

Evaluation of Efficacy of 1% Curcuminoids as Local Application in Management of Oral Lichen Planus – Interventional Study

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ABSTRACT

Introduction: Oral Lichen Planus (OLP) is a chronic inflammatory mucocutaneous disease affecting the oral cavity which has been associated with severe burning sensation which in turn affects the quality of life of the patients. Currently, the effective treatment of choice remains the use of corticosteroids. The chronicity and recalcitrant nature of the disease demand the long term use of these drugs with ensuing adverse effects. Turmeric and its active ingredient, “curcumin”, have been found to have anti-inflammatory, antioxidant and anticancer properties. Hence, this intervention study was done to evaluate the efficacy of curcumin oral gel in the management of oral lichen planus.

Aim: The study was conducted to compare the efficacy of 1% curcumin gel with the conventional mid-potent topical corticosteroid, triamcinolone acetonide 0.1% in managing the signs and symptoms of OLP.

Materials and Methods: An intervention study was conducted on 75 patients diagnosed with OLP divided into three groups, Group 1 (0.1% triamcinolone acetonide oral paste thrice daily

in tapering doses), Group 2 (curcumin oral gel thrice daily) and Group 3 (curcumin oral gel six times daily). The patients were analysed for the symptom (burning) and sign (erythema and ulceration) using the numerical rating score and Modified Oral Mucositis Index (MOMI) for a period of three months on a bimonthly basis. The results were analysed using Students t-test and unpaired t-test.

Results: Intragroup comparison using paired t-test showed statistically significant reduction in burning sensation ($p < 0.001$) as well as erythema and ulceration ($p < 0.001$) in all the three groups. However, when the three groups were compared Group 1 showed the maximum reduction in burning sensation (77%) and erythema and ulceration (67%). Among the curcuminoid group, increased frequency was found to be more beneficial.

Conclusion: Curcumin oral gel can bring about clinical improvements in OLP patients; however it cannot be used as a mainstay drug. Instead, it can be used as a maintenance drug after the patient is treated with an initial course of corticosteroids. Further studies with larger sample size and increased drug concentrations may be required.

Keywords: Anti-inflammatory, Antineoplastic, Autoimmune, Antioxidant, Corticosteroids, Herbal

INTRODUCTION

Since, the start of mankind plant products have been used as effective medications for the treatment of various illnesses. Documented evidence of use of herbal products for treatment of various diseases dates back to 5000 years when the Sumerians used plants like thyme, caraway as effective medications [1]. Over the years, herbal medications lost the race against the synthetic medications as there was lack of scientific evidence supporting their efficacy and mechanism of action. But, the recent years have witnessed an “herbal renaissance” with increasing number of people returning back to herbal as well as natural products for the treatment of various ailments as the efficacy of these medications have been proved scientifically and they have negligible adverse effects when compared to the synthetic preparations.

OLP is a chronic inflammatory and immune mediated disease that affects the mucous membranes and is manifested as erosive or ulcerative mucosa and desquamative gingivae with interlacing diffuse white striations [2]. The patients usually present with oral pain and soreness that is exacerbated with spicy foods as well as ulceration and bleeding [3]. Extensive research and numerous trials have been conducted to determine the most efficacious and safe treatments for OLP, but currently there exists no definite treatment protocol for the management of OLP [4]. Currently available treatment options mainly aim at alleviation of the symptoms and monitoring for any dysplastic changes [5]. A wide variety of therapeutic modalities have

been used either alone or in combination topically, intralesionally or systemically based on the severity of the lesion. The current accepted mode of treatment is the use of corticosteroids [6]. The chronic and recalcitrant nature of the disease demands the use of these drugs for long durations with subsequent increase in dose. However, the topical drugs result in various side effects which include thinning of the oral mucosa, secondary candidiasis, stomatopyrosis and altered taste sensation while the systemic steroids cause suppression of hypothalamic pituitary axis, diarrhea, fluid retention, osteoporosis, hypertension, diabetes mellitus and increased susceptibility to infection [7]. Therefore, there has been a constant search for an alternative natural or herbal drug with anti-inflammatory properties which could be taken as monotherapy or in combination with the mainstay drugs used in the treatment of lichen planus on a long term basis with minimal side effects. This would help in controlling the disease and prevent recurrence of the lesion.

