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Evaluating the Efficacy of the Er,Cr:YSGG Fractional Laser Before Treatment With Triamcinolone NN Ointment in Oral Lichen Planus Lesions

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Abstract

Introduction: It has been demonstrated that laser technology can enhance topical drug absorption. This study aimed to determine the effects of Er,Cr:YSGG laser radiation before the application of topical corticosteroids in the healing of oral lichen planus.

Methods: In this double-blind split-mouth clinical trial, 32 lesions were chosen from eight patients affected by oral lichen planus (OLP). The oral lesions were randomly categorized into two groups. The first group had topical treatment with triamcinolone NN ointment and the second group had laser radiation (Er,Cr:YSGG) for eight weeks before starting the ointment. For each lesion, the irritating level based on the VAS score, the lesion level based on the Thongprasom scale score, and the healing time were measured, and the collected data were analyzed by the Friedman test and the Wilcoxon's statistical test.

Results: The mean healing time based on the verbal analog scale (VAS) score was not significantly different between the two treatment groups ($P>0.05$). The mean healing time based on Thongprasom scale scores did not show any significant difference between the two treatment groups ($P>0.05$).

Conclusion: The application of the Er,Cr:YSGG laser before treatment with triamcinolone NN ointment did not show any advantage for the average healing time compared to a medicine regimen with only triamcinolone NN ointment.

Keywords: Oral lichen planus; Corticosteroid; Laser; Er,Cr:YSGG.

Introduction

The oral lichen planus (OLP) is a chronic autoimmune skin and mucosa disease it represents with clinical types, namely reticular, papular, plaque-like, erythematous, erosive, or bullous lesions.[1,2] The prevalence of OLP has been reported, ranging from 0.5% to 2.6% in the general population.[3] The goal of OLP healing is a reduction in the levels of symptoms, the prevention of degenerated tissue, and a reduction of probable dysplasia, and it would progress as a malignancy if left untreated.[4]

Corticosteroids have been the first-line therapy for the treatment of OLP, applied topically or systemically.[5] In one-third of the patients with OLP treated with topical corticosteroids, secondary candidiasis is developed.[6,7] Another disadvantage to using corticosteroid treatment is the potential tachyphylaxis and the diminishment of biologic effectiveness of drugs.[8] Improving the side effects of these drugs can result in better control of the disease with a reduction of treatment duration, but when the OLP lesion is resistant to topical corticosteroids, systemic drugs will be inevitably selected, but they have also indicated some side effects including osteoporosis, glaucoma, hypertension, and so on; therefore, it is necessary that other therapeutical procedures be studied with possibly fewer side effects.[9,10] Recently, different profiles of laser radiation have been studied for the treatment of oral lesions, including lichen planus.[11]

Ablative fractional lasers (AFXLs) present an innovative procedure used to overcome the epidermal barrier in a contact-free, controlled, and standardized manner and to improve the penetration of previously applied topical agents in terms of laser-assisted drug delivery (LADD).[12] The increase of laser-assisted drug penetration results in more effective healing compared to passive drug delivery. In this technique, there is shortened healing duration. Moreover, the drug dose and subsequently adverse side effects are reduced.[13]

The LADD technique provides enhanced drug permeability using a low-level laser without necessary contact with the skin. According to recent literature, fractional erbium laser radiation has enhanced the impacts of topical corticosteroids on the healing of colloid

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affected-skin lesions.

In previous studies, fractional erbium laser radiation has been suggested to improve the efficacy of topical corticosteroids in the treatment of colloidal skin lesions.[14-16] Moreover, the AFXL technique was applied in the studies to treat actinic keratosis, actinic cheilitis, Bowen's disease, basal cell carcinoma, vitiligo, viral warts, hemangioma, and atrophic scars, to improve response to vaccination, and to treat melasma and macular amyloidosis.[17,18]

Although topical corticosteroids have responded to many lesions, resistance cases have also been reported.[9,10] Due to the fact that the use of laser radiation before topical corticosteroids can heal skin lesions,[12-15] it seems that there is no study on the effect of laser radiation on increasing the effect of corticosteroids in the oral mucosa. On the other hand, there is a difference between the histological structure of the skin and oral mucosa.[19] This study aimed to evaluate the impacts of Er,Cr:YSGG laser radiation before the topical application of corticosteroids in the treatment of OLP.

Materials and Methods

This double-blind split-mouth study was carried out on patients with erosive, atrophic or ulcerative OLP in more than one region of their mouth, and the selected 32 OLP lesions were treated. These patients were diagnosed clinically by the presence of reticular or papular forms of lichen planus.[20] To be included in the study, the patients were required to have symmetrical bifocal OLP lesions and written consent. Those patients who had a history of recurrent disease, skin mucosa involvement, use of medications being effective in the healing of OLP during the previous month, a history of head and neck cancer, a history of proliferative diseases including cancers, atherosclerosis, rheumatoid arthritis, psoriasis, scleroderma, and a history of thyroid disease, pregnancy, and OLP lesions with a complete keratotic nature or with location fitting Amalgam fillings were excluded from this study.

First, written consent was obtained from each patient, and then the evaluation criteria of lichen planus were studied. The verbal analog scale (VAS) ranging from 0 to 10 was used to evaluate the levels of pain and irritation, 0 being none irritating and 10 being most irritating.

The Thongprasom sign scoring system was used to clinically evaluate OLP planus lesions, and based on this system, OLP lesions on each side were scored separately between 0 and 5; with 0 = no observed lesion/normal mucosa; 1 = mild white striae; 2 = white striae with atrophic and erythematous areas (< 1 cm^2); 3 = white striae with atrophic and erythematous areas (> 1 cm^2); 4 = white striae with ulcerative areas (< 1 cm^2); and 5 = white striae with ulcerative areas (> 1 cm^2).[21]

Large diameter lesions were measured by Collis with a caliper and periodontal probe. The symmetrical bifocal lesions were randomly divided into two groups for treatment regimens according to the mucosal type in the mouth. The "symmetrical" term means that the keratinized lesions occur bilaterally. The lesions were divided into two groups. Each group was represented with two lesions for the same patient. Triamcinolone NN ointment was applied in the medicine regimen of lesions for the studied patients.

In the first group, the topical application of triamcinolone NN ointment was designed for a maximum of eight weeks. The mentioned ointment was covered over the total surface of the lesion(s) with an applicator three times a day after a meal. The second group received a very long-pulsed Er,Cr:YSGG laser (2780 nm) using a MZ8 tip (Waterlase iPlus®, BIOLASE Technology, Inc, USA; 1.75 J/cm^2, 70% water, 80% air, a non-contact pattern medical device at 1 mm distance, 1.5 minutes) once a week before and during the medicine regimen (this group received this laser pulse weekly for a maximum of eight weeks). Then, they were treated with a medicine regimen like the first group for eight weeks.[22]

To blind the control patients to their treatment, a placebo laser light was radiated on the other side. Laser radiation was carried out by a person who was not the lesion data collector, and the recorder of the lesion data was not informed about which side was radiated by laser light. In every therapy session, the mentioned data of the VAS and Thongprasom sign scoring criteria were recorded for each patient, and if the patients scored on Thongprasom sign scoring criteria as 1 before the complete eight sessions, the therapy was ended. The healing times alongside the reduction of symptoms (50% reduction of pain and irritation) and the achieved Thongprasom sign scoring scale (scored as 0 or 1) were compared in the two treatment groups (Figures 1-4).

The collected data were analyzed using the Friedman statistical test and Wilcoxon's test in SPSS Statistics version 24.

Results

According to the researcher's and clinical observations, the difference between the two groups was considered 50%.[22] Therefore, to find this difference between conventional treatment and combination laser treatment, in terms of

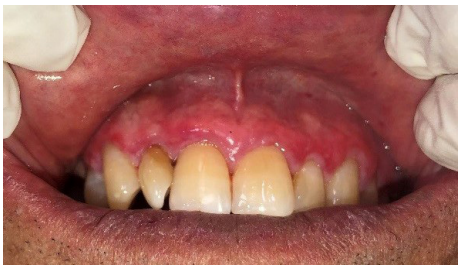

Figure 1. First Week, Before the Treatment of the Marginal Gingiva in Atrophic Lichen Planus.

