

Effects of Beclomethasone and Adcortyl in the treatment of Erosive Oral Lichen planus lesions: A Comparative Study

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Abstract

Introduction: Lichen planus (LP) is a common chronic immune-mediated mucocutaneous disease, the exact cause of which is unknown. One of the common treatments for erosive lichen planus (ELP) is the use of topical corticosteroids of adcortyl ointment (triamcinolone in orabase). On the other hand, beclomethasone spray as a topical corticosteroid is easy to use in the mouth. The purpose of this comparative study was to investigate the effects of beclomethasone and adcortyl in the treatment of erosive oral lichen planus lesions (EOLP).

Materials and Methods: The present single-blind clinical trial was conducted on 50 patients with EOLP lesions with a mean age of 40.55 years at Jondishapur University of Medical Sciences, Iran. Beclomethasone and adcortyl were co-administered on lesions in both sides of the mucosa of the cheek, gums or margin of tongue for 3 to 6 weeks, after which the dose was adjusted. Visual analogue scale was used to evaluate the effect of drugs. Data were analyzed by paired t-test, Wilcoxon and Kolmogorov-Smirnov tests ($\alpha = 0.05$).

Results: The results of this study showed that there was no difference between applying beclomethasone and adcortyl in terms of reducing the extent and severity of EOLP lesions, and adcortyl was more effective than beclomethasone in relieving pain symptoms ($P < 0.05$).

Conclusion: The therapeutic effects of the adcortyl and beclomethasone were similar in controlling the EOLP lesions. Adcortyl was more effective than beclomethasone in relieving pain and irritation symptoms.

Keywords: Oral lichen planus, Erosive, Topical corticosteroid, Beclometasone, Adcortyl

Introduction

Lichen planus (LP) is a common immune-mediated mucocutaneous disease, first described by British Physician Wilson Erasmus in 1869 (1, 2). The LP as a chronic autoimmune condition affects various surfaces, including the skin, scalp, nails, and mucous membranes (2, 3). Although the

exact cause is unknown, several factors have been reported, including immunological disorders, stress, dental material, genetic factors, allergies, drugs, hepatitis C, hypertension, malignant neoplasms and diabetes (2, 4-9).

The prevalence of oral lichen planus (OLP) is reported to be 1-2% in different communities (10), which is more common in people aged

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30 to 60 years and women (2, 3, 11). In a study of 420 patients with OLP in Iran, 64.9% of patients were women with an average age of 41.6 years (12).

Some of the most important and serious complications of OLP are the possibility of pre-cancerous lesions and dysplastic changes in them, which can eventually lead to carcinoma in the mouth. The rate of malignant changes in OLP is reported to be 0.4-3.3% (13, 14). In addition, lesions tend to become chronic, which can cause discomfort, pain and irritation in patients. Therefore, correct diagnosis and control of the disease, as well as its differentiation from other chronic lesions, reduces the consequences of the disease, including the impact on the quality of life of patients due to reducing pain and irritation and elimination of chronic lesions leading to malignancy (13). The treatment of OLP disease, due to its unknown etiology, is to reduce or eliminate the symptoms of the lesion. Currently, topical steroids are the first step in treating these lesions because of effective therapeutic effects with minimal side effects (15).

When the symptoms of the disease are very severe, systemic steroids are used from the beginning of treatment. The topical use or topical injection of a steroid is also administered successfully to treat OLP, especially erosive-bullous type. The topical corticosteroids such as triamcinolone, betamethasone, clobetasol and fluocinolone improve pain and irritation within 1-2 weeks (16). Adcortyl (Bristol-Myers Squibb-USA) Kenacort A, 1 mg/g, contains the mid-strength triamcinolone acetonide, which is prepared as an orabase for longer shelf life on the lesion. The mechanism of action of this drug is to interfere with cytoplasmic receptors of steroid and has anti-inflammatory and anti-itch effects. Beclomethasone (Beclotis NS, 50 mcg/dose containing 200 dose, Shandong Jewin pharmaceutical Co.Ltd-India) is a topical

steroid with high activity and low side effects. Each container of this spray contains 200 puffs and each puff contains 50 micrograms of beclomethasone dipropionate. The spray should be kept at a temperature below 30°C, away from direct sunlight and heat. A study showed that the doses of 400 to 800 mcg of this drug did not cause adrenal suppression (13).

One of the common treatments for erosive oral lichen planus (EOLP) is the use of topical corticosteroids of adcortyl ointment (triamcinolone in orabase), which is an imported and expensive pharmaceutical product and is usually available in the market as a paste. Moreover, due to the fact that topical steroids are mostly used as mouthwashes, gels, ointments and sprays, they are easier for patients to use; therefore, this study aimed to investigate the clinical effects of adcortyl and beclomethasone in the control and treatment of EOLP lesions.

Materials and Methods

The present single-blind clinical trial was conducted on 50 patients with EOLP lesions with a mean age of 40.55 ± 5.53 years referred to Oral Diseases Department of Dentistry Faculty at Jondishapur University of Medical Sciences. A written consent was obtained from all patients. Diagnosis of all lesions was based on clinical symptoms and biopsy. Beclomethasone spray is a class of corticosteroids. The study used BECLEX spray (containing 50 micrograms of beclomethasone dipropionate per dose), and adcortyl mucosal adhesive (Triamcinolone topical), a class of corticosteroids.

Inclusion criteria were patients with EOLP lesions who, in addition to their definitive clinical diagnosis, had their histopathological diagnosis confirmed by the pathologist, non-use of other therapies for EOLP lesions; absence of any systemic disease that causes oral symptoms similar to EOLP lesions such

as lupus erythematosus, secondary syphilis, Lichenoid Drug Eruption, erythema multiforme, and graft-versus-host disease (GVHD).

Exclusion criteria were uncooperative patients regarding recurrence of lesions, and the use of other topical or systemic corticosteroids concurrent with the desired medications.

Patients' pain experience was determined by the visual analogue scale (VAS). Due to the fact that OLP lesions are known to have bilateral distribution in the oral cavity, in order to know how much this feeling of pain and tenderness exists on each side, after stimulating the lesions on both sides separately (by pulling the cotton roll on the lesion site) the VAS test was recorded for pain and irritation for each side. Also in each patient, the shape and borders of the lesions were drawn on each side. Thus, after drying the site of the lesion, a translucent sheet disinfected with deconex spray was placed on the lesion, and then the shape and boundaries of the lesion were drawn and recorded in the patient's file. The entire erosive lesion surface was measured by a flexible ruler or probe.

In order to homogenize the samples in the present study, the scale of mucosal lesions was the same in all individuals and on both sides. After recording all the information, first, the lesions of one side in each patient were randomly determined by a person other than the examiner to use adcortyl and the other side to use beclomethasone, and the examiner was unaware of this choice. The topical treatment was administered to each patient at the same time as adcortyl and beclomethasone, with beclomethasone on one side and adcortyl on the other. To prevent the two drugs from mixing when used, patients were instructed to first put the adcortyl on the desired side and then bring the beclomethasone completely closer to the desired site. Adcortyl was prescribed four times daily after each meal and before

bedtime and beclomethasone four times daily after each meal and before bedtime. After taking the medication, eating was avoided for an hour. After starting the treatment, the patients were called every week for up to three consecutive weeks, and the response rate of the lesions to the treatment was recorded according to the criteria already stated, and was assessed as a second questionnaire. If symptoms of candidiasis occur, treatment with oral nystatin will begin for the patient. After the end of the third week of drug treatment, the rate of improvement of the symptoms and the recurrence of the lesions were evaluated using the evaluation of the response to the treatment listed below. In cases where the mucosal lesions were completely or partially removed within three weeks, the dose was gradually reduced; otherwise treatment was continued for up to six weeks. To adjust the medication, the adcortyl dose was first reduced to twice daily and the beclomethasone dose to three times daily for three weeks, and the lesions were evaluated for non-recurrence. If the lesions did not recur, adcortyl would have given once daily for three weeks and beclomethasone twice daily. After reassessment, adcortyl was used for three weeks every other day and beclomethasone once daily. Finally, the drugs reached adcortyl maintenance twice a week and beclomethasone three times a week, and the medication was discontinued if not recurred (13).

