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PHOTODYNAMIC THERAPY AND TOPICAL STEROID EFFECTS UPON IMMUNE REGULATORY CELLS AMONG PATIENTS WITH ORAL LICHEN PLANUS

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ABSTRACT

Objective: To evaluate the effectiveness of the photodynamic therapy (PDT) in comparison with topical corticosteroids upon immune regulatory cells of patients oral lichen planus. **Subjects and methods:** Twenty patients with clinical and histological diagnosis of EOLP were divided into two equal groups. Group A: (control group) were instructed to use topical corticosteroid, Group B :(study group) received PDT using diode laser 635 nm mediated by toluidine blue (TB), and before starting the treatment five milliliters of peripheral venous blood was taken from both patients groups and withdrawn into an EDTA- containing test tube to prevent coagulation. These procedures were performed after three months and six months of treatment for both topical corticosteroids and PDT treated patients to detect changes occurs before and after treatment. **Results:** a statistically significant difference was reported between baseline and follow -up periods. Where both groups showed a remarkable reduction in pain, size of lesions, and CD4:CD8 ratio showed statistically significant decrease during follow up periods. **Conclusions:** Photodynamic therapy is an effective treatment and it can be considered as an alternative method for TC in treatment of erosive-atrophic OLP and effectively regulates the distribution of CD4+ T cells and CD8+ T cells.

KEYWORDS: Oral lichen planus, photodynamic therapy, topical steroid, immune regulatory cells.

INTRODUCTION

Oral lichen planus (OLP) is a chronic mucocutaneous disease of unknown etiology, that affects 0.5%-2% of the general population[(1)], in particular, it affects adults over the age of 30-year-old with a slight female predication [(2)]. Although mucosal site can be affected, the buccal mucosa is most common affected site, followed by tongue and gingiva[(3,4)] . Oral lichen planus can present clinically in different patterns: reticular, atrophic, and bullous erosive form; each have specific characteristics and can be found isolated or associated together. The most prevalent type is reticular type; characterized by the presence of Wickham striae, which are typically symmetric, bilateral, asymptomatic, and found in the buccal mucosa. The erosive form, despite being less frequent, presents greater

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clinical significance because the lesions are usually symptomatic, starting from a minimal discomfort to episodes of severe pain[5].

OLP pathogenesis is thought to be a T-cell mediated autoimmune disease, involving specific and non-specific antigen specificity [6] . Antigen-specific mechanisms in OLP include antigen presentation by basal keratinocytes and antigen-specific keratinocytes killing by CD8+cytotoxic T-cells. Non-specific mechanisms include mast cell degranulation and matrix metalloproteinase (MMP) activation in OLP lesions. These mechanisms may combine to cause T-cell accumulation in the superficial lamina propria, basement membrane disruption, intra-epithelial T-cell migration, and keratinocyte apoptosis in OLP [7, 8].

Topical and systemic corticosteroid has been considered as the foremost widely accepted treatment modality for OLP. However, because the chronic nature of OLP, long-term use of corticosteroids associated with development of certain local and systemic complications, include mucosal atrophy, oral candidiasis, adrenal insufficiency, gastrointestinal disorders, hypertension, as well as diabetes [9,10]. Hence, thinking about other treatment modalities to avoid these complications would be of value in this regard.

Photodynamic therapy (PDT) has been proposed as promising therapeutic modality for several medical and dental conditions[11]. PDT involves topical or systemic administration of a light-sensitive drug, termed as a photosensitizer, followed by light irradiation with a specific wave length that corresponds to the absorbance band of the drug, and the interaction in the presence of tissue oxygen can produce cytotoxic oxygen free radicals that are suggested to be responsible for the therapeutic action of PDT [12]. In this respect, many studies have been performed to evaluate the efficacy of PDT in management of OLP. Mostafa et al [13] reported better improvement in signs and symptoms of OLP among PDT-treated group compared to corticosteroid group. Additionally, another study[14] reported that PDT was as effective as topical corticosteroid in management of OLP. Jajarm et al [15], found that topical uses of dexamethasone and PDT showed significantly decrease of pain and size of lesion. In view of these data, the present study was designed to evaluate the effect of photodynamic therapy and topical steroid upon immune regulatory cells in patients suffering from oral lichen planus.

