

Comparative Efficacy of Topical Curcumin and Triamcinolone for Oral Lichen Planus: A Randomized, Controlled Clinical Trial

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Abstract

Objectives: Lichen planus (LP) is a chronic inflammatory mucocutaneous disease. Its treatment is often symptomatic and includes topical and systemic corticosteroids. Although corticosteroid therapy is usually successful, it has side effects and thus, an alternative treatment is favorable. The aim of this study was to compare the efficacy of topical curcumin and triamcinolone for treatment of oral lichen planus (OLP).

Materials and Methods: In this study, 50 patients (36 women and 14 men) in the age range of 38 to 73 years with OLP were randomly divided into two groups. Each group received 0.1% triamcinolone or 5% curcumin oral paste three times a day for four weeks. Assessment of the appearance score and severity of pain was done at baseline and at the end of two and four weeks and recorded in the patients' questionnaires. The data were analyzed by SPSS 17 software, using the Mann-Whitney and Spearman's tests.

Results: With respect to pain reduction, nine patients (36%) in the curcumin group and eight patients (32%) in the triamcinolone group showed complete remission. With respect to the appearance score, one patient (4%) in each group showed complete remission. No statistically significant difference was noted between the two groups.

Conclusion: Application of curcumin is suggested for treatment of OLP because of its desirable anti-inflammatory effects and insignificant side effects.

Keywords: Curcumin; Lichen Planus; Triamcinolone

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INTRODUCTION

Oral lichen planus is an immune-mediated disease of unknown etiology with the mediation of T cells [1], in which the symptoms of patients decrease with an increase in CD4⁺ counts [2]. Oral lichen planus lesions can be of reticular, papular, plaque-like, bullous, erythematous (atrophic) and ulcerative forms.

Ulcerative lesions are the most debilitating form of OLP [3], which develop painful symptoms and interfere with eating, speaking, swallowing and tooth brushing [4]. Corticosteroids are usually successful for controlling the symptoms of the disease [5]; but because of the side effects of long-term corticosteroid therapy such as secondary candidiasis, telangiectasia,

hypothalamic–pituitary–adrenal suppression [6,7], muco-cutaneous atrophy and increased potential of systemic absorption, it may be better to avoid their long-term use [8].

Curcuma longa is a perennial plant belonging to Zingiberaceae family [9]. It has been used for centuries in the Indian traditional medicine for its anti-inflammatory effects [10]. Its main constituents include three curcuminoids including curcumin (the primary ingredient and the one responsible for its yellow color and anti-inflammatory effect), demethoxycurcumin and bisdemethoxycurcumin.

Chainani-Wu in a systematic review [11], and others [9, 12-16] confirmed the anti-inflammatory, antioxidant, wound healing and anticarcinogenic effects as well as safety of curcumin.

Clinical studies assessing curcuminoids have evaluated its utilization in inflammatory conditions such as rheumatoid arthritis, postsurgical inflammation and chronic uveitis [11]. The curcuminoids are safe even in high doses and only a few side effects have been reported [11].

Since oxidative stress may play a role in pathophysiology of OLP [17], and by noting that OLP is a chronic inflammatory disease [18], the herbs which have both anti-inflammatory and antioxidant properties may efficiently control OLP.

Chainani-Wu et al, in 2007 and 2012 assessed the efficacy of systemic administration of curcuminoids for treatment of OLP [10, 19]. Efficacious results were obtained in controlling the signs and symptoms of OLP using high doses of this herb. Concerning noticeable side effects reported by patients who used corticosteroids [20], chronic nature of OLP, risk of oral candidiasis upon usage of topical corticosteroids, and fewer side effects, safety and anti-inflammatory properties of curcuminoids, we aimed to clinically evaluate the efficacy of curcuminoids for treatment of OLP, compared with conventional corticosteroid therapy.

MATERIALS AND METHODS

This clinical trial was conducted on 50 patients (36 women and 14 men) in the age range of 38 to 73 and a mean age of 50.66 years. The patients had clinical signs of OLP (atrophic and ulcerative forms), and the disease was confirmed by clinical and histopathological examination.