Four conditions were expected in patients:

- 1) Complete removal of the lesions: The patient's symptoms are completely resolved, the lesions are completely removed, and only white lines are seen.
- 2) Partial removal of the lesions: The patient's symptoms are reduced and the white lines and areas of mild erythematosus are seen.
- 3) Lack of response to treatment: The patient's symptoms do not eliminate and the lesions remain stable or increase.

4) Changes in the diameter of the lesions: The diameter of the lesions changed.

This study was approved by the Ethics Committee of the Deputy of Research at Jondishapur University of Medical Sciences. The necessary information was confidentially collected. In this project, basic information about the research was first explained to patients and they were asked to sign informed consent to participate in the research. In this study, there was no financial or physical burden to the patients, and their information and names were anonymous and kept completely confidential. The following items were also observed: 1) Oral health education was also considered during the examination. 2) Patients were informed of the presence of any oral or dental lesions that needed to be treated or the risk of any infection or malignancy and any other lesions that would endanger a person's life.

Statistical Analysis

After collecting the questionnaires, the data were analysed using SPSS version 20 software. Paired-Sample t-test, Wilcoxon and Kolmogorov-Smirnov tests were used for descriptive statistics. The significance level in all statistical tests was $P < 0.05$.

Results

According to the findings of this study, the mean maximum diameter of pre-treatment lesions was 18.78 ± 6.17 mm on the side of applying beclometasone and 17.47 ± 4.05 mm on the side of applying adcortyl. The dependent t-test showed that the two groups of beclometasone and adcortyl had no statistically significant difference before treatment.

The lesions were completely eliminated by the end of the third week in 5 patients in the beclomethasone group and in 7 patients in the adcortyl group. The mean maximum lesion

diameter after treatment (at the end of the third week) was 4.92 ± 2.99 mm in the beclometasone group and 5.18 ± 3.32 mm in the adcortyl group. The dependent t-test showed that there was no significant difference between beclomethasone and adcortyl groups after treatment. The mean percentage of reduction in the maximum lesion diameters in beclometasone and adcortyl groups was 73.02 ± 18.57 mm and 68.69 ± 19.50 mm, respectively. These values showed no significant difference after treatment in two groups in accordance with independent t-test. By the end of the twelfth week, all the lesions treated with adcortyl were eliminated. In the beclomethasone group, only two lesions with a maximum diameter of 4 mm remained.

The mean pain intensity based on VAS on the sides of applying beclomethasone and adcortyl prior to treatment was 5.90 ± 2.48 mm and 6.02 ± 2.23 mm, respectively. The dependent t-test showed that there was no significant difference in pre-treatment pain intensity between beclomethasone and adcortyl groups ($P = 0.08$).

After treatment (at the end of the third week) the pain was completely relieved in 28 patients and decreased in 22 patients in the beclometasone group; these results were 36 and 14 in the adcortyl group, respectively. The Wilcoxon test showed that the pain intensity was significantly different between the two groups of beclomethasone and adcortyl after treatment ($P = 0.02$).

The Wilcoxon test showed that the percentage of pain reduction on the side of applying adcortyl was significantly higher than on the side of applying beclometasone ($P = 0.02$). By the end of the twelfth week, no patients in both groups had pain in one or both sides.

Regarding the response to treatment in the beclometasone group at the end of the third week, the patient's symptoms were completely eliminated, the lesion was

completely removed, and only white lines were seen in 5 patients, the patient's symptoms were decreased and white lines and areas of mild erythematosis were seen in 15 patients, and the diameter of the lesion also was changed and decreased in 30 patients. Three types of response were seen: Complete removal of the lesion: 1) The patient's symptoms are completely resolved, 2) the lesion is completely removed, and 3) only white lines are seen.

Partial removal of the lesion: The patient's symptoms are reduced and the white lines and areas of mild erythematosis are seen.

Changes in the diameter of the lesion: only the diameter of the lesion changes.

Regarding the response to treatment in the ad cortyl group at the end of the third week, the patient's symptoms were completely eliminated, the lesion was completely removed, and only white lines were seen in 7 patients, the patient's symptoms were decreased and white lines and areas of mild erythematosis were seen in 12 patients, and the diameter of the lesion also was changed and decreased in 31 patients.

Discussion

Because OLP, especially erosive, atrophic and bullous types, can cause pain and discomfort to patients for years, the relief of resulting pain and irritation is of particular importance in improving the quality of life of these patients (17). On the other hand, OLP is considered a precancerous lesion. Therefore, disease control is very important in order to prevent irreversible dysplastic changes and eliminate symptoms such as pain and irritation and also reduce the size of lesions and improve the patient's quality of life (18-20) Thus, the efficacy of drugs against their side effects has led to many studies using a variety of drugs to control this disease (1). Accordingly, primary treatment is usually the use of topical corticosteroids, which can

improve symptoms and eliminate lesions with minimal side effects. One of these drugs is ad cortyl, which is considered an accepted drug in the treatment of OLP lesions. On the other hand, among the topical corticosteroids, few studies have been performed on the drug form of the spray. It seems that due to the ease of use of the spray, the level of acceptance and cooperation of the patient is higher, especially in the posterior and out of reach areas. In the study of Azimi et al., the two groups of beclomethasone and ad cortyl had no statistically significant difference before treatment. Both drugs reduced the maximum diameter of the lesions, and there was no significant difference between the two groups in terms of mean reduction in the maximum diameter of lesions and pain intensity. But the rate of pain reduction in the ad cortyl group was significantly higher than in the beclomethasone group and no patient in either group had pain on one or both sides at the end of the twelfth week (13). Results of this study were in line with the present study. Even though the studied patients were any type of OLP but patients of present study were erosive type of OLP.

In the study of Azizi et al., the ad cortyl and triamcinolone mouthwash were compared in treatment of OLP. Both groups showed significant reduction in the size and severity of pain indicating the positive effect of two methods in the treatment and control of the disease. But the differences between two groups were not significant (1). These results are not far-fetched and are consistent with the present study.

Xia et al., studied the effects of triamcinolone on ulcerative OLP, similar results were obtained, relief of sign & symptoms and reduction in size after 4 weeks were seen. No side effects were seen as in the present study (20). On the other hand Lee et al. in their study about effects of Triamcinolone on OLP found significantly improve in pain and burning sensation in mouth but reduction in

size of lesions were not measured. They also reported some cushingoid features as side effects of using corticosteroids. This can be due to the method of applying the drug that was intralesional injection. It seems that some degrees of systemic absorption have been occurred (21).

Liu et al., have compared effects of intralesional triamcinolone and betamethasone on OLP patients. Betamethasone had better result than triamcinolone in management of OLP (22).

Borahan et al., studied the effect of methylprednisolone acetate on a case of erosive OLP and significant improvement were seen. But some degree of Abscess formation and mucosal atrophy were occurred due to intralesional injection method (23). Another reported side effects were atrophy and persistent erythema in the case report of Metwalli et al., in which effects of intralesional Triamcinolone acetate on OLP patients were evaluated and significantly improvement was seen (24).

Alerraqi in a study compared the effects of three different types of corticosteroids as the mainstay of treating OLP, including intralesional Triamcinolone, topical Betamethasone and systematic glucocorticosteroid. All groups showed remission and there were no significant differences between groups (25). So because of the side effects of systemic types of

corticosteroids topical ones are preferred as we used in the present study.

Sethi-Ahuja et al., in their study compared intralesional corticosteroid and platelet rich plasma (PRP) in the treatment of OLP. No significant differences in terms of pain reduction, size of lesions and erythema scores were seen between two methods. So PRP has comparative effectiveness with corticosteroids with the advantage of no side effects (26). Another comparative study was done by Lavaee et al. between photodynamic therapy and topical corticosteroid (Triamcinolone). But no significant differences between groups were observed and both groups improved significantly. Photodynamic therapy can be considered as a new and alternative method with no known side effects (27).