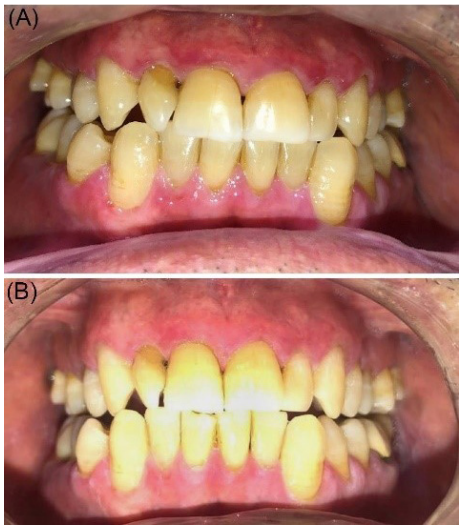

Figure 2. (A) Forth and (B) Eighth Week, Right Area of The Maxilla From Mesial of Central to Distal of canine treatment With Er,Cr:YSGG and Ointment of Triamcinolone NN and Left Area of Maxilla Treatment With the Ointment of Triamcinolone NN.

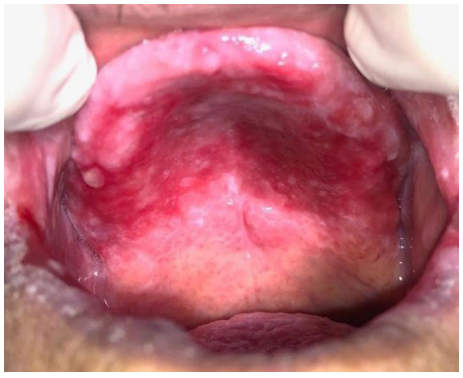

Figure 3. First Week Before the Treatment.

type I error ($\alpha = 0.05$, z1- α / 2 = 1.96) and type II error ($\beta = 0.2$, z1-$\beta = 0.84$) in each group the number of samples are 15 according to the formula.

$$n = \frac{(z1-\frac{\alpha}{2}+z1-B)^2\ (P1(1-p1)+p2(1-p2)}{(P1-P2)^2} = 15$$

$\alpha = 0.05$, $\beta = 0.2$, $p_1 = 0.25$, $p_2 = 0.75$

In this study, 10 patients who met the inclusion criteria were recruited in the study, but 2 patients (with 4 lesions) were excluded from the study for their refusal to cooperate. Thus, the data were obtained from 8 patients (male: 3, female: 5). The mean age of the patients was 56.25 ± 10.63 years. 32 lesions of these patients were included in the study, and the lesion on one side was studied along with the lesion on the other side in order to evaluate the effects of both medication regimens. Also, in certain subjects, a couple of lesions were examined. The clinical diagnosis was confirmed for 7 patients with lichen planus papules and reticulate white lines observed in their clinical profiles. In addition, one patient was diagnosed through histopathologic evaluation.

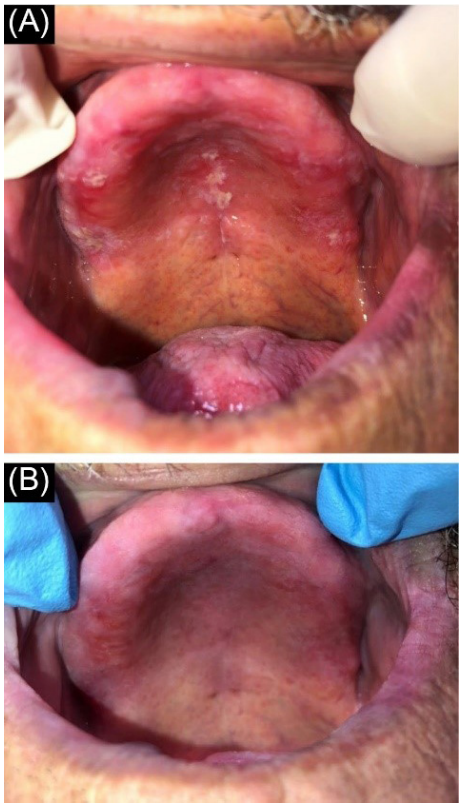

Figure 4. (A) Forth and (B) Eighth Week, Left Area of the Hard Palate Treatment With the Er,Cr:YSGG Laser and the Ointment of Triamcinolone NN and Right Area of the Hard Palate With the Ointment of Triamcinolone NN.

