Lasers Med Sci (2015) 30:1475–1480
DOI 10.1007/s10103-014-1694-1

ORIGINAL ARTICLE

A comparative study of toluidine blue-mediated photodynamic therapy versus topical corticosteroids in the treatment of erosive-atrophic oral lichen planus: a randomized clinical controlled trial

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Received: 21 April 2014 / Accepted: 17 November 2014 / Published online: 9 December 2014

Abstract Recently, photodynamic therapy (PDT) has been suggested as a new treatment option that is free from side effects for erosive-atrophic oral lichen planus (OLP). The purpose of this study was to compare the effect of toluidine blue-mediated photodynamic therapy (TB-PDT) with local corticosteroids on treatment of erosive-atrophic OLP. In this randomized clinical trial, 25 patients with keratotic-atrophic-erosive oral lichen planus were allocated randomly into two groups. Group 1 (experimental): topical application of toluidine blue with micropipette was applied, and after 10 min, the patients were treated with a 630-nm GaAlAs laser (power density: 10 mW/cm^2) during two visits. Group 2 (control) used mouthwash diluted with dexamethasone (tab 0/5 in 5 ml water) for 5 min, and then, it was spat out, and after 30 min, the mouth was rinsed with 30 drops of nystatin 100,000 units for 5 min and again spat out. Demographic data, type, and severity of the lesions and pain were recorded before and after treatment and then at the 1-month follow-up visit. Response rate was defined based on changes in intensity of the lesions and pain. In the experimental and control groups, sign scores of changes significantly reduced after treatment respectively (p=0.021) and (p=0.002), but between the two groups, no significant difference was observed (p= 0.72). In the experimental (p=0.005) and control groups (p= 0.001), the intensity of lesions significantly reduced after treatment and there was a significant difference between the two groups (p=0.001). The mean amount of improvement in pain was significantly greater in the control group compared with the experimental group (p<0.001) (α=0.05). Our study showed that TB-PDT with laser was effective in the management of OLP.

Keywords Corticosteroid therapy · Photodynamic therapy · Oral lichen planus

Introduction

Lichen planus is a chronic inflammatory mucocutaneous disease and estimated to affect 0.5 to 2 % of the general population. Oral lichen planus (OLP) occurs more frequently than cutaneous lesions and tends to be more resistant to treatment. OLP is classified as erosive, reticular, popular, plaque-like, atrophic, or bullous type [1]. Erosive-atrophic OLP manifests as diffuse, erythematous patches surrounded by fine white lines (Wickham striae). Reticular lesions are asymptomatic and require no treatment, but patients with erosive-atrophic forms of OLP experience significant discomfort; therefore, they often seek treatment [2, 3]. Malignant transformation also seems to be more

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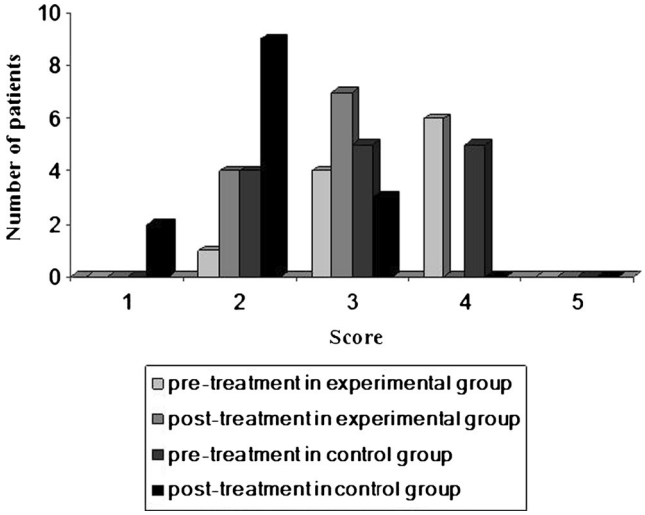

Fig. 1 Sign score distribution in the experimental and control groups before and after treatment based on Thongprasom sign scoring. Score *5* white striae with an erosive area=1 cm^2, score *4* white striae with an erosive area <1 cm^2, score *3* white striae with an atrophic area >1 cm^2, score *2* white striae with atrophic area <1 cm^2, score *1* mild white striae only, score *0* no lesions, normal mucosa

probable in erosive lesions [4]. Unlike cutaneous lesions, which generally improve spontaneously, OLP requires long-term treatment and follow-up [5]. Different treatment procedures are available such as surgical intervention or laser therapy; however, pharmacologic therapy is the most common procedure [6]. The most widely accepted pharmacologic treatment for OLP lesions includes topical and systemic corticosteroids. Topical corticosteroids are the drug of choice in treating mild to moderately symptomatic lesions [2, 7]. Due to the chronic nature of OLP and the need for long-term use of corticosteroids, complications such as candidiasis, adrenal insufficiency, gastrointestinal disorders, hypertension, and diabetes may occur [7, 8].