SUBJECTS AND METHODS

Twenty patients diagnosed clinically and histologically as erosive oral lichen planus of both sexes from Oral Medicine and periodontology department in Faculty of Dental Medicine, Al-Azhar University in a randomized parallel study design after signed Informed consent. They were chosen consistent with the subsequent inclusion and excluding criteria

Inclusion criteria, Patients with histologically proven diagnosis of OLP according to modified WHO criteria [16].

Exclusion criteria: Patient on treatment of immunosuppressive, chemotherapy or history of radio therapy for the last 6 months, Pregnant and lactating ladies**,** Patients with uncontrolled diabetes and or hypertension, Patients with history of positive HCV or HBs Ag, Patients treated by drugs that could cause Lichenoid reaction, Patients were received topical treatment for oral Lichen planus in the last 2 weeks or systemic treatment for OLP in the past 3 months, and Heavy smoker's subjects.

Sample size calculation: According to previous clinical study [17], 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 following formula: n= 2(Za+Zb) 2 x(S) 2/ (d) 2.where S = 2.27 and d = 2.

Patients were divided into two groups; Photodynamic group: ten selected patients who received PDT mediated by toluidine blue (TB). At first application of toluidine blue on both sides of lesional area was performed. After ten minutes PDT was performed by using a semiconductor laser 635 nm. Application of 635 nm wavelength was transmitted to the lesion via an optical fiber equipped with a diffuser tip. The laser power from the top of the glass fiber didn't exceed 300 mW. Each session of PDT was applied for 10 min. The total dose 120 J/cm2 for each sitting. The procedure was repeated on 3rd, 7th and 15th day. Then the patients were followed up at the end of fourth week, 3 months and 6 months of treatment. After each laser session, a chilly diet was recommended. The healing process after each laser treatment was uneventful, with no pain, edema, or bleeding. No side effects were observed at any time during the treatment and follow up. Corticosteroid group: ten patients were instructed to use the topical corticosteroid in orabase (kenakort A-orabase). They were educated to put a very thin layer of corticosteroid three times a day without eating or washing for half an hour after application (after meals and before bed time).

Clinical assessment

The clinical data was scored according to the criteria scale described by Thongprasom et al (1992) [17]. Then the severity of symptoms of lesions was recorded using the visual analog score (VAS), graduated from zero to ten, where zero = no pain, and 10 = extremely painful [18]. Digital photographs were taken at the initial presentation, after treatment, and at the follow up periods for visual documentation of changes. The improvement (total resolution of the clinical signs) was defined as the disappearance of all erosive lesions, regardless of any persisting hyperkeratotic lesions; partial response, meant reduction in pain and size of the lesion compared to baseline; and no improvement defined as no changes in the lesion.

Peripheral blood lymphocyte subsets assessment:

Five millilitres of peripheral venous blood was taken from each patient and withdrawn into an EDTA- containing test tube to prevent coagulation, before starting treatment. Samples were taken at an equivalent time, within the morning after the patient fasted overnight. This is important because cortisol levels (which might influence lymphocyte subsets) vary over the day. Lymphocyte phenotype analysis was performed by means of 2-color, 4-parameter flow cytometry using FACS Calibur (Becton Dickinson).

Lymphocyte phenotype analysis was performed by using monoclonal antibodies to distinguish cells expressing CD4, CD8 antigens. The protocol used was as follows: The required amount (5, 10, or 20μL) of the appropriate fluorescein isocyanate-labeled or phytoerythrin-labeled monoclonal antibody was added to a 10 μL sample of blood that had been treated with EDTA to stop coagulation. After incubation at room temperature in the dark for 30 minutes, 2 mL of lysing agent (Facs, Becton Dickinson) was added. The sample was then incubated in the dark for a further 10 minutes, and then washed by centrifugation at 1200 rpm for 10 minutes. The pellet was re-suspended in 1 mL of phosphate-buffered saline (PBS) solution, and then washed again at 1200 rpm for 10 minutes. The pellet was re-suspended in 1 mL of (PBS), and fluorochrome-labeled cells were then counted by flow cytometry in a FACS calibur cytometer (Becton Dickinson). The cytometer data were analysed with the help of the program Cell-Quest (Becton Dickinson). When leukocytes are added to the reagent, the fluorochrome- labeled antibodies bind to leukocyte surface antigens. During acquisition, the cells travel past the beam and scatter the laser light. The stained cells fluoresce. These scatter and fluorescence signals, checked by cytometer, provide information about the cell‟s size, internal complexity, and relative fluorescence intensity. Cells were considered to be positive for tested antigens if they revealed higher fluorescence intensity than cells stained with the isotype-matched control antibody. The results were

presented as the percentage of cells gated in forward scatter and side scatter (FSC/SSC) lymphocyte-gate expressing the assessed antigens. These procedures mentioned above are performed after three months, six months of treatment with topical corticosteroids and PDT for detection of changes occurs before and after treatment.

