Methylene Blue-Mediated Photodynamic Therapy: A Possible Alternative Treatment for Oral Lichen Planus

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Background and Objectives: In this study, methylene blue-mediated photodynamic therapy (MB-PDT) was used as a possible alternative method for the treatment of oral lichen planus (OLP).

Study Design/Materials and Methods: Thirteen patients with 26 OLP lesions were enrolled in this study. Patients were instructed to gargle a 5% methylene blue solution in water for 5 minutes. Ten minutes later, irradiation was performed by laser light ($\lambda = 632$ nm, light exposure dose $= 120$ J/cm^2). Lesions were evaluated pre and post-operatively and at follow-up sessions by changes in sign and symptom (pain) scores, and size of lesions.

Results: 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%.

Conclusion: MB-PDT seems to be an effective alternative treatment for control of OLP. In our opinion, this preliminary result warrant further studies in order to show the efficacy of MB-PDT in control of OLP for a longer period of time. Lasers Surg. Med. 38:33–38, 2006.
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Key words: methylene blue; oral lichen planus; pain severity; photodynamic therapy; sign score

INTRODUCTION

Lichen planus is a relatively common chronic inflammatory mucocutaneous disease. Although the cause is not well known, T-cell-mediated autoimmune phenomena are involved in the pathogenesis of lichen planus [1].

Two basic types of lesions occur in oral lichen planus (OLP): totally white (keratotic) and white with red (keratotic+atrophic, erosive, bullous). Although, it is not usually a presenting symptom of hyperkeratotic lesions, OLP may be painful, especially in the atrophic and erosive forms or where a desquamative gingivitis is present [2].

OLP is reported to occur in 0.5%–2.2% of the normal population, with a peak incidence in the 30–60 years of age and with a female predominance of 2:1 [1]. Unlike cutaneous lesions, which are self-limiting in the majority of cases, oral lesions are chronic and are a potential source of significant morbidity. Furthermore, compared to cutaneous lesions, oral lesions are more difficult to control and are often refractory to conventional therapies [3]. The reported frequency of malignant transformation varies greatly from 0.4% to more than 5% over a period of 0.5 to more than 20 years [4]. Treatment options for OLP are numerous, including topical, intralesional and systemic corticosteroids, topical cyclosporine and tacrolimus, topical and systemic retinoids, however, outcomes are often disappointing.

Photodynamic therapy (PDT) is an effective therapy for premalignant and malignant cutaneous lesions [5]. It has also been used for non-oncologic purposes like psoriasis [6,7]. PDT involves in situ photo-activation of photosensitizers (PSs) by light at appropriate wavelength, generating highly active and short-lived oxygen derived species [8]. These cytotoxic species, including singlet oxygen and free radicals, induce direct oxidative damage to cellular organelles, destruction of microvasculature, and promotion of apoptosis [9]. PDT may also impart an immunological effect as well as a local apoptotic effect [10]. Many clincially used photosensitzers arise from three families: porphyrins, chlorophylls, and dyes such as methylene blue (MB) [11]. In this study, we are reporting the results of a single session of methylene blue-mediated photodynamic therapy (MB-PDT) for the treatment of OLP which has not been reported before to the best of our knowledge.

MATERIALS AND METHODS

Patient Selection

This is an open before-after study enrolling 26 lesions of 13 patients with clinical and histopathological diagnosis of OLP. The lesions had previously failed to

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respond to corticosteroid therapy (triamcinolone and methyleprednisolone as topical and systemic corticosteroid, respectively) and other treatments (topical cyclosporine). They were recently referred to the Clinic of Oral Medicine at the School of Dentistry in Tehran University of Medical Sciences (TUMS), Tehran, Iran for regular visits; during the period of September 1, 2004 to May 1, 2005. The protocol was approved by Medical Ethics Board in TUMS and Academic Center for Education, Culture and Research (ACECR).

Patients with systemic diseases, drug consumption, pregnancy, photosensitivity, age less than 20 years, and who had lesion/lesions with dysplasia and who received treatment for OLP at least 1 month previous to beginning the study were excluded. Lesions adjacent to amalgam filling site were not eligible to the study.

Patients were evaluated by an oral medicine specialist for demographics, medical history, symptoms, duration of disease, type, site, size of the lesions (cm^2), and history of cutaneous lesion and these data were recorded. Then those who were eligible to inclusion and exclusion criteria were referred to the clinic of Iranian Center for Medical Laser (ICML), ACECR, to undergo MB-PDT. Then the whole study process and its experimental nature were described to the patients. Informed consent was sought and obtained from each patient.

