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Research Article

# Photodynamic Therapy versus Topically Applied Corticosteroids in the Treatment of Oral Lichen Planus

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## Abstract

**Objective**

To compare the efficacy of photodynamic therapy (PDT) versus topical corticosteroids in the treatment of patients with erosive oral lichen planus (EOLP).

**Subjects and Methods**

Randomized clinical trials included twenty patients with EOLP clinical and histological diagnosis. They were divided into two groups of equal size: Ten patients in Group A (the control group) were

instructed to use a topical corticosteroid (kenakort A-orabase). Ten patients in Group B (study group) received PDT using a diode laser at 635nm mediated by toluidine blue (TB).

**Results**

Both groups showed a statistically significant difference from the baseline to the follow-up periods. Whereas both groups demonstrated a significant reduction in pain and lesion size.

**Conclusion**

Toluidine blue-mediated photodynamic therapy with a 635-nm diode laser was found to be effective and could be used as an alternative therapy for TC in the treatment of erosive-atrophic OLP.

## Abbreviations

EOLP: Erosive Oral Lichen Planus
TC: Topical corticosteroid
PDT: Photodynamic therapy
TB: Toluidine blue
IL-6: Interleukin-6
TNF-α: Tumor necrosis factor-α
GM-CSF: granulocyte-macrophage colony-stimulating factor
IL-8: Interleukin-8
INF-γ: Interferon Gamma
HPV: Human papilloma virus
PUVA: photochemotherapy
VAS: Visual analog score
Hepatitis CV AB: Hepatitis C virus antibody
Hepatitis Bs Ag: Hepatitis B virus antigen
CO2 laser: Carbon dioxide laser
MB: Methylene blue

## Introduction

Oral lichen planus (OLP) is a chronic mucocutaneous inflammatory disease that affects 0.5 to 2% of the total population [1]. Typically, it affects adults over the age of 30-year-old with a slight female prediction [2]. Although any mucosal site can be affected, the buccal mucosa, tongue, and gingiva are the most commonly affected [3]. It can present clinically in three patterns: reticular, atrophic, and bullous erosive; each has distinct characteristics and can be found alone or in combination. The most common type is the reticular type, which is distinguished by the presence of Wickham striae, which are typically symmetric, bilateral, asymptomatic, and primarily found in the buccal mucosa. Despite its rarity, the erosive form is more clinically significant because the lesions are usually symptomatic, ranging from minor discomfort to episodes of severe pain [4].

OLP is thought to be a T-cell mediated autoimmune disease with both specific and non- specific antigen specificity [5]. Antigen specificity includes antigen presentation by basal keratinocytes and antigen-specific keratinocytes by CD8+cytotoxic T-lymphocytes, whereas non-specific antigen includes mast cell degranulation and matrix metalloproteinase activation [6]. Interleukin-6 (IL-6), tumour necrosis factor (TNF- α), and granulocyte-macrophage colony- stimulating factor (GM-CSF) are all released and cause a local inflammatory response [7]. The most widely used treatment for OLP is topical and systemic corticosteroids. Nevertheless due to the chronic nature of OLP, long-term use of corticosteroids is associated with certain local and systemic complications that include mucosal atrophy, oral candidiasis, adrenal insufficiency, gastrointestinal disorders, hypertension, and diabetes [8].

Photodynamic therapy (PDT) has been proposed as a modern and promising therapeutic modality for a variety of medical and dental conditions [9]. PDT entails the topical or systemic administration of a photosensitizer, a light-sensitive drug, followed by light irradiation with a specific wavelength that corresponds to the drug's absorbance band. In the presence of tissue oxygen, the interaction generates cytotoxic oxygen free radicals, which are thought to be responsible for PDT's therapeutic action [10]. Several studies have been conducted to assess the efficacy of PDT in the treatment of OLP. Mostafa *et al* [11] found that the PDT-treated group improved more than the corticosteroid-treated group in terms of signs and symptoms of OLP. Furthermore, Bakhtiari *et al* [12] reported that PDT was just as effective as topical corticosteroids in treating OLP. In contrast, Jajarm *et al*, [13] found that topical uses of dexamethasone and PDT showed significantly decrease of pain and size of lesion. In light of this, the current study on 20 patients compared the clinical effect of photodynamic therapy mediated by toluidine blue (TB- PDT) on signs and symptoms of erosive oral lichen planus (EOLP) lesions to conventional topical corticosteroids (TC) treatment in an attempt to overcome the disadvantages of TC.