The results of this study showed that there was no difference between applying beclomethasone and adcortyl in terms of reducing the extent and severity of EOLP lesions, but adcortyl was more effective than beclomethasone in relieving pain symptoms.

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References

1. Azizi A, Lavaf S, Amani B. Comparison of the Effects of Adcortyl Ointment (Triamcinolone in Orabase) and Triamcinolone Mouthwash on Oral Lichen Planus. Shiraz Univ Dent J. 2009; 10 (1): 25-30.
2. Gholizadeh N, Sheykhbahaei N, Mansourian A, Amini-Shakib P, Sadrzadeh-Afshar M, Fooladvand S. Lack of association between Estrogen and progesterone receptors and Oral Lichen Planus. J Kerman Univ Med Sci, 2020; 27(1): 24-35. doi: 10.22062/jkmu.2020.89593.
3. Crincoli V, Di Bisceglie MB, Scivetti M, Lucchese A, Tecco S, Festa F. Oral lichen planus: update on etiopathogenesis, diagnosis and treatment. Immunopharmacol Immunotoxicol.

- 2011; 33 (1): 11-20. doi: 10.3109/08923973.2010.498014.
4. Yiannias JA, el-Azhary RA, Hand JH, Pakzad SY, Rogers RS, 3rd. Relevant contact sensitivities in patients with the diagnosis of oral lichen planus. *J Am Acad Dermatol.* 2000; 42 (2 Pt 1): 177-82. doi: 10.1016/S0190-9622(00)90123-3.
 5. Boorghani M, Gholizadeh N, Taghavi Zenouz A, Vatankhah M, Mehdipour M. Oral lichen planus: clinical features, etiology, treatment and management; a review of literature. *J Dent Res Dent Clin Dent Prospects.* 2010; 4 (1): 3-9. doi: 10.5681/joddd.2010.002.
 6. Gupta S, Jawanda MK. Oral Lichen Planus: An Update on Etiology, Pathogenesis, Clinical Presentation, Diagnosis and Management. *Indian J Dermatol.* 2015; 60 (3): 222-9. doi: 10.4103/0019-5154.156315.
 7. Srinivas K, Aravinda K, Ratnakar P, Nigam N, Gupta S. Oral lichen planus - Review on etiopathogenesis. *Natl J Maxillofac Surg.* 2011; 2 (1): 15-6. doi: 10.4103/0975-5950.85847
 8. Nogueira PA, Carneiro S, Ramos-e-Silva M. Oral lichen planus: an update on its pathogenesis. *Int J Dermatol.* 2015; 54 (9): 1005-10. doi: 10.1111/ijd.12918.
 9. Issa Y, Duxbury AJ, Macfarlane TV, Brunton PA. Oral lichenoid lesions related to dental restorative materials. *Br Dent J.* 2005; 198 (6): 361-6. doi: 10.1038/sj.bdj.4812176.
 10. Gonzalez-Garcia A, Diniz-Freitas M, Gandara-Vila P, Blanco-Carrion A, Garcia-Garcia A, Gandara-Rey J. Triamcinolone acetonide mouth rinses for treatment of erosive oral lichen planus: efficacy and risk of fungal over-infection. *Oral Dis.* 2006; 12 (6): 559-65. doi: 10.1111/j.1601-0825.2006.01238.x.
 11. Chainani-Wu N, Silverman S, Jr., Lozada-Nur F, Mayer P, Watson JJ. Oral lichen planus: patient profile, disease progression and treatment responses. *J Am Dent Assoc.* 2001; 132 (7): 901-9. doi: 10.14219/jada.archive.2001.0302.
 12. Pakfetrat A, Javadzadeh-Bolouri A, Basir-Shabestari S, Falaki F. Oral Lichen Planus: a retrospective study of 420 Iranian patients. *Med Oral Patol Oral Cir Bucal.* 2009; 14 (7): E315-8.
 13. Azimi S, Rafieian N, Abdolsamadi HR. Comparative evaluation of the effects of beclomethasone and ad cortytle in the treatment of oral lichen planus. *J Isfahan Dent Sch.* 2011; 7 (3): 256-64.
 14. Javadzadeh A, Vatanpour H, Delavarian Z, Momajed A, Esmaeily H, Vatanpour M, et al. Efficacy of clobetasol, ketoconazole and amitryptiline mouthwash on Oral Lichen Planus. *IJPR.* 2008; 7 (3): 171-8. doi: 10.22037/IJPR.2010.762.
 15. Thongprasom K, Dhanuthai K. Sterioids in the treatment of lichen planus: a review. *J Oral Sci.* 2008; 50 (4): 377-85. doi: 10.2334/josnusd.50.377.
 16. Gholizadeh N, Sadrzadeh-Afshar MS, Sheykhbahaei N. Intralesional corticosteroid injection as an effective treatment method for oral lesions: a meta-analysis. *Braz J Pharm Sci.* 2020;56:e18077. doi: 10.1590/s2175-97902019000418077.
 17. Gholizadeh N, Sadrzadeh-Afshar MS, Mansourian A, Fooladvand S. The Relationship Between The Oral Lichen Planus and Endocrine Hormnes: A Review of Literature. *Ann Dent Spec.* 2018;6(3):352-6.
 18. Agha-Hosseini F, Sheykhbahaei N, Sadrzadeh-Afshar MS. Evaluation of Potential Risk Factors that contribute to Malignant Transformation of Oral Lichen Planus: A Literature Review. *J Contemp Dent Pract.* 2016;17(8):692-701. doi: 10.5005/jp-journals-10024-1914.

