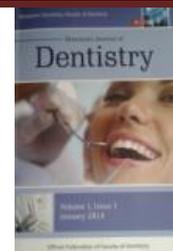




Photodynamic Therapy of Oral Erosive lichen Planus in Diabetic and Hypertensive Patients



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Abstract:

Objectives: To assess the clinical evaluation of the effectiveness of the photodynamic therapy (PDT) in comparison with topical corticosteroids in the management of diabetic and hypertensive patients with oral erosive lichen planus.

Methods: A total of sixteen patients suffering from oral erosive lichen planus were selectively collected for contribution in the present study. They were divided into two groups. This study was performed using a split-mouth design in which the photodynamic therapy was applied on the right side and topical corticosteroid ointment in the left side.

Results: our results show that there was statistically significant difference between the time zero and the end of the 2nd and 4th week in the subjective and objective scores in addition to areas of ulcerations, erythema, reticulation and total area of the lesions in both groups.

Conclusions: PDT has a quick and significant beneficial effect in the control of the main symptoms and signs of oral lichen planus.

Keywords: Lichen planu, diabetic, hypertensive, Photodynamic therapy.

Introduction

Oral lichen planus (OLP) is a relatively common chronic dermatological disease characterized by relapses and remissions. It is a cell-mediated autoimmune condition of unknown aetiology, in which T lymphocytes accumulate beneath the epithelium of the oral mucosa and cause damage to the basal keratinocytes that are recognized as being antigenically foreign or altered [1]. Psychological disturbances, such as depression, anxiety and stress, have been investigated in the etiopathogenesis of OLP, since patients with this disease report a more frequent development or exacerbation of lesions during periods of greater emotional tension [2]. Familial occurrence of lichen planus LP is a well-recognized but rare event, with an incidence varying from 1% to 11% of all LP patients [3].

An association has been described between oral lichen planus, diabetes mellitus, and hypertension. This triad is referred to as a Grinspans syndrome [4]. There is a relation between some medications and Oral lichenoid reactions (OLR) which are considered variants of OLP. Oral and cutaneous involvements have been reported. The Systemic medications such as, anti-malarial drugs [5], non-steroidal anti-inflammatory drugs (NSAIDs) [6], antihypertensive agents [7]. Many reports have suggested the association of lichen planus and HCV infection. The prevalence of this association varies from 0% to 62% with conflicting results [8].

The diagnosis of OLP should be done by clinical and histological examination. However, in classical lesions, it is possible to achieve the diagnosis based solely on clinical appearance. Upon inspection, OLP may present with white striae (Wickham's striae) in the surface of the mucosa, white papules or plaques, atrophic, erosive or vesicular lesions. The erosive, atrophic or bullous OLP has diverse painful symptoms [9]. The most commonly affected areas are the mucosa of the cheek, dorsum of the tongue, gingiva, labial mucosa [10]. Intraoral lesions OLP has six classical clinical presentations described in the literature: reticular, erosive, atrophic, plaque-like, papular and bullous [11].

The classic histopathologic features of OLP include the dense, band-like subepithelial inflammatory infiltrate consisting of lymphocytes beneath the basement membrane,

increased number of intraepithelial lymphocytes and liquefactive degeneration of basal keratinocytes [12]. Eosinophilic colloid bodies (Civatte bodies) are formed by degenerating basal keratinocytes and immunocomplexes, and they are often identified in the supra-basal epithelial area. The ultrastructure of these colloid bodies suggest that they are apoptotic keratinocytes, which is shown by demonstrating of DNA and nuclear fragmentation and immunoglobulins, especially IgM in these cells [13].

A wide variety of therapeutic modalities have been employed to treat oral lichen planus which include corticosteroids, retinoids and its derivatives [14], immunosuppressors as cyclosporine, levamisole and azithioprine [15], antifungal agents like griesofulvin and PUVA therapy [16]. These agents are either prescribed alone or in combination, the choice purely depends on professional judgment. Corticosteroids have been found to be the most predictable and successful agents in treatment of oral lichen planus. They can be used topically, intralesionally or systemically [17]. The efficacy of corticosteroids for treatment of lichen planus is mainly attributed to its anti-inflammatory and immunosuppressive actions.

Light has been used as a therapeutic agent for many centuries. In ancient Greece the sun was used in heliotherapy or the exposure of the body to the sun for the restoration of health. The Chinese used to treat such conditions as rickets, skin cancer and even psychosis. This use of light for treatment of various pathologies is referred as Phototherapy [18]. PDT is a medical treatment modality involving the administration of a photosensitizing compound, which selectively accumulates in the target cells, followed by local irradiation of the lesion with visible light. The combination of two absolutely nontoxic elements, i.e. drug and light, in the presence of oxygen results in the selective photodamage and cell death [19].

