

Evaluation of the Efficacy of Curcumin in the Treatment of Oral Lichen Planus: A Randomized Controlled Trial

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ABSTRACT

Introduction: Oral Lichen Planus (OLP) is a chronic immunological, mucocutaneous disease with a wide range of clinical appearances. The treatment of oral lichen planus is often difficult and disappointing.

Aim: We have studied the efficacy of curcumin, a low molecular weight flavonoid with anti-inflammatory and anti-oxidant activities, in the treatment of OLP.

Materials and Methods: In this study, a randomized, double-blind, placebo-controlled trial was conducted with a total of 20 OLP patients. The patients were randomly divided into two groups, each treated with curcumin tablets at a dose of 2000 mg/day or placebo for a period of four weeks. Furthermore, the patients of both groups received routine treatment for OLP (i.e. Mouthwash Dexamethasone 0.5 mg and suspension

Nystatin 100,000 Units). The baseline data were recorded for each patient. Patients were evaluated on day 14 and after completing the course of treatment. Pain and burning sensation were measured based on the Visual Analogue Scale, and the Thongprasom Index was used for clinical improvement and healing. Mann-Whitney and independent t-test were used to compare the responses between the two groups, p-value < 0.05 was considered statistically significant.

Results: Our analyses demonstrated no significant difference between the curcumin and placebo treated groups.

Conclusion: In conclusion, curcumin had no detectable effect in the treatment of OLP. However, a higher dose of curcumin administration and other forms of curcumin with improved bioavailability may be considered in future studies.

Keywords: Anti-inflammatory, Clinical trial, Erosive

INTRODUCTION

Lichen planus is a T-cell mediated autoimmune disease that affects the skin and the mucus membrane. Oral Lichen Planus (OLP) is the mucosal counterpart of cutaneous lichen planus. It presents frequently in the fourth decade of life with women predilection [1,2]. Reticular, papular, plaque-like, erosive, atrophic or bullous types are the clinical features of OLP. The most involved areas of the mouth are the buccal mucosa, tongue and the gingiva [3].

Although the etiology of OLP is still uncertain, a growing number of evidences indicate that a dysregulation of T-cell mediated immunity, which leads to the attack of activated CD8+ lymphocytes on basal keratinocytes, has an important role in the pathogenesis of OLP [4].

It has been demonstrated that blocking the activity of IL-12, IFN- γ , TNF- α , RANTES, or MMP-9, or up-regulating TGF- β 1 activity may contribute to the pathogenesis of OLP with therapeutic value [5,6].

Although various treatments have aimed to improve the lesions and reduce the associated pain, corticosteroids are the mainstay and most common drug for OLP management which have been widely used. Calcineurin inhibitors, retinoids, dapsone, hydroxychloroquine, mycophenolatemofetil and enoxaparin are also applied for OLP treatment [7].

However, side effects including high blood pressure, adrenal suppression, etc., may occur through corticosteroids therapy, thus trends toward drugs of natural or herbal origin with antioxidant and anti-inflammatory properties, with or without corticosteroids, have been considered for the treatment of OLP [8].

As a natural product, curcumin is nontoxic and has diversified effects in various oral diseases. Curcumin has been identified as a natural phytochemical and active principle in turmeric, the ground

powder of the rhizomes of *Curcuma longa*. Curcumin exhibits antioxidant, anti-inflammatory, antimicrobial, and anticarcinogenic activities [9]. Moreover, curcumin is safe even at very high doses. Curcumin mediates its anti-inflammatory effects through the downregulation of inflammatory transcription factors (such as nuclear factor-kappa B), enzymes (such as cyclooxygenase 2 and 5,lipoxygenase) and cytokines (such as TNF- α , IL-1, IL-6 and IL-8). Furthermore, curcumin produces its antioxidant effect through inhibition of free radicals and nitric oxide [10].

Despite the progress in researches on OLP, the successful treatment is still difficult to obtain. As control and reduction of symptoms is the main purpose for OLP treatment, in the present study we attempted to evaluate the efficacy of curcumin (in addition to topical corticosteroids) administration in treatment of erosive- atrophic OLP and compare the response rate before and after treatment.

MATERIALS AND METHODS

Patients

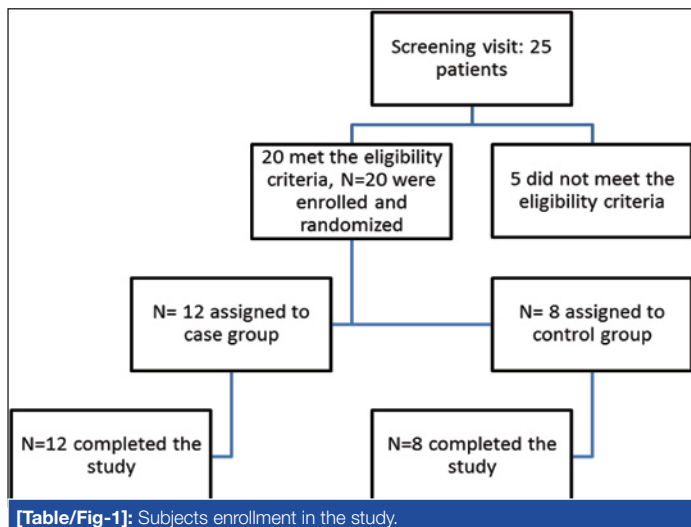
Subjects were recruited from the Department of Oral Medicine, Mashhad Dental School, Iran, between October 2012 to June 2013, with clinical signs of erosive-atrophic OLP which was confirmed by clinical or histopathological examination.

Patients were screened by review of their medical history, medications used, current symptom score (for OLP), and an oral examination.

The exclusion criteria included pregnancy, lactation, current use of anticoagulants or antiplatelet agents [11], current orthodontic treatment, history of gastric ulcers, duodenal ulcers, gallstones [12], hepatic diseases [13], any existing malignancy or viral infection in mouth, receiving any topical treatment for OLP in the

past two weeks or any systemic treatment for OLP in the past four weeks, use of azathioprine, cyclosporine or receiving PUVA, UVA or UVB in the last month, a history of allergy to corticosteroids or curcumin.

A total of 25 patients with symptomatic OLP were screened for this study. Twenty of these patients (7 male, 13 female) who met the eligibility criteria, were enrolled in our study, [Table/Fig-1].



Three subjects for gastric ulcers and duodenal ulcers, one for anticoagulant agent consumption and one for pregnancy were excluded from the study.

The clinical data comprised of age, gender, lesion site, medical background, and symptoms of OLP including severity of burning and pain, for all cases were recorded.

Study Design

This randomized, placebo-controlled, double-blind clinical trial was approved by the Ethics Committee of Mashhad University of Medical Sciences. All the study participants signed the written informed consent and were well informed about the aim and method of this study.

Intervention and Randomization

Patients were randomly divided into two treatment groups (Case Group (n=12) and Control Group (n=8) receiving curcumin or placebo respectively. Randomization was performed using a computer-generated random number table. Study medication tablets with 95% curcuminoids (Samilabs Limited, Bangalore, India) and identical placebo tablets (containing lactose) were prepackaged by a university pharmacist in identical containers. During treatment, both of the practitioners and the patients were unaware of medications they were using.

The first group of patients (n=12) received curcumin tablets, provided as 500 mg tablets, whereas the second group (n=8) received placebo tablets. The patients used four placebo or curcumin tablets two times a day for a period of four weeks.

Furthermore, the patients of both groups received routine treatment for OLP (i.e., Mouthwash Dexamethasone 0.5 mg (Iran-Hormone Co., Iran) three times a day and suspension Nystatin 100,000 Unit (Jaber Ebne Hayyan Co., Iran, three times a day). It should be noted that after topical steroid application an environment for candidiasis development is established. Therefore, antifungal drugs should be prescribed as a prophylactic treatment.

Data Collection

At the baseline and subsequent visits, symptom and sign intensity over the previous week were recorded.

The Visual Analog Scale (VAS) is represented by a horizontal line, with the left end marked as no symptoms and the right end marked

as the worst imaginable symptoms. The length from the left end to the vertical mark, made by the patient to indicate intensity of symptoms, was measured in millimeters using a millimeter ruler [14]. An oral examination was conducted, and the atrophic and erosive changes were quantified based on the severity of the change and the number of sites involved by Thongprasom criteria [Table/Fig-2] [15].

Each of these two assessments was conducted for each patient at three different time points: (i) at baseline (day 0); (ii) at the first visit after 2 weeks (day 14); (iii) at the second visit after 4 weeks (day 28).

Absence of any inconvenience was recorded as complete remission of symptoms (no symptoms). Partial remission, worsening and persistence of the patient's condition were defined as decrease, an increase, or no change, respectively. The Visual Analog Score (VAS) was used to investigate the severity of patient's symptoms.

At each visit, any therapeutic side effect was evaluated and recorded.

STATISTICAL ANALYSIS

Mann-Whitney and independent t-test were used to compare the responses between the two groups and p-value < 0.05 was considered statistically significant.

RESULTS

Twenty patients (Control Group, n=8; Case Group, n=12) with erosive-atrophic lichen planus were evaluated in this study. The buccal mucosa and tongue were the most common sites for OLP lesions followed by gingival and labia mucosa. Demographics and clinical characteristics are provided in [Table/Fig-3]. There were no significant differences between the two groups for the baseline characteristics including age, gender, history of previous treatment, skin involvement, site of lesions and systemic diseases (p-value > 0.05) [Table/Fig-3].