19. Agha-Hosseini F, Moosavi MS, Sadrzadeh-Afshar MS, Sheykhbahaei N. Assessment of the Relationship Between Stress and Oral Lichen Planus: A Review of Literature. *JIDAI*. 2016; 28(2): 78-85. doi:10.30699/jidai.29.78.
20. Xia J, Li C, Hong Y, Yang L, Huang Y, Cheng B. Short-term clinical evaluation of intralesional triamcinolone acetonide injection for ulcerative oral lichen planus. *J Oral Pathol Med*. 2006;35(6):327-331. doi: 10.1111/j.1600-0714.2006.00441.x.
21. Lee SH, Yoon HJ. Intralesional infiltration of corticosteroids in the treatment of localized Langerhans cell histiocytosis of the mandible: report of two cases. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2013;116(4):e255-60. doi: 10.1016/j.oooo.2011.11.035.
22. Liu C, Xie B, Yang Y, Lin D, Wang C, Lin M, et al. Efficacy of intralesional betamethasone for erosive oral lichen planus and evaluation of recurrence: a randomized, controlled trial. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2013;116(5):584-90. doi: 10.1016/j.oooo.2013.07.023.
23. Borahan MO, Fisekcioglu E, Alpay MS. A complication after intralesional methylprednisolone acetate application to oral mucosa: A case report. *Balk J Dent Med* 2014;18:154-156.
24. Metwalli MI, Marei AM, Toama MA, Soliman MI, Fawzy MM. Bacillus Calmette-Guerin polysaccharide nucleic acid extract versus triamcinolone acetonide intralesional injection in the treatment of oral lichen planus: a comparative study. *Egyptian J Dermatol Venerol*. 2018;38(1):1-11. doi: 10.4103/ejdv.ejdv_12_17.
25. Alerraqi E. Steroid Therapy in Oral Lichen Planus. *J Steroids Horm Sci*. 2016; 7(2):1-10. doi: 10.4172/2157-7536.1000173.
26. Sethi Ahuja U, Puri N, More CB, Gupta R, Gupta D. Comparative evaluation of effectiveness of autologous platelet rich plasma and intralesional corticosteroids in the management of erosive oral Lichen planus- a clinical study. *J Oral Biol Craniofac Res*. 2020;10(4):714-718. doi: 10.1016/j.jobcr.2020.09.008.
27. Lavaee F, Shadmanpour M. Comparison of the effect of photodynamic therapy and topical corticosteroid on oral lichen planus lesions. *Oral Dis*. 2019;25(8):1954-1963. doi: 10.1111/odi.13188.