PDT involves three components: a photosensitizer, light and oxygen. A photosensitizer or its metabolic precursor is administered to the patient. Methylene blue (MB) is a heterocyclic aromatic chemical compound. It has been used in medical practice for more than 10 years and is said to have very low tissue toxicity. Unlike other photosensitizers, MB can be administered topically and orally. It has strong absorption at wavelengths longer than 620

nm, where light penetration into tissue is optimal, hence used as photosensitizer in PDT [20].

In recent times, PDT that utilizes visible light source delivered promising results for refractory OLP. It has been used with various success rates in the field of oncology, especially in head and neck tumours. The selective uptake and retention of a local or systemically administered photosensitizer in tumour tissue is the main principle behind PDT. Intracellular activation of the photosensitizer, using light of proper wavelength, results either in the production of free radicals (type I mechanism) or the formation of intracellular singlet oxygen (type II mechanism), which causes cell death by vascular shut down mechanisms and intracellular oxygenation [21].

It has been suggested that PDT may have immunomodulatory effects and may induce apoptosis in the hyperproliferating inflammatory cells which are present in psoriasis and lichen planus. This may reverse the hyperproliferation and inflammation of lichen planus. Thus, PDT seems to be a promising alternative for the control of OLP without any adverse effects and can be used for cases resistant to steroids or when steroids are contraindicated [22].

Patients and methods

Sixteen patients with the age ranging from 30-60 years attended to the department of Oral Medicine and Periodontology, Faculty of Dentistry, Mansoura University were suffering from the clinical signs and symptoms of intra-oral erosive lichen planus. Some of these patients had a history of unresponsiveness to currently available therapy. The patients were selected after histopathological confirmation to be participants in this study.

Inclusion criteria were as follows:

1-Presence of oral erosive lichen planus lesions bilaterally on the buccal mucosa.

2-Clinical and histopathological diagnosis of oral lichen planus based on a modified definitions of the World Health Organization (WHO) [23].

3-Diabetic and hypertensive patients were included in the present study.

-Diabetic patients were controlled type 2 (non insulin dependent) patients.

-Hypertensive patients were essential hypertension type.

Study design

Treatment protocol

For each patient, the right side of the buccal mucosa was considered as the test side, while the left side was the control side.

Group1

It included 8 patients

In the right side (test side): Methylene blue (MB) mouth path solution in water of 5% concentration was applied for 5 minutes, then after 10 minutes, A focal red light (wavelength 660nm, Intensity 100-130mW/cm²) was applied on the lesional area for 2 minutes with total dose delivery for each visit (15.6)J/cm².

In the left side (control side): Topically applied betamethazone valerate 100mg (ointment) was rubbed on the lesional area 3 times daily.

Group2

It included 8 patients

In the right side (test side): A focal red light (wavelength 660nm, Intensity 100-130mW/cm²) was applied on the

lesional area for 2 minutes with total dose delivery for each visit (15.6)J/cm².

In the left side (control side): Topically applied betamethazone valerate 100mg (ointment) was rubbed on the lesional area 3 times daily.

This treatment protocol was applied for four weeks.

Clinical assessment

Clinical evaluations were performed at the start of the study, and baseline parameters were recorded. The lesions were re-assessed at the end of the second and fourth weeks of treatment.

Objective response

Lesions of oral lichen planus are scored according to these criteria,⁽²³⁾ using a scaled tongue blade:

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;

5 = white striae with erosive area >1cm².

Lesions are also measured with a flexible transparent grid, divided into calibrated squares of 4 mm², and a thin indelible, ink marker. The grid was placed over the lesion, and area of ulceration, erythema, and reticulation was traced with the ink marker (Fig:2). Quantitative measurements were calculated from the grid by multiplying the number of squares by 4mm² to obtain the total area of the lesion [24].

Subjective response

Discomfort scores as well as questionnaire documenting any possible adverse effects was completed. Patients are asked to rank the severity of their discomfort on a visual analogue scale rating from 0 to 3 as follow:

0 = no pain;

1 = mild pain;

2 = moderate pain;

3 = severe pain.

Subjective and objective responses were measured at the start of the study and at the end of the second and fourth week of treatment. Digital photographs were taken at the initial presentation and at the ends of the 2nd and 4th weeks of treatments for visual documentation of changes.