According to the Friedman test, within a period of time from one to eight weeks, the VAS scores decreased significantly in both of the two treatment regimens in the groups receiving triamcinolone NN ointment (without laser therapy) or triamcinolone NN ointment + laser therapy ($P < 0.0001$). No significant difference was observed when the mean VAS scores were compared between the two treatment groups at different times ($P > 0.05$; Table 1).

The Mann-Whitney test indicated that there were no significant differences in the average healing time according to the VAS scores between the two treatment groups ($P = 0.819$; Table 2).

According to the Friedman test, within a period of time from one to eight weeks, the Thongprasom scale scores decreased significantly in both of the two treatment regimens in groups receiving triamcinolone NN ointment (without laser therapy) or triamcinolone NN ointment + laser therapy ($P < 0.0001$). No significant difference was observed when the mean Thongprasom scale scores were compared between the two treatment groups at different times ($P > 0.05$; Table 3).

The Mann-Whitney test suggested no significant differences in the average healing time according to the Thongprasom scale scores between the two treatment groups ($P = 0.410$; Table 4).

Based on the lesion location on the lips and gingival

Table 1. The comparison of VAS Scores Between the Two Treatment Groups During the 8-Week Study

Week	Triamcinolone NN Ointment	Triamcinolone NN Ointment + Laser Therapy	*P* Value
	Mean ± SD	Mean ± SD	
1	4.69 ± 3.53	4.75 ± 3.61	0.923
2	2.38 ± 2.03	2.19 ± 1.87	0.704
3	1.25 ± 1.61	0.94 ± 1.29	0.551
4	0.38 ± 0.72	0.19 ± 0.75	1.000
5	0.31 ± 1.25	0.00 ± 0.00	0.956
6	0.00 ± 0.00	0.00 ± 0.00	1.000
7	0.00 ± 0.00	0.00 ± 0.00	1.000
8	0.06 ± 0.25	0.00 ± 0.00	0.780
P value	< 0.0001	< 0.0001	

Table 2. The Average Recovery Time (Weeks) Based on VAS Scores and Treatment Regimens

Treatment Regimens	Mean ± SD	*P* Value
Triamcinolone NN ointment	1.15 ± 1.56	0.819
Triamcinolone NN ointment + laser therapy	1.09 ± 1.50	

Table 3. The Comparison of Thongprasom Scores Between the Two Treatment Groups During the 8-Week Study

Week	Triamcinolone NN Ointment	Triamcinolone NN Ointment + Laser Therapy	*P* Value
	Mean ± SD	Mean ± SD	
1	3.19 ± 0.40	3.25 ± 0.45	0.674
2	2.25 ± 1.06	2.19 ± 0.98	0.872
3	2.25 ± 0.93	2.06 ± 0.93	0.662
4	1.75 ± 1.18	1.56 ± 1.15	0.551
5	0.81 ± 0.98	0.88 ± 1.03	0.850
6	0.69 ± 1.07	1.03 ± 1.03	0.657
7	0.75 ± 1.12	0.56 ± 1.10	0.423
8	0.75 ± 1.12	0.56 ± 1.10	1

Table 4. The Mean Recovery Time (Week) Based on Thongprasom Scores and Treatment Regimens

Treatment Regimens	Mean ± SD	*P* Value
Triamcinolone NN ointment	1.82 ± 5.12	0.410
Triamcinolone NN ointment + laser therapy	1.86 ± 4.56	

region, there was not a significant difference in healing time observed between the two treatment groups according to the VAS scores ($P > 0.05$). However, the healing time obtained based on the Thongprasom scale scores in the treatment group with triamcinolone NN ointment on the lips was significantly shorter than that in the gingiva (*P* value = 0.016), but in the treatment regimen with Er,Cr:YSGG laser + triamcinolone NN ointment, there was no significant difference between lips and gingiva ($P > 0.05$; Tables 5 and 6).

