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The Efficacy of Topical Triamcinolone Acetonide in Combination with Retinoic Acid in Orabase in the Treatment of Oral Lichen Planus: a clinical trial Study

Narges Gholizadeh, D.D.S., M.Sc.[1], Mahnaz Sahebjamee, D.D.S., M.Sc. [2], Massoud Amanlou, Ph.D.[3], Shamsoulmolouk Najafi D.D.S., M.Sc.[4*]

1- Associate Professor, Department of Oral & Maxillofacial Medicine, School of Dentistry, Tehran University of Medical Science, Tehran, Iran

2- Professor, Department of Oral & Maxillofacial Medicine, School of Dentistry, Tehran University of Medical Science, Tehran, Iran

3- Professor , Drug Design and Development Research Center, The Institute of Pharmaceutical Sciences (TIPS), Tehran University of Medical Sciences, Tehran, Iran

4- Associate Professor Department of Oral Medicine, School of Dentistry, Tehran University of Medical Sciences, Tehran, Iran (Corresponding author: Email: najafi_drsh@yahoo.com)

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Abstract

Background: There are many therapeutic modalities for oral lichen planus under trial; however, none has resulted in complete remission of lesions yet. The aim of this study was to evaluate the combination therapy with topical triamcinolone acetate comparing to topical triamcinolone acetate alone in the treatment of oral lichen planus.

Methods: Patients were randomly divided into the two groups to receive either 0.1% triamcinolone alone (group TO) or 0.1% triamcinolone with 0.05% retinoic acid (group TRO). Participants were instructed to apply medication thrice daily and were visited at baseline and after 1, 2, 3, and four weeks of treatment. The size of lesions and symptoms were recorded at each session. Relaps was followed up in a 2-month period. Data were analyzed using Mann–Whitney U-test and through SPSS 13.0 software.

Result: The decrease in pain and burning sensation in both groups was similar four weeks after the treatment (P=0.71). All patients in the TRO group (100%) and 85% of patients in the TO group were improved to score 1 & 0. The decrease in the size of keratosis, atrophic, and erosive form of lesions were different in the two groups significantly (P<0.0001). In the 2nd month follow up, 10% of the TRO group and 15% of the TO group had relapsed which was not statistically significant (P=1).

Conclusion: According to the results, retinoid improves the efficacy of the corticosteroid in the suppression of inflammation in oral lichen planus patients and combination of them improves lichen planus lesions more than triamcinolone acetonide alone.

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Introduction

Oral lichen planus (OLP) is a chronic inflammatory disease affecting oral mucosa and characterized by relapses and remissions. Although reticular, popular, and plaque-like forms are asymptomatic, patients may complain of a slight roughness of the affected sites. Moreover, atrophic and erosive lesions may produce various symptoms ranging from a mild burning sensation to intense pain (1, 2). OLP is a T-cell-mediated autoimmune disease in which CD8+ cytotoxic T cells trigger the apoptosis of keratinocytes (3-5)

Currently, its treatment is usually palliative and targets relieving symptoms and healing of severe lesions and other discomforts. Sometimes OLP lesions can be difficult to manage and may be resistant to topical or systemic therapies.

There are several topical and systemic medications for the treatment of OLP such as steroids, retinoid, cyclosporine, tacrolimus, pimecrolimus immunomodulatory, steroid-sparing agents (hydroxychloroquine, azathioprine, mycophenolate mofetil) and ultraviolet phototherapy. All of them are nonspecific and merely have a temporary effect on lesions **(**6).

Corticosteroids are probably the most common treatment modalities that are widely utilized in the treatment of OLP. They can be utilized in the forms of systemic, topical and, intra-lesional. Topical steroids including Triamcinolone acetonide 0.1%, Betamethasone valerate, Fluocinonide, Clobestasol propionate, and Dexamethasone have provided the basis for the management of lichen planus (7- 11).

There are multiple forms such as mouthwash, ointment, gel, and orabase. Among these forms, orabase is the most effective compared to the gel or ointment. Orabase is a mucoadhesive paste consisting of gelatin, pectin, carboxymethylcellulose sodium, and plasticized hydrocarbon gel including polyethylene and mineral oil gel base.