Results

In comparing the mean of the degree of improvement between the right and left sides of group 1 in the subjective and objective responses of the patients in the 2nd week, the right side was higher than the left side, while at the 4th week they were in right side less than in the left side. While in group 2 the mean of the degree of improvement of the subjective and objective responses at the 2nd and 4th weeks were lower in right side than left side. In comparison between the right and left sides of group 1, the mean degree of improvement in area of ulceration, erythema, reticulation and total area of the lesions at the 2nd week in the right side was higher than in the left side, while at the 4th week the left side was higher than in the right one. In group 2 the mean degree of improvement in area of ulceration, erythema, reticulation and total area of the lesions at the end of the 2nd and 4th weeks of treatment are higher in the left side than right side (Fig. 1,2,3,4).

Discussion

Oral lichen planus (OLP) is a chronic inflammatory disease that affects the mucus membrane of the oral cavity. It is a T-cell mediated autoimmune disease in which the cytotoxic CD8+ T cells trigger apoptosis of the basal cells of the oral epithelium [25].

Photodynamic therapy (PDT) is a minimally invasive treatment that has shown promising results in treating lesions of the head and neck [26]. PDT involves a cold photochemical reaction that is activated when photosensitizing drugs are exposed to light at a specific wavelength and it results in cellular destruction by a free radical oxidative process. The photochemical reaction has no effect on the connective tissues [27].

After histopathological examination of the lesions, patients with any histological signs of dysplasia were excluded from the study. Diabetic and hypertensive patients were included in this study with the age ranging between thirty three to sixty years old as lichen planus is common to be seen in this age. Diabetic patients were of type 2 and hypertensive patients were of essential hypertensive type. Some authors believe that certain oral manifestations are related to inadequate metabolic control of diabetes [28,29]. Others believe that it might be due to immunological response, such as lower chemotaxis and phagocytosis, and the involvement of microcirculation with the reduction of blood supply, which contributes to diabetic patients becoming more prone to infections and alterations in the oral cavity [30]. Lichen planus was suggested to be found in hypertensive patients as a drug reaction to antihypertensive drugs [31].

This study was applied on diabetic and hypertensive patients only because Systemic corticosteroids shouldn't be used in these patients, as it cause sodium and water retention and there is a reduced carbohydrate tolerance accompanies corticosteroid use. Glucocorticoids increase gluconeogenesis and blood glucose increases by 10–20%. Glucose tolerance and sensitivity to insulin is decreased but if pancreatic function is normal no diabetes should develop. However, hyperglycaemia and glycosuria should be checked for as one fifth of patients may develop “steroid diabetes” [32]. So other safe treatment modalities like PDT is mandatory for better management of diabetic and hypertensive patients with OLP.

Considering the right side of group 1, our results show that there was statistically significant difference between the time zero and the end of the 2nd and 4th week in the subjective and objective scores in addition to areas of ulcerations and reticulations and total area of the lesions.

These results are in agreement with a study conducted by Aghahosseini et al [20] in which MB-PDT was used as a possible alternative method for the treatment of OLP. Results showed that there was significant Improvement in sign scores was achieved in 16 lesions. Four keratotic lesions disappeared completely. There was a statistically significant decrease in sign and symptom scores 1 week after treatment and at follow-up sessions up to 12 weeks. Average reduction in size of lesions was 44.3%.

Those findings indicate that PDT was beneficial on the treatment of oral erosive LP. It may be attributed to that

PDT has immunomodulatory effects and may induce apoptosis in the hyperproliferating inflammatory cells, which are present in lichen planus. This may reverse the hyperproliferation and inflammation of lichen planus [20].

Our results showed that MB-PDT has a quick and significant beneficial effect in the control of the main symptoms and signs of OLP with minimal adverse effects. Size of the lesions decreased in patients who responded satisfactorily to the treatment protocol too. We observed no scarring after treatment as well.

As UVB light was used in treatment of oral erosive LP without using photosensitizer [33], we tried to test the effect of red light on oral erosive LP without using photosensitizer in the right sides of group 2 and comparing its effect with the topical corticosteroids. Our results show that application of red light alone without the photosensitizer resulted in statistically significant difference between the time zero and the end of the 2nd and 4th week in the subjective and objective scores in addition to areas of ulcerations and erythema and total area of the lesions.

As the red light is a part of the visible light, studies concluded that visible light can cause cell dysfunction through the action of reactive oxygen species on DNA and that this may contribute to cellular aging, age-related pathologies. However, studies have demonstrated that visible light can induce cellular dysfunction and cell death both in vitro and in vivo. Irradiation of mammalian cells with visible light induces cellular damage primarily via reactive oxygen species (ROS). ROS such as the hydroxyl radical, superoxide anion, and singlet oxygen can be produced when visible light excites cellular photosensitizers. Whereas photosensitizers such as melanin and lipofuscin in pigmented cells and retinoids in photoreceptor cells have been identified. However, a number of options exist, including flavin-containing oxidases, the cytochrome system, heme-containing proteins, and tryptophan-rich proteins. The interaction of these chromophores with light can generate ROS, which in turn can damage lipids, proteins, and DNA [34].

