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**ORIGINAL ARTICLE**

# The Efficiency of Photodynamic Therapy in the Management of Pain in Patients with Oral Lichen Planus

Mona Abdallah Sabry[*1], Ali Mohamed Saafan[2], Hanaa Mohamed El-Shennawy[3], Amal Ali Hussine[4], Doaa Mohamed Abd El- Aziz[5], Doaa Ahmed Abdel Fadeel[6]

[1] *Assistant Researcher, Surgery and Oral Medicine Department, National Research Center (NRC), Giza, Egypt*

[2] *Professor of Dental Laser applications, National Institute of Laser Enhanced Sciences (NILES), Cairo University, Egypt*

[3] *Professor of Oral & Dental Laser applications, Surgery and Oral Medicine department, National Research Center (NRC), Giza, Egypt*

[4] *Associate professor of Oral Medicine & Periodontology, Faculty of Oral &Dental Medicine, Cairo University, Egypt*

[5] *Associate professor of Chemical & Clinical Pathology, Faculty of Medicine, Ain Shams University, Egypt*

[6] *Lecturer of Laser Applications in Pharmaceutical Sciences, National Institute of Laser Enhanced Sciences (NILES), Cairo University, Egypt*

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**KEYWORDS**

Oral lichen planus;
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**ABSTRACT:** Photodynamic therapy (PDT) which is a type of photochemotherapy is a new method of treatment used in cases of erosive/atrophic oral lichen planus (OLP) to reduce symptoms of the disease. Assessment of the effect of PDT on pain scale in patients having erosive / atrophic oral lichen planus.30 patients having erosive/atrophic OLP were recruited in this study. The oral lesions were subjected to PDT twice per week for 2 months. Methylene blue (MB) oral gel was used as a photosensitizer applied to the oral lesions, then diode laser of 650 nm WL and 150 mW (milli Watts) powers was used in a non- contact mode for 2:30 minutes. Visual analogue scale (VAS); pain scale was used for clinical assessment. The results showed improvement in the severity of pain over the duration of treatment. There was a gradual decrease of the mean VAS score over 8 weeks duration from 8±1 to 4±2. The decrease was statistically significant in the mean VAS score in the first month from 7±2 to reach 5±2 by the end of the second month ($p<0.001$). The use of photodynamic therapy was found to be effective in management of erosive / atrophic OLP; it showed improvement in the subjective as well as objective signs and symptoms of the disease with no side effects.

## INTRODUCTION

Lichen planus is a chronic mucocutaneous autoimmune disease of unknown etiology. OLP is believed to be due to abnormal T- cell mediated immune response against the basal cell layer which was recognized foreign as a result of changes in the antigenicity of the cells [1]. Although the etiology of OLP is still unclear, there is evidence that it is a complex immunologic disease mediated by cytotoxic cells and directed against basilar keratinocytes and resulting in vacuolar degeneration and lysis of basal cells [2]. It affects skin, oral mucosa, genital mucosa, nails and scalps [3]. About 0.5- 2% of the populations are affected and females of the middle age commonly suffer from this disease [4]. Intraorally, the posterior buccal mucosa is most commonly affected, the

*Corresponding author: sabry.mona@gmail.com (M. Abdallah Sabry)
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lateral border of the tongue and the gingiva, but other areas may be affected, mainly the palate, lip, and floor of the mouth [5].

Erosive/atrophic (OLP) appear in the form of irregular ulcers, most commonly associated with pain and burning sensation. It is aggravated by trauma, acidic, hot and spicy food causing severe discomfort to the patients and affecting their quality of life [6], unlike plaque, reticular and papular forms which are asymptomatic. Moreover, high risk of malignant transformation was observed in erosive/atrophic type than in other types of OLP [7]. This clinical picture is associated with periods of remissions and exacerbations [8]. That's why we recorded the visual analogue scale (VAS) as a method of pain evaluation during and after treatment.

PDT is one recent promising modality introduced for the treatment of oral lichen planus as an alternative method to conventional standard management without any adverse effects [9]. It can be used for cases resistant to steroids or when steroids are contraindicated [10]. PDT involves a triad; a photosensitive agent, a photosensitizer (PS) and a light source at a specific wavelength [11]. When the PS is administered into the tissues it accumulates selectively in the target cells followed by irradiation of the lesion by a source of light at a definitive wavelength in the presence of oxygen. This will result in cell death [12] as a result of production of free radicals and singlet oxygen. Direct or indirect oxidative damage is induced by these cytotoxic species to the cellular organelles promoting programmed cell death [13].