Photodynamic therapy (PDT) is a procedure based on the activation of molecules of various chemical agents called photosensitizers by light emitting radiation using a selected wavelength. After activation, cytotoxic free radicals are released and subsequently result in the destruction of targeted cells [9–11]. PDT has been used to treat various lesions such as malignancies and infections [12, 13]. PDT has also been used for OLP lesions, and this method is successful in reducing signs and symptoms of the disease [11, 14]. It has been suggested that PDT may induce apoptosis in inflammatory proliferative cells that exist in psoriasis and lichen planus [11]. Toluidine blue is a cationic photosensitizer, and its maximum absorbance is at 630 nm [15]. Luan et al. demonstrated that toluidine blue-mediated PDT had an antimicrobial effect in periodontal tissue without any destructive potential on other tissues [10]. Therefore, PDT may be an alternative and effective treatment with minimal side effects for patients suffering from erosive-atrophic OLP. The aim of our study was to compare the effect of toluidine blue-mediated PDT with topical corticosteroids on treatment of erosive-atrophic OLP.

Table 2 Mean of age in two groups

Group	Number	Mean	Standard deviation
Experimental	11	48.71	13.53
Control	14	43.73	10.01
Result of *t* test	t=1.02, p value=0.318		

Materials and method

Adult patients with atrophic-erosive biopsy-proven OLP in the tongue or buccal mucosa (size ≤3 cm) who presented at the Department of Oral Medicine (Mashhad Dental Faculty) between April 2008 and March 2009 participated in this study.

Patient exclusion criteria included those presenting with systemic diseases, drug consumption, pregnancy, photosensitivity, patients younger than 20 years, and patients who had lesions with dysplasia or had received treatment for OLP at least 1 month prior to the beginning of the study.

First, 30 patients were selected based on clinical examinations and exclusion criteria, but after performing biopsies, five patients were excluded from the study. Finally, 25 patients were randomly (by coin toss) allocated into an experimental

Table 1 Distribution of patients based on gender in two groups

Gender	Group					
	Experimental		Control		Total	
	Number	Percent	Number	Percent	Number	Percent
Male	3	27.3	5	35.7	8	32
Female	8	72.7	9	64.3	17	68
Total	11	100	14	100	25	100
Result of Fisher's exact test	p=1.00					

Table 3 Distribution of patients based on the history of systemic drugs use in two groups

History of drug use	Experimental		Instance		Total	
	Number	Percent	Number	Percent	Number	Percent
Had	1	9.1	5	35.7	6	24
Had not	10	90.9	9	64.3	19	76
Total	11	100	14	100	25	100
Result of Fisher's exact test	p=0.18					

group (11 patients) and a control group (14 patients). All of the selected patients completed the treatment. The sample size was calculated based on Jajarm et al. study [16].

Each patient signed a detailed informed consent form, and the study protocol was approved by the Institutional Ethics Committee of the University of Mashhad.

Patients in the experimental group were treated by a topical application of 50 μl toluidine blue (1 mg/ml) with micropipette and after 10 min treated by laser irradiation (exposure time 2.5 min; fluence 1.5 J/cm^2 per session; power density 10 mW/cm^2; one illumination point 1 cm^2 area).

A GaAlAs laser was used as a light source (Mustang 2000, Russia, KLO3 probe, 630 nm, 10 mW/cm^2, continuous wave, spot size: 1 cm^2). This treatment was done in two sessions, two times weekly for 1 month. If patients had multiple lesions in different locations of the buccal mucosa and lateral border of the tongue, each location was treated separately.

Patients in the control group were treated by topical corticosteroids consisting of dexamethasone (0.5 mg in 5 ml water) mouthwash for 5 min, followed 30 min later by a mouthrinse with 30 drops of Nystatin (100,000 units) for 5 min. This treatment was repeated four times a day for 1 month, and patients were followed up weekly during this period.

Sign scores were assessed by the Thongprasom sign scoring as follows [17]: score 5 (white striae with an erosive area= 1 cm^2), score 4 (white striae with an erosive area <1 cm^2), score 3 (white striae with an atrophic area >1 cm^2), score 2 (white striae with atrophic area <1 cm^2), score 1 (mild white striae only), and score 0 (no lesions, normal mucosa) (Fig. 1). The size of the lesions was determined by using a digital caliper (accuracy 0.01 mm). The severity of the lesions in each site was recorded based on the presence of reticular/hyperkeratotic, atrophic, or erosive/ulcerative lesion(s). For patients with more than one lesion, a sign score was derived by the summation of the scores of all four areas (right and left buccal mucosa and right and left border of the tongue). The scores are recorded as follows: reticular score= R, atrophic score= A, and erosive/ulcerative score= E (RAE score) with a total weighted score of $(R\times1)+(A\times1.5)+(E\times2)$.

