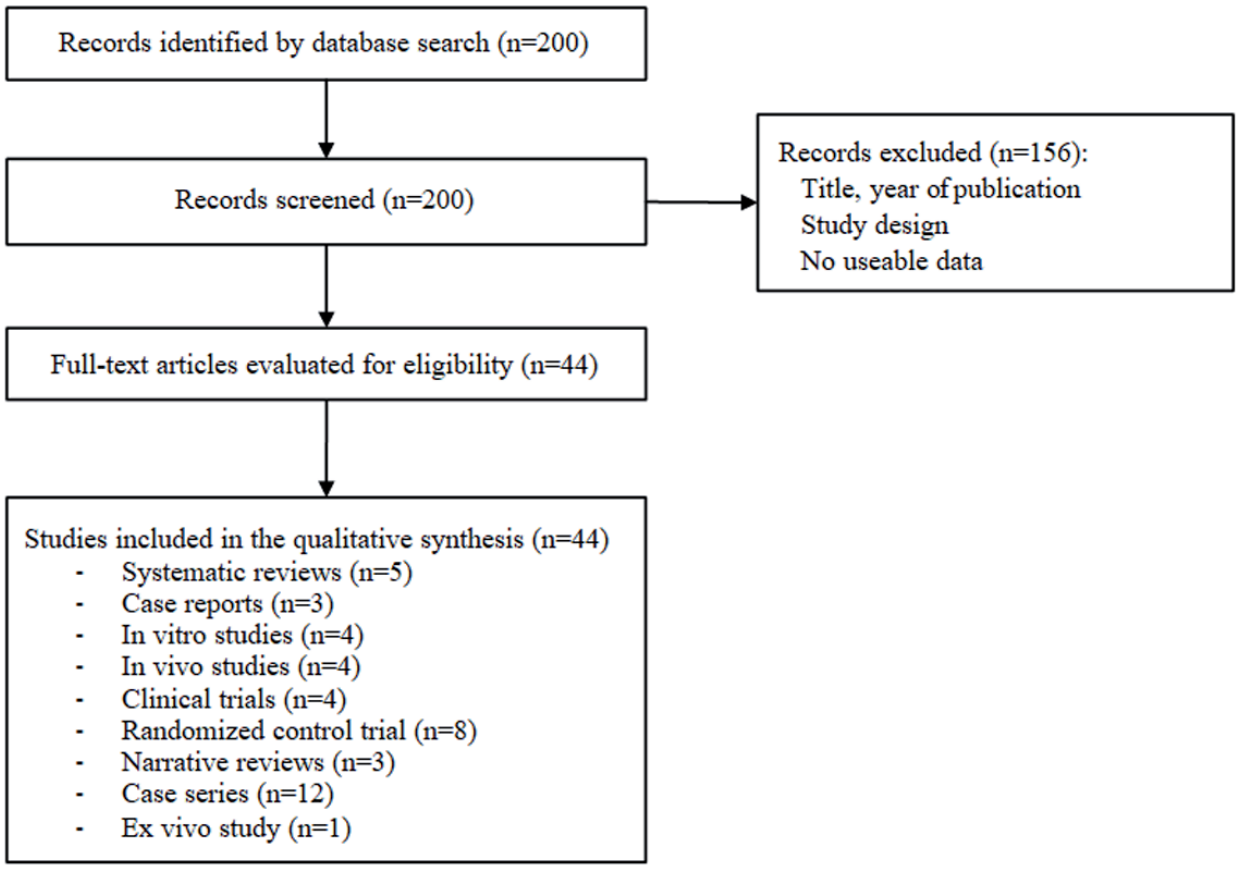

Fig. 1. Flowchart of the systematic review

Table 1. Quality assessment for systematic review

Systematic reviews	Nr. of studies	Type of lesions	Localization of lesions	Treatment	Parameters	Follow-up	VAS	Outcome
- Peplow et al. 2010 (7)	47	Wounds	Different areas	Different types of lasers	Different parameters	-	-	PBM, at a range of dosage parameters (median 4.2 J/cm^2), has a significant benefit for wound healing.
- Al-Maweri et al. 2017 (8)	6	Reticular and erosive-atrophic OLP	Different areas	Diode laser with wavelengths from 630 to 970 nm for 4 to 12 sessions	Power from 10 mW to 3 W	From 3 to 12 months	Different VAS scores	PBM is effective in reducing signs and symptoms of OLP.
- Jajarm et al. 2018 (9)	13	OLP	Different areas	Different types of laser	Different parameters	-	Different VAS scores	PBM reduces pain and sign scores. PDT do not reveal statistically significant differences between the sizes of lesions before and after the treatment.
- Najeeb et al. 2016 (10)	9	Aphthous ulcers	Different areas	Different types of laser	Different parameters	-	-	Various types of lasers have succeeded in providing immediate pain relief to patients.
- Pavlic et al. 2014 (11)	15	OLP	Different areas	Different types of laser	Different parameters	-	4 years	Phototherapy techniques have limited effects but PBM reduced pain and clinical score.

Table 2. Quality assessment for narrative review

Narrative review	Nr. of studies	Type of lesions	Localization of lesions	Treatment	Parameters	Follow-up	VAS	Outcome
- Katayoun et al. 2019 (12)	10 studies (9 RCT; 1 Clinical series)	OLP	Intraoral	PBM	10 mW; 40 mW; 1 W; 2 W; 3 W 0.28 J/cm^2; 0.3/0.5 J/cm^2; 1.5 J/cm^2; 4 J/cm^2; 6 J/cm^2	-	-	Low dose laser treatment can be used as an alternative method in treating symptomatic and erosive OLP.