The advantages of mucoadhesive microspheres are enhancing drugs owing to a high surface-to-volume ratio, a much more close contact with the mucus layer and efficient absorption, high bioavailability, and specific targeting of drugs at the involved site without any systemic side effects (7). Triamcinolone acetonide 0.1 % (mid-potency steroid) is commonly used for the treatment of localized and symptomatic OLP in both forms of a mouth rinse and an Orabase paste (5, 12).

A topical high-potency corticosteroid such as disodium betamethasone phosphate or Clobetasol propionate can be used in disseminated OLP; however, they can be systemically absorbed leading to pituitary-adrenal axis suppression. Long-term use of topical steroids (more than two weeks continuously) may result in oral candidiasis, mucosal atrophy, and an increase in the systemic absorption (5).

Retinoids are synthetic versions of vitamin A. They have anti-inflammatory, anti-keratinizing, and immunomodulating effects. Therefore, their synthetic and natural analogs may be useful in the treatment of the OLP and accelerating of the healing process. Topical retinoids and corticosteroids have shown promising effects in the treatment of OLP (12). However, limited clinical trial studies have examined the effect of their combination in the treatment of oral lichen planus.

Therefore, the aim of this study was the evaluation efficacy of topical triamcinolone acetonide in combination with retinoic acid in orabase for treatment of oral lichen planus.

Material and Method

Forty patients with non-erosive and erosive OLP, including 28 females and 12 males with the age range of 21–62 years (mean age 41 ± 2 years) were randomly selected in a randomized control double-blind clinical trial. Participants were selected from those referred to the Department of Oral Medicine, Faculty of Dentistry, Tehran University of Medical Sciences**.** Inclusion criteria were OLP diagnosed using the clinical and histopathologic examinations according to the modified World Health Organization (WHO) criteria. The informed consent according to the Helsinki Declaration II was signed by each individual prior to the intervention. The present study was approved by the Ethics Committee of Tehran University of Medical Sciences (Ethical code number: 880369885458816) and Registered in the Clinical Trials Registration Center of Iran (IRCT201211062464N6). Exclusion criteria were receiving any localized and systemic treatment for oral lichen planus in the last month, presence of dysplasia in the histopathologic figure, history of lupus, hepatitis C, hepatitis B, diabetes, thyroid diseases and any systemic conditions causing such lesions as lichen planus, pregnancy or breastfeeding and having contraindication for biopsy. In the present study, a new formula as 0.1% triamcinolone acetonide combined with 0. 05% Retinoic acid in Orabase has been examined. The drugs used in our study were 1) Triamcinolone acetonide 0.1%, and 2) combination of Triamcinolone acetonide 0.1% (KENALOG®), and Retinoic Retino-A®) both in an Orabase past, formulated by the Department of Medicinal Chemistry, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran (patent number: A61K31/573). The composition of the oral past was gelatin, pectin, carboxymethylcellulose sodium, plasticized hydrocarbon gel prepared from polyethylene and mineral oil gel base in different ratios. To achieve the desired viscosity and maximum adherence to oral lesions, different ratios of the above-mentioned ingredients and active compound (Retinoic acid and Triamcinolone acetonide) were mixed and tested. The best formulation for oral past containing gelatin (16.5 %), pectin (16.5 %), carboxymethylcellulose sodium (16.7 %) and plasticized hydrocarbon gel (50.3%) represented the satisfactory results. Appropriate amount of oral past and active materials were mixed, poured in 30g capacity tubes in the absence of air, labeled, and kept at room temperature. The selected patients (n=40) were randomly divided into the two groups of TO (n=20) and TRO (n=20), according to Block Randomization (www.randomization.com). The TRO group (15 women and 5 men) was treated with the combination of Triamcinolone acetonide 0.1%and Retinoic acid 0.05 % in Orabase, and TO group (13 women and 7 men) received triamcinolone acetonide 0.1% in Orabase. The lesion's size was scored from 0 (without lesion) to 5 (large lesion) as follow (10):

Score 0: No lesion, normal mucosa

Score 1: Mild white striae, no erythematous area

Score 2: White striae with atrophic area less than 1 cm^2

Score 3: White striae with atrophic area more than 1 cm^2

Score 4: White striae with erosive area less than 1 cm^2

Score 5: White striae with erosive area more than 1 cm^2

A scaled wooden tongue blade which was divided into 5 cm sections equally, was utilized to measure the size of the lesions. The visual analog scale (VAS) was used for evaluating the severity of the subjects' pain and discomfort (symptom), which ranged from 0 (showing no pain) to 100mm (demonstrating extreme pain):