Methylene blue (MB) which is a tricyclic phenothiazine dye is an aromatic chemical compound with the chemical formula C16H18CIN3S and molecular weight (MW) 319.85. It has a very low tissue toxicity which can be administered topically and orally. That's why it is preferred for superficial skin lesions and oral cavity [14]. It has its strongest absorption at wavelengths longer than 620 nm [10] and it is best absorbed at a wavelength of 665 nm [14]. Different light sources are used in topical PDT, meanwhile lasers, most commonly diode lasers are considered as an ideal light source for PDT. Diode lasers are considered ideal because of their coherence and monochromacity, that's why they are used commonly nowadays in dental clinics as they are also compact and portable [15].

Various new agents have been recently suggested to treat OLP. They include the following: topical amitriptyline, amlexanox, bacillus Calmette–Guerin polysaccharide nucleic acid (BCG-PSN), hyaluronic acid, ignatia, low-intensity laser therapy, lycopene, psychiatric therapy, purslane extract, and topical thalidomide [16]. Others like topical aloe-vera gel, topical pimecrolimus and oral curcuminoids seem to be promising [17].

Diode lasers have been recently used in the medical field. It has several advantages over other laser types such; small size of the device, wide range of spectrum and its transmission through fibro-optics makes it more liable to be used in inaccessible areas [18]. It has a wavelength range from 810 - 940 nm which allows superficial laser energy absorption by the tissues thus producing its effect on the surface tissue lesions [19]. The use of such lasers is called "LOW LEVEL LASER THERAPY" LLLT [20]. LLLT has been frequently used due to its bio-stimulatory effects as a result of increased cellular metabolism, tissue regeneration and proper wound healing [21]. The aim of treatment is to alleviate symptoms of pain in case of symptomatic atrophic/erosive OLP.

## MATERIALS AND METHODS

Thirty patients were recruited in this study (21 females, 9 males) with an age range of 35-55 years old with an average of 5-10 years duration of OLP. Patients were suffering from erosive/atrophic OLP with severe pain, burning sensation and difficulty in eating. They came for the first time seeking for treatment. They were randomly selected from the outpatient clinic of dermatology at National Research Centre (NRC) and from dermatology hospital (El Hod El Marsoud). The study protocol was approved by the Ethical Committee of the NRC by the no. (15023). All patients were informed about the treatment plan and they all submitted a written informed consent before enrollment.

### *Inclusion criteria*

Patients clinically and histologically diagnosed with OLP were included in the study based on a modified definition of the World Health Organization (WHO) criteria [22]. They were free from any systemic diseases and those

with controlled diabetes and/or controlled hypertension participated in this study.

***Exclusion criteria***

Pregnant and lactating women are those of history of topical steroids in the last two months, and systemic steroids in the last six months or any other treatment that would interfere with our results and patients with uncontrolled diabetes or hypertension. The patients are having malignant lesions under treatment and those suffering from viral infections e.g. AIDS.

***Treatment protocol***

Patients included in this study were scheduled for proper scaling and root planning together with oral hygiene measures and mouth wash to reduce bacterial load prior to treatment.

Patients were subjected to PDT twice per week for two months with a maximum of 16 sessions. Figure (1) showed an ulcerative lesion on the lateral border of the tongue as the patient complained from severe pain which was dramatically reduced after PDT sessions where obvious healing was seen as in figure (2). Methylene blue (MB) muco-adhesive oral gel was applied to the oral lesions one at a time using cotton swabs and left for 15 minutes after proper isolation of the area to be treated.

The muco-adhesive oral gel was prepared at the National Institute of Laser Enhanced Sciences (NILES), Cairo University using carbopol 940 and methyl paraben sodium that were purchased from NORMEST Co. for scientific development, Egypt [23, 24].

Then laser was applied to the oral lesions in non-contact mode. Laser used in this study was diode laser of a wave length of 650 nm & power 150mW, with 6mm diameter of the working probe of the hand piece. Laser was applied to each oral lesion for duration of 2:30 mins. Two times per week for a duration of 2 months with max of 16 sessions. Laser was applied with slight overlapping motion in order to evenly distribute energy covering all mucosal lesions and also peri-lesional tissues. Laser device was manufactured at the National Institute of Laser Enhanced Sciences (NILES), Cairo University (S.N.15012). The gel was then removed by asking the patients to rinse after laser exposure to avoid undue exposure to other lesions and to guarantee standardization.