Research studies both ex vivo and in vivo suggest that curcuminoids, the major constituent of turmeric, has anti-inflammatory, antioxidant and anticancer properties [8]. Curcumin tones down the inflammatory response by depressing the activity of Cyclooxygenase-2 (COX-2), lipoxygenase and inducible Nitric-Oxide Synthase enzymes (iNOS). It also inhibits the production of the inflammatory cytokines- tumor necrosis factor, interleukins 1, 2, 6, 8, 12 and migration inhibitory protein [9,10]. The inhibition of inflammatory cytokines is brought about by suppressing the activity of nuclear factor kappa B which

in turn also causes inhibition of COX-2 and iNOS [11]. A search through literature revealed few studies using curcuminoids in the management of lichen planus and comparing their efficacy with the commonly used corticosteroid gel. Hence, the present study was undertaken to assess the efficacy of 1% curcuminoids in the form of oral gel in the management of OLP.

MATERIALS AND METHODS

Study Design

This prospective interventional study was carried out in the Department of Oral Medicine, Amrita School of Dentistry, Kochi, Kerala, India, from December 2013 to August 2015. Ethical clearance was obtained from the Institutional Ethical Committee and informed consent was taken from all the participants of the study.

Study Population

The subjects consisted of 75 patients who were diagnosed clinically as well as histopathologically with erosive OLP. The inclusion and exclusion criteria have been listed in [Table/Fig-1].

All the patients meeting the eligibility criteria were interviewed and examined in the dental clinic and their data was recorded in a standard case sheet proforma. The selected 75 patients were allocated into three groups of 25 subjects each by simple randomization. Members of Group 1 were asked to apply 0.1% triamcinolone acetonide thrice daily over the lesion and the lesions were assessed in every two weeks and the dose was tapered accordingly. Members of Group 2 and Group 3 were asked to apply the Curenex Oral Gel three times and six times daily respectively over the lesions.

Drugs Used

Control drug– Tess Buccal Paste (Troika Pharmaceuticals) each gram of which contains 0.1% triamcinolone acetonide.

Test medication– Curenex Oral Gel (Piramel, Health Care, India) each gram of which contains curcuma longa extracts 10 mg, Colours – brilliant blue FCF, erythrosine and titanium dioxide.

The burning sensation in the mouth was recorded by using Numerical Rating Scale (NRS) by asking the patients to assign a

Inclusion Criteria	Exclusion Criteria
Clinically and histopathologically confirmed Oral lichen Planus without dysplasia in histopathologic evaluation and willing to take part in the study. Clinical diagnosis was based on the presence of interlacing white striations with intermixed erythematous or ulcerative areas. Histopathologic diagnosis was based on presence of hydropic degeneration of basal cell layer, dense subepithelial inflammatory infiltrate.	Evidence of lichenoid reaction in clinical or histopathological assessment
	Patients having extra oral manifestations of oral lichen planus
	Patients on long term glucocorticosteroid therapy for other systemic diseases
Patients with symptomatic oral lichen planus i.e., burning sensation and who had not under gone any previous treatment for the same in the last six months	Patients with other white lesions like leukoplakia, SLE along with oral lichen planus.
	Pregnancy, lactation
	History of allergic reactions to corticosteroids or herbal preparations

[Table/Fig-1]: Patient selection criteria.

