Clinical assessment of the effects of lycopene in the management of oral lichen planus

Ramayan Prasad Kushwaha¹, Gajendra Prasad Rauniar¹, Jyotsna Rimal²

¹Department of Clinical Pharmacology and Therapeutics, B. P. Koirala Institute of Health Sciences, Dharan, Nepal; ²Department of Oral Medicine and Radiology, CODS, B.P. Koirala Institute of Health Sciences, Dharan, Nepal

Abstract

Background: Oral lichen planus (OLP) is a common subacute, chronic inflammatory mucocutaneous disease of the oral mucosa with unknown etiopathogenesis. Currently, the antioxidants such as retinoids, β-carotenoids, Aloe vera, purslane, turmeric, and lycopene are being successfully used in the treatment of OLP lesions, suggesting the role of oxidative stress in the pathogenesis of OLP.

Aims: The aim of this study was to assess the clinical effects of lycopene in the management of OLP lesions.

Materials and Methods: After obtaining written informed consent, 13 patients with symptomatic OLP and proven by biopsy were received capsule lycopene 4 mg/day for 8 consecutive weeks. The assessment was done at 0, 2, 4, 6, and 8 weeks of the interval using Thongprasom clinical sign scores to record the improvement in the clinical sign and symptoms of OLP lesions. Complete remission of the disease was defined as a complete absence of symptom and clinical sign scores of OLP lesions.

Results: Among 13 patients, seven patients were male. The age ranged from 27 to 74 years. At baseline, the mean Thongprasom clinical sign score was 2.77 ± 1.74 that became 0.85 ± 0.37 (69%) after 8 weeks of treatment with lycopene, which was statistically significant (P = 0.005). Complete remission of the lesions was seen in two patients, and partial remission was seen in 11 patients after 8 consecutive weeks of treatment with lycopene.

Conclusion: The result of this study was encouraging. In contrast to other management modalities for OLP, lycopene offers a safe, efficacious, and reliable treatment that yields a significant improvement in the signs and symptoms of the patients, which may be due to its antioxidant and anti-inflammatory activity. Therefore, lycopene can be recommended as a good treatment option in the prevention and management of OPL lesions.

Clinical Significance: Finding from this study may help the dentist and clinician to choose lycopene as an alternative drug with less reported adverse effect for the effective management and prevention of OLP lesions.

Introduction

Oral lichen planus (OLP) is a chronic inflammatory mucocutaneous disorder of the oral mucosa. It is characterized by hyperkeratotic white or gray thread-like papules in linear, annular, or reticiform arrangement forming typical reticular patches over the oral mucosa. The prevalence of OLP in the general population ranges from 0.5% to 2.2%.[1,2] The disease presentation is usually observed between 30 and 60 years and is more common in female than male.[3] Clinically, mucosal lesions of OLP are usually multiple and almost always have a bilateral, symmetrical distribution. It commonly affects the buccal mucosa, tongue and gingiva. Atrophic and erosive forms of OLP lesions may cause intense pain and may interfere with speaking, eating, and swallowing. Thus, the symptomatic OLP requires treatment to reduce pain and burning sensation.

The etiopathogenesis of OLP is still unknown, but it is reported that several antigen-specific and non-specific inflammatory mechanisms are involved, in which the functions of the Langerhans cells, keratinocytes, and T lymphocytes are

Key words:
Antioxidant, lycopene, oral lichen planus, reactive oxygen species, treatment, β-carotenoid
altered. These activated cells release different kinds of cytokines such as interleukin (IL-2, IL-10, and IL-6), interferon gamma, and tumor necrosis factor, promoting chronic inflammation and apoptosis of the oral epithelial cells. These inflammatory cells and keratinocytes generate various amounts of free radicals and reactive oxygen species, which increase lipid peroxidation, proteins, and nucleic acid oxidation in the surrounding cells. Increased oxidative stress and reduced antioxidant defense system may contribute to damage the extracellular matrix proteins and may inhibit collagen and proteoglycan synthesis. Currently, the use of antioxidants such as retinoids, β-carotene, Aloe vera, purslane, turmeric, and lycopene is being successfully used to treat the OLP lesions, suggesting that the oxidative stress has an important role in the genesis of OLP lesions.