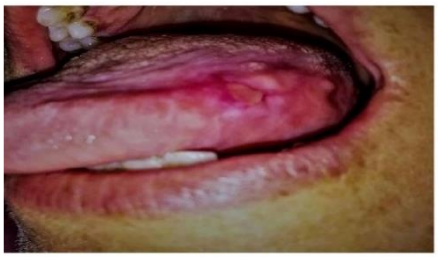

**Figure 1.** Showing the lesion on the lateral border of the tongue.

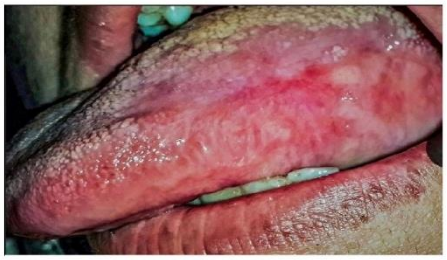

**Figure 2.** Showing improvement of the lesion after PDT sessions.

***Clinical evaluation***

Visual analogue scale (VAS) which is graduated from zero to ten, where zero= no pain, and 10=extremely painful [25] was used. The VAS was recorded before, during and after treatment.

Data management and statistical analysis were performed using the Statistical Package for Social Sciences (SPSS) version 24.

Data were explored for normality by checking the data distribution and using Kolmogorov-Smirnov and Shapiro-Wilk tests and it showed normal distribution. Comparison overtime was done by repeated measure ANOVA using generalized liner methods followed by paired t-test for pairwise comparison. ANOVA was done to compare more than two related variables. Non-parametric analogue Friedman test and pairwise difference were detected by the Wilcoxon rank test were done to ensure robustness of results. Adjustments of p-value were done using the Bonferroni method for multiple testing. All p-values are two-sided. P-values $\leq 0.05$ were considered significant.

## RESULTS

Thirty patients with OLP were included in the study. Patients received 2 laser sessions per week for 2 months. They were 21 females and 9 males. The mean age ±SD of patients was 45.9±6.8 years and ranges from (35-55 years).

The mean VAS score at the first week was 8±1 with median of 7 and range of 6to10 that decreased gradually over 8 weeks to reach a mean of 4±2 by the end of the 8th week with range of 2-8, this was statistically significant ($p<0.001$).

Pair-wise comparisons revealed that all time periods were statistically significant from each other except comparing week 5 to week 6 and week 6 to week 7 (Table 1 & Figure 3).

During the first month, the mean VAS score was 7±2 with median 6 and range of 4 to 10 that decreased to mean of 5±2 by the second month with range of 2 to 8, this showed statistical significance ($p<0.001$) (Table 2).

**Table 1.** Statistical analysis of VAS score for pain intensity all over the study time/week

| | Mean | SD | Median | Minimum | Maximum | P value |
|---|---|---|---|---|---|---|
| **W1** | 8 | 1 | 7 | 6 | 10 | <0.001 |
| **W2** | 7 | 2 | 7 | 4 | 10 | |
| **W3** | 6 | 2 | 6 | 4 | 10 | |
| **W4** | 6 | 2 | 5 | 3 | 10 | |
| **W5** | $5^{a}$ | 2 | 5 | 3 | 9 | |
| **W6** | $5^{a-b}$ | 2 | 5 | 2 | 8 | |
| **W7** | $5^{b}$ | 2 | 5 | 2 | 8 | |
| **W8** | 4 | 2 | 3 | 2 | 8 | |

SD: standard deviation, similar letters indicate statistically non-significant difference