Conclusion

In conclusion, we found that PDT may be effective in treatment of OLP and may increase the duration of symptom free period; therefore, it can be used as an alternative therapy alongside standard treatment methods.

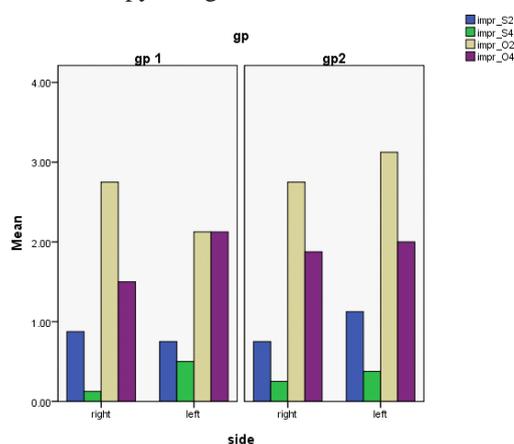


Figure 1: Mean improvement level according to the side in both groups.

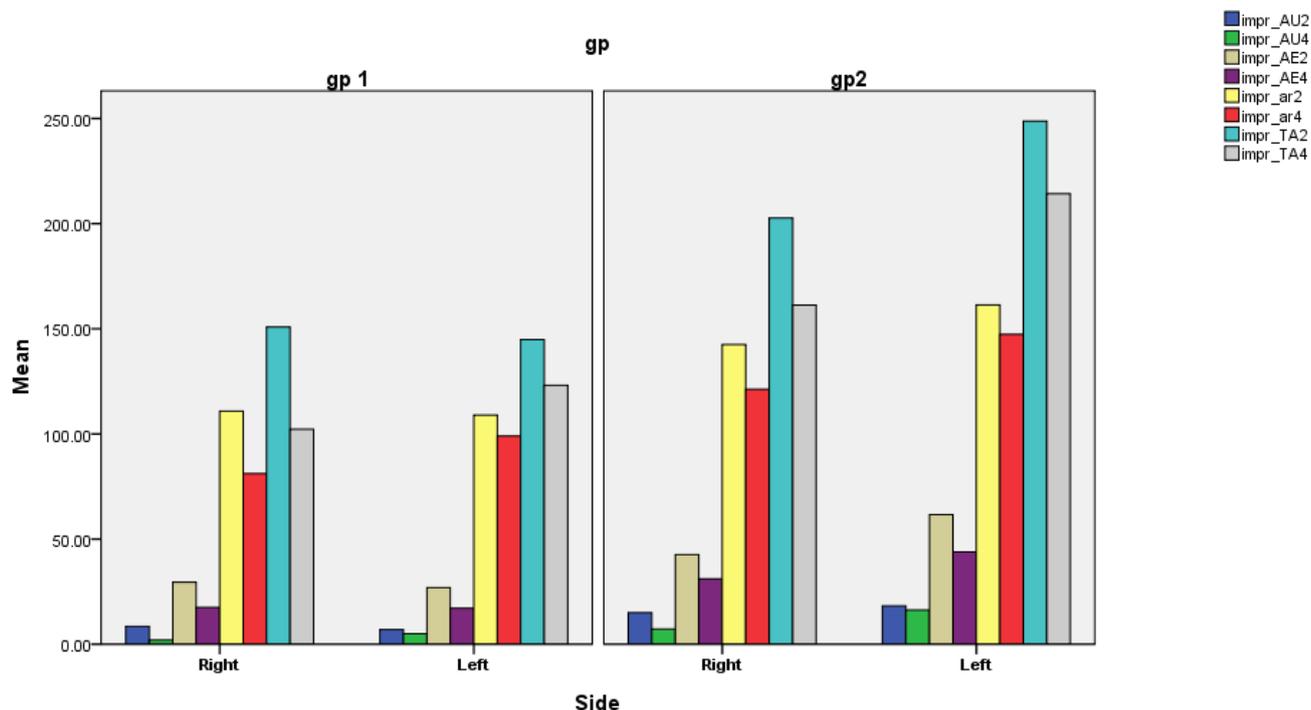


Figure 2: Mean improvement level according to the side in both groups.



Figure 3: Erosive type of lichen planus on right buccal mucosa of a 35 years old woman with 3 months disease duration in group one at time zero, 2nd week and 4th week respectively.



Figure 4: Erosive type of lichen planus on right buccal mucosa of a 45 years old man with 1 year disease duration in group 2 at time zero, 2nd week, 4th week respectively.

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