Score for erythema		Score for erythema	
Intensity	Interpretation	Intensity	Interpretation
0	Normal	0	No ulcerations
1	Mild erythema	1	Between 0-0.25 cm ²
2	Moderate erythema	2	Between 0.25-1 cm ²
3	Severe erythema	3	1.0 cm ² or greater

[Table/Fig-2]: Modified oral mucositis index – scoring criteria [12].

numerical score representing the intensity of their burning sensation on the scale from 0 to 10, with 0 being no burning sensation and 10 being worst imaginable burning sensation [12]. Similarly, clinical signs of OLP were measured using a semi quantitative scale i.e., MOMI [Table/Fig-2] developed by Schubert MM et al., [13]. Sixteen different oral sites were examined and scores for erythema as well as ulcerations were recorded separately. The total score for clinical signs was obtained by summing the scores for these 16 sites. The score at the initial visit was taken as the baseline value.

In each group, the patients were recalled every two weeks for a period of three months. On each follow up visit, the NRS Score as well as the MOMI score were recorded. Patients were enquired about any adverse drug reactions during the study period.

STATISTICAL ANALYSIS

All the collected data were subjected to statistical analysis using SPSS software. The demographic data including age, sex, systemic illnesses and medications were recorded and represented in pie charts. The baseline NRS Score and MOMI score as well as post treatment NRS Score and MOMI Score between the groups were compared using independent t-test. The pre and post treatment NRS Scores and MOMI Index within the groups were compared using paired t-test.

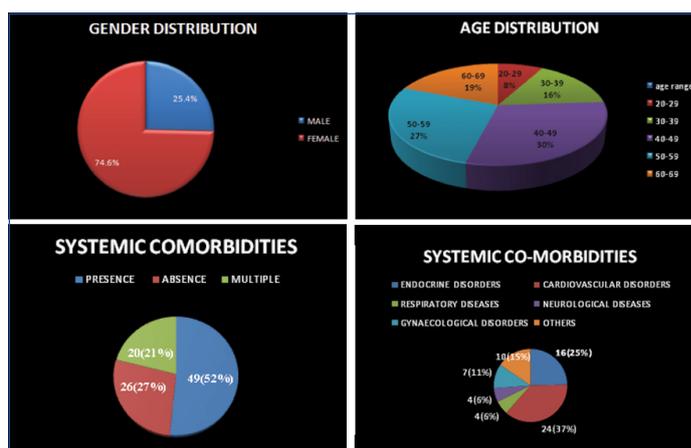
RESULTS

The selected patients were in the age range 20 to 70 years and the demographic data has been discussed in [Table/Fig-3].

The baseline NRS Score and MOMI score between the groups and the post treatment results were compared using independent t-test and showed no significant difference (p-value > 0.05). [Table/Fig-4,5].

The pre and post-treatment NRS Scores and MOMI Index within the groups were compared using paired t-test [Table/Fig-6].

In Group, 1 there was a 77.3% reduction in the burning sensation and 67.8% reduction in the erythema and ulceration score following application of the drug after three months. Group, 2 showed 54.4% reduction in the burning sensation and 46.6% reduction in the erythema and ulceration score following application of the drug for



[Table/Fig-3]: Demographic data.

Group	N	Mean±SD (NRS score)	p-value	Mean±SD (MOMI score)	p-value
Group-1	25	5.68±0.748	0.556	11.52±1.636	0.595
Group-2	25	5.52±1.122		11.08±3.774	
Group-1	25	5.68±0.748	0.184	11.52±1.636	0.418
Group-3	25	5.32±1.108		11.04±2.441	
Group-2	25	5.52±1.122	0.529	11.08±3.774	0.965
Group-3	25	5.32±1.108		11.04±2.441	

[Table/Fig-4]: Pre-treatment comparison for NRS score and MOMI Index between the three groups.

