PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Efficacy of photobiomodulation on oral lichen planus: a protocol study for a double-blind, randomized controlled clinical trial
AUTHORS	Ferri, Elza; Gallo, Camila; Abboud, Clery; Yanaguizawa, Wellington; Horliana, Anna Carolina; Silva, Daniela; Pavani, Christiane; Bussadori, Sandra; Nunes, Fabio; Ferrari, Raquel; Fernandes, Kristianne; Rodrigues, Maria Fernanda

VERSION 1 – REVIEW

REVIEWER	Dr Santosh R Patil College of Dentistry, Jouf Univeristy, KSA
REVIEW RETURNED	21-May-2018

GENERAL COMMENTS	The authors should mention what type of oral lichen planus patients included Inclusion criteria Exclusion criteria

REVIEWER	Paolo G. Arduino University of Turin, Italy
REVIEW RETURNED	05-Jun-2018

GENERAL COMMENTS	Dear editor, thanks for the opportunity to review this study procotol about the efficacy of photobiomodulation on oral lichen planus. The study desing is well performed. I do only suggest some minor changes: INTRODUCTION: please state some of the limits of previous study about PBM and OLP. M&M: inclusion criteria (please give the name of some of the most common medication associated with lichenoid lesions; otherwise, give some references)_pag 7 line 7 M&M: experimental design (please give some explanation about you decide to use clobetasol 3 times daily for 1 month and nystatin only 1 daily: in literature other proposed regimen have been published, different from this). Give some ref and explain your choice _ pa 7 line 40-42 M&M: secondary outcomes (please give better explanation about methods of sampling saliva)_ pag 9 line 36 There are some typos all over the manuscript.

REVIEWER	Maria Siponen Institute of Dentistry, University of Eastern Finland, Finland
REVIEW RETURNED	19-Jun-2018

GENERAL COMMENTS	1. Please state more clearly what is the hypothesis of the study (noninferiority or equivalent trial)

	2. You could consider intention to treat analysis instead of excluding the participants who discontinue or deviate from intervention protocols. This way the sample size is not reduced if a participant discontinues or deviates from protocol. 3. In the Clinical Trials register the estimated enrollment should be 44 instead of 22

REVIEWER	Lopez Jornet Pia University of Murcia
REVIEW RETURNED	23-Jul-2018

GENERAL COMMENTS	Efficacy of photobiomodulation on oral lichen planus: a protocol study for a double-blind, randomized controlled clinical trial Not all oral lichen planus produce symptom (summary clinical characteristics were scored using example Thongprasom Index Thongprasom K, Luengvisut P, Wongwatanakij A, Boonjatturus C. Clinical evaluation in treatment of oral lichen planus with topical fluocinolone acetonide: a 2-year follow-up. J Oral Pathol Med 2003; 32: 315–322. Symptoms were evaluated using visual analogue scales (VAS) It should indicate that pain (VAS) was included Treatment period was short Response to treatment according to criteria???? no standardized methods for evaluating the severity You must indicate the degree of compliance with the treatment Adherence to treatment was assessed with the Adherence Scale ???

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:
Reviewer: 1
Reviewer Name: Dr Santosh R Patil
Reviewer's comment: The authors should mention what type of oral lichen planus patients included in Inclusion criteria and Exclusion criteria.
Answer: We thank the reviewer for the suggestion. We have added the information regarding the type of oral lichen planus included in the study in the Inclusion and Exclusion criteria as described below.
"The participants in this study will be male and female (over 18 years of age) diagnosed with symptomatic lesions of reticular, atrophic or erosive oral lichen planus, based on the clinical and histopathological criteria of the World Health Organization (1978) and modified by van der Meij and van der Waal18."
Reviewer: 2
Reviewer Name: Paolo G. Arduino
Dear editor, thanks for the opportunity to review this study procotol about the efficacy of photobiomodulation on oral lichen planus. The study desing is well performed.
I do only suggest some minor changes:
Reviewer's comment: INTRODUCTION: please state some of the limits of previous study about PBM and OLP.