- Hamblin et al. 2018 (13)	94 with oropharynx, nasopharynx, hypopharynx cancer	Mucositis	Oral mucosa	PBM progression free survival	660 nm, 100 mW, 4 J/cm^2 and spot size 0.24 cm^2	41 months	-	Patients subjected to PBM had better progression-free survival than those in the placebo group (p=0.03) and had a tendency for better overall survival .
- Walsh et al. 1997 (14)	-	Wound	Intraoral	PBM	-	-	-	Acceleration of the healing, PBM selectively inhibits a range of nociceptive signals arising from peripheral nerves.

Table 3. Quality assessment case report

Case report	Nr. of patients	Type of lesions	Localization of lesions	Treatment	Parameters	Follow-up	VAS	Outcome
- Derikvand et al. 2017 (15)	1	Reticular OLP	Left buccal mucosa	980 nm diode laser for 4 sessions/then continued to 10 sessions (3 in a week)	0.3 W, 6J, 20 sec, CW, 6 J/cm^2 / 0.2 W, 4 J, 20 sec, CW, 4 J/cm^2	1 month	80%	Resolution of lesion after one month.
- Madhavi et al. 2013 (16)	2	Erosive/atrophic OLP	Left buccal mucosa/left tongue border	630 nm red diode laser 3 days for a month	10 mW, 1.5 J/cm^2, 150 sec	3 months	10/10 - 7/10	No significant change / regression of lesion.
- Misra et al. 2013 (17)	1	Reticular OLP	Right and left buccal mucosa	940 nm diode laser twice weekly for 2 months	-	7 months	7/10	Complete remission of burning sensation and pain.

Table 4. Quality assessment for ex vivo studies

Ex vivo study	Nr. of samples	Type of lesions	Localization of lesions	Treatment	Parameters	Follow-up	VAS	Outcome
- Prabhu et al. 2012 (18)	75 albino Mice	Wound	-	5 groups: 1st group: non-illuminated; the other 4 groups: He-Ne laser (632.8 nm)	7 mW, 4.02 mW/cm^2, CW, Spot size 15 mm Duration of irradiation: - 2nd group: 2 min 08 sec – 0.5 J/cm^2 - 3rd group 4 min 15 sec – 1 J/cm^2 - 4th group: 6 min 23 sec – 1.5 J/cm^2 - 5th group: 8 min 32 sec – 2.0 J/cm^2	15 days	-	Significant increase in collagen deposition along with the reduced edema, leukocytes, increased granulation tissue, and fibroblast number.

Table 5. Quality assessment for in vitro studies

In vitro study	Nr. of lesions	Type of lesions	Localization of lesions	Treatment	Parameters	Follow-up	VAS	Outcome
- Pinheiro et al. 2002 (19)	Hep2 cells defrosted	-	-	635 nm or 670 nm diode laser for 7 days	0.04, 0.06, 0.08, 1.2, 2.4, and 4.8 J/cm^2	-	.	Irradiation with 670 nm laser applied at doses between 0.04 and 4.8 J/cm^2 increases the proliferation of cells.
- Liu et al. 2004 (20)	HepG2 and J-5 cells (SCC9)	-	-	Diode GaAlAs 808 nm	130 mW, CW	-	-	Proliferation of HepG2 and J-5 cells was inhibited.
- Frigo et al. 2009 (21)	B16F10 melanoma cells	Melanoma	-	In-Ga-Al-AsP – 660 nm, 3 times for 3 consecutive days	Treatment Group: 150 J/cm^2 with an irradiance of 2.5 W/cm^2 for 60 sec. 2nd group: received sessions with an PBM dose of 1050 J/cm^2 with an irradiance of 2.5 W/cm^2 for 420 sec.	24, 48, and 72 hours after irradiation	-	There were no statistically significant differences between the in vitro groups, except for an increase in the hypodiploid melanoma cells at 72 hours post irradiation.
- Sperandio et al. 2013 (22)	oral dysplastic cells (DOK) and oral cancer cells (SCC9 and SCC25)	Dysplasia and oral cancer	-	GaAlAs -660 nm or 780 nm	Irradiated at 40 mW with different energy density of 2.05, 3.07, and 6.15 J/cm^2	12, 24, 48, and 72 hours	-	PBM modified the expression of proteins related to progression and invasion in all the cell lines, and could aggravate oral cancer cellular behavior.

Table 6. Quality assessment for in vivo studies

In vivo study	Nr. of samples	Type of lesions	Localization of lesions	Treatment	Parameters	Follow-up	VAS	Outcome
- Gal et al. 2006 (23)	49 rats	-	-	670 nm diode laser	25 mW/cm^2 in CW	-	-	Laser stimulation shortened the inflammatory phase and stimulated the regeneration of epidermis.
- Rhee et al. 2016 (24)	30 mice	Thyroid cancer	-	650 nm diode laser	15 or 30 J/cm^2 in CW	4 weeks	-	PBM decreases TGFβ1 and increases p-AKT/HIFα1.
- Frigo et al. 2009 (21)	21 mouse	Melanoma	-	660 nm diode laser, 3 times daily for 3 days	50 mW, CW, beam spot size 2 mm^2, irradiance of 2.5 W/cm^2 1st group for 60 sec (dose 150 J/cm^2) and 2nd group for 420 sec (dose 1050 J/cm^2)	15 days	-	PBM irradiation over melanomas with a combination of high irradiance (2.5 W/cm^2) and high dose (1050 J/cm^2) significantly increased melanoma tumor growth.
- Gavish et al. 2009 (25)	38 mice	Abdominal aortic aneurysm	-	780 nm diode laser	4 mW/cm^2 for 9 min	4 weeks	-	PBM has a substantial effect on arterial wall elasticity.