0= Asymptomatic (no pain)

25= Low level of symptoms, does not interfere with usual daily activity (mild)

50= Symptoms interfere with regular daily activity (moderate)

75= Sore and painful; greatly interferes with regular daily activity (severe)

100= Impossible to live with the severe symptoms (very severe) Participants were asked to apply the base on lesion sites three times a day for four weeks. They were instructed to place the ointment on the lesion after each meal and after rinsing the mouth and drying the area with a cotton roll and avoiding eating and drinking for half an hour. The examiner, patient and the analyzer were all three blinded (triple blind). All participants in the two groups were visited at baseline and after 1, 2, 3, and four weeks of treatment. During each session, clinical examination along with photography was performed, and the patients' response rates were determined using pain scores and overall clinical improvement was determined using lesion score or sign stage. The symptomatic response for each patient was calculated by subtracting the final pain score from the initial score. The clinical response was estimated through subtraction of the lesions score obtained in the first and last examination sessions. Positive and negative values were considered as improvement and worsening, respectively. All data were recorded in the questionnaires at the end of each week. Analysis and comparison of pain scores, size of the lesions and clinical and symptomatic response rates between the two groups were performed using Mann–Whitney ***U***-test and through SPSS 13.0 computer software. A value of $p<0.013$ was considered as statistically significant.

Results

Forty patients, 28 women and 12 men, with the mean age of 41 ± 2 years (range 21–62 years) were enrolled. Before the start of the treatment, the participants had lesions lasted for two months to eight years, with a mean of 28 months. The buccal mucosa was the most common site for OLP, followed by the gingiva, tongue, labial mucosa (Table1). The patients in both groups were similar in age and location of the lesions. Before starting therapy, there was no statistically significant difference in the scores of signs and symptoms between the two groups (Table1). The use of medications in the two groups led to a decrease in pain and burning sensation severity of OLP and 95% of patients in the TRO group and 90% of the patients in TO group were asymptomatic (no pain) after three weeks. The difference between the two groups was not statistically significant (P =0.71, Table2). After three weeks of treatment, all patients in the TRO group (100%) and 60% of participants in the TO group improved to score 1 & 0. Decrease in the size of keratotic, atrophic and erosive OLP lesions were significantly different in the two groups (P<0.0001, Table2). Thus, after 2 to 3 weeks, the decrease in the size of keratotic and atrophic/erosive lesions was greater in the experimental group compared to the control group. In the two-month follow up of

the patients, 10% of the TRO group and 15% of the TO group relapsed and there was no significant difference between the two groups (P=1, Table3). There were no side-effects in either of the groups throughout the entire intervention period.

Table 1. Basic characteristics of the studied patients and their pain severity and sign score before the treatment

Variable	TO group	TRO group
Sex		
male	7 (35%)	5 (25%)
female	13 (65%)	15 (75%)
mean age (year)	44.6±2	45.8±2
Location of lesions		
Cheek	20 (100%)	20 (100%)
Gingiva	9 (45%)	12 (60%)
Tongue	7 (35%)	5 (25%)
lip	2 (10%)	3 (15%)
Pain severity		
Mild	3 (15%)	3 (15%)
Moderate	9 (45%)	10 (50%)
Severe	3 (15%)	4 (20%)
Very severe	5 (25%)	3 (15%)
Sign Score		
Score1	-	-
Score2	1 (5%)	0 (0%)
Score3	2 (10%)	5 (25%)
Score4	9 (45%)	8 (40%)
Score5	8 (40%)	7 (35%)