Statistical analysis of the data:

Quantitative data were carried out by using range (minimum and maximum), mean, standard deviation and median significance of the obtained results was judged at the 5% level. The used tests were Student t, ANOVA with repeated measures, Mann Whitney test and Friedman test.

RESULTS

Twenty patients with biopsy-proven and clinically diagnosed erosive OLP were divided into 2 equal groups; their demographic data were presents 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. On comparing the two studied groups regarding age, it was found that there was a statistically non-significant difference between the two groups regarding the mean age.

TABLE (1) Comparison between the two studied groups according to age.

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

The comparison between the two groups regarding the pain score recorded at different 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).

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)

Regarding Absolute count of CD4, % of change after 3 and 6 months, there was statistically non-significant difference between groups (p=0.529, and 0.353 respectively).

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*		

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*		

Regarding absolute count of CD8, % of change after 3 and 6 months, there was statistically non-significant difference between groups (p=0.971, and 0.529 respectively).

Regarding CD4:CD8 ratio, % of changes after 3 and 6 months, there was statistically non-significant difference between groups (p=0.218 and 0.165 respectively).

TABLE (4) Summarizes comparison between the two studied groups according to absolute count of CD4&CD8:

	Photodynamic (n = 10)	Corticosteroid (n = 10)	Test of Sig.	P
Absolute count of CD4				
Before	1524.9 ± 363.2	1387.6 ± 331.5		
After 3M	1256.1 ± 363.8	1230.4 ± 331.6		
After 6M	938.5 ± 189.5	972.2 ± 157.4		
% of change				
After 3M	-10.92 ± 40.57	-7.69 ± 30.58	U=41.50	0.529
After 6M	-33.96 ± 26.39	-25.42 ± 23.61	U=37.0	0.353
Absolute count of CD8				
Before	417.9 ± 107.0	471.5 ± 144.7		
After 3M	400.9 ± 95.73	437.8 ± 102.5		
After 6M	427.8 ± 126.0	428.4 ± 139.8		
% of change				
After 3M	4.93 ± 47.25	2.0 ± 44.98	U=49.0	0.971
After 6M	7.45 ± 38.85	-1.95 ± 41.85	U=41.0	0.529
CD4:CD8 ratio				
Before	3.75 ± 0.88	3.12 ± 0.93		
After 3M	3.09 ± 0.37	2.92 ± 0.40		
After 6M	2.26 ± 0.87	2.40 ± 0.75		
% of change				
After 3M	-14.70 ± 14.79	-1.39 ± 22.25	U=33.50	0.218
After 6M	-33.62 ± 40.23	-14.80 ± 43.68	U=31.0	0.165

DISCUSSION

Oral lichen planus is a chronic mucocutaneous disease and it was speculated that cell- mediated immunity and cytokines, produced by keratinocytes and lymphocytes, play an effective role in its pathogenesis. These cytokines (TNF-α, IL-8, INF-γ) cause increased activity of lymphocytes and apoptosis of keratinocytes. Hence, systemic and local corticosteroid therapies are the cornerstone in its treatment However; these treatments have plenty of side effects such as candidiasis, xerostomia, sore throat, osteoporosis, adrenal insufficiency, hypertension, and diabetes mellitus [18]. Treatment of OLP is aimed primarily at reducing the length and 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 [19].

Currently, PDT has been applied for the treatment of a spread of lesions like skin and breast cancers, immunologic diseases (such as acne, psoriasis, lichen planus, and scleroderma), and infectious diseases (such as HPV, osteomyelitis, and candidiasis) [20]. PDT is widely used to treat oral lesions including potentially malignant lesions (erythroplakia, verrucous carcinoma), head and neck cancers, and periodontal disease [21]. PDT involves a chilly chemical reaction that's activated when photosensitizing drugs are exposed to light at a selected wavelength and it leads to cellular destruction by a free radical oxidative process. The photochemical reaction has no effect on the connective tissues [22]. PDT has 3 main constituents: oxygen, a photosensitizing drug, and light. The drug is activated by light and interacts with molecular oxygen to supply excited state reactive oxygen. As PDT is a cold photochemical process it does not affect proteins such as collagen and elastin so the integrity of underlying structures can be maintained[23].