The exclusion criteria were pregnancy and lactation, current use of anticoagulants or antiplatelet agents (curcumin has inhibitory effects on platelet aggregation) [21], current orthodontic treatment, history of gastric ulcers, duodenal ulcers, gallstones (curcumin may induce gastric irritation and stimulate gall bladder constrictions) [22], hepatic diseases (curcumin may cause hepatotoxicity in some mammals including mice and rats) [11], any existing malignancy or viral infections in the mouth, history of topical treatment for OLP in the past two weeks or any systemic treatment for OLP in the past four weeks, taking azathioprine, cyclosporine or receiving Psoralen plus ultraviolet A (PUVA), ultraviolet A (UVA) or ultraviolet B (UVB) radiation in the past month and history of allergy to corticosteroids or curcumin [6].

The crushed roots of *C. longa* L. were purchased from a drugstore in Rasht city in Iran and identified by a research fellow.

The ground herbal root (1g) was extracted using 10 mL of 96% ethanol boiling in a water bath for three minutes and the least volume of solvent was added to the given aliquot. Each sample was centrifuged at 8000g for 10 minutes; then the supernatant was filtered with a syringe filter (0.45µm). This mixture included curcumin, demethoxycurcumin and bisdemethoxycurcumin in lower amount.

Patients were given complete information about their disease and also about curcumin and triamcinolone pastes and then they were asked to participate in the study by signing an informed consent form approved by the Ethics Committee of Guilan University of Medical Sciences.

This clinical trial was also registered under the code IRCT2001105012950N2. The patients were randomly divided into two groups of 25. The sample size of 25 was chosen based on expected and actual enrollment of study subjects over a two-month time period. Because of feasibility reasons the enrollment was stopped at 25 subjects. A blocked randomization (block size of six) was used. The pharmacy of Guilan University of Medical Sciences supplied curcuminoids and triamcinolone in the form of similar oral pastes and generated the randomization sequence using the random number generator in Microsoft Excel (Microsoft Corp, Seattle, WA). Both participants and investigators were blinded to the treatment assignment. All the patients were examined and the age, sex, medical history, smoking status, form and location of oral lesions, duration of the disease, type of treatment received, severity of pain and appearance score were all recorded. Then, the patients received 0.1% triamcinolone or 5% curcumin paste for four weeks and were asked to apply it three times a day after eating and brushing, and then they were advised to avoid eating for 20 minutes. Measurement of the appearance score and severity of pain was done at baseline and at the end of two and four weeks and recorded in the patients' questionnaires.

To determine the severity of pain, we used a visual analog scale (VAS) and patients ranked the severity of pain on a 10-cm horizontal line graded from 0 to 10; 0 indicated no pain and 10 indicated the most severe pain [23]. To determine the appearance score, we used the criteria by Thongprasom et al, with the below mentioned classification:

0: No lesion, normal mucosa

1: Mild white striae, no erythematous area

2: White striae with atrophic area less than 1cm²

3: White striae with atrophic area more than 1cm²

4: White striae with ulcerative area less than 1cm²

5: White striae with ulcerative area more than 1cm² [24].

In this study, complete remission was defined as 100% reduction in signs and symptoms, Good response was defined as 50% or more reduction in signs and symptoms but still less than 100%. Poor response was defined as less than 50% reduction in signs and symptoms. If the status of lesions showed no change, the case was considered as no response.

The data were analyzed by SPSS version 17 software using the Mann-Whitney and Spearman's correlation tests. P<0.05 was considered statistically significant.

Table 1. Baseline characteristics of the study participants

	Curcumin N=25	Triamcinolone N=25
Age: mean (standard deviation)	49.24 (8.17)	52.08 (9.20)
Males: N (%)	10 (40)	4 (16)
Females: N (%)	15 (60)	21 (84)
Duration of oral lichen planus (in months)	23.96±15.49	28.52±15.72
Lesion type	Ulcerative: N (%)	16 (64)
	Atrophic: N (%)	9 (36)
Mean severity of pain at baseline (VAS score)	5.84±2.01	5.47±3.12
Mean size of lesion at baseline (cm ²)	3.88±0.78	3.95±1.07

RESULTS

Fifty-five patients participated in this study. Five patients were lost to follow up. The remaining 50 patients consisted of 36 females and 14 males (female to male ratio was 2.57) with a mean age of 49.24 years and age range of 38-73 years. The curcumin group consisted of 15 women and 10 men with a mean age of 49.24 years (range 38-73 years), while 21 women and four men with a mean age of 52.08 years (range 38-73 years) formed the triamcinolone group.