The efficacy of treatment was evaluated according to Severity of pain and burning (VAS score) as well as type and severity of lesion (Thongprasom score).

Score	Clinical signs
0	no lesion, normal mucosa
1	mild white striae, no erythematous area
2	white striae with atrophic area less than 1cm ²
3	white striae with atrophic area more than 1cm ²
4	white striae with ulcerative area less than 1cm ²
5	white striae with ulcerative area more than 1cm ²

[Table/Fig-2]: Thongprasom criteria.

	Placebo n=8	Curcumin n=12
Age (mean±S.D.)	52.75± 9.43	49.42± 11.22
Male	5 (62.5%)	2 (16.7%)
Female	3 (37.3%)	10 (83.3%)
History of previous treatment	5 (62.5%)	4 (33.3%)
Skin involvement	1 (12.5%)	2 (16.7%)
Site of OLP		
Buccal	8 (62%)	10 (47%)
Tongue	4 (31%)	6 (25%)
Gingiva	0	5 (23%)
Lip	1 (7%)	1 (5%)
Systemic disease	4 (50%)	7(58.3%)
Pain and sensation score (mean±S.D.)	4.63±3.20	6.5±2.15
Thangprasom score	3±1.30	3.17±1.03

[Table/Fig-3]: Baseline characteristics of the study participants.

Complete remission of atrophic/erosive lesions (score 0 or 1 using the scale of Thongprasom et al.), was observed in nine cases of 12 case group patients (75%) compared to five cases of eight (62.5%) control group patients [Table/Fig-4]. According to Mann-Whitney test, the observed difference was not statistically significant (p-value=0.77).

The VAS score and the Thongprasom score were reduced in both groups at first and second visits with statistically significant difference (p<0.05); however, no statistically significant difference was observed between the two studied groups. [Table/Fig-5-7(a&b)] demonstrate the detailed data for both groups at each visit compared to the baseline. In addition, no side effects were reported by the patients after the treatment course.

DISCUSSION

Topical and/or systemic corticosteroids are the most common treatments for OLP. Despite the therapeutic effects of corticosteroids, due to their role in modulating inflammation and immune response, they are associated with adverse significant adverse which reduce the efficacy of treatment [7].

Interestingly, recent studies have reported increased oxidative stress and imbalance in the antioxidant defense system in patients with OLP. This in turn leads to disturbed antioxidant defense, lipid

peroxidation and increased oxidative DNA damage in epidermis, as well as oxidative modification of proteins in dermis of OLP patients. Thus, factors capable of inhibiting the defects of this balance may prevent the associated symptoms [16,17].

Curcumin is a low molecular weight and hydrophobic polyphenol extracted from rhizomes of the herb curcuma longa (turmeric). Anti-inflammatory, anti-oxidative and anti-tumour properties are the several reported biological activities of this agent [18].

Curcumin is a strong anti-oxidant agent, comparable to vitamins C and E, which has significant preventive and curative effects in a number of diseases such as cancer, diabetes and atherosclerosis. Curcumin acts as a potent scavenger of various Reactive Oxygen Species (ROS) including superoxide anion radicals and hydroxyl radicals that play a central role in atherosclerosis and cancer diseases.

Curcumin has been shown to mediate anti-inflammatory effects through the inhibition of different macromolecules involved in inflammation including phospholipase, cyclooxygenase 2, lipoxygenase, prostaglandins, interleukins 1 and 2, and tumour necrosis factor [19-21].

Padmanaban et al., suggested that curcumin may have effects on management of infectious diseases through immunomodulation [22].

Rai et al., demonstrated the anti-pre-cancer properties of curcumin in oral leukoplakia, submucous fibrosis and lichen planus. They reported that salivary and serum levels of malonaldehyde (MDA), 8-hydroxydeoxyguanosine (8OHdG), and vitamins C and E were increased after curcumin consumption [23].

Singh V et al., evaluated 10 patients who were confirmed as patients of oral lichen planus. They used the extract of turmeric in the ointment form twice a day for three months. Decrease of VAS

	Clinical response			Total
	Complete remission	Partial remission	Resistance to treatment	
Curcumin group N=12	9 (75%)	1 (8.3%)	2 (16.7%)	12
Placebo group N=8	5(62.5%)	3(37.5%)	0(0%)	8
p-value=0.77, Z=-0.28*				20