Table 2. The outcomes of treatment assessed during the treatment period

	1st week		2nd week		3rd week		4th week	
	TO	**TRO**	**TO**	**TRO**	**TO**	**TRO**	**TO**	**TRO**
Pain score								
No pain	6 (30%)	12 (60%)	11 (55%)	12 (60%)	18 (90%)	19 (95%)	19 (95%)	20 (100%)
Mild	7 (35%)	7 (35%)	5 (25%)	5 (25%)	2 (10%)	1 (5%)	1 (5%)	0 (0%)
Moderate	4 (20%)	1 (5%)	4 (20%)	3 (15%)	2 (10%)	0 (0%)	0 (0%)	0 (0%)
severe	2 (10%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)
Very severe	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
P value	0.024		0.738		0.718		0.799	
Sign score								
Score 0	0 (0%)	0 (0%)	0 (0%)	4 (20%)	4 (20%)	14 (70%)	6 (30%)	17 (85%)
Score 1	1 (5%)	9 (45%)	5 (25%)	12 (60%)	8 (40%)	6 (30%)	11 (55%)	3 (15%)
Score 2	3 (15%)	8 (40%)	7 (35%)	4 (20%)	6 (30%)	0 (0%)	3 (15%)	0 (0%)
Score 3	8 (40%)	2 (10%)	5 (25%)	0 (0%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)
Score 4	6 (30%)	1 (5%)	3 (15%)	0 (0%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)
Score 5	2 (10%)	0(0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
P value	<0.001		<0.001		<0.001		<0.001	

Table 3. Relapse rate in the two studied groups

relapse	**RO**	**TO**	**P value**
1 mouth	0 (0%)	0 (0%)	-
2 mouth	2 (10%)	3 (15%)	1

Discussion

Based on the present study, combination of corticosteroid and retinoid in Orabase (thrice applications daily for 2 to 3 weeks) was more effective in decreasing the size of keratotic, atrophic and erosive OLP lesions than triamcinolone acetonide alone. These two components have entirely different modes of action and have synergistic effects when combined in a single

formulation, which lead to more rapid clearing and are notably effective in the treatment of OLP. A number of studies have reported that topical retinoid might be a preferred therapeutic medication in the treatment of hyperkeratotic lesions such as OLP and leukoplakia (13). According to Sahebjamee & Arbabi, innon-keratotic and even keratotic oral lichen planus, topical triamcinolone acetonide 0.1% in oral base reduces the severity of atrophic and erosive oral lesions more effectively than topical retionoic acid 0.05% in orabase. In the mentioned study, the clinical efficacy of retinoic acid 0.05% was less than triamcinolone acetonide 0.1% (11). This might be due to different immuno-modulating mechanisms of the two drugs (12). A study on intralesional triamcinolone acetonide injection and its efficacy in treating ulcerative OLP reported that 84.4% of patients demonstrated complete response in ulceration size and their results suggest that this method is effective and safe in achieving lesion and pain regression (10). Furthermore, the efficacy of Retinoic acid in Orabase (0.05%) has been compared with fluocinolone acetonide in Orabase (0.1%), in the treatment of atrophic and erosive OLP and it has been found that fluocinolone acetonide 0.1% reduces the severity of OLP more efficiently than retinoic acid 0.05% (10). The results of the above studies show that the use of retinoid compounds alone in the treatment of oral lichen planus is less efficient than corticosteroids and studies on the combined effects of these drugs are needed. Although anti-inflammatory effects of retinoic acid have been reported, triamcinolone acetonide seems to be more effective in inflammation. On the other hand, the primary use of retinoids is dissuaded and limited due to their side effects and low remission rates. Both systemic and topical retinoid are suggested to be used as adjuvant (2). The corticosteroid-retinoid combination of the invention decreases inflammation by two entirely different mechanisms, acting in concert. One mechanism by which the corticosteroid works is by inhibiting the release of enzymes that initiate the inflammatory cascade, whereas the effect of the retinoid is less specific and perhaps through interfering with the arachidonic acid cascade. Among these, is the ability of retinoid to promote wound healing and to stimulate the formation of angiogenesis, thus increasing the local blood supply (8, 13). Dalirsani et al, revealed that combination of 0.2% triamcinolone acetonide and vitamin A mouthwash and triamcinolone acetonide mouthwash alone were effective in reducing lesion size, pain and irritation of oral erosive lichen planus (14) which is consistent with the results of our study. Another interesting reason for using retinoid compounds in the treatment of lichen planus is the OLP's tendency for malignant transformation to SCC in the long term (15) and long-term, follow-up is essential (5,16). Since the treatment of oral lichen planus often requires long-term use of immunosuppressive and cytotoxic agents, it can be a trigger for malignant transformation. For example, cyclosporine and tacrolimus can stimulate cancer progression (17, 18), while therapeutic modalities with topical or systemic steroids, such as retinoids, do not have any effect on the risk of malignant transformation (10, 18). According to multiple studies, Vitamin A can

play a role in the prevention of oral cancer and cause regression of premalignant leukoplakia (10, 19). Conclusion According to the present study findings, the combination of triamcinolone acetonide and retinoic acid in Orabase was more effective than triamcinolone acetonide in Orabase in the treatment of OLP which may be the result of their synergistic effect. This treatment method could be used in the treatment of OLP.