Table 7. Quality assessment for clinical trial

Clinical trial	Nr. of subjects	Type of lesions	Localization of lesions	Treatment	Parameters	Follow-up	VAS	Outcome
- Ozcelik et al. 2008 (26)	20	Gingival Hyperplasia	Maxillary and mandibular anterior areas	Diode laser 588 nm for 7 days	120 mW, irradiance of 4 J/cm^2 for 5 min in CW	15 days	-	PBM enhances epithelization and improves wound healing.
- El Shenawy et al. 2015 (27)	24	Erosive-atrophic OLP	Different areas	Two groups: 1st group: twice weekly with 970 nm diode laser for 2 months; 2nd group: with topical corticosteroids (0.1% TAO) 4 times daily for 1 month	4 applications for 2 min each, power of 3.0 W, frequency of 30 Hz	1st group: 2 months 2nd group: one month	-	Topical steroids are more effective than PBM. PBM may be used as an alternative treatment for symptomatic OLP when steroids are contraindicated.
- Othman et al. 2016 (28)	24	Different clinical forms of OLP	Different areas	Two groups: 1st group: treated with diode laser (970 nm) twice weekly for 10 sessions; 2nd group treated with topical corticosteroids (0.1% TAO) 4 times daily for 1 month	2 W in CW, in a non-contact mode. 8 min in 4 subsequent sessions	-	-	Topical steroids reduce pain, reticular, atrophic, erosive RAE score and TNF-α serum level more than laser treatment.
- Thongprassom et al. 1992 (29)	40	Erosive-atrophic OLP	Different areas	Two groups: 1st group: 0.1% TAO orobase; 2nd group: with 0.1% FAO orobase. Four application daily for 1 month	-	1st group: 2 weeks; 2nd group: 1 month	-	FAO is better in the treatment of OLP and has no serious clinical side effects except candidiasis.

Table 8. Quality assessment case series

Case series	Nr. of subjects	Type of lesions	Localization of lesions	Treatment	Parameters	Follow-up	VAS	Outcome
- Kvaal et al. 2013 (30)	14	Different clinical forms of OLP	Different areas	Methyl-5 aminolevulinate (MAL) with red light using LED from 600 to 660 nm	75 J/cm^2 of red light and 37 J/cm^2 for large areas	4 years	-	MAL is absorbed and converted to PpIX in T cells. OLP treated with MAL-PDT (Photodynamic Therapy) showed an improvement after a single treatment.
- Sadaksharam et al. 2012 (31)	20	Atrophic-erosive OLP	Different areas	5% methylene blue (MB) with a Xenon arc lamp (630 ±5 nm)	Total dose: 120 J/cm^2, 3 times; each session 20 min	6 months	-	MB in combination with PDT reduced signs and symptoms of OLP without side effects.
- Rhodus et al. 2006 (32)	13	Erosive-ulcerative OLP	Different areas	0.1% dexamethasone mouthwash 3 times per day for 6 weeks	-	6 weeks	-	The levels of TNFα, IL-I-α, IL-6 decrease d significantly; also VAS value decreased.
- Cafaro et al. 2010 (33)	13	Atrophic-erosive OLP	Different areas	Ga-AL diode laser 904 nm, 2 sessions weekly	4 J/cm^2 energy per minute	6.46 months	Different values	PBM could be a possible treatment for unresponsive OLP.
- Cafaro et al. 2014 (34)	30	Atrophic-erosive OLP	Different areas	Ga-AL diode laser 980 nm, one laser irradiation weekly until the resolution of signs	4 J/cm^2, 300 mW, for 3.73 sec for each lesion	26 months	6.57 on average (T0)	Significant reduction in clinical scores of the treated lesions and in reported pain.

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- Elshenawy et al. 2015 (35)	10	Different clinical forms of OLP	Different areas	Diode laser 970 nm twice weekly for 2 months	Power at (3 W), frequency of 30 Hz, energy of 180 J for 8 min in 4 subsequent sessions	2 months	7 on average	PBM improved lesion size and showed complete remission of burning sensation and pain.
- Kundoor et al. 2015 (36)	10	Leucoplakia and different clinical forms of OLP	Different areas	Diode laser 980 nm	4 W in CW	6 months	6-7 for 3 patients and 3-5 for 7 patients	Diode lasers provide acceptable clinical improvement of potentially malignant lesions with minimal side effects.
- Mutafchieva et al. 2018 (37)	12	Erosive-atrophic OLP	Different areas	Diode laser 810 nm, 3 times a week for one month	0.5 W, 30 sec, 1.2 J/cm^2	-	Different values	PBM improved pain and sign scores.
- Prassana et al. 2015 (38)	16	Oral leucoplakia (OL) and OLP	Different areas	5% MB for 5 min and exposed to red light at 630 ±10 nm twice a week, 4 weeks for OLP lesions	Dose of 120 J/cm^2	3 months	Different values	MB-PDT is an effective modality in management of OLP and OL.
- Sobaniec et al. 2013 (39)	23	Different clinical forms of OLP	Different areas	20% chlorin e6 and 10% dimethyl sulfoxide 1 hour before illumination and exposed to a semiconductor laser (660 nm) for 10 sessions	Power of 300 mW, and with a density of 90 J/cm^2	-	-	PDT can be useful in the treatment of OLP lesions.
- Trehan et al. 2004 (40)	8	Different clinical forms of OLP	Different areas	Excimer laser 308 nm once a week with a maximum of 30 treatments	Starting dose at 100 mJ/cm^2 and after increased by 50 mJ/cm^2	Weekly follow-up	Different values	Low dose of excimer laser can be effective in treating symptomatic OLP.
- Aghaosseini et al. 2006 (41)	13	Different clinical forms of OLP	Gingival and buccal areas	5% MB for 5 min mouthwash and irradiation with diode laser (632 nm)	Dose 120 J/cm^2 for 2 min	3 months	Different values	MB-PDT seems to be an effective alternative treatment for OLP in the reduction of signs and symptoms.

Table 9. Quality assessment for randomized control trial (RCT)

RCT	Nr. of subjects	Type of lesions	Localization of lesions	Treatment	Parameters	Follow-up	VAS	Outcome
- Kardash et al. 2008 (42)	50	Hip disease	Hip	40 mg of dexamethasone	-	1 month	-	Single dose of dexamethasone 40 mg had an effect on the inflammatory response and decreased pain 24 hours after hip arthroplasty.
- Agha-hosseini et al. 2012 (43)	28	Different clinical forms of OLP	Different areas	One group with CO_2 laser; second group with diode laser with 2 probes: infrared light (Ga-Al 890 nm) and the other red light (633 nm) for 5 sessions every other day	Infrared light: 0.3- 0.5 J/cm^2; Red light: CW, 0.3-0.5 J/cm^2	3 months	Different values	PBM displayed better results than CO_2 laser treatment.
- Dillenburg et al. 2014 (44)	42	Atrophic-erosive OLP	Different areas	Two groups: 1st group clobetasol propionate gel (0.05%) three times a day, PBM group (n=21): application of laser irradiation using InGaAlP diode laser three times a week. diode laser (InGaAlP 660 nm)	Power output of 40 mW, density 1000 mW/cm^2, energy density of 6 J/cm^2, 6 sec exposure time per point, and 0.24 J of total energy per point	2 months	Different values	PBM proved more effective than topical clobetasol 0.05% for the treatment of OLP.
- Jajarm et al. 2011 (45)	30	Atrophic-erosive OLP	Tongue and buccal mucosa	Two groups: 1st group with diode laser (630 nm) 2 times a week, for a maximum of 10 sessions; 2nd group with 0.5 mg desamethasone mouthwash for 5 min followed by 30 drops of nystatin for 5 min. All of this 4 times a day for 1 month	Fluence 1.5 J/cm^2, irradiance of 10 mW/cm^2 for 2.5 min	1 year	Different values	PBM had the same efficacy as topical corticosteroids in the treatment of OLP.