Lycopene is a potent polyunsaturated β-carotenoid, which contains 11 conjugated double bonds, responsible for its antioxidant activity. Antioxidant effect of lycopene is mainly attributed to the physical and chemical quenching of free radicals. Lycopene is an efficient singlet oxygen quenching carotenoids. Due to its antioxidant, immunomodulatory, and free radical scavenging properties, it is used in the management of oral cancer or premalignant conditions such as oral leukoplakia, oral submucous fibrosis, and periodontal diseases, including OLP where the oxidative stress and lipid peroxidation are increased, and while antioxidant activities are decreased. The aim of this study was to assess the clinical effects of lycopene in the management of OLP in terms of elimination of clinical signs and symptoms of the patients. This study was motivated by the need for a monotherapeutic agent with a minimal or no reported adverse effects for a long-term use in the treatment of OLP lesions.

Materials and Methods

This study was conducted at the Bisheshwar Prasad Koirala Institute of Health Sciences, Dharan, Nepal, in the Department of Oral Medicine and Radiology, College of Dental surgery. In this study, 13 patients with age more than 18 years, clinically with presence of signs and symptoms, and histopathologically diagnosed with the disease of OLP were enrolled, after approval from the Institutional Ethical Review Board (no.636). Each patient was explained about the disease condition and its precancerous potential, which helped to reduce the patient’s psychological stress. Each patient was asked to sign written informed consent form and to perform complete oral prophylaxis before enrollment into the study. Patients with lichenoid reactions, presence of other mucosal diseases, renal or hepatic diseases, pregnancy, and breastfeeding were excluded from the study. Those with the habit of chewing guthka, lime, betel nut, pan, and tobacco smoking were also excluded from the study. Patients receiving any kind of systemic or local drug therapy for the same or treatment likely to modify OLP lesions such as systemic steroids, antifungals, immunosuppressants, and antioxidant were asked to discontinue their medication for a minimum of 4 weeks before enrollment into the study.

No concomitant intake of other medication and alcohol were permitted during the study period.

A single oral medicine specialist recorded the patient’s demographic data, previous treatment records, and clinical history and performed an examination to record lesion number, types, size (in cm²), and site of involvement in the oral mucosa. A punch biopsy was taken from the most affected lesion site along with some normal mucosa. The biopsy specimen was submitted to the central pathology department of the institute for the histopathological examination. Clinically and histopathologically diagnosed OLP patients received capsule lycopene 4 mg/day (LycoRed 2 mg capsule, Jagsonpal Pharmaceuticals, New Delhi, India) orally for 8 consecutive weeks. On each appointment, the reduction of the Thongprasom clinical sign scores was recorded based on the criterion described and modified by Thongprasom et al. as shown in Table 1.

Reticular/hyperkeratotic, erythematous/atrophic, and erosive/ulcerative areas were readily distinguished from each other because they were white, red, and yellow, respectively. The lesion size was determined using transparent grid calibrated to 1 mm² and using the University of North Carolina-15 periodontal probe (UNC-15).

The marker lesion was defined in case of OLP as a lesion extended to the multiple sites. Part of the oral mucosa that was highly affected by the OLP lesions was considered as the marker lesion. Different clinical types of lesions were found in the same patient, such as reticular and erosive forms, and in this case, the most severe erosive form of the lesion was considered to determine the type of lesion. The size of the lesion was determined by measuring the maximum distance between two opposite largest outside edges of the lesion. The cross-sectional area of the lesion was calculated by multiplying the length x width of the two opposite largest outside edges of the lesion. In case of multiple lesions, at the same site, their surface areas were added to obtain the total surface area. The overall treatment response was recorded at the baseline and at the 2 weeks’ interval for 8 consecutive weeks. Complete remission of the disease was defined as a complete absence of symptoms and clinical sign scores of the patients. Partial remission, worsening, and persistence of the disease were defined as a decrease, an increase, or no change, respectively, in patient’s symptoms and clinical sign scores. Patients were asked open-ended questions to ascertain the nature and severity of any adverse effects. Statistical software package SPSS 11 version (SPSS Inc., Chicago, IL, USA)

| Table 1: Clinical sign scores based on Thongprasom criterion[11,12] |
|------------------|----------------------------------|
| Score | Clinical signs |
| 0 | No lesions or normal mucosa |
| 1 | Mild white strie only, no erythematous area |
| 2 | White strie with an erythematous/atrophic area of<1 cm² |
| 3 | White strie with an erythematous/atrophic area of>1 cm² |
| 4 | White strie with erosion/ulceration area of<1 cm² |
| 5 | White strie with erosion/ulceration area of>1 cm² |
was used for data analysis. Descriptive statistics such as mean, standard deviation, and percentages were calculated. Wilcoxon signed-rank test was used to compare the data of follow-up weeks. P < 0.05 at a confidence interval of 95% was considered statistically significant.

