Efficacy of laser phototherapy in comparison to topical clobetasol for the treatment of oral lichen planus: a randomized controlled trial

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Abstract. Oral lichen planus (OLP) is a relatively common chronic mucocutaneous inflammatory disease and a search for novel therapeutic options has been performed. We sought to compare the efficacy of laser phototherapy (LPT) to topical clobetasol propionate 0.05% for the treatment of atrophic and erosive OLP. Forty-two patients with atrophic/erosive OLP were randomly allocated to two groups: clobetasol group (n = 21): application of topical clobetasol propionate gel (0.05%) three times a day; LPT group (n = 21): application of laser irradiation using InGaAlP diode laser three times a week. Evaluations were performed once a week during treatment (Days 7, 14, 21, and 30) and in four weeks (Day 60) and eight weeks (Day 90) after treatment. At the end of treatment (Day 30), significant reductions in all variables were found in both groups. The LPT group had a higher percentage of complete lesion resolution. At follow-up periods (Days 60 and 90), the LPT 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. These findings suggest that the LPT proved more effective than topical clobetasol 0.05% for the treatment of OLP. © 2014 Society of Photo-Optical Instrumentation Engineers (SPIE) [DOI: 10.1117/1.JBO.19.6.068002]

Keywords: oral lichen planus; clobetasol propionate 0.05%; laser phototherapy; recurrence; treatment; randomized controlled trial; topical corticosteroid.

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1 Introduction

Lichen planus is a relatively common chronic mucocutaneous inflammatory condition that affects ~0.3% to 2.3% of adults.1–3 Clinically, oral lichen planus (OLP) is classified into three major types: reticular, atrophic, and erosive.4,5 The reticular form is the most common and is typically asymptomatic. In contrast, the atrophic and erosive forms present erythematous, ulcerative areas leading to symptoms ranging from a burning sensation to severe pain.4,5 Patients with OLP often experience periods of remission and exacerbation, which may be related to psychological disorders and emotional stress, although divergent opinions are found regarding the psychological component.6–8

Although there is no cure for OLP, a number of treatments with topical or systemic corticosteroids, immunosuppressors, and immunomodulators are available to improve the clinical appearance of the lesions and reduce the degree of pain.8–15 Despite the clear potential for controlling OLP, few studies16–20 have used laser phototherapy (LPT) for this purpose. LPT has been widely used in several inflammatory conditions.21–27 The main effects of this therapy are analgesia, biomodulation, and the acceleration of wound healing.26–37 LPT has advantages over current OLP therapies such as noninvasiveness and the absence of side effects.

The aim of the present study was to compare the efficacy of LPT in comparison to a topical corticosteroid for the management of signs and symptoms of atrophic and erosive OLP. Analyses were performed regarding the resolution of atrophic/erosive lesions, chewing function, swallowing, fluid intake, and altered sense of taste. Moreover, the association of these data with the degree of anxiety in the patients was evaluated.

2 Methods

2.1 Study Design

The present single-center, randomized, controlled, single-blind study received approval from the Human Research Ethics Committee (HCPA protocol 11-0365). All participants signed a statement of informed consent prior to any clinical procedure.

2.2 Participants, Interventions, Randomization, and Blinding

Forty-two consecutive adult patients with OLP were enrolled in the study between February 2012 and November 2012. The sample size was calculated according to previously published...
Inclusion criteria were age 21 years or older, symptomatic atrophic/erosive OLP, and histopathological diagnosis of OLP based on the criteria proposed by the World Health Organization. The exclusion criteria were pregnant or nursing women, histological signs of dysplasia, OLP therapy in the previous three months, amalgam restoration near the lesions, and the use of medications associated with oral lichenoid reaction. Tabagism was not considered exclusion criteria for this study.

The patients were randomly assigned to one of the two treatment groups using computer-generated random number tables. Only one researcher knew in which group the patients were allocated. This unblinded researcher was not involved in any evaluation during and after the treatments. The patient was not blinded to the treatment.

The clobetasol group consisted of 21 subjects who received topical clobetasol propionate gel (0.05%), and the LPT group consisted of 21 subjects submitted to laser therapy. Figure 1 displays the study flowchart. The participants received verbal and written instructions on how to apply all the medications used.