Table 5. The Mean Recovery Time of Lips and Gums in Two Treatment Regimens, Triamcinolone NN or Er,Cr:YSGG laser + Triamcinolone NN Based on VAS scores

Treatment Regimens	Lesion Location	Number of Lesions	Mean	*P* Value
Triamcinolone NN ointment	Lips	4	2	0.48
	Gum	6	1.17	
Triamcinolone NN ointment + laser therapy	Lips	5	2	0.42
	Gum	6	1.17	

Table 6. The Mean Recovery Time of Lips and Gums in Two Treatment Regimens, Triamcinolone NN or Er,Cr:YSGG Laser + Triamcinolone NN Based on the Thongprasom Scale

Treatment Regimens	Lesion Location	Number of Lesions	Mean	*P* Value
Triamcinolone NN ointment	Lips	4	3.75	0.016
	Gum	6	6.17	
Triamcinolone NN ointment + laser therapy	Lips	5	3.8	0.182
	Gum	6	0.182	

Discussion

The aim of this study was to evaluate the efficacy of laser radiation before the medicine regimen with topical corticosteroids in healing OLP lesions. Although the effect of fractional laser radiation has previously been demonstrated to improve the local absorption of topical medicine through the skin,[23-26] there is little evidence to suggest that this procedure has an impact on the absorption of drugs via the oral mucosa. According to the results of this study, laser radiation applied prior to the treatment with topical corticosteroids did not show any difference in healing lesions of OLP compared to a regimen without laser light based on the speed and extent of lesion healing.

The rate of molecules when passed through the membrane layer can be described according to Fick's first law of diffusion as follows: ($J = Km \times Dm \times CL$), where Km is a factor of those molecules capable of passing through the membrane layer, Dm is a factor of the diffusion capability of molecules passing through the membrane, and LCL is the concentration gradient of the molecule on both sides of the membrane divided by the diffusion distance. Fractional laser treatment is capable of increasing Km or the number of molecules passing through the mucosa, and consequently, the local medicine absorption is enhanced.[14]

According to the mentioned equation, the LADD system has promoted the impacts of topical medication in many studies despite these findings in our study.[12]

Possible reasons for differences observed between the results in this study and those in other studies include as follows:

Unlike previous studies, which were mostly designed with the raised lesions (viral warts, keloids), skin plaques or intact skin and mucosa (for the promoted effect of anesthesia and vaccination),[27] the present study was done with ulcerative or atrophic OLP lesions. As the ulcerative and atrophic lesions are manifested with a disrupted

uniform structure of epithelium and a decreased number of epithelial layers respectively, it may significantly reduce the diffusion length for drug release. Therefore, the impact of the laser light, including an increase in the absorption of medicine molecules followed by boosted medicine efficacy in normal, hypertrophic, and hyperkeratotic mucosal tissues, would be fruitless.

Given an increase of mucosal blood flow under the wound lesions,[28] the topical medication that penetrates into the lesion areas is rapidly moved away by blood flow to the area of inflammation or diluted in concentration. Therefore, the increased drug molecules are more easily eliminated from the area without sufficient time for medications like corticosteroids to be processed. However, repeating laser radiation could enhance drug molecules over time with increased impacts of the medicines.

In this study, OLP lesions were assessed using two criteria, the subjective ones developed based on VAS scores and the objective ones designed based on the Thongprasom scores. As the change ranges of these two criteria are limited, the Thongprasom criteria ranged from 0-5 and the mean VAS scores between two groups slightly differs, therefore difference between the two healings falls in a narrow range, and such difference requires a larger sample size to be established between two medication regimens. Shorter healing times were found in the healing group than in the control group, although the observed difference was statistically non-significant.

The distribution of OLP lesions in the oral mucosa is widely dispersed,[3] and given study limitations, it was not feasible to match study patients. But when the analysis was performed on the recovery of the developed lesions in the lips and gingiva by the Thongprasom criteria, it was determined that there was not a significant difference in the duration of lesion recovery occurring in the gingiva and lips where they were exposed to laser radiations before the consumption of corticosteroids. However, in lesions treated only with corticosteroids, the lip lesions recovered more quickly. Therefore, it seems that in oral keratinizing mucosa with more mucosal thickness, using laser radiation is more effective before corticosteroid that it can be considered in the treatment of OLP lesions.

Conclusion

The Er,Cr:YSGG laser applied before the treatment with Triamcinolone NN ointment topical did not show any effects on the average recovery time compared to if Triamcinolone ointment was utilized by itself.

Conflict of Interests

The authors declare that they have no conflict of interest.

Ethical Considerations

This clinical trial study was reviewed and approved by the Biomedical Research Ethics Committee of the School of Dentistry - Shahid Beheshti University of Medical Sciences (Ethics Code: IR.SBMU.DRC.REC.1398.166) and was registered at the Iranian Registry of Clinical Trials (identifier: IRCT20200119046187N1).

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