## Patients and Methods

In a randomized parallel study design, twenty patients with clinical and histological diagnosis of erosive oral lichen planus of both sexes were selected from the Oral Medicine and Periodontology department at Al-Azhar University's Faculty of Dentistry. They were included according to the following.

**Inclusion Criteria:** Patients who have a histologically proven diagnosis of OLP based on modified WHO criteria [14].

**Exclusion Criteria:** (a) Patient on the treatment of immunosuppressive, chemotherapy or history of radiotherapy for the last 6 months,(b)- Pregnant and lactating ladies,(c)- Patients with uncontrolled diabetes and or hypertension, with positive Hepatitis CV AB or Hepatitis Bs Ag. (d)- Patients taking any medications that may cause a lichenoid reaction, those who have had topical treatment for oral lichen planus in the last two weeks or systemic treatment for OLP in the last three months, and (e)-heavy smokers. After providing detailed information and a description of the study, each patient provided informed consent.

**Sample Size Calculation:** According to previous clinical study [15], sample size calculation was undertaken via G*power version 3.1 statistical software based on the following pre-established parameters: an alpha-type error of 0.05, a power tests of 0.80 a total sample of at least 40 sites. According to the formula below: n= 2(Za+Zb) 2 x(S) 2/(d) 2.where S = 2.27 and d = 2.

Diagnosis of erosive OLP was based on:

**Clinical Examination:** It included documented patient data, intraoral examination (signs and symptoms, onset and duration of disease, site, and size of the lesions) and skin examination of any dermatological sign of lichen planus.

**Histological Examination:** The incisional biopsy specimen was obtained under local anesthesia, placed at once in a suitable fixing solution (10% neutral buffered formalin), and sent to the pathologic laboratory to confirm the diagnosis. Laboratory investigations were performed after diagnosis and before treatment (Complete blood picture-Fasting blood glucose level-Liver tests).

**Grouping and Intervention:**

The chosen patients were divided into two groups based on a randomized selection process: Group A (the control group) consists of the following individuals: Ten patients were told to use the standard TC in orabase (kenakort A-orabase). They were instructed to apply a very thin layer of TC three times per day and to refrain from eating or washing for 30 minutes after application (after meals and before bedtime).Group B (study group): ten patients received PDT mediated by toluidine blue (TB). At first application of toluidine blue on both sides of the lesional area was performed, after ten minutes PDT was performed by using a semiconductor laser 635nm. An optical fiber with a diffuser tip was used to deliver a 635nm wavelength to the lesion. The laser power from the end of the optical fiber did not exceed 300mW.

Each session of PDT was applied for 10 min with a total dose of 120 J/cm$^2$ for each session. The procedure was repeated on the 3$^{rd}$, 7$^{th}$, and 15$^{th}$ day. The patients were followed up on at the end of the fourth week, three months, and six months of treatment. A cold diet was advised after each laser session. There was no pain, edema, or bleeding after each laser treatment. There were no side effects observed at any time during the treatment or follow-up.

**Clinical Assessment**

The clinical data were scored using the Thongprasom *et al* [15] criteria scale. Lesions of oral lichen planus were scored according to these criteria by using a scaled tongue blade where: 0 = no lesion, 1 = mild white striae without erythematous area, 2 = white striae with atrophic area <1cm2,3 = white striae with atrophic area >1cm2, 4 = white striae with erosive area <1cm2, and 5 = white striae with erosive area >1cm2.

The severity of the symptoms of the lesions was recorded using the visual analog score (VAS) which graduated from zero to ten, where zero = no pain, and 10 = extremely painful [16]. Discomfort ratings and a questionnaire documenting any potential side effects were completed. Patients were asked to rank the severity of their discomfort on a visual analog scale rating from 0 to 10; responses were measured at the start of the study, after treatment and at the follow-up periods. Total improvement (complete resolution of clinical signs) was defined as the disappearance of all erosive lesions, regardless of any remaining hyperkeratotic lesions; partial response was defined as a decrease in pain and size of the lesion compared to baseline; and no improvement was defined as any changes in the lesion.

### Statistical Analysis of the Data

Range (minimum and maximum), mean, standard deviation, and median were used to describe quantitative data. The significance of the obtained results was determined at the 5% level. Student t, ANOVA with repeated measures, Mann Whitney test, and Friedman test were the tests used.