Procedure

MB was used as PS. MB is a commercially available medical dye. It is a tricyclicphenothiazine dye with chemical formula C16H18CIN3S and molecular weight (MW) 319.85. Peak absorption of MB is maximum at 652 nm. The fluorescence spectrum is centered at 683 nm [12]. Ten minutes prior to laser irradiation, patients were instructed to gargle a MB solution in water of 5% concentration for 5 minutes. A diode laser (Lumina®,Russia; 632 nm, CW, 1 W) was used as the light source. The lesions and 0.5 cm of their surrounding marginal zone were illuminated with a spot size of 1 cm^2. Large lesions were illuminated with multiple spots. A light exposure dose of 120 J/cm^2 was used for 2 minutes.

Assessments

Lesions were exactly measured and digital photographs were taken before PDT and at follow up sessions weekly

TABLE 1. Description of Type and Location of OLP Lesions

Type of lesions	Location Gingival	Buccal	Total
Keratotic	5 (19.2%)	4 (15.4%)	9 (34.6%)
Atrophic	2 (7.7%)	1 (3.8%)	3 (11.5%)
Erosive < 1 cm^2	1 (3.8%)	—	1 (3.8%)
Erosive ≥ 1 cm^2	9 (34.6%)	4 (15.4%)	13 (50%)
Total	17 (65.4%)	9 (34.6%)	26 (100%)

up to 12 weeks. At the follow up sessions, lesions were examined by an oral medicine clinician and a dermatologist to detect any residue, recurrence or change in lesions.

Response rates were assessed clinically by three measures: the reduction in sign and symptom (pain) scores, and the amount of reduction in size of the lesions. Treatment outcomes were defined as changes in sign and symptom (pain) scores, and size of the lesions before and 1 week after a single session of MB-PDT treatment.

Reduction in sign scores were assessed by Thongprasom sign scoring as follows [13]: score 5 (white striae with erosive area ≥ 1 cm^2), score 4 (white striae with erosive area < 1 cm^2), score 3 (white striae with atrophic area > 1 cm^2), score 2 (white striae with atrophic area < 1 cm^2), score 1 (mild white striae only), score 0 (no lesions, normal mucosa). Symptom (pain) of lesion was scored by 0–10 visual analogue scale (VAS) before treatment and at each follow-up session. Reductions in size of lesions were assessed by scaled tongue blade.

Statistical Analysis

Data were analyzed using SPSS version 11.5 (SPSS Inc., Chicago, IL). Wilcoxson sign test was used for evaluation the difference between sign score of lesions before and 1 week after treatment. Paired-sample t-test was used for assessing the changes in symptom (pain) score and size of the lesions.

RESULTS

Thirteen adult patients (12 females, 1 males, mean age = 42.5) with 26 OLP lesions, confirmed histopathologically, participated in this study (Table 1). The mean

TABLE 2. Sign Scores Before and 1 week After a Single Session of Methylene Blue-Mediated Photodynamic Therapy (MB-PDT)

Sign score (before)	Sign score (after) Score 5	Score 4	Score 3	Score 2	Score 1	Score 0
Score 5 ($n = 13$)	2	3	8	—	—	—
Score 4 ($n = 1$)	—	1	—	—	—	—
Score 3 ($n = 3$)	—	—	2	1	—	—
Score 1 ($n = 9$)	—	—	—	—	5	4

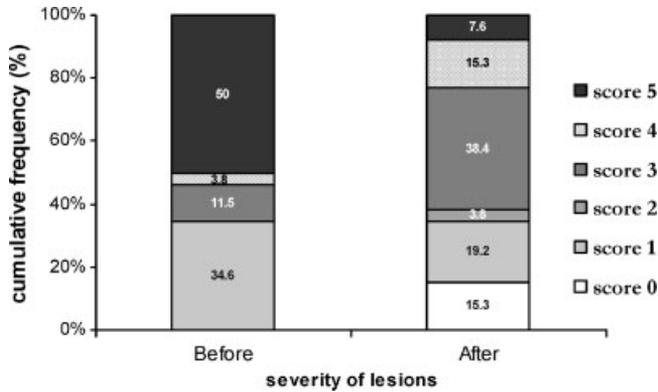Wilcoxon's rank sum test: significant ($P = 0.0001$).

Fig. 1. Changes in the sign score of OLP lesions before and 1 week after methylene blue-mediated photodynamic therapy (MB-PDT).

duration of lesions was 3.5 years (range 1–10 years). As shown in Table 1, erosive lesions with surface area greater than 1 cm² (score 5) on gingiva were the most frequent ones.

OLP sign score decreased in almost all scoring groups and it was statistically significant ($P = 0.0001$) (Table 2 and Fig. 1). Improvement of sign score was noted in 16 lesions. Eight lesions improved 2 score, 8 lesions improved 1 score, and 10 lesions showed no reduction in sign score.

Of 13 erosive lesions (score 5), 8 showed improvement to score 3 (Figs. 2, 3, and 4) and 3 others improved to score 4. Complete remission (score 0) achieved only in four reticular lesions (score 1) (Fig. 5). No complete remission was found in other scoring groups. There was a significant reduction in sign score immediately 1 week after MB-PDT (Table 2).

In patients with painful OLP, improvement in symptom (pain) score measured by VAS was achieved. This is shown by general downward shift in the symptom (pain) score to 0 at the end of the follow up (Table 3). The mean of symptom (pain) score decreased 1 week after treatment and it was statistically significant in lesions with score 3 and 5 ($P = 0.001$).

Size of lesions statistically decreased in the lesions classified in score 1 and 5 ($P = 0.001$). Although size of the lesions classified in score 3 and 4 decreased, it was not statistically significant. In this study mean reduction in size was about 44.3 %. There was no statistical significant association between location of lesions ($P = 0.152$) and response to treatment.

These improvements in sign and symptom scores, and size of the lesions achieved at 1 week after a single session of MB-PDT were constant through out the rest of follow-up period.

There were not any serious intra and post-operative complications. Few patients just complained about a mild burning sensation during the therapy. We have not seen any others side effects during the follow-up period.

DISCUSSION

OLP is a chronic immunological disease which has no definite cure at present [14]. In this clinical trial, we evaluated the efficacy of a new procedure, Methylen Blue-mediated Photodynamic Therapy (MB-PDT), in the treatment of the OLP. 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. Complete responses were also found in four reticular OLP lesions after a single session of MB-PDT. Since, even keratotic symptomless OLP lesions always carry the risk of transformation to atrophic and erosive types, it can be assumed a significant result.

Erosive lesions also changed to atrophic lesions (decrease of score from five to three in eight patients). Keeping in mind that the later has less premalignant potential than the former, it can be presumed that MB-PDT can decrease the risk of malignant transformation.

At present the management of OLP is not satisfactory in all cases and there is no definitive treatment. Among many treatments available, high potency topical corticosteroids

Fig. 2. Male 65 years old with painful erosive lesion (score 5) on right upper gingival (left) improved to painless atrophic lesion (score 3) (right) after 1 week of MB-PDT. The improvement was persistence up to 12 weeks of follow-up.
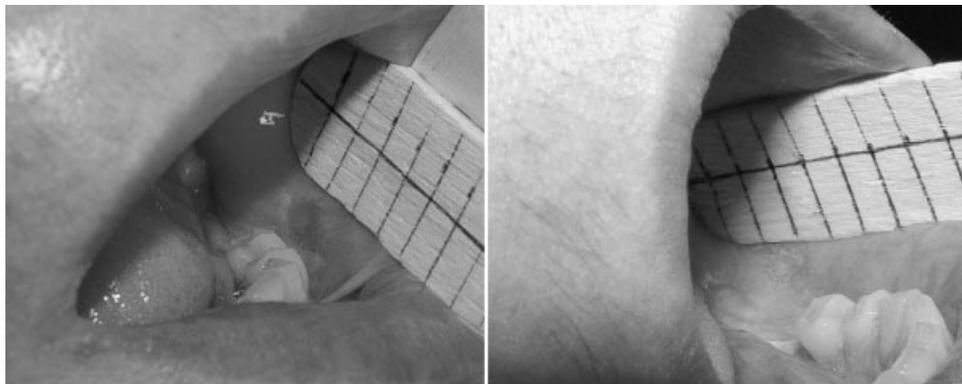
Fig. 3. Female 45 years old with painful erosive lesion (score 5) on left buccal (left) improved to painless atrophic lesion (score 3) (right) after 1 week of MB-PDT. The improvement was persistence up to 12 weeks of follow-up.

remain the most reliable and effective modality, though topical cyclosporin, topical tacrolimus, or systemic corticosteroids may be indicated in patients whose conditions are unresponsive to topical corticosteroids [15]. Corticosteroids are also systemically used for erosive-ulcerative OLP lesions but with the risk of severe adverse reactions [16]. Oral PUVA therapy with low-dose UVA is effective in treating the various forms of OLP, but it seems to have too many side effects, mainly nausea and the potential for carcinogenicity. Topical application of psoralen is promising, but still experimental [17]. There was several case series which showed that treatment with the 308-nm excimer laser might be an additional treatment option for OLP [18–20]. However the results are still disappointing, so searching for new treatment modalities seems quite rational.