Answer: We thank the reviewer for the suggestion and we have included in the Introduction a paragraph to describe some limitations of previous studies about PBM and OLP as described above.
“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 randomization 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. “
Reviewer’s comment: M&M: inclusion criteria (please give the name of some of the most common medication associated with lichenoid lesions; otherwise, give some references)pag 7 line 7
Answer: We thank the reviewer for the suggestion and we have included in the M&M the medications that seems to be causative of lichenoid drug reactions according to the systematic review of Fortuna, Aria and Schiavo, published on European Journal of Clinical Pharmacology (2017).
“Patients with ongoing cancer, pregnant or breastfeeding women, patients with a history of corticosteroids or NSAIDS 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, IFN-alpha, 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.
Fortuna G, Aria M, Schiavo JH. Drug-induced oral lichenoid reactions: a real clinical entity? A systematic review. Eur J Clin Pharmacol. 2017 Dec;73(12):1523-1537. doi: 10.1007/s00228-017-2325-0.

Reviewer’s comment: M&M: experimental design (please give some explanation about you decide to use clobetasol 3 times daily for 1 month and nystatin only 1 daily: in literature other proposed regimen have been published, different from this). Give some ref and explain your choice _ pa 7 line 40-42
Answer: According to the review performed by Gøtzsche and Johansen, published in the Cochrane Database of Systematic Reviews (2014), the effect of nystatin was similar to that of placebo on fungal colonization in severely immunodepressed patient. In addition,

in the study performed by Marable et al. (2016), no significant difference in the incidence of oral fungal infection between OLP patients treated with a preventive antimycotic therapy and those not treated prophylactically was observed in a cohort of 315 patients. However, this study observed that patients using clobetasol had a significantly higher incidence of oral fungal infection compared to other steroid therapies. Thus, based in our clinical experience and in the literature, we have included the preventive use of nystatin once a day during the treatment of OLP patients.
Marable DR, Bowers LM, Stout TL, Stewart CM, Berg KM, Sankar V, DeRossi SS, Thoppay JR, Brennan MT. Oral candidiasis following steroid therapy for oral lichen planus. Oral Dis. 2016 Mar;22(2):140-7.
Gøtzsche PC, Johansen HK. Nystatin prophylaxis and treatment in severely immunodepressed patients. Cochrane Database of Systematic Reviews 2014, Issue 9. Art. No.: CD002033. DOI: 10.1002/14651858.CD002033.pub2.
Reviewer’s comment: M&M: secondary outcomes (please give better explanation about methods of sampling saliva) pag 9 line 36
Answer: We thank the reviewer for the suggestion. We have included the paragraph bellow to describe the methods of saliva sample collection.
Five ml 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 400xg 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 TNFα -α via Enzyme Linked Immune Sorbent Assay (ELISA), according to manufacturer’s instructions (R&D).
Reviewer’s comment: There are some typos all over the manuscript.
Answer: We apologize for the typos and we have corrected them.