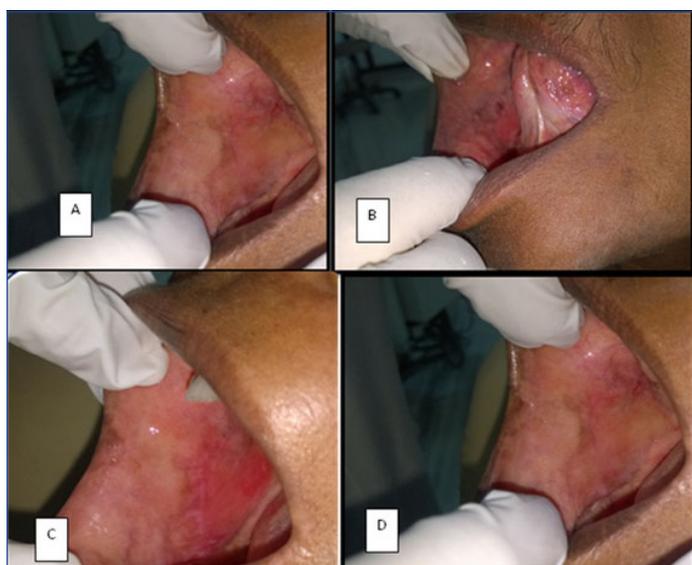
Baseline comparison made by independent t-test
p>0.05 not significant

Group	N	Mean±SD (NRS score)	p-value	Mean±SD (MOMI score)	p-value
Group 1	25	1.36±1.114	<0.001	3.72±2.227	<0.006
Group 2	19	2.47±0.841		5.95±2.887	
Group 1	25	1.36±1.114	0.053	3.72±2.227	<0.082
Group 3	25	1.96±1.020		4.80±2.062	
Group 2	19	2.47±0.841	<0.001	5.95±2.887	<0.001
Group 3	25	1.96±1.020		4.80±2.062	

[Table/Fig-5]: Post-treatment comparison for NRS score and MOMI Index between the groups. • Independent t-test • p-value<0.05

Group	Mean±SD (NRS score)		% change	p-value	Mean±SD (MOMI score)		% change	p-value
	Baseline	After three months			Baseline	After three months		
Group-1	5.68±0.78	1.36±1.11	77.39	<0.001	11.52±1.63	3.72±2.22	67.8	<0.001
Group-2	5.26±1.098	2.47±0.841	54.4	0.184	10.63±3.67	5.95±2.877	46.6	<0.001
Group-3	5.32±1.108	1.96±1.02	64.99	0.529	11.04±2.44	4.80±2.06	58.36	<0.001

[Table/Fig-6]: Pre and Post-treatment comparison for NRS score and MOMI Index within the three groups. Comparison using paired t-test p-value <0.05



[Table/Fig-7]: Clinical photographs: a) pre treatment photograph of patient in Group 2; b) post-treatment photograph of patient in Group 2; c) pre-treatment photograph of patient in Group 3; d) post-treatment photograph of patient in Group 3.

three months. In Group 3, there was a 64.99% reduction in the burning sensation and erythema and ulceration score by 58.36% following application of the drug for three months. Though, there was a significant reduction in both NRS score and MOMI score in each group ($p < 0.001$), Group 1 showed the maximum reduction in NRS score (burning sensation) and MOMI Index (erythema and ulceration score) after three months of application. Among Group 2 and Group 3, Group 3 patients (Cure next oral gel six times daily) showed a greater reduction in NRS score and MOMI index when compared to Group 2 (Cure next oral gel thrice daily) [Table/Fig-7]. Six patients in Group 2 did not complete the study as there was no reduction in signs and symptoms and they were given a more potent drug whereas, in Group 1 and 3 all the 25 patients completed the study.

DISCUSSION

OLP is a relatively common chronic inflammatory mucocutaneous disease that occurs in about 0.5% to 2.2% of the adult population and has been managed mainly with systemic or topical corticosteroids [14].