2.3 Topical Clobetasol Propionate 0.05%

The medication was prepared with a hydroxyethyl cellulose gel and packaged (15 g) in a labeled tube by a pharmacist. Only two nonconsecutive missing applications were accepted.

To evaluate possible systemic absorption, blood cortisol levels were monitored at 8:00 am in the second (Day 14) and fourth (Day 30) week of treatment considering a normal range from 5.0 to 25 μg/dl.

2.4 Laser Phototherapy

LPT was administered by a single professional using a continuous wave diode laser (InGaAlP; MM Optics, São Carlos, São Paulo, Brazil) with a wavelength of 660 nm (visible red). Irradiation was performed in punctual contact mode with a spot size of 0.04 cm², power output of 40 mW, output density of 1000 mW/cm², energy density of 6 J/cm², 6-s exposure time per point, and 0.24 J of total energy per point. The number of points varied based on lesion size; therefore, it was not possible to calculate the total dose for all the cases. LPT was administered three times a week (Monday, Wednesday, and Friday) for four consecutive weeks, totaling 12 sessions. The output power of the equipment was checked using a power meter (Laser Check; MMOptics LTDA, São Paulo, Brazil).

2.5 Candidiasis Prevention

All patients received prophylactic anti-mycotic medication (Nystatin oral suspension 100,000 USP/ml. Micostatin®; Bristol-Myers Squibb Brasil S.A, São Paulo, Brazil) administered three times daily. The medication was delivered in individual 5-ml dispensers. The patient used an anti-mycotic during all the days of treatment with clobetasol and LPT. During follow-up, the medication was discontinued.

2.6 Clinical Evaluation

All patients were evaluated at baseline (Day 0), once a week during treatment (Days 7, 14, 21, and 30) as well as at four weeks (Day 60) and eight weeks (Day 90) after the discontinuation of treatment (follow-up period) (Fig. 2). Evaluations were performed by a single professional who was blinded to the allocation of the participants to the different treatment groups. Evaluations involved the recording of symptoms, clinical signs, functional scores, Beck anxiety inventory (BAI), and photography. At each evaluation, the patients in both groups were asked to report any unusual effects that might have been related to the therapy protocol.

2.6.1 Clinical scores

The clinical data were scored: Score 0: no lesions; Score 1: hyperkeratotic lesions; Score 2: atrophic area ≤1 cm²; Score 3: atrophic area >1 cm²; Score 4: erosive area ≤1 cm²; and Score 5: erosive area >1 cm².
2.6.2 Symptom scores
Symptom scores were determined using a visual analogue scale (VAS).

2.6.3 Functional scores
Functional scores analyzed the chewing function; swallowing, fluid intake, and altered sense of taste were assessed. The functional scores were recorded as described by Lilleby et al.\(^{41}\) no difficulty = 0 points; mild difficulty = 1 point; moderate difficulty = 2 points; severe difficulty = 3 points; and impossible = 4 points.

2.6.4 Clinical resolution (CR) and recurrence rates (RR)
The CR score was evaluated at Day 30 and classified\(^{42}\) as: Complete resolution—absence of symptoms and the remission of all atrophic/erosive lesions regardless of any persisting hyperkeratotic lesions. Partial resolution—decrease in but not the complete remission of atrophic/erosive areas and symptoms. No response—maintenance or worsening of the baseline condition.

The RR was analyzed on Days 60 and 90 by comparisons to the patient’s condition on Day 30. The absence of recurrence was recorded when the patient maintained the same clinical aspect as that found on Day 30 and recurrence was recorded in the presence of new atrophic and/or erosive lesions at the same site in the follow-up period.

2.6.5 Beck anxiety inventory
The BAI is a questionnaire with 21 multiple-choice items addressing how the patient felt in the previous week regarding common symptoms of anxiety. The score ranges from 0 to 63 and is classified as minimal anxiety (score: 0 to 10), mild anxiety (score: 11 to 20), moderate anxiety (score: 21 to 30), and severe anxiety (score: 31 to 63). The BAI was administered at every evaluation day.

2.7 Statistical Analysis
Statistical analysis was carried out using the SPSS version 18.0 (SPSS Inc., Chicago, Illinois). Data were analyzed using a generalized estimating equations (GEE) test, which combined tests for treatment differences and changes in treatment response over time. The GEE followed by Bonferroni’s posthoc test was used to determine the significance of differences between therapies over time considering the VAS score, CS, functional scores, and CR score. The chi-squared test was used to analyze the RR. All statistical tests were performed with a significance level of 5% (\(p < 0.05\)). The statistical tests used took into account the correlated nature of the repeated measures of each patient. Analyses were performed on an intention-to-treat basis.

3 Results
Table 1 summarises the characteristics of the patients. All patients completed the treatment period and underwent the evaluation on Day 60. Nine patients (five in the clobetasol group and four in the LPT group) did not undergo the evaluation on Day 90 (Fig. 1).

3.1 Clinical Scores
The CS results are graphically represented in Fig. 3. At baseline (Day 0), the patients exhibited lesions with atrophic and erosive areas associated or not to hyperkeratotic lesions, with a similar mean CS in both groups. The CS remained similar in both groups, decreasing progressively through to Day 21. However, from Day 30 to the end of the follow-up period (Day 90), the LPT group had significantly lower scores in comparison to the clobetasol group (\(p < 0.001\)). At Day 90, the LPT group exhibited more hyperkeratotic lesions and fewer atrophic/erosive lesions than the clobetasol group (\(p < 0.001\)). Moreover, the clobetasol group demonstrated a worsening of clinical aspects, with the recurrence of atrophic and erosive lesions. Figure 4 illustrates the CS findings in a patient from the LPT group.

3.2 Symptom Score
All patients had symptoms at baseline (Day 0). The overall mean VAS score was 6.6 (±2.0), with no statistically significant difference between groups. The mean VAS scores decreased significantly in both groups by Day 14 (\(p < 0.001\)) (Fig. 5). The change in mean VAS scores did not differ significantly between groups during treatment. In the follow-up period, the LPT group maintained a stable mean VAS, whereas a significant increase was found in the clobetasol group, leading to significant differences groups (\(p < 0.05\)).

3.3 Functional Scores
On Day 0, both groups exhibited moderate difficulty in chewing and fluid intake as well as an altered sense of taste. Both groups demonstrated significant improvements in the four aspects analyzed throughout treatment (\(p < 0.001\)). At Day 30, improvements were found in both groups in all functional scores. In the follow-up period, a significant difference between groups...
was found only with regard to altered sense of taste, for which the clobetasol group had a worse behavior (Fig. 6).

3.4 Clinical Resolution and Recurrence Rates

Partial or complete CR was achieved in both groups. Complete resolution at Day 30 occurred in 28.6% (6 patients) of the clobetasol group and 61.9% (13 patients) of the LPT group. Table 2 displays the RR in both groups. At Day 60, only one case of recurrence (4.8%) was found in the LPT group, whereas 10 cases (47.6%) were found in the clobetasol group ($p < 0.001$). At Day 90, the LPT group had a higher percentage of patients with no signs of recurrence, but the difference between groups did not achieve statistical significance ($p = 0.276$).

3.5 Beck Anxiety Inventory

The overall mean BAI score at baseline (Day 0) was $34.02 \pm 9.46$ (32.9 in the clobetasol group and 35.1 in the