## Results

Twenty patients with biopsy-proven and clinically diagnosed erosive OLP were divided into 2 equal groups; their demographic data were presented in table 1. They were ranged in age between 38.0 - 65.0 years with a mean age of 51.80 ± 9.34 years in the photodynamic group and ranged in age between 36.0 - 65.0 years with a mean age of 51.60 ± 9.58 years in the corticosteroid group. When the two studied groups were compared in terms of age, it was discovered that there was a statistically non-significant difference in the mean age between the two groups.

***Table 1:*** *Shows a comparison of the two studied groups based on age*

| Age (years) | Photodynamic (n = 10) | Corticosteroid (n = 10) | t | p |
|---|---|---|---|---|
| Min. - Max. | 38.0 - 65.0 | 36.0 - 65.0 | 0.047 | 0.963 |
| Mean ± SD. | 51.80 ± 9.34 | 51.60 ± 9.58 | | |
| Median | 53.50 | 52.0 | | |

The comparison of the two groups in terms of pain scores recorded at various periods of follow-up. Both groups (right and left) showed a statistically non-significant decrease in mean pain measurements after 1 month. Both groups (right and left) showed a statistically significant decrease in mean pain measurements after 3 and 6 months (Table 2).

***Table 2:*** *Comparison between the different time periods in each group according to VAS*

| | Pain | | | | Fr | p |
|---|---|---|---|---|---|---|
| | Before | After 1m | After 3m | After 6m | | |
| **Photodynamic Right** | 9.60 ± 0.70 | 5.90 ± 2.18 | 1.80 ± 3.82 | 1.60 ± 2.50 | 26.528* | <0.001* |
| **$p_0$** | | 0.166 | <0.001* | <0.001* | | |
| **Left** | 9.0 ± 0.82 | 5.20 ± 2.10 | 1.70 ± 3.59 | 1.50 ± 3.17 | 27.414 | <0.001* |
| **$p_0$** | | 0.166 | <0.001* | <0.001* | | |
| **Corticosteroid Right** | 9.60 ± 0.70 | 5.80 ± 2.25 | 1.90 ± 3.35 | 1.80 ± 1.93 | 27.574* | <0.001* |

| | | | | | | |
|---|---|---|---|---|---|---|
| **$p_0$** | | 0.166 | <0.001* | <0.001* | | |
| **Left** | 9.20 ± 1.14 | 5.40 ± 2.50 | 2.10 ±3.75 | 1.90 ± 3.25 | 27.574* | <0.001* |
| **$p_0$** | | 0.166 | <0.001* | <0.001* | | |

Both groups (right and left) showed a statistically non-significant decrease in the mean THONGPRASOM Scale after 1 month. Both groups (right and left) showed a statistically significant decrease in the mean THONGPRASOM Scale after 3 and 6 months (Table 3).

***Table 3:*** *Comparison between the different time periods in each group according to THONGPRASOM Scale*

| | **THONGPRASOM Scale** | | | | **Fr** | **P** |
|---|---|---|---|---|---|---|
| | **Before** | **After 1m** | **After 3m** | **After 6m** | | |
| **Photodynamic Right** | 5.0 ± 0.0 | 3.40 ± 0.97 | 2.20 ± 1.62 | 1.80 ± 1.93 | 21.203* | <0.001* |
| **$p_0$** | | 0.100 | 0.002* | <0.001* | | |
| **Left** | 4.40 ± 0.52 | 3.0 ± 1.15 | 2.0 ± 1.49 | 1.60 ± 1.58 | 20.663* | <0.001* |
| **$p_0$** | | 0.100 | 0.003* | <0.001* | | |
| **Corticosteroid Right** | 5.0 ± 0.0 | 3.70 ± 0.82 | 2.0 ± 1.70 | 1.70 ± 2.11 | 20.711* | <0.001* |
| **$p_0$** | | 0.141 | 0.002* | <0.001* | | |
| **Left** | 4.50 ± 0.71 | 3.20 ± 1.23 | 1.80 ± 1.32 | 1.80 ± 1.93 | 22.097* | <0.001* |
| **$p_0$** | | 0.141 | <0.001* | <0.001* | | |