Curcumin, the principal curcuminoid in turmeric is known to possess anti-inflammatory, antioxidant, chemopreventive and chemotherapeutic properties. The present study compared the efficacy of topical 1% curcuminoids gel and 0.1% triamcinolone acetonide in the management of OLP. It was found that even though

1% curcuminoids was effective in reducing the signs and symptoms of OLP and its efficacy increased with frequency of application, but it was not as effective as 0.1% as triamcinolone acetonide. Hence as per our study it cannot be used as a substitute for corticosteroids but can be used only as a maintenance drug. Further studies with increased dosages or concentrations may be needed to see whether it can completely substitute corticosteroid therapy.

Topical application of curcumin gel was well tolerated without

any toxic manifestations or worsening of the disease, making it a potential therapeutic agent. This finding is consistent with the study conducted by Singh V et al., and Chainani-Wu N who also reported the efficacy of curcumin in management of OLP without any evident side effects [15,16].

The mean age of the study population was 47.7 years which conforms to the inference obtained by the study done by Chitturi RT et al., wherein a group of 58 OLP patients of Indian origin had a mean age of 45.7 years [17]. Studies in various parts of the world show a difference in the mean age of occurrence and this difference could be attributed to ethnicity and geographic locations. The increased prevalence of OLP in older subjects could be due to higher stress level. Also, as age advances, patients become more medically compromised and take multiple drugs which could also have contributed to lichenoid reactions.

In the present evaluation among the 75 patients, 19 (25%) were males while 56 (75%) were females which points to a female predilection for OLP. These results are in conjunction with the results obtained by Kumar T et al., (64%), Omal PM et al., (63%) and Silvermann S et al., (68%) as they too suggest a female predilection for the disease [18-20]. This could be due to the influence of hormones like oestrogen.

Burning sensation while eating spicy food or even normal food is one of the common complaint reported by patients with OLP. Although, the exact mechanism causing burning sensation is not clear, intolerance to spices could be due to the atrophic and permeable epithelium [21]. In Group 1, there was 77% reduction in the mean NRS score and a 67% reduction in MOMI score after three months of regular application. Thus, the above mentioned data suggest that topical application of 0.1% triamcinolone acetonide in tapering doses was highly effective in reducing the burning sensation as well as the clinical signs of the disease.

The mean NRS scores for burning sensation for Group 2 showed a reduction of 54% and the mean score for erythema or ulceration, MOMI Index showed a reduction of 46% after application of the drug for a period of three months. The mean NRS score for burning sensation in Group 3 showed a reduction by 64% and the MOMI Index showed a reduction of approximately 58% from the baseline value.

The findings of our study coincide with the findings of Singh V et al., who evaluated 15 OLP patients treated with turmeric which was made in the ointment form and was used for local application on the lesion for a period of three months [15]. However, all the patients obtained complete resolution of the lesion as against our study in which only 45-67 % of the lesions were reduced on application of the drug. This could be attributed to the difference in concentration

of the curcumin as the curcumin used in their study was a crude extract which was mixed with glycerin in the ratio of 75:25. The drug used in our study had only 1% of curcumin suggesting that increased concentration causes more reduction in signs and symptoms. Since curcumin poses negligible adverse effects, increasing the concentration would not result in any detrimental effects in the patient.

In the study conducted by Chainani–Wu N et al., high dose curcuminoids (6000 mg/day in divided doses) was given systemically in 20 patients with OLP resulted in greater decrease in the signs and symptoms of OLP when compared to our study. But, in their study they had followed up the patient only for a period of two weeks and in the two weeks a reduction of approximately 22% was obtained. The concentration of the drug used was much higher (6000 mg/day) as preliminary studies done by the same author revealed that higher concentration of the drug was required for its beneficial action [22].

The reduction of the burning sensation and the clinical signs of OLP (erythema and ulceration) reflected by the MOMI Index and NRS score in our study could be attributed to the anti-inflammatory property of curcumin. Though, the exact aetiopathogenesis of OLP cannot be pointed out, it is said to be a chronic inflammatory disease with the immune system having a primary role in the development of the disease, as there is a dense subepithelial inflammatory infiltrate which is dominated by T-lymphocytes [23]. According to Rao CV et al., curcumin is a dual inhibitor of arachidonic acid metabolism, as it inhibits both cyclooxygenase and lipoxygenase pathways of inflammation, thus, inhibiting the products of inflammation such as prostaglandins and leukotrienes thereby, minimizing the signs and symptoms of inflammation [24].