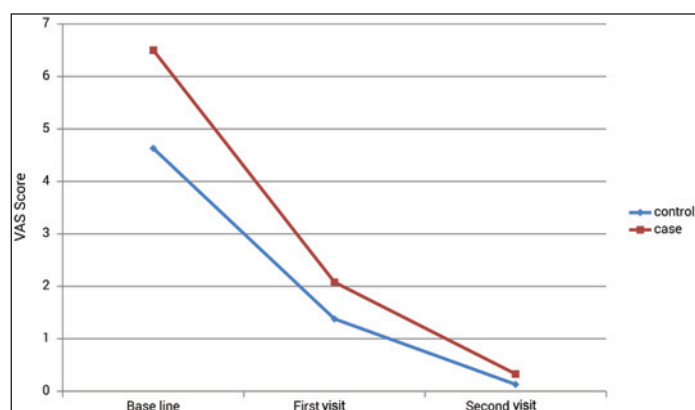
[Table/Fig-4]: Comparison of clinical response between studied groups. * Mann-Whitney test.

	Placebo n=8				Curcumin n=12			
	VAS score		Thangprasom		VAS score		Thangprasom	
	Baseline	First visit	Baseline	First visit	Baseline	First visit	Baseline	First visit
Mean±SD	4.63±3.20	1.38±1.68	3±1.30	2.5±1.41	6.5±2.15	2.08±1.38	3.17±1.03	2.25±1.13
p-value	0.027*		0.002*		0.046*		0.005*	

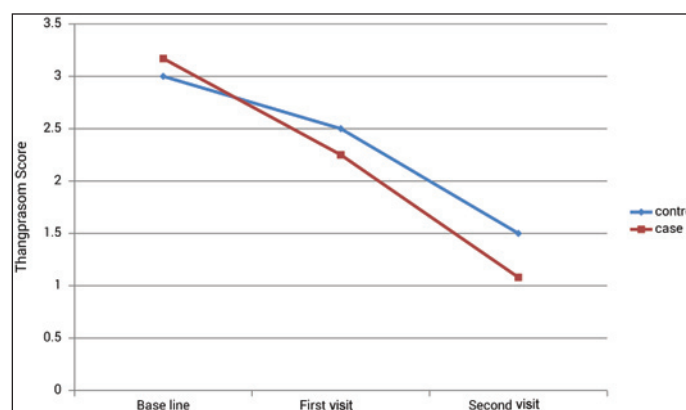
[Table/Fig-5]: Comparison of VAS score and Thongprasom score at baseline and first visits in the studied groups. * Mann-Whitney test.

	Placebo n=8				Curcumin n=12			
	VAS score		Thangprasom		VAS score		Thangprasom	
	Baseline	Second Visit	Baseline	Second Visit	Baseline	Second Visit	Baseline	Second Visit
Mean±SD	4.63±3.20	0.13±0.35	3±1.30	1.5±1.06	6.5±2.15	0.33±0.65	3.17±1.03	1.08±0.66
p-value	0.026*		0.008*		0.002*		0.002*	

[Table/Fig-6]: Comparison of VAS score and Thongprasom score at baseline and second visits in the studied groups. *Mann-Whitney test.



(a)



(b)

[Table/Fig-7]: The VAS score (a) and the Thongprasom score (b) were reduced in both groups upon treatment with statistically significant difference (p<0.05).

in all participants and improvement in clinical symptoms in nine patients were reported after three months [24].

The efficacy of curcumin in the treatment of OLP has been also evaluated in a randomized double-blind clinical trial by Chainani-Wu N et al., in 2007.

In this study, a high dose of curcumin (6000 mg/day in three divided doses) or placebo were administrated to 20 patients for 12 days. Here, the curcumin group exhibited a greater reduction in signs and symptoms as compared with the placebo group. Diarrhea was the most frequently reported side effect [25].

As our study has been conducted with a lower dose of curcumin (2000 mg/day) but for a longer period (four weeks) compared to the study by Chainani-Wu N et al., it appears that curcumin can only be effective at high doses and this could explain the significant difference in the results of the two studies.

Major reasons contributing to poor bioavailability are rapid metabolism and rapid systemic elimination. Curcumin nanoparticles, liposomal curcumin, structural analogues of curcumin, curcumin phospholipid complexes or the combination of curcumin with adjuvants (e.g. Piperine) are some of approaches by which researches attempted to improve the bioavailability of this agent [18].

It is noted that the administration of corticosteroids in the both studied groups, due to ethical issues, might have masked the presumable positive effect of curcumin. Therefore in future studies, the treatment by curcumin may have to be conducted without using corticosteroid in the regimes of the patients.

LIMITATION

Further studies with a larger number of patients, a higher dose of curcumin, and a longer period of treatment can give more valuable information.

CONCLUSION

As significant difference was not observed between groups, curcumin had no detectable effect in the treatment of OLP. However, a higher dose of curcumin administration and other forms of curcumin with improved bioavailability may be considered in future studies.

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