<table>
<thead>
<tr>
<th>Baseline characteristic</th>
<th>Clobetasol group ($n = 21$)</th>
<th>LPT ($n = 21$)</th>
<th>Total ($n = 42$)</th>
<th>$p$-value$^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, $n$ (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3 (14.3%)</td>
<td>4 (19%)</td>
<td>7 (16.7%)</td>
<td>NS</td>
</tr>
<tr>
<td>Female</td>
<td>18 (85.7%)</td>
<td>17 (81%)</td>
<td>35 (83.3%)</td>
<td>NS</td>
</tr>
<tr>
<td>Age, year, mean SD</td>
<td>61.33 ($\pm 11.85$)</td>
<td>55.14 ($\pm 15.96$)</td>
<td>58.2 ($\pm 14.23$)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean duration, months</td>
<td>48.48 ($\pm 39.64$)</td>
<td>44.81 ($\pm 51.05$)</td>
<td>46.6 ($\pm 44.6$)</td>
<td>NS</td>
</tr>
<tr>
<td>VAS, mean SD</td>
<td>6.52 ($\pm 1.74$)</td>
<td>6.74 ($\pm 2.27$)</td>
<td>6.63 ($\pm 2.0$)</td>
<td>NS</td>
</tr>
<tr>
<td>Site of involvement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tongue</td>
<td>54 (53.5%)</td>
<td>47 (46.5%)</td>
<td>101 (45.1%)</td>
<td>NS</td>
</tr>
<tr>
<td>Buccal mucosa</td>
<td>33 (47.8%)</td>
<td>36 (52.2%)</td>
<td>69 (30.8%)</td>
<td>NS</td>
</tr>
<tr>
<td>Lips / Labial mucosa</td>
<td>13 (36.1%)</td>
<td>23 (63.9%)</td>
<td>36 (16.1%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Floor of mouth</td>
<td>1 (14.3%)</td>
<td>6 (85.7%)</td>
<td>7 (3.1%)</td>
<td>NS</td>
</tr>
<tr>
<td>Gingiva</td>
<td>4 (66.7%)</td>
<td>2 (33.3%)</td>
<td>6 (2.7%)</td>
<td>NS</td>
</tr>
<tr>
<td>Palate</td>
<td>1 (33.3%)</td>
<td>2 (66.7%)</td>
<td>3 (1.3%)</td>
<td>NS</td>
</tr>
<tr>
<td>Alveolar ridge</td>
<td>0</td>
<td>2 (100%)</td>
<td>2 (0.9%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Clinical aspects of lesions

| Reticular              | 11 (10.4%)                  | 23 (19.5%)    | 44 (18.8%)      | 0.06         |
| Erosive                | 53 (50.0%)                  | 72 (61.0%)    | 125 (53.4%)     | 0.06         |
| Atrophic               | 42 (39.6%)                  | 23 (19.5%)    | 65 (27.8%)      | 0.04         |

was found only with regard to altered sense of taste, for which the clobetasol group had a worse behavior (Fig. 6).
LPT group), demonstrating severe anxiety. Similar significant decreases were found in both groups throughout treatment ($p < 0.001$). At Day 90, the clobetasol group demonstrated an increase in anxiety, whereas the LPT group maintained a constant mean score, with a significant difference between groups ($p < 0.05$) (Fig. 7).

### 3.6 Side Effects

Three patients (14.3%) of the clobetasol group reported a transient local burning sensation immediately after the first two days of drug application and two (9.5%) reported gastrointestinal distress, which was resolved with the concomitant intake of omeprazole. The mean cortisol level in the clobetasol group was 8.85 ± 3.59 on Day 14 and 10.67 ± 3.96 on Day 30, which were within the normal endogenous cortisol pattern (5.0 to 25 μg/dl). No side effects were reported in the LPT group.

### 4 Discussion

Among the therapeutic options available to OLP, corticosteroids are the most widely accepted, but a definitive cure has not yet been achieved. A search for alternative methods that are capable of modulating the inflammatory response related to the disease seems reasonable. LPT is a promising modality that has been employed in different adverse health conditions. Few studies have employed LPT as a treatment for OLP. The present investigation compared the efficacy of clobetasol and LPT in the treatment of atrophic and erosive OLP. Overall, both topical clobetasol 0.05%, and LPT were effective in the management of OLP, with reductions in clinical, symptom, functional and BAI scores throughout the treatment period. These results were considered a successful outcome based on the conversion of symptomatic erosive lesions into reticular lesions with barely any symptoms.
The recurrence of OLP lesions after the end of treatment with clobetasol has been described as a rebound effect that can occur when the corticosteroid is abruptly discontinued,\textsuperscript{14} as found in the present study. Moreover, the literature describes that systemic administration of corticosteroid led to improvements in all variables analyzed of OLP, despite the inferior performance of clobetasol in comparison to LPT especially during follow-up periods. These findings are in agreement with data described in the previous studies, which report rates of improvements in clinical signs and symptoms ranging from 56\% to 100\% associated to corticosteroid\textsuperscript{13,46–48} local side effects with the use of this medication. In the present study, clobetasol was well tolerated and caused no change in endogenous cortisol levels. However, local adverse effects were reported, such as a burning sensation and gastrointestinal discomfort, which is in agreement with data described in the previous studies.\textsuperscript{13,48} These effects were mild and transient and did not force patients to abandon the study, which demonstrates that topical clobetasol treatment for 30 days is a safe treatment modality with few side effects.