Yadav VS et al., has demonstrated the immunomodulatory effect of curcumin which involves the activation of the host macrophages and natural killer cells and modulation of lymphocytes mediated function. This effect of OLP would be beneficial as the pathogenesis of OLP is by T-lymphocyte mediated cytotoxicity and any immunomodulatory effect would be beneficial in reducing the severity of the disease [25].

Curcumin also holds a promising future in the treatment of OSMF. Hastak K et al., had done preliminary studies and concluded that turmeric to be effective in the amelioration of clinical signs and symptoms in patients with OSMF [26]. Das BA et al., reported that curcumin has a fibrinolytic action in OSMF and concluded that there was a statistically significant and equal reduction of palpable fibrotic bands in patients with OSMF [27]. Joshi J et al., reported symptomatic relief and clinical improvement in the opening of jaw with turmeric extract and turmeric oil in 30 cases of OSMF in a pilot study [28].

In a study done by Abdolsamadi H et al., in 36 patients diagnosed with OLP and 36 healthy controls, it was proved that OLP patients had decreased total salivary antioxidant level which results in increased presence of reactive oxygen species in the saliva which could contribute to oxidative stress. This produces damaging effect on the cell membrane and may be implicated in the pathogenesis of OLP [29]. Priyadarshini KI et al., has demonstrated the scavenging effect of curcumin on superoxide radicals, hydroxyl radicals and lipid peroxidation which would help in the reduction of damage caused by oxidative stress [30]. Thus, the effects brought about by the treatment regimen using curcumin oral gel could be a synergism of their anti-inflammatory and antioxidant properties.

OLP is considered to be a premalignant disorder, though, the incidence is not more than 0.2% per year. The chemopreventive action of curcumin would be beneficial in such circumstances as curcumin enhances the activities of detoxifying enzymes like glutathione transferases and NADPH and cytochrome p450, thereby, modulating its chemopreventive action [31].

In the present study, the comparison of mean post-treatment score for burning sensation as well as symptom score (MOMI) amongst

Group 1 and Group 2 revealed that Group 1 had an increased and faster rate of improvement of signs and symptoms when compared with Group 2. However, the comparison of mean post-treatment score for burning sensation as well as symptom score (MOMI) amongst Group 1 and Group 3 revealed that the rate of reduction of signs and symptoms amongst the two groups was almost comparable. So, the application of curcumin oral gel six times daily was almost as effective as application of triamcinolone acetonide. The application of a drug six times a day poses a compliance issue as patients would find it difficult to comply with the therapy.

The results obtained from the study has opened newer vistas for further research as there is evidence stating that OLP can be treated with natural preparations like curcumin. Further studies should aim at determining effective concentrations in reduced frequencies. Studies with patients of different variants of OLP in each group must also be conducted. Since, curcumin produces minimal side effects, an extended release preparation in the form of a muco-adhesive patch can also be developed so that its therapeutic effect can be extended. This may even eliminate the need of an initial course of corticosteroid.

CONCLUSION

Based on the results obtained, it would be difficult to suggest curcumin as a primary modality of treatment in the place of corticosteroids. Since, curcumin showed reduction in sign and symptoms along with relief from burning sensation, this choice of therapy is beneficial, affordable and noninvasive to those affected with OLP, probably after an initial short course of topical or systemic steroids. Also, long term steroid application as a part of maintenance regime would result in side effects which can be minimized by keeping the patient on natural products like curcumin oral gel. Future trials must be conducted for longer durations and evaluation of recurrences must be also incorporated in the aims of the study.

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