Results

Of 13 patients, seven patients were male and six were female. The age of the patients ranged from 27 to 74 years. Buccal mucosa was the most common site for the presentation of the disease followed by gingiva, tongue, labial mucosa, and hard palate [Figure 1]. Different types and forms of the lesions coexisted in the same patient. All of them had reticular forms of the lesion, while six had atrophic and four had erosive forms of the lesions. The duration of the lesions ranged from 1 month to 4 years. Among 13 patients, 11 patients who had received topical steroid therapy had recurrence or relapse of the disease.

At the baseline, the mean Thongprasom clinical sign score was 2.77 ± 1.74. After 8 weeks of treatment, the baseline score became 0.85 ± 0.37 (P = 0.005), which was lowered by 69% [Table 2]. However, the mean change of clinical sign score was seen to be statistically significant (P = 0.011) in patients treated with lycopene after 6 weeks of treatment [Figure 2].

Complete remission of the lesions, complete absence of symptoms, and clinical sign scores were seen in two patients after 8 consecutive weeks of treatment with lycopene. The rest of the patients had experienced a partial remission of the lesions. No patients had worsened or persistence of the lesions. The most common adverse effects reported in these patients were flatulence and nausea. Mild abdominal pain or cramps, increased appetite, diarrhea, headaches, dizziness, and dry mouth were less frequently reported other adverse effects.

Discussion

The single, effective treatment for OLP is still unknown. Some authors have recommended topical and systemic corticosteroids as the most effective treatment, whereas others have recommended numerous other pharmaceutical and non-pharmaceutical agents such as different types of immunosuppressants, immunomodulators such as levamisole, retinoids, β-carotenoid, and lycopene, along with other free radical scavenging agents. However, the side effects of many pharmaceutical agents cannot be ignored in the long-term use.

Recent literature reported increased oxidative stress, an imbalance in the antioxidant defense system, increased lipid peroxidation, oxidative damage to DNA, and proteins as the causative factors in the genesis of OLP lesions. Some researchers have advocated the use of purslane, A. vera and turmeric along with lycopene for the treatment of OLP lesions because of antioxidant properties. Even, Nagao et al reported that there was a significant decrease in the level of lycopene in patients having atrophic and erosive forms of lesions. Therefore, it is always a “quest” for the search for an effective treatment of OLP with little or no side effects. This study was done to evaluate the clinical effectiveness of antioxidant-rich lycopene in the management of OLP lesions.

In our study, based on previous studies, the selected dose of lycopene was 4 mg/day. Various previous studies have used lycopene at the dose of 4–8 mg/day for 2–32 weeks for successful management of potentially malignant oral lesions such as oral leukoplakia, OLP, and periodontal diseases and for reversal of hyperkeratosis of the oral epithelium. Furthermore, some studies have also supported the daily intake of 5–10 mg of lycopene to maintain circulating levels of lycopene at sufficient levels, to combat the oxidative stress, and to prevent chronic diseases. The selection of lycopene 4 mg/day was
based on the fact that patients with low level of lycopene at baseline responded better to low doses of lycopene than those with elevated baseline lycopene level.\(^{20}\) Therefore, in our study, lycopene 4 mg/day was selected for 8 consecutive weeks for the treatment of OLP.

In our study, OLP lesions were seen more commonly in patients of age group 27–74 years with slightly male predominance. Similar findings were reported by Saawarn et al.,\(^6\) where OLP was more common in the age group of 14–75 years with male predominance. However, studies by Agha-Hosseini et al.,\(^5\) Mansourian et al.,\(^7\) Pratihha et al.,\(^14\) and other various studies have reported that the common age group of OLP lesions was 19–75 years with female predominance. This difference may be due to the differences in patient selection and the prevalence of OLP in their setting.

Our study results have shown that there was a decrease in the clinical sign scores by 44% and 69% from the baseline after 6 and 8 weeks of treatment with lycopene, respectively. Patients have reported the reduction of pain or discomfort after starting treatment. Complete remission of lesions was seen in two (15.5%) patients, while remaining (n = 11, 84.6%) had partial remission of lesions after 8 consecutive weeks of treatment with lycopene. