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Lycopene in the management of oral lichen planus: A placebo-controlled study

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Abstract

Context: Oxidative stress has been implicated in the pathogenesis of lichen planus, and a lower level of lycopene has been reported in erosive and atrophic oral lichen planus (OLP) patients. However, its efficacy in the management of OLP has not been reported.
Aim: This study was designed to assess the efficacy of systemic lycopene in the management of OLP.
Settings and Design: This prospective, randomized, double-blind, placebo-controlled study was done in the Oral Medicine Department of a postgraduate teaching dental hospital in India.
Materials and Methods: Thirty symptomatic OLP patients, randomly divided into two groups of 15 each, were administered lycopene 8 mg/day and an identical placebo, respectively, for 8 consecutive weeks. Burning sensation using visual analogue scale and overall treatment response using Tel Aviv-San Francisco scale were recorded at every visit. The data obtained were analyzed statistically using Wilcoxon Rank test, Mann-Whitney and Fischer's Exact test.

Results: A higher (84%) reduction in burning sensation was seen in lycopene than in the placebo group (67%). All 15 (100%) patients in the lycopene group showed 50% or more benefit and 11 (73.3%) patients showed 70-100% benefit, while this number was only 10 and 4 (26.7%), respectively, in the placebo group.
Conclusion: Lycopene was very effective in the management of OLP, and oxidative stress may have a role in disease pathogenesis.

Keywords: Antioxidant, free radicals, lycopene, oral lichen planus, oxidative stress

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Lichen planus (LP) is a chronic inflammatory mucocutaneous disease of unknown etiology that occurs in about 0.2-4% of the adult population, affecting the skin and/or oral mucosa. [1] Clinically, oral lichen planus (OLP) presents in various forms such as reticular, papular, plaque like, atrophic, erosive and bullous, [2] of which erosive and atrophic forms are usually symptomatic and need therapeutic interventions. [1] The etiology is not known, but there are several hypotheses involving genetic, infectious, psychogenic and autoimmune factors. The pathogenesis has been extensively studied and the disease appears to be a result of a cell-mediated immune reaction in which Langerhans cells, keratinocytes and activated T lymphocytes are involved. [3]

Currently, there is no definite cure for this disease entity, and the large number of therapeutic agents studied reflects the inadequacy of any one agent to control the symptoms in all the patients. Further, most of the therapeutic agents studied have their own associated adverse effects, which need to be monitored, thus making the choice of treatment modality in majority of cases a difficult decision. [2],[4]

The role and importance of oxidative stress has been suggested in the pathogenesis of LP. A study done on erosive vulval LP tissues showed increased oxidative stress and decreased antioxidant enzyme expression. [5] Bernanan *et al.*, found increased expression of inducible nitric oxide synthase in 9 out of 30 OLP cases studied. [6] Vahlaquist *et al.*, reported lower levels of serum carotenoids in LP patients, [7] and Nagao *et al.*, reported a significantly lower level of serum lycopene in the erosive and atrophic OLP cases. [8] Despite these evidences, there are no published reports on the use of antioxidants in the management of OLP, except for the use of vitamin A and its analogues. [1],[2],[3],[4]

Lycopene is a red-colored, fat-soluble carotenoid, which gives tomatoes and several other fruits their deep red color. [9],[10] Lycopene does not have the pro-vitamin A activity [11] and its various

benefits on human health can be explained based on its properties of antioxidant activity, inhibition of cancer cell proliferation, interference with growth factor stimulation, inducing phase II enzymes, regulation of transcription and restoration of gap junctions. [9] Lycopene exerts its antioxidant activity by physical and chemical quenching of free radicals and is the most efficient singlet oxygen quenching carotenoid. [9],[10]

Though there are several studies assessing the role of lycopene in general health, very few studies have assessed its role in prevention and treatment of oral diseases. [9],[10],[11],[12] It has shown to be effective in the management of oral leukoplakia and to play a role in the chemoprevention of oral cancer. [13],[14] Its role in the management or prevention of OLP has not been investigated. However, as significantly decreased levels of lycopene have been reported in patients with atrophic and erosive OLP, [8] its role in the disease pathology needed further investigation. Further, by virtue of its antioxidant and anticancer properties, [9] it may be useful in the prevention of malignant transformation in the OLP.