For determining the efficacy indices (EI) of the treatment (improvement of lesions), the following formula was used: [100 %×(total score of lesion before treatment − total score of lesion after treatment)]/total score of lesion before the start of treatment. The EI were evaluated on a five-rank scale [18] as such: healed EI=100 %, marked improvement 75 %≤EI< 100 %, moderate improvement 25 %≤EI<75 %, mild improvement 0 %<EI<25 %, and no improvement=0.

Evaluation of experienced pain was performed by means of the 0-to-10 visual analog scale (VAS). The amount of improvement in experienced pain was calculated by the following formula: N=[100 %×(pretreatment VAS score−posttreatment VAS score)]/pretreatment VAS score. This result was classified as follows: score 5: (lack of pain or discomfort N= 100 %), score 4: (marked improvement 75 %≤N<100 %), scores 3 and 2: (moderate improvement 25 %≤N<75 %), score 1: (mild improvement 0 %<N<25 %), and score 0: (no improvement N=0).

Table 4 Mean of duration of lesions in two groups

Group	Statistical indices		
	Number	Mean	Standard deviation
Experimental	11	17.36	15.27
Control	14	14.36	15.46
Result of t test	t=1.485, p value=0.632		

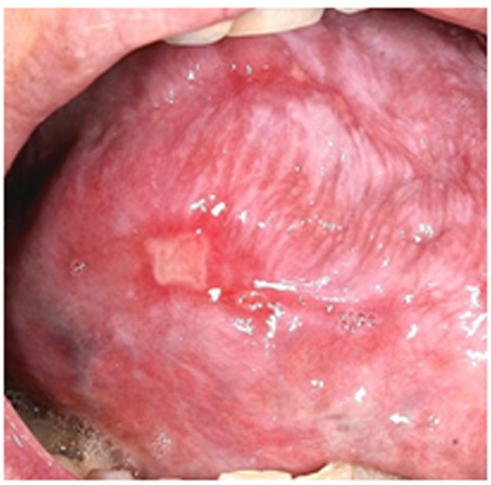

Fig. 2 Clinical view of the lesion before treatment

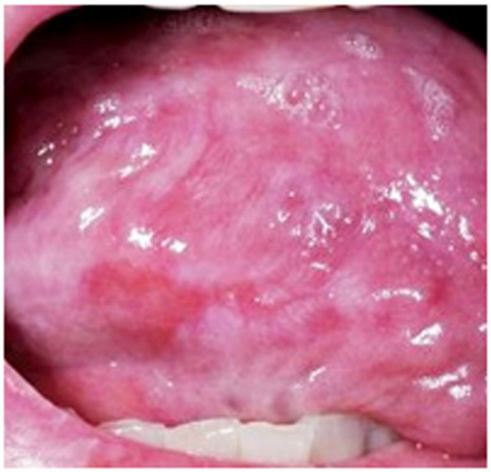

Fig. 3 Clinical view of the lesions after toluidine blue-mediated photodynamic therapy

The rate of improvement for each patient was evaluated weekly during the time of treatment and then was followed up 2, 3, and 4 weeks after completion of treatment to evaluate any relapse.

All collected data were analyzed with the chi-square, Mann-Whitney, Student's *t* test, Fisher's exact, and Wilcoxon test using SPSS software version 15 (SPSS Inc, Chicago, Il.).

Results

Statistical analysis showed no significant difference between the two groups regarding gender representation, age, marital status, and pretreatment duration of disease, lesion location, or previous treatments (Tables 1, 2, 3, and 4).

The Wilcoxon test showed a significant difference in sign score changes before and after the treatment in the experimental group (p=0.021) and in the control group (p=0.002) (Figs. 2 and 3). However, the Mann-Whitney test showed no significant difference between the two groups before and after treatment (Fig. 1).

Mean amount of improvement in pain was significantly greater in the control group in comparison with the experimental group (p<0.001) (Table 5). Efficacy indices significantly increased after treatment in the experimental (p=0.005) and control groups (p=0.001). However, there was a significant difference between the two groups, and the efficacy index of the control group improved significantly more than the experimental group (p=0.001) (Table 6).

In the experimental group (72.7 %) and in the control group (100 %), the patients did not show any relapse at their follow-up sessions and there was a statistically significant difference between the two groups (p=0.042) (Table 7).

There were no intra- or postoperative complications in both groups, and no side effects were observed during the follow-up period.