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 [24], and it is suggested that PDT induces apoptosis in proliferated inflammatory cells [25]. By considering the inflammatory pathogenesis of OLP and the immunomodulatory effect of PDT, photodynamic therapy may be an effective alternative treatment procedure. Wavelength is that the most vital think about all kinds of photo therapies and so, the foremost appropriate wavelength should be selected to get the simplest results. The present study was designed to evaluate the value of photodynamic therapy and topical steroid on immune regulatory cells in oral lichen planus patients. A 635-nm laser was used as it the most effective wavelengths for wound healing and no side effects were reported [26]. In addition, although many studies have used methylene blue as a photosensitizer, in this study, toluidine blue was used because it absorbs at 635nm[27]. TB is a cationic photosensitizer that has a strong absorption at 635nm, which is a proper optical range for light penetration into the damaged tissue [28].

The obtained results showed that both groups had statistically significant differences from baseline to follow-up periods. The results of the present study were in accordance with study[15], who showed that sign scores of pain and size of the lesions significantly reduced in both groups treated by TB-PDT (630 nm wavelength and exposure dose of 120J/cm2) for two visits and corticosteroid mouth wash .therefore, they mentioned that, LLLT was as effective as topical corticosteroid therapy. Trehan et al [29], used an excimer laser (308 nm) in eight patients suffering from symptomatic OLP lesions, and after the treatment, five patients had marked improvement in experiencing pain. In the present study, all patients in the experimental group had marked 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.

Additionally, a study[30], performed on 20 patients with systemic OLP. PDT with xenon arc light of 630±5 nm wavelength and total dose of 120 J/cm2 in four visits and photosensitizer of MB was done. A significant reduction in lesions over a prolonged period without any side effects had been reported. 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 and post-operative complications; there was no postoperative bleeding or scaring after TB-PDT application.

Currently, it has been emphasized that, LP disease is a cell-mediated immune response and considered as type of autoimmune disease [31]. Where, large number of lymphocytic infiltrates, mainly T cells, has been present at the site of lesion of the LP as the main types [32]. Where, these lymphocytes showed to be activated in local lesions occur at skin and mucous membranes, thereby increasing the secretion of various adhesion molecules and cellular kinases [33,34]. In normal states, CD4+ T cells and CD8+ T cells subsets should be in dynamic equilibrium [35]. With the progression of OLP, the increase in CD4+ T cells and CD8+ T cells is more pronounced. Therefore, OLP is believed to be mainly caused by invasion of the oral mucosa by CD4+ T cells and CD8+ T cells, inducing killing of superficial and basal cells to accelerate the progression of the injury [36,37]. In the present study the photodynamic treated group showed statistically significant decrease in mean absolute count of CD4 after 6 months and statistically non-significant decrease in mean absolute count of CD8 at the same period. The result can postulated that there was statistically significant decrease in mean CD4:CD8 ratio after 6 months. On the other hand, corticosteroid group showed statistically significant decrease in mean absolute count of CD4 after 6 months and statistically non-significant decrease in mean absolute count of CD8 after 6 months. This means there is statistically non-significant decrease in mean CD4:CD8 ratio after 6 months.

The present result also was consistent with the results of other study [38], conducted to determine the immunological efficacy of PDT in the treatment of OLP lesion through clinical and immunohistological evaluation. They found that, there was a reduction of infiltrating CD4 and CD8 cells in mucosal lesions of OLP. The PDT led to a significant decrease of peripheral blood CD4+CD137+ and CD8+CD137+ T- cells in OLP patients and to indicate the anti-inflammatory effect of PDT.

CONCLUSIONS & RECOMMENDATIONS

Toluidine blue-mediated photodynamic therapy with a 635-nm diode laser is as effective as corticosteroid therapy for the treatment of OLP. Besides, PDT wouldn't cause unwanted side effects. Both treatment modalities reduced CD4+ and CD8+ T cells in OLP lesion. More clinical trials with large number of patients, long follow-up periods and different sources of light and photosensitizers are required to determine the ideal parameters of PDT treatment for OLP.

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