Reviewer: 3
Reviewer Name: Maria Siponen
Reviewer's comment: Please state more clearly what is the hypothesis of the study (noninferiority or equivalent trial).
Answer: We would like to thank Reviewer for pointing this out. We expect that both treatments have equal efficacy. Thus we included sentence bellow in the Introduction.
"In this context, this double-blind, randomized 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."
Reviewer's comment: You could consider intention to treat analysis instead of excluding the participants who discontinue or deviate from intervention protocols. This way the sample size is not reduced if a participant discontinues or deviates from protocol.
Answer: We thank the reviewer for the suggestion. 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. We write this statement in the Material and Methods section as described below.
"The statistical distribution of the data will be analyzed 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 is 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 Software (version 7.0, La Jolla, CA, USA).
Reviewer's comment: In the Clinical Trials register the estimated enrollment should be 44 instead of 22.
Answer: We thank the reviewer for the correction. We have changed the number of patients in the Clinical Trial.
Reviewer: 4
Reviewer Name: Lopez Jornet Pia
Reviewer's comment: Not all oral lichen planus produce symptom (summary clinical characteristics were scored using example Thongprasom Index; Thongprasom K, Luengvisut P, Wongwatanakij A, Boonjatturus C. Clinical evaluation in treatment of oral lichen planus with topical fluocinolone acetonide: a 2-year follow-up. J Oral Pathol Med 2003; 32: 315–322.
Answer: We have included the sentences bellow in the Summary.
Methods and analysis: Forty-four patients with symptomatic and histopathological diagnosis of OLP will be randomized into 2 experimental groups in a double-blind manner: Control group (n=22) - clobetasol propionate 0.05% + placebo PBM and Experimental group (n=22) – PBM (λ = 660nm, power 100mW, radiant exposure: 177J/cm2, and 0.5J per point) + placebo gel. Laser will be applied 2x/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 and 60 days of follow up. Pain will be evaluated using Visual Analogue Scale (VAS) and clinical characteristics will be scored using the Thongprasom Index.
Reviewer comment: Symptoms were evaluated using visual analogue scales (VAS) It should indicate that pain (VAS) was included.
Answer: We thank the author for the suggestion. We have included the sentence bellow in the Summary.
"Pain will be evaluated using Visual Analogue Scale (VAS) and clinical characteristics will be scored using the Thongprasom Index."
Reviewer's comment: Treatment period was short.

Answer: In the recent systematic review performed by Maweri et al. (2017), the number of sessions with PBM in the literature varied from 5 to 12. Moreover, the study performed

by Dillenburg et al. (2014), which was included in the systematic review and showed moderate estimated risk of bias, have demonstrated that PBM was more effective as propionate clobetasol (0.05%) when the OLP patients were treated three times a week during four consecutive weeks totaling 12 sessions. The present protocol was based in this study but some modifications were needed as the patients were unable to go to the clinic three times a week. Thus, PBM with 0.5J per point will be used twice/week for four consecutive weeks, totaling 8 treatment sessions.
Reviewer's comment: Response to treatment according to criteria???? no standardized methods for evaluating the severity
Answer: The response to treatment will be evaluated according to Carrozzo et al. (1999). Thus, 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. In addition, the Thongprason Index will be used to evaluate the severity of OLP according to the clinical presentation (reticular, atrophic or erosive).
Carrozzo M, Gandolfo S, Lodi G, Carbone M, Garzino-Demo P, Carbonero C et al. Oral lichen planus in patients infected or noninfected with hepatitis C virus: the role of autoimmunity. J Oral Pathol Med. 1999; 28(1): 16-19.
Reviewer's comment: You must indicate the degree of compliance with the treatment.
Answer: We would like to thank the reviewer for the suggestion. We expect higher degree of patient's compliance with the treatment because they have been followed up by the Stomatology Clinic of the University of São Paulo, Brazil, every two months since their diagnostic.
Reviewer's comment: Adherence to treatment was assessed with the Adherence Scale ???
Answer: We will add the adherence scale to treatment according to Nguyen et al. (2016). Thus, we will apply the Medication Adherence Questionnaire as suggested by the reviewer.
Nguyen TM, La Caze A, Cottrell N. Validated adherence scales used in a measurement-guided medication management approach to target and tailor a medication adherence intervention: a randomised controlled trial. BMJ Open. 2016 Nov 30;6(11):e013375.

VERSION 2 – REVIEW

REVIEWER	Paolo G. Arduino University of Turin
REVIEW RETURNED	21-Aug-2018

GENERAL COMMENTS	No more comments

REVIEWER	Pia Lopez Jornet University of Murcia .Spain
REVIEW RETURNED	19-Aug-2018

GENERAL COMMENTS	The paper is incomplete There is no results section. There are no data .No tables no figures