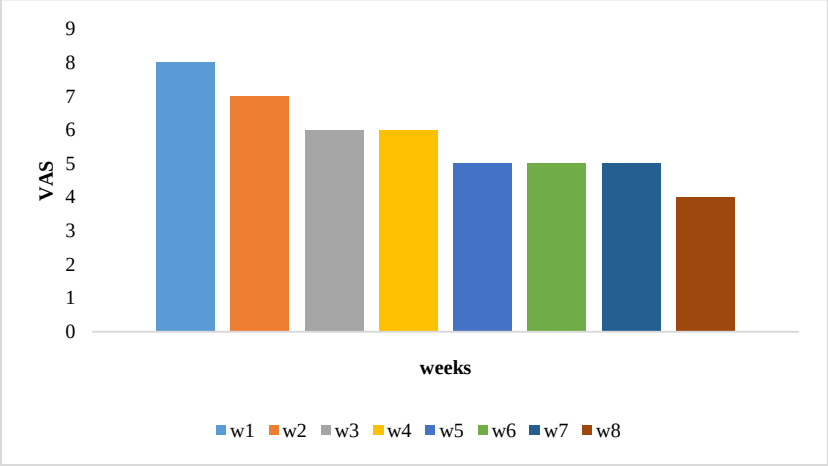


**Figure 3.** shows the VAS score over the study duration in weeks

**Table 2.** Statistical analysis of VAS score for pain intensity/month

| | Mean | SD | Median | Minimum | Maximum | P value |
|---|---|---|---|---|---|---|
| **Month1** | 7 | 2 | 6 | 4 | 10 | <0.001 |
| **Month2** | 5 | 2 | 4 | 2 | 8 | |

SD: standard deviation, $p \leq 0.05$ statistically significant

## DISCUSSION

PDT is considered a new modality for treatment of a large number of oral lesions. Few studies have investigated the efficacy of PDT in treatment of OLP, by using VAS PDT is capable of alleviating pain in patients

suffering from OLP and assisting in clinical improvement of OLP lesions during treatment as well as during the follow-up period [26, 27].

Therefore, the safety and efficacy of PDT in OLP should be determined, analyzing its clinical picture, symptoms, the quality of life and recurrence rate, as well as the modulation of cytokines involved in the pathogenesis of OLP to get to know how this therapeutic tool works [28].

VAS is used to evaluate pain as infinite studies have used this scale to assess OLP symptoms. VAS is considered as one of the most commonly used methods in literature as it is a patient-dependent measure [29]. Despite the clinical picture of OLP, patients with symptomatic lesions were involved in our study. Patients with OLP suffer from discrete burning sensation to severe pain; the quality of life of patients can be significantly affected.

The treatment of symptoms of OLP was carried out by several treatment modalities as: topical steroids like dexamethasone, clobetasol, betamethasone and triamcinolone, topical calcineurin inhibitors (TCIs) such as tacrolimus, pimecrolimus, retinoids such as tretinoin and photo-chemotherapy [11].

PDT is a special type of treatment that combines two components: a photosensitizer (PS) and a harmless source of light at a specific wavelength [30]. The visible light irradiation forms biochemical interaction in the presence of PS and oxygen causing excitation and production of toxic oxygen species such as singlet oxygen and free radicals which lead to cellular destruction, membrane lysis and protein activation [22].

Sobaniec et al., carried out a study on 23 patients with 48 lesions using PDT & photolon photosensitizer in a gel form for treatment of OLP. Diode laser of WL 660 nm and power of 300mW was used in their study. The appointments were scheduled at 2-weeks interval for 10 sessions. PDT was found beneficial in this study and there was a significant decrease by 55% in the size of clinical lesions [9].

Diana et al. conducted a study on 20 patients, where the study group received PDT using diode laser of WL 660 nm and P.D 100-130 mW $cm^{2-1}$. There was a highly remarkable decrease in VAS scores immediately after treatment in the study group p=0.0001 and all over the periods of follow up; 1, 2, 4 weeks & 2 months [31].

Aghahosseini et al. estimated PDT as an alternative treatment for OLP in 13 patients with 26 mucosal lesions. Low- energy laser of 632 nm WL and an energy dose of 120 J $cm^{2-1}$ were applied to OLP lesions. Evaluation was carried on 3, 7, 15 days and 1to 9 months after PDT. The mean reduction of the size of the mucosal lesions was 44.3%. There was a 50% clinical improvement of the lesions with obvious reduction in their signs and symptoms [32].

In our study, the efficacy of PDT was used to reduce pain intensity in patients with OLP. In comparing the pain intensity in different sessions, the comparison revealed that all time periods showed statistical significance from each other except comparing session 3 to 4, session 4 to 5, session 5 to 6, session 8 to 12, session 9 to 11, session 10 to 11 and session 12 to 13.

In the first week the mean VAS was 8±1 decreased gradually to 4±2 over the $8^{th}$ week with a statistical significance ($p<0.001$). All time periods showed statistical significance of pain intensity from each other except comparing week 5 to week 6 &week 6 to week 7. In comparing the pain intensity in month time, it was 7±2 and decreased to 5±2 with statistical significance ($p<0.001$) in the first month. The results of our study correlated with studies conducted by different researchers [31, 32 & 9].