Table 5 Mean and standard deviation of improvement in experienced pain in two groups after treatment (based on VAS score)

Groups	After treatment $\overline{X} \pm$ SD
Experimental	25.09 %±15.4 %
Control	53.71 %±18.63 %
Result	Z=−3.59
Mann-Whitney	p<0.001

Discussion

Lichen planus is a chronic mucocutaneous disease. Cell-mediated immunity and cytokines, which are 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 [1]. With regard to the immunologic pathogenesis of OLP, systemic and local corticosteroid therapies are the cornerstone in its treatment [2, 7]. However, these treatments have plenty of side effects such as candidiasis, xerostomia, sore throat, osteoporosis, adrenal insufficiency, hypertension, and diabetes mellitus [7, 8] Therefore, an alternative treatment modality should be introduced. As an alternative for the treatment of OLP, low-level laser therapy (LLLT) has been introduced and it controls inflammation in the oral cavity by modulating the mast cells function and decreasing the production of pro-inflammatory prostaglandin E2 [19].

Recently, 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) [13]. Also, PDT is widely used to treat oral lesions including premalignant lesions (erythroplakia, verrucous carcinoma), head and neck cancers, and periodontal disease [12]. The basis of PDT is a combination of light and photosensitizing and then the release of reactive oxygen species. In this procedure, after applying the photosensitizers locally or systematically, the light at a specific wavelength is emitted on the targeted tissue and the products that are produced by photosensitizing cause a specific reaction on the tissue [12]. It is suggested that PDT induces apoptosis in proliferated inflammatory cells [11]. By considering the inflammatory pathogenesis of OLP and immunomodulatory effect of PDT, photo dynamic therapy may be an effective alternative treatment procedure. Wavelength is the most important factor in all types of photo therapies, and so, the most appropriate wavelength should be selected to

Table 6 Mean and standard deviation of clinical severity of the lesions in the two groups before and after treatment

Groups	Before treatment $\overline{X} \pm SD$ (%)	After treatment $\overline{X} \pm SD$ (%)	Difference $\overline{X} \pm SD$ (%)	Paired *t* test
Experimental	13.36±9.33	28.18±16.34	14.82±13.64	$t=-3.6$ $p=0.005$
Control	5.36±10.11	46.29±15.26	40.93±18.77	$Z=-0.19$[a] $p=0.001$
Result Independent *t* test	$Z=-2.29$[a] $p<0.033$	$t=2.85$ $p=0.009$	$t=3.87$ $p=0.001$	

EI=100 %, marked improvement 75 %≤EI<100 %, moderate improvement 25 %≤EI<75 %, mild improvement 0 %<EI<25 %, no improvement=0

[a] Mann-Whitney

obtain the best results. In this study, a 630-nm laser was used because this is one of the most effective wavelengths for wound healing and no side effects have been reported in studies using this wavelength [19–21]. In addition, although many studies have used methylene blue as a photosensitizer, in our study, toluidine blue was used because it absorbs at 630 nm [15].

Limited clinical studies have examined the effect of photodynamic therapy in treating erosive-atrophic OLP [11, 14]. In our study, there was no significant difference in sign score changes between the control and experimental groups. Although, there were significant differences in symptom improvement and efficacy indices and amount of relapse between the two groups and the control group showed better results than the experimental group. Therefore, these results show that conventional corticosteroid therapy is more effective than PDT.

Jajarm et al. compared the effect of low-level laser therapy (LLLT) and topical corticosteroid, and they determined that LLLT was as effective as topical corticosteroid therapy [16].

Sadaksharam et al. evaluated the effect of methylene blue-mediated PDT on OLP in 20 patients. This study, which only examined the severity of lesions, showed a significant reduction in their clinical severity [22]. However, in our study, symptom improvement and efficacy index was also evaluated. Aghahosseini et al. showed a significant reduction in size and pain score of OLP lesions after treatment with methylene blue-mediated PDT [14]. Trehan et al. 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 [23]. In our study, two patients in the experimental group had marked improvement. These differential findings maybe a result of the difference in applied doses and energy as well as the use of photosensitizers in our study.

Conclusion

Under this study circumstances, the results have shown that toluidine blue-mediated photodynamic therapy with a 630-nm GaAlAs laser is an effective treatment and it can be considered as an alternative for erosive-atrophic OLP. However, it should be noted that traditional corticosteroid therapy showed better results than TB-PDT.

More randomized clinical trials to compare the effect of photosensitizer-mediated PDT and low-level laser therapy are needed.

Table 7 Survival of improvement in experienced pain after treatment in the two groups

Survival of improvement in experienced pain	Experimental		Control		Total	
	Number of patients	Percentage	Number of patients	Percentage	Number of patients	Percentage
2 weeks	2	18.2	0	0	2	8
3 weeks	1	9.1	0	0	1	4
4 weeks	8	72.7	14	100	22	88
Total	11	100	14	100	25	100
Mann-Whitney		$Z=-2.04$ $p=0.042$				

Acknowledgments This research was financially supported by the research vice chancellor of the Mashhad University of Medical Sciences.

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