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References

1. Ismail SB, Kumar SK, Zain RB. Oral lichen planus and lichenoid reactions: etiopathogenesis, diagnosis, management, and malignant transformation. J Oral Sci 2007; 49(2):89-106.
2. Alrashdan MS, Cirillo N, McCullough M. Oral lichen planus: a literature review and update. Arch Dermatol Res 2016; 308(8):539-51.
3. Lavanya N, Jayanthi P, Rao UK, Ranganathan K. Oral lichen planus: An update on pathogenesis and treatment. J Oral Maxillofac Pathol 2011; 15(2):127-32.
4. Carrozzo M, Uboldi de Capri M, Dametto E, Fasano ME, Arduino P, Broccoletti R, et al. Tumor necrosis factor-alpha and interferon-gamma polymorphisms contribute to susceptibility to oral lichen planus. J Invest Dermatol 2004; 122(1):87-94.
5. Carrozzo M, Thorpe R. Oral lichen planus: a review. Minerva Stomatol 2009; 58(10):519-37.
6. Nisa SU, Saggu TK. To estimate the efficacy of 0.1% tacrolimus with Colgate Oraguard-B paste for the treatment of patients with symptomatic oral lichen planus. Indian J Dent 2016; 7(1):23-27.
7. Monajjemzadeh F, Gholizadeh N, Yousefzadeh Mobaraki N, Jelvehgari M. Physicochemical and in vitro mucoadhesive properties of microparticles/discs of betamethasone for the management of oral lichen planus. Pharm Dev Technol 2016; 21(8):996-1005.
8. Al Haj Zen A, Nawrot DA, Howarth A, et al. The Retinoid Agonist Tazarotene Promotes Angiogenesis and Wound Healing. Mol Ther. 2016;24(10):1745-1759.
9. Laeijendecker R, Tank B, Dekker SK, Neumann HA. A comparison of the treatment of orallichen planus with topical tacrolimus and triamcinolone acetonide ointment. Acta Derm Venereol 2006; 86(3):227-9.
10. Thongprasom K, Dhanuthai. Steroids in the treatment of lichen planus: a review. J Oral Sci 2008; 50(4):377-85.
11. Sahebjamee M, Arbabi Kalati F. Management of oral lichen planus. Archives of Iranian medicine 2005; 8(4):252-6.
12. Sahebjamee M, Amanlou M, Bakhshi M. Efficacy of topical retinoic acid compared with topical triamcinolone acetonide in the treatment of oral lichen planus. Acta Medica Iranica 2004; 42(2):108-13.
13. Mabire D, Adelinet CH, Csoka IC. Retinoic acid mimetic anilides. [cited 2019 Oct 20] Available from:

https://patents.google.com/patent/US6936626B2/en.

14. Dalirsani Z, Taghavi Zenouz A, Mehdipour M, Alavi F, Javadzadeh Y. Comparison of the effect of combination of triamcinolone acetonide and vitamin a mouthwash with triamcinolone mouthwash alone on oral lichen planus. J Dent Res Dent Clin Dent Prospects 2010; 4(1):21-4.
15. Gholizadeh N, Emami Razavi A, Mohammadpour H, Tavakol F, Sheykhbahaei N. Association of MAPK and its regulatory miRNAs (603, 4301, 8485, and 4731) with the malignant transformation of oral lichen planus. Mol Biol Rep 2020; 47(2):1223-32.
16. Mattila R. Molecular markers of oral lichen planus [dissertation]. Turku, Finland: University of Turku; 2009.
17. de Sousa FA, Paradella TC. Malignant potential of oral lichen planus: a meta-analysis. Revista Odonto Ciência 2009; 24(2):194-7.
18. Mattsson U, Magnusson B, Jonell M. Squamous cell carcinoma in a patient with oral lichen plants treated with topical of application tacrolimus. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2010; 110(1):e19-25.
19. Greenberg MS, Glick M, Ship JA. Burket's Oral Medicine. 11th ed. USA: PMPH USA; 2008.