The LPT positive effects on erosive and ulcerative OLP lesions could be explained by its biological activity in a diversity of cell types, such as fibroblasts\textsuperscript{36,37} and epithelial cells,\textsuperscript{34,49} which are key participants in the mucosal healing process. LPT activates signaling pathways that lead to cell proliferation and migration,\textsuperscript{34,35} controls oxidative stress,\textsuperscript{28} modulates the production of several cytokines,\textsuperscript{31–33,50} and regulates several genes that are closely involved in the wound healing process.\textsuperscript{34} However, it is difficult to compare the results of the present study with data from the literature, as few studies have analyzed the effect of LPT on OLP\textsuperscript{16–20} and only one randomized clinical trial compared LPT with standard therapy (dexamethasone).\textsuperscript{18} The previous studies also found significant pain and clinical improvements in OLP with the use of LPT.\textsuperscript{16–20} In the present investigation, the most striking finding was the maintenance of the improvement in clinical signs and symptoms up to two months after the end of treatment with LPT, demonstrating longer control of OLP in comparison to that achieved with clobetasol.

In the present study, the patients in both groups exhibited significant improvements in psychological factors. This finding can be attributed to the reduction in symptoms, improvement in oral functions, and the attention that patients received during the

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|}
\hline
Recurrence & No recurrence & Total \\
\hline
Clobetasol & 10 (47.6) & 11 (52.4) & 21 \\
LPT & 1 (4.8) & 20 (95.2) & 21 \\
Total & 11 (26.2) & 31 (73.8) & 42 \\
\hline
Clobetasol & 6 (37.5) & 10 (62.5) & 16 \\
LPT & 3 (17.6) & 14 (82.4) & 17 \\
Total & 9 (27.3) & 24 (72.7) & 33 \\
\hline
\end{tabular}
\caption{Recurrence rate in clobetasol and LPT groups at follow up (Days 60 and 90); significant worsening in CS in clobetasol group at Day 60.}
\end{table}

Fig. 6 Mean functional scores (standard error of mean) in clobetasol and LPT groups during experimental period; Both groups demonstrated significant improvements in chewing (a), fluid intake (b), swallowing (c) and altered sense of taste (d) throughout treatment, with significant (*) difference between groups in fluid intake at Day 7 (B). Significant (*) worsening in sense of taste in clobetasol group during follow-up period (Days 60 and 90).
four weeks of treatment. Although few studies have investigated the association between the BAI score and OLP, this question is a helpful tool for analyzing the clinical course of psychological symptoms in patients with this condition. Considering the interplay between one’s emotional state and the course of OLP, psychological support should be considered as a complementary strategy in the management of OLP, particularly in patients who do not respond well to treatment.

The suggestion that OLP can undergo malignant transformation into oral squamous cell carcinoma has been debated for decades. Some authors have reported that the use of clinical and histopathological criteria are sufficient for an accurate diagnosis and that cases associated to OLP transformation are generally related to a failure to fulfill these criteria.53–56 Premalignant oral epithelium is typically defined by histopathologic criteria as different grades of epithelial dysplasia depending on the severity of the microscopic changes. According to Van der Meij et al.,56 only oral lichenoid lesions are endowed with malignant transformation, but not OLP. All patients included in this study were biopsied and only cases without dysplasia that fulfill all criteria for OLP were selected.

The safety in using LPT in the oral mucosa is always a concern. We have recently shown that the low doses of irradiation do not induce genomic instability as judged by two distinct markers for genomic integrity.27 Indeed, a lack in the accumulation of DNA double strand breaks or absence of the BRCA1 DNA damage repair molecule suggests that the low energy densities of LPT can serve as a safe therapeutic strategy for lesions and ulcers from the oral mucosa.37

To the best of our knowledge, this is the first clinical trial to evaluate the effects of LPT in comparison with topical clobetasol 0.05% for the treatment of OLP involving the analysis of clinical behavior, symptoms, oral function, and psychological aspects. The results indicate that the LPT is more effective than clobetasol for treating OLP lesions and preventing their recurrence. The data also strongly indicate that the LPT is a promising therapeutic strategy for OLP. The only disadvantage in the use of LPT is the upfront equipment costs and required specialized training that surpasses the costs of using clobetasol. Further studies are currently underway to investigate the mechanisms underlying the effects of LPT on OLP as well as the mechanisms involved in the pathobiology of this condition.

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