## Discussion

Lichen planus is a chronic mucocutaneous disease and it was speculated the cell- mediated immunity and cytokines produced by keratinocytes and lymphocytes play an effective role in its pathogenesis. These cytokines (TNF- α, IL-8, and INF-γ) stimulate lymphocyte activity and induce keratinocyte apoptosis. Hence, systemic and local corticosteroid therapies are the cornerstone in its treatment. However these treatments have plentiful side effects such as candidiasis, xerostomia, sore throat, osteoporosis, adrenal insufficiency, hypertension, and diabetes mellitus [17]. The primary goal of OLP treatment is to shorten and lessen the severity of symptomatic outbreaks. Various modalities have been presented to relieve the symptoms such as tacrolimus, systemic and topical retinoids, calcineurin inhibitors, cryotherapy, CO2 laser, PUVA therapy, and toluidine blue-mediated photodynamic treatment [18].

Currently, PDT has been applied for the treatment of a variety of lesions such as skin and breast cancers, immunologic diseases (such as acne, psoriasis, lichen planus, and scleroderma), and infectious diseases (such as HPV, osteomyelitis, and candidiasis) [19]. PDT is widely used to treat oral lesions including potentially

malignant lesions (erythroplakia, verrucous carcinoma), head and neck cancers, and periodontal disease [20]. PDT is a cold photochemical reaction that occurs when photosensitizing drugs are exposed to light of a specific wavelength, resulting in cellular destruction via a free radical oxidative process. The connective tissues are unaffected by the photochemical reaction [21]. PDT has 3 main constituents: oxygen, a photosensitizing drug, and light. The drug is activated by light, and then it interacts with molecular oxygen to produce excited state reactive oxygen. Because PDT is a cold photochemical process, it has no effect on proteins like collagen and elastin, preserving the integrity of the underlying structures [22].

In PDT, photosensetizer absorbs the transferred light and converts the light energy into a chemical reaction which in turn leads mainly to the formation of singlet oxygen. Cytotoxic effects of PDT on tumoral cells or activated lymphocytes are mediated through these oxidative products [23], and it is suggested that PDT induces apoptosis in proliferated inflammatory cells [24]. By considering the inflammatory pathogenesis of OLP and the immunomodulatory effect of PDT, photodynamic therapy may be an effective alternative treatment procedure. Because wavelength is the most important factor in all types of phototherapies, the most appropriate wavelength should be chosen to achieve the best results. A 635-nm laser was used because it has the highest efficacy for wound healing, and no side effects were reported [25,26]. Furthermore, while methylene blue has been used as a photosensitizer in many studies, toluidine blue was used in this study because it absorbs at 635nm [27]. TB is a cationic photosensitizer that has a strong absorption at 635nm which consider a proper optical range for light penetration into the damaged tissue [28].

The findings revealed statistically significant differences between the two groups from the baseline to the follow-up periods. The results of the present study were in accordance with Jajarm *et al* [13], who showed that sign scores of pain and size of the lesions significantly reduced in both groups treated by TB-PDT (630nm wavelength and exposure dose of 120J/cm$^2$) for two visits and corticosteroid mouth wash . As a result, they stated that LLLT was just as effective as topical corticosteroid therapy. Trehan *et al* [29] used an excimer laser (308nm) in eight patients suffering from symptomatic OLP lesions, and after the treatment, five patients had marked improvement in experiencing pain. In the current study, all patients in the experimental group showed significant improvement. These differential findings may be a result of the difference in applied doses and energy as well as the use of photosensitizers in our study.

In addition, a study [30] of 20 patients with systemic OLP was conducted. PDT was performed in four visits with a xenon arc lamp of 630nm wavelength and a total dose of 120 J/cm$^2$ and MB photosensitizer. They were able to achieve a significant reduction in lesions over a long period of time with no side effects. It should be mentioned that patient's carelessness about the instruction of topical corticosteroid application and the need for its continuous application may affect the evaluation scores. Thus, VAS maybe not a reliable score to evaluate the patients pain, especially in the elderly and illiterate patients. There were no serious intra- or post-operative complications; there was no postoperative bleeding or scarring following TB-PDT application.

## Conclusion & Recommendation

Under this study circumstances toluidine blue-mediated photodynamic therapy with a 635nm diode laser was an effective treatment and it can be considered as an alternative therapy for erosive-atrophic OLP. The

study samples reflected the findings in these selected groups of patients only. More studies with larger samples and long duration of follow-up periods are needed to confirm these results.

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