PDT is a minimally invasive treatment available for palliation or eradication of several cancers. It can be applied alone or together with surgery, radiation therapy, or chemotherapy. PDT is also valuable for premalignant conditions such as oral leukoplakia, mucosal dysplasia, or carcinoma in situ [21]. It has also been used for non-oncologic purposes like psoriasis [6,7].

In PDT, a PS absorbs the transferred light and converts the light energy into a chemical reaction which in turn leads mainly to formation of singlet oxygen. Cytotoxic effects of PDT on tumoral cell or activated lymphocytes are mediated through these oxidative products [8,9]. In clinical practice, PSs arise from three families: porphyrins, chlorophylls, and dyes [11]. In the present study, we used MB as a topical PS.

Nearly a century ago, the antibacterial characteristics of MB which is a phenothiazine dye were described and attributed to its photodynamic properties. MB itself has been used in medical practice for more than 100 years and is recognized as having very low tissue toxicity. Clinical uses of MB include the treatment of ifosfamide encephalopathy, methemoglobinemia, urolithiasis, and cyanide poisoning [22,23]. Even intravenous administration of MB is FDA approved for methemoglobinemia. MB can be administered in human beings orally or intravenously in high doses without any toxic effects [22]. Unlike other PSs; MB can be administered topically and orally, and it may be a preferred

Fig. 4. Female 40 years old with erosive OLP lesion (score 5) of the upper gingival before (left) and after (right) MB-PDT with partial response (score 3). The improvement was persistence up to 12 weeks of follow-up.

Fig. 5. Atrophic and keratotic lichen planus lesion on the left upper gingival before photodynamic therapy (PDT) (left). Complete response after 9 months follow-up (right).

choice for superficial lesions in skin and oral cavity. The fact that MB has a strong absorption at wavelengths longer than 620 nm, where light penetration into tissue is optimal, has led to the using of MB as a promising candidate for PDT [24–27].

The exact mechanism of action of PDT is unclear. It would appear to act on hyperproliferating cells, such as those present in malignancies which selectively uptake the PSs [28]. 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 [28]. This may reverse the hyperproliferation and inflammation of lichen planus.

We could find one report of the use of PDT for hypertrophic lichen planus of the penis. Kirby et al. [29] used ALA-mediated PDT twice for treating the lesion. The lesion had completely resolved after 4 weeks. At 6-month follow-up there was no recurrence. However, pervious studies showed that ALA-mediated PDT, in addition to being a somewhat painful therapy, the drug when topically applied does not penetrate deeply [11].

PDT appears to have the potential to improve the management of OLP. Patients with OLP often have to apply the topical agents on a daily basis for significant periods of time. Therefore, a treatment modality that can result in extended periods of remission can have a profound impact on patients' quality of life. In this study we used MB-PDT just once for every lesion, but PDT can be repeated several times without any side effect. We presume that this may result in complete remission even in erosive lesions. It seems that PDT, compared to other treatment modalities, induces long time remission.

In conclusion, we found that PDT may be effective in treatment of OLP and may increase the duration of symptomfree period; therefore, it can be used as an alternative therapy alongside standard treatment methods. However, there are some limitations from which this study suffers. Since our patients were not willing to use local steroid therapy anymore even on one of their lesions (as control) due to previous inefficient use of these agents for a pretty long time (range 1–10 years), we had no other choice except for selecting the study design as before-after open trial which has already been used for evaluating a new treatment modality for OLP [14,18]. So to determine the exact effect size of MB-PDT on treatment of OLP, it is necessary to put it into further randomized controlled clinical trials with large sample size and long follow-up by blinded evaluator.

TABLE 3. Changes in the Size of Lesions and Symptom (pain) Score Before and 1 Week After MB-PDT

Sign score	Lesions area			Symptom score (VAS)	
	Before (cm^2)	After (cm^2)	Mean of area reduction (%)	Before	After
Score 5 ($n = 13$)	2.1 ± 0.5	1.5 ± 0.9	34.2%	5 ± 1.5	0.7 ± 1.3
Score 4 ($n = 1$)	0.75	0.50	33.3%	6	1
Score 3 ($n = 3$)	2.3 ± 0.7	1.4 ± 0.6	41.1%	5.3 ± 3.2	1.6 ± 2.8
Score 1 ($n = 9$)	1.3 ± 0.6	0.4 ± 0.6	61.3%	0	0
Total	1.8 ± 0.7	1 ± 0.9	44.3%	5.1 ± 1.7	0.9 ± 1.5

Pair t-test: significant ($P = 0.001$).

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