The mean duration of the disease before beginning the study was 23.96 ± 15.49 months in the curcumin group and 28.52 ± 15.72 months in the triamcinolone group; 21 patients had atrophic lesions (42% or nine patients in the curcumin group and 12 patients in the triamcinolone group) and 29 patients had ulcerative lesions (58% or 16 patients in the curcumin group and 13 patients in the triamcinolone group). All the patients complained of pain. The mean severity of pain was 5.84 ± 2.01 (VAS) in the curcumin group and 5.47 ± 3.12 (VAS) in the triamcinolone group (Table 1). The buccal mucosa was the most common site for OLP followed by the gingiva, tongue, palate, labial mucosa and floor of the mouth (Table 2).

Table 2. Percentage of involved sites in the curcumin and triamcinolone groups

Involved site	Curcumin (n=25)	Triamcinolone (n=25)	Total (n=50)
Buccal	10 (20%)	8 (16%)	18 (36%)
Gingiva of maxilla	7 (14%)	9 (18%)	16 (32%)
Gingiva of mandible	2 (4%)	4 (8%)	6 (12%)
Tongue	2 (4%)	1 (2%)	3 (6%)
Palate	1 (2%)	2 (4%)	3 (6%)
Labial mucosa	1 (2%)	1 (2%)	2 (4%)
Floor of the mouth	2 (4%)	0	2 (4%)

The mean VAS score was 5.84 ± 2.01 in the curcumin group at baseline, which decreased to 3.08 ± 2.01 and 2.64 ± 2.98 at the second and third follow-ups, respectively. The mean VAS score in the triamcinolone group was 5.47 ± 3.12 at baseline, which decreased to 1.90 ± 1.58 and 1.76 ± 1.78 at the second and third visits, respectively.

The mean Thongprasom score was 3.88 ± 0.78 in the curcumin group at baseline, which decreased to 3.28 ± 1.36 and 2.64 ± 1.29 at the second and third visits, respectively. The mean Thongprasom score was 3.95 ± 1.07 in the triamcinolone group at baseline, which decreased to 3.38 ± 1.07 and 2.95 ± 0.97 at the second and third visits, respectively.

In evaluation of pain reduction in the curcumin group, nine patients (36%) had complete remission, four patients (16%) had good response, six patients (24%) had poor response and six patients (24) showed no response to treatment. In the triamcinolone group, eight patients (32%) had complete remission, eight patients (32%) had good response, four patients (16%) had poor response and five patients (20) showed no response to treatment. There was no significant difference between the two groups in each of the follow up visits (Mann-Whitney; VAS at baseline: $P=0.17$; VAS two weeks later: $P=0.3$; VAS four weeks later: $P=0.46$; power of analysis =0.74, calculated by Minitab 16 software, Table 3). In evaluation of the appearance score in the curcumin group, one patient (4%) had complete remission, six patients (24%) had good response, 12 patients (48%) had poor response and six patients (24) showed no response to treatment. In the triamcinolone group, one patient (4%) had complete remission, two patients (8%) had good response, 12 patients (48%) had poor response and 10 patients (40) showed no response to treatment. The two groups had no significant difference according to the Thongprasom criteria scores (Mann-Whitney test; baseline: $P=0.77$, two weeks later: $P=0.92$, four weeks later: $P=0.31$, Table 3).

Using the Spearman's correlation test, there was no meaningful correlation between the mean severity of pain and the mean appearance score in the two groups with age, sex and duration of the disease ($0.058 < P \text{ value} < 0.97$).

At the end of the study in the curcumin group, a few patients complained of burning sensation, itching, mild swelling and xerostomia, which were disappeared at the end of the first week of drug consumption. Most of the patients also complained of undesirable yellow color of the drug particularly on the gingiva. In the triamcinolone group, only one patient complained of burning sensation in the first week of applying the drug, and one patient complained of mucosal desquamation in the entire duration of treatment.

DISCUSSION

Oral lichen planus is a chronic autoimmune mucocutaneous condition, which commonly involves the oral mucosa. This lesion can cause oral discomfort and even in some cases, transform into squamous cell carcinoma. Therefore, OLP is considered to be a potentially dangerous and malignant disease and has attracted the attention of clinicians [25].