FOLLOWS

- Jajarm et al. 2015 (46)	25	Keratotic-atrophic-erosive OLP	Tongue and buccal mucosa	Two groups: 1st group with 50 µl of toluidine blue (TB) mediated with GA-Alas diode laser (630 nm) 2 times weekly for 1 month; 2nd group with 0.5 mg of dexamethasone mouthwash for 5 min followed with 30 drops of nystatin for 5 min. All of this 4 times a day for 1 month	Power density 10 mW/cm^2 and fluence 1.5 W/cm^2 for 2.5 min	1 month	Different values	TB-PDT (Photodynamic Therapy) is an effective treatment for OLP, but topical corticosteroids show better results.
- Kalakonda et al. 2016 (47)	20	Inadequate vestibular depth	Inadequate vestibular depth	Two groups: 1st group: scalpel blade n 15; 2nd group: with 808 nm wavelength diode laser for surgical treatment and also for biostimulation	Power setting of 1 W for 30 sec for biostimulation	72 hours	Different values	Laser can be a safe and effective alternative to traditional vestibuloplasty performed with the scalpel.
- Kazancioglu et al. 2015 (48)	120	Atrophic-erosive OLP	Tongue or buccal mucosa	Three groups: 1st group with ozone therapy with a concentration of 10~00 µg/ml; 2nd group with diode laser 808 nm. Both 2 times a week for a maximum of 10 sessions; 3rd group: dexamethasone mouthwash for 5 min, followed with 30 drops of nystatin solution, 4 times daily for 1 month	1st group: the ozone generator had an intensity of 60% for 10 sec; 2nd group: fluence, 1.5 J/cm^2, irradiance of 10 mW/cm^2, dose 120 J/cm^2 for 2.5 min	6 months	Different values	Ozone and corticosteroid therapies were more effective than 808 nm PBM in the treatment of OLP.
- Mirza et al. 2018 (49)	45	Atrophic-erosive OLP	Tongue or buccal mucosa	Three groups: 1st group with 50µl toluidine blue with micropipette and PDT laser irradiation using GaAlAs laser (630 nm) two times weekly for 1 month; 2nd group: diode laser (630 nm) two times a week, for a maximum of 10 sessions; 3rd group: dexamethasone 0.5 mg mouthwash for 5 min and after 30 drops of Nystatin for 5 min, 4 times a day for 1 month	1st group: fluence of 1.5 J/cm^2 per session, power density of 10 mW/cm^2 for 2.5 min 2nd group: fluence of 1.5 J/cm^2 per session, irradiance of 10 mW/cm^2 for 2.5 min	1 year	Different values	PDT and PBM are effective in the treatment of erosive-atrophic forms of OLP in adult patients.

Results of Individual Studies

Analysis of the studies – in particular five systematic reviews, three narrative reviews, three case reports, one ex vivo study, four in vitro studies, four in vivo studies, four clinical trials, 12 case series, and eight randomized clinical trials – enabled the determination that laser treatment allowed excellent management of lesions from OLP. In addition, after measuring the pain sensation through the VAS scale, a significant reduction in algic sensation and a significant reduction in lesion size was described at the follow-up. (15,17) When case reports were analysed, each one concluded that although there were positive effects of PBM on observed patients, further scientific insights into a wider sample of patients would be needed. (12-15) (Tab. 9)

In a review conducted in December 2019 by Katayoun et al., the efficacy of PBM on OLP lesions was once again demonstrated: articles have been studied since April 2019 and all are in agreement on the reduction of signs and symptoms with PBM treatment on this type of lesion. (12)

In the case series, results are generally on the same trend: there was a significant reduction in pain and burning sensation. (33,35,37,40) In a study of Kundoor et al., pain disappeared after the first week of treatment. (36) Cafaro et al. study treated 30 patients for a total of 82 lesions and 64 of these had a complete resolution without complications and, in the follow-up at 26.6 months, 15 patients had no new lesions. (34)