In view of these data which highlight the potential usefulness of lycopene in OLP and also in recognition of the need for a specific therapeutic regimen for OLP, this study was conducted to assess the response of treatment with lycopene in OLP.

Materials and Methods

The present prospective, randomized, placebo-controlled, double-blind study was conducted in the Department of Oral Medicine and Radiology, College of Dental Sciences, Davangere, India. Thirty systemically healthy persons of either sex with clinically and histopathologically diagnosed and symptomatic OLP were included in the study. Patients who were on any treatment for the OLP were asked to stop the same 2 weeks prior to the administration of study medications.

Ethical and legal approvals were obtained from the Legal and Ethical Committee of the institute, headed by the Dean of the institute.

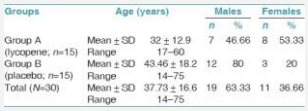
Patients were randomly allocated into two groups, group A and group B of 15 each, and were administered softgel capsule lycopene 8 mg/day (Lycored® 2 mg, Jagsonpal Pharmaceuticals, New Delhi, India) in two divided doses and an identical placebo, respectively, for eight consecutive weeks. Burning sensation using Visual Analogue Scale (VAS) of score 0-100, and the overall treatment response were recorded at baseline, at 2 weeks intervals and 30 and 60 days after completion of the therapy. The overall treatment response was recorded using Tel Aviv-San Francisco scale as follows: *Score 4* ⇒90-100% remission of sign and symptoms; *Score 3* ⇒70-80% benefit, treatment not required; *Score 2* ⇒50% benefit; *Score 1* ⇒ 30-50% improvement, treatment still needed; *Score 0* ⇒ little improvement or no change; *Score -1* ⇒ deterioration or regression. [1]

The data so obtained were analyzed statistically. The comparative analysis was carried out by using Wilcoxon Rank Test for intra-group comparison and Mann-Whitney Test and Fischer's

Exact Test for inter-group analysis.

Results

The study group comprised 19 males and 11 females, showing slight male predilection with a male to female ratio of 1.72:1. The mean age of the patients enrolled in the study was 37.73 ± 16.6 years, with an age range of 14-75 years [Table 1].



Groups		Age (years)	Males		Females	
			n	%	*n*	%
Group A (lycopene; *n*=15)	Mean ± SD	32 ± 12.9	7	46.66	8	53.33
	Range	17–60				
Group B (placebo; *n*=15)	Mean ± SD	43.46 ± 18.2	12	80	3	20
	Range	14–75				
Total (*N*=30)	Mean ± SD	37.73 ± 16.6	19	63.33	11	36.66
	Range	14–75				

Table 1: Age and sex distribution of patients

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The statistical analysis of the pre-treatment data revealed no statistically significant differences between both the groups at the start of the study.

The mean score for the burning sensation in group A (lycopene) reduced significantly by 84% (P=0.001) after the treatment, with 47.0 ± 20.4 at baseline to 7.6 ± 9.2 at the end of 8 th week. The post-treatment follow-up at 1 st and 2 nd months did not reveal any significant change in the severity of symptoms [Table 2].

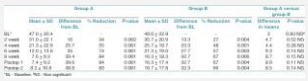

Table 2: Comparison of burning sensation before and after treatment (VAS scores)

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In group B (placebo) too, the mean score for the burning sensation reduced significantly by 67% (P=0.006) after the treatment, i.e. from 49.0 ± 22.9 at baseline to 16.3 ± 18.3 at the end of 8 th week. However, one patient showed deterioration with increase in VAS score of 30 at baseline to 70 at the end of 8 th week, and another patient did not show any improvement. The post-treatment follow-up at 1 st and 2 nd months did not reveal any significant change in the severity of symptoms [Table 2].

Thus, though there was significant reduction in the mean scores of burning sensation in both the groups after the treatment, this reduction was more in lycopene group (84%) as compared to the placebo group (67%) [Table 2].

As per Tel Aviv-San Francisco scale, at the end of the treatment, all the patients in group A showed 50% or more benefit, with 11 (73.3%) patients showing 70-100% relief in signs and symptoms and did not require further treatment [Table 3].

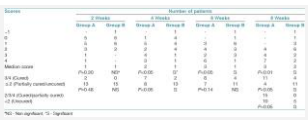

Table 3: Comparison of overall treatment response as per the Tel Aviv-San Francisco scale

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In the placebo group, though 10 (66.7%) patients showed 50% or more benefit, only 4 (26.7%) patients showed 70-100% relief in signs and symptoms and did not require further treatment. Two patients showed little or no improvement, with one of them showing deterioration of signs and symptoms [Table 3].

If stages 3 and 4 are taken together as cured and stage 2 or lesser as partially cured/uncured, then at the end of the treatment, 11 (73.3%) patients in group A were cured and 4 (26.7%) remained partially cured or uncured, while in group B, 4 (26.7%) and 11 (73.3%) patients fell in these categories, respectively, showing a statistically significant (P=0.02) difference [Table 3].

Upon further modifying the criteria and taking stages 2, 3 and 4 together as partially/completely cured and 1, 0 and −1 as uncured, all the 15 patients in group A were partially/completely cured in comparison to only 10 in group B [Table 3]. This difference in the treatment response too was statistically significant (P<0.05).

Thus, with respect to overall treatment response, patients in lycopene group showed significantly better (P<0.01) results than patients in placebo group.

Discussion

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LP is a chronic inflammatory mucocutaneous disease that occurs in about 0.2-4% of the general population, affecting skin and/or mucosa. [1]

Although the exact etiology of the disease is unknown, the role of free radicals and oxidative stress has been implicated in its pathogenesis. [6],[15],[16] Further, an affirmative treatment remains elusive and a vast array of empirical treatments reported in the literature indicates the continuing search for the solution. [2],[3],[4]

The role of lycopene, a potent antioxidant being used in the management of various systemic and few oral diseases including cancer and precancerous lesions, suggested to be caused by the oxidative stress, [9],[10],[11],[12],[13] has not been assessed in the prevention or treatment of OLP. However, one study has reported significantly decreased levels of lycopene in patients with atrophic and erosive OLP, [8] and its role in the disease pathology needs further investigation.

In our study, we treated 15 OLP patients with lycopene 8 mg/day and another 15 with an identical placebo.

The doses of lycopene used for the various conditions reported in the literature vary in the range of 6-60 mg/day. [9],[10],[11],[12],[13]

A dose regimen of 8 mg/day was found effective for the management of oral leukoplakia. [13] LP

is a chronic condition and various studies have reported longer duration of treatment, ranging from 2 to 32 weeks, and most of the studies, using retinoids, have used the medications for 8 weeks. [1],[2],[3],[4] Therefore, we decided to use 8 mg/day of lycopene for a period of 8 weeks.

Relief from the symptoms or burning sensation is an important goal in the management of OLP. In our study, patients in both lycopene and placebo groups showed a significant reduction in the burning sensation at the end of the treatment (84% and 67%, respectively). However, this reduction in burning sensation was higher in lycopene group than in the placebo group.

The better relief seen in the medicine group can be attributed to the effects of the drug, while the relief seen in the placebo group can be related to the spontaneous remission of the disease, which occurs infrequently in OLP as a natural course of disease process, [17] or to the positive psychological effect of undergoing treatment and continuous reassurance by the treating clinicians.

The overall treatment response measured by the Tel Aviv-San Francisco scale evaluating both signs and symptoms was significantly better in lycopene group than in placebo group (P=0.01). At the end of the treatment, all the patients showed 50% or more benefit (total or partial cure), with 11 (73.3%) patients showing 70-100% relief (total cure) and did not require further treatment. In contrast, in the placebo group, only 10 patients showed 50% or more benefit and only 4 patients showed 70-100% relief. In one patient, no improvement was seen, while one patient deteriorated. Even patients with severe erosive cases showed a good response from lycopene therapy [Figure 1] and [Figure 2].