While in another study conducted by Maloth et al. 8 patients with 20 OLP lesions were divided into 2 groups (control & study groups). The regimen of PDT included 5- ALA as a photosensitizer which was topically applied and irradiated by blue LED light of 420 nm at several sessions for 4 weeks. Results showed that 80% of lesions showed partial response while 20% showed no response at all [33].

Jajram et al. carried out a study where TB photosensitizer was topically applied and after 10 minutes the lesions were exposed to GaAlAs laser of 630 nm WL & P.D of 10 mW $cm^{2-1}$ for 2.5 minutes twice per week for 1 month. Control group received dexamethasone for 5 minutes 4 times daily for 1 month. Results showed that traditional corticosteroids showed better results than TB-PDT. These different findings may be due to variation in applied doses and energy used, also the different photosensitizers used [34].

Magdalena S et al. conducted a study where 12 females were treated by PDT using ALA gel which was applied directly onto the oral lesions. A high-power LED providing 630 nm as a light source and 300 mW as its power were used. Ten sessions were performed once weekly with duration of 2.5 minutes each. The mean reduction in lesions' size was 8.05% which was of no statistical significance although pain was less intense [35]. These studies were inconsistent with our study [33-35].

The possible reasons could be the light source, where the above study used LED as light source but we used laser, the Ps used here is ALA while we used MB. The number of sessions in this study was 10 sessions where in our study it was 16 sessions. Moreover, the use of TB photosensitizer for 1 month duration, 8 sessions in the study carried out by Jajram et al., resulted into controversy results with our study due to different PS, number of sessions and duration of the study [34].

As for the study conducted by Maloth et al., the use of ALA as a photosensitizer, blue LED light as a light source and 420 nm as a wave length resulted in inconsistent results in comparison to our study [33].

PDT produces cytotoxic effects through cellular, vascular and immunological responses. These effects depend on tissue- oxygen availability, the photosensitizer and the illumination program used [10]. PDT has an effect on inflammatory cytokines as interleukin IL-6, and IL-10, it also increases number of neutrophils.

It should be noted that the process of healing of the oral mucosa is directly affected by PDT due to activation of the signaling pathways of the cells leading to cellular migration and proliferation, leucocytic influx controlling, cytokines modulation, production of chemokines, and oxidative stress [36]. That's why the study of the different inflammatory cytokines will greatly help us to identify more about the PDT different therapeutic mechanisms [28].

Lynch et al. conducted a study and proved that PDT leads to systemic immune-suppression. The suppressor cells were finally identified as macrophages in this study. Furthermore, the observed effect could be adoptively transferred by viable splenocytes from PDT-treated mice [37]. In PDT-mediated immunosuppression the role of IL-10 was studied, where Simkin et al. investigated the immunosuppressive effects of PDT using BPD (Benzoporphyrin-derivative) as a photosensitizer in normal and IL-10-deficient mice [38].

The authors found out that IL-10 has a potent role in BPD-PDT-mediated immune-suppression. In a study by Qin et al. the immune-suppressive effects of peritoneal PDT resulted in marked reduction of peritoneal lymphocytes and that macrophage activation and phagocytosis were significantly increased [39].

The immunosuppressive effects of PDT were examined in a disease occurring in mice called adjuvant enhanced arthritis which is an autoimmune disease [40]. This disease is similar to the human auto-immune arthritis found in systemic lupus erythematosus (SLE) disease. Mice treated by PDT showed decreased severity of arthritis as well as delayed onset of the disease in comparison to untreated mice. Bone tissue and cartilage damage was prevented by PDT; this was attributed to selective destruction of lymphocytes found in the circulation as well as in the joints, which showed highly beneficial effects [41].

PDT has an immunosuppressive effect similar to that of topical steroids which is considered the gold standard for treatment of OLP.

Finally, the use of PDT was found to be an efficient alternative method compared to corticosteroids in OLP therapy. In addition to its curative role, it has the advantage of being safe.

## CONCLUSIONS

PDT showed remarkable effects in pain relief in OLP patients, thus it is a reliable and valuable treatment modality. Pain scale was obviously improved during the treatment course of the disease, therefore PDT is considered beneficial in improvement of the quality of life of OLP patients.

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***Conflict of interest***

All authors declare no conflict of interest in this study.

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