In systematic reviews, the evidence from the studies suggested that the use of a red or infrared wavelength in a range of dosing parameters (median 4.2 J/cm^2) leads to significant benefits in measured wound healings. (7) An analysis was made to understand the role of corticosteroids, and a comparison was made between the efficacy of PBM vs corticosteroids. In all the studies analysed by Al-Maweri (8), including the study of Dillenburg et al. and Otham et al, it has been reported that the PBM is effective in reducing signs and symptoms of OLP. (8,28,44) Dillenburg et al. showed significantly better improvement in the signs and symptoms of OLP in the laser treated group compared to clobetasol treated group. (44)

It is important to remember that there are some side effects resulting from the use of topical corticosteroids, but, nevertheless, these effects appear to be limited and generally well tolerated. Adverse reactions include secondary candidiasis, nausea, mucous atrophy, xerostomia, dysgeusia, and delayed healing of oropharyngeal wounds during treatment. (50-52) In a study of Thongprassom et al, two types of corticosteroids, Fluocinole Acetonide (FAO) and Triamcinolone Acetonide (TAO), were compared and it has been shown that there are better results with FAO. However, some side effects, such as candidiasis, could occur. (29)

Therefore, laser therapy plays an important role in the management of OLP lesions since its ability to reduce painful symptoms, anxiety levels, lesion size, and side effects compared to corticosteroids. (44) Othman et al. and Jajarm et al. experienced a marked improvement in TNF-alpha parameters in both PBM and corticosteroid. (8,28,45)

By contrast, Kazancioglu et al. and Elshenawy et al. noticed a much more significant decrease in pain in the corticosteroid group in both studies than in the PBM group. (8,27,48) Although these studies used different types of corticosteroids, the results yield the conclusion that there is still decreased pain and lesion size. (8,32,41)

In this review, a comparison was also made between PDT and PBM, and their effectiveness was compared: in general, PDT and PBM were effective in the treatment of erosive-atrophic forms of OLP in adult patients. In fact, PDT and PBM could improve clinical signs and symptoms of OLP, and, compared to steroid therapy, appear to be a therapeutic mode with few or no side effects. The underlying principle of PDT is that the light activates the photosynthesizer that acts in a chemical reaction and then, by combining with the oxygen of the tissue, it releases free radicals leading the target cells to apoptosis. (46)

Moreover, in a review of Pavlic et al. some studies have been reported a reduction in algic sensation and a decrease in pain and burning sensation, with an improvement also in the size of the lesion. (11,31,38) Dabrowski et al. also showed how PDT manages to direct the effect of light on a very precise target. (53) Furthermore, in a study by Mirza et al, it was found that although the PBM is useful in the management of OLP, the efficacy index, namely the improvement of symptoms, of the PDT group is significantly better than in the PBM group ($p=0.001$) and in the corticosteroid group ($p=0.001$). (49)

The question was whether PBM could lead to the transformation of already dysplastic and potentially malignant lesions into carcinoma. In addition, the study by Sperandio et al. showed that the line of oral dysplastic cells (DOK) treated with laser and red light (660 nm) or near infrared (780 nm) showed increased cell proliferation during all experimental periods, wavelengths and laser doses used. In addition to proliferation, an increase in specific proteins related to cancer invasion and progression has been observed, such as Pakt, Hsp90, pS6ser/244 and cycline D1. (22)

Therefore, PBM could modify cellular behavior with a dose-dependent trend (18,25), which is why it is generally counterproductive in the treatment of proliferating or dysplastic lesions that can potentially turn into neoplasm. (19) In vivo studies were also performed with regard to the PBM capability to cause a malignant transformation. Frigo et al. exposed in their paper that the low dose (150 J/cm^2) reduced the size of the tumor (not statistically significant), while the high dose (1050 J/cm^2) significantly increased the size of the tumor. (21) A study of Rhee et al. also showed that tumor growth was faster in PBM; HIF-1a and Pakt groups increased, while TGF-b1 expression decreased. (24)