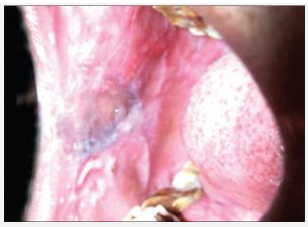

Figure 1: Case of erosive lichen planus before therapy

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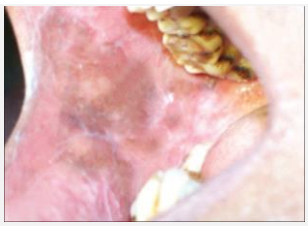

Figure 2: Postoperative photograph of same case after treatment with lycopene for 8 weeks

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Thus, our study indicates that lycopene was effective in controlling the signs and symptoms in the OLP patients.

Since no other study has assessed the role of lycopene in the management of LP, the results of our study could not be compared directly with the results of any other study. However, various retinoids with pro-vitamin A activity, which are shown to have antioxidant properties, have been used in the management of OLP. [1],[2],[3],[4]

Gorskey *et al.*, [1] and Hersle *et al.*, [17] in their study using systemic etretinate, obtained results similar to our study, with more than 50% and 92% patients, respectively, showing improvement in signs and symptoms of the disease. However, Fergueson *et al.*, [18] using the same medication, and Camiesa *et al.*, [19] using systemic isotretinoin, found the beneficial effects to be minimal.

Patients in all these studies showed severe adverse effects, [1],[17],[18],[19] which has proved to be a major disadvantage and limiting factor of the retinoid therapy. In contrast, lycopene is a safe drug with no reported adverse effects, [20] and none of the patients in our study showed any adverse effects. Thus, it can be a better alternative than other retinoids in the management of OLP.

Further, most of these studies reported recurrences, in most of the cases, within 2-3 months of the completion of the treatment. [1],[2],[3],[4],[17],[18],[19] Though none of the patients showed any recurrence of lesions in our study, the follow-up period was short and further studies with longer follow-up periods are warranted.

Corticosteroids are the mainstay in the treatment of OLP. [2],[3],[4] However, here too, the associated adverse effects are a limiting factor. Therefore, the safety of lycopene can be an advantage over corticosteroids for the management of OLP.

The results obtained from 8 mg/day systemic lycopene in the management of oral leukoplakia were similar to our study, with 80% of the patients showing resolution of signs and symptoms. [13] The results of this study and our study suggest that lycopene can be beneficial in the management of various oral premalignant lesions and conditions.

The beneficial effect shown by lycopene in our study can be attributed to its ability to scavenge free radicals, [9],[10],[11],[12] and various studies have shown an evidence for the role of oxidative stress in the pathogenesis of LP. [6],[15] Also, lycopene deficiency has been reported in the patients with erosive or atrophic OLP, [8] and lycopene supplementation may have shown positive results, suggesting a role of decreased lycopene levels in the disease pathogenesis.

Further, the drug used in the study, "Lycored", also contained Vitamin A, α-tocopherol, zinc and selenium, which are known to have antioxidant properties, and might have added synergistically to the positive effects of lycopene.

The marginal benefit shown by the patients in placebo group can be attributed to the spontaneous remission of the disease or the psychological effects, as discussed above.

To conclude, the results obtained from our study are encouraging; the use of lycopene has shown favorable results in OLP patients. The therapeutic effect of a potent antioxidant like lycopene also indirectly substantiates the hypothesis of the role of oxidative stress in the pathogenesis of LP. Therefore, our results justify the need for the addition of this therapeutic regimen (lycopene) to the armamentarium for the management of OLP.

However, since the sample size in our study was small, further studies are recommended on a larger sample size with a longer follow-up period, possibly along with the evaluation of

oxidative stress markers and antioxidant enzyme level assessments at pre- and post-treatment stages to further elucidate the role of antioxidants in the management of this disease and the role of oxidative stress in its pathogenesis.

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Figures

[Figure 1], [Figure 2]

Tables

[Table 1], [Table 2], [Table 3]