Most of the previous studies assessed the effects of corticosteroids [4,6,26] and one immunosuppressive drug and in all of them the results in both participating groups were the same and equally successful; but since topical use of corticosteroids may lead to oral

candidiasis and other side effects and also considering the chronic nature of OLP, it would be better to find an alternative treatment. Also, it has been reported that tacrolimus and pimecrolimus may increase the risk of malignancy in patients using these drugs topically for their cutaneous psoriasis. These medicines should be used in limited cases and their consumption is advised to be in minimal doses and for a limited time [3, 27-30].

In the current study, we used curcumin; its safety, anti-inflammatory and antioxidant effects have been confirmed in many previous studies [9,11-16].

The clinical efficacy of curcumin was compared with that of a topical corticosteroid, which is the standard treatment for OLP. It was concluded that in addition to effectiveness of curcumin for treatment of OLP, its effects were similar to those of topical corticosteroids, and thus, it can be a suitable alternative to corticosteroids. Chainani-Wu et al. in 2007 [10] used curcumin for treatment of OLP in a placebo controlled clinical trial. Curcuminoids were prescribed as tablets, at a dosage of 2000mg/day for seven weeks.

They concluded that systemic administration of curcumin was not successful for treatment of OLP. Systemic administration of curcumin in the study by Chainani-Wu et al. [10] was different from its topical administration in the current study; the topical administration increases the efficacy of the drug.

Table 3. Pain reduction and clinical response in the curcumin and triamcinolone groups

Response rate	Pain reduction		Clinical response	
	Curcumin (n=25)	Triamcinolone (n=25)	Curcumin (n=25)	Triamcinolone (n=25)
Complete remission	9 (36%)	8 (32%)	1 (4%)	1 (4%)
Good response	4 (16%)	8 (32%)	6 (24%)	2 (8%)
Poor response	6 (24%)	4 (16%)	12 (48%)	12 (48%)
No response	6 (24%)	5 (20%)	6 (24%)	10 (40%)

Chainani-Wu et al. [10] administered a primary dose of systemic prednisone (60 mg/day for the first week) in both groups, which was not done in our study and could have affected their final results. Long periods of observation not only can interfere with patient compliance and cooperation (less subject retention until the end of study), but also can affect the treatment outcomes. For this reason, they recommended future studies with shorter follow-ups. In the current study, the final follow up session was at four weeks. The dosage of curcumin that Chainani-Wu et al, in 2012 [19] used in their study for treatment of OLP was higher than the dosage of curcumin in our study. They used systemic curcumin, with a dose of 6000mg/day. Interestingly, they found curcumin to be effective for controlling the signs and symptoms of OLP. It was well tolerated by the patients and its safety was also confirmed at this dosage.

The observation period was reduced to two weeks in their latter study, which was closer to our study, compared to seven weeks in their former study. Our sample size was similar to their latter study, as they enrolled 20 patients. Concerning their findings, erythema, mucositis and ulceration significantly decreased after using curcuminoids. An interesting finding of our study was the insignificant difference between the two groups in the reduction of pain and appearance score (there was no statistically significant difference between the two groups). The number of patients reporting reduction in appearance score in the curcumin group was more than that in the triamcinolone group (76% in the curcumin group versus 60% in the triamcinolone group); but the number of patients reporting reduction in severity of pain in the triamcinolone group was more than that in the curcumin group (80% in the triamcinolone group versus 76% in the curcumin group). This difference may be explained as:

Some of the patients complained of burning sensation when applying the curcumin that might have affected the pain and burning sensation during the treatment.

Half the patients who did not report pain reduction by applying curcumin recalled the same problem with triamcinolone paste previously; this might be due to the topical application of drugs, because the same patients did not have any problem with corticosteroid mouthrinse. At the end of the study, we asked the patients in the curcumin group whether they had used corticosteroids in the form of Orabase or mouthrinse, to compare their efficacy with that of curcumin. Twenty patients (80%) preferred triamcinolone in Orabase to curcumin. Seven patients (35%) had only problems with undesirable yellowish color of curcumin particularly on the gingiva or other exposed areas. The remaining 13 patients (65%) had experienced burning sensation when applying curcumin.

CONCLUSION

Corticosteroids as the conventional treatment for OLP may lead to noticeable side effects and development of other conditions like oral candidiasis. Herbal medicines can be suitable alternatives to synthetic drugs. Application of topical curcumin can be suggested for treatment of OLP because of its desirable anti-inflammatory effects and insignificant side effects. Future studies with larger sample sizes and the drug in the form of mouthrinse are recommended.

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