Finally, the review of Hamblin et al. showed that although there are some articles that suggest that PBM therapy can be harmful in animal models of tumors, there are also many articles that suggest the opposite, proving that the laser light can directly damage the tumor by enhancing other anticancer therapies and stimulating the host's immune system. In addition, there are two clinical trials that show increased survival in cancer patients who received PBM. (14)

Discussion

The aim of this review is to understand the efficacy of PBM on OLP lesions. Since PBM has the ability to stimu-

late cell differentiation and improve wound healing and re-epithelization, PBM was proposed for the treatment of this disease. (23,26) PBM plays a key role in the production of ß-endorphins and enkephalins and in reducing levels of bradykinin and histamine, thus contributing to an analgesic and pain-relieving effect. The analgesic effect of PBM is also corroborated by its action on C fibers, reducing their activity and leading to a reduction in the conduction of pain stimuli. (47)

The reduction of clinical signs of OLP after PBM could be explained by PBM biological activity in enhancing proliferation, differentiation, and migration of fibroblasts and ultimately in the stimulation of epithelial cells, which are considered key factors in the healing process of the oral mucosa. (10)

In addition, PBM plays a crucial role in immunomodulation because it improves the release of leukocytes in oral tissues, controlling inflammation of the oral mucosa. (14) Therefore, all the reported studies show positive effects of PBM with a significant reduction of signs and symptoms from OLP lesions. (8,9,12-17,28,33-37,44) The studies generally concluded there was reported wide heterogeneity in the parameters of the lasers used and the follow-up in some cases was too short. In this way, it is not possible to assert that PBM is the best therapy and the only one to be exploited in the control of the OLP; also because, as reported in some studies, better results are expected with both PDT and corticosteroids than with PBM. (48,49) Analysis of available literature found that doses between 0.001 and 10 J/cm^2 provide the ideal therapeutic window for biostimulation. (54) It is also important to say that, according to the literature, besides performing the same laser parameters for all patients undergoing this treatment, it is necessary for the effective dose to be between 2 and 3 J/cm^2 in order to have a positive effect on the various lesions. (55) However, despite this, there are still the effects of PBM: analgesic effects going to compete with C-fibers and thus allowing the decrease of painful conduction (10) and the decrease of the size of the lesion. PBM is able to stimulate the production of fibroblasts, which may play a key role in tissue healing. (47)

The wide heterogeneity of the study projects, and the parameters for laser applications, made the treatment results of these studies the limit of this review. Effectiveness of PBM is influenced by various factors, such as wavelength, output power, energy density, treatment duration, and operating mode. Of all these factors, the one that has a fundamental role appears to be the dose of application, but nevertheless, taking the diversity of the laser parameters into consideration, an effective dose with precise values has not yet been established (56,57).

Conclusions

There are many positive biological effects promoted by the use of laser therapy and only a few side effects are reported, especially in comparison with the side effects related to the use of corticosteroids. (50,51) Therefore, it has been demonstrated that this treatment is much less invasive than traditional pharmacological treatments; however, better results will be necessary in proving this assessment. As already mentioned, establishing settings and application timings is necessary, by testing them on extended samples. In fact, the use of procedures, settings, fluences, pulsation frequencies, and wavelengths are extremely variable in many available studies. Standardized guidelines and protocols should therefore be established for OLP lesions treated with PBM.

Regarding the question of whether there is actual development of carcinogenic oral dysplastic cells or not, opinions remain divided. Through in vitro studies, it was found that there is a high proliferation of dysplastic cells and an increase in akt/mtor/cyclamen D1 proteins following treatment with PBM up to 72 hours after the laser session and with a single dose. For this reason, additional studies will be necessary both in vitro, to determine whether higher doses of PBM can produce results that go beyond 72 hours, and in vivo in order to understand whether and how dysplastic cells in patients may undergo malignant transformation.

Conflict of interest

There is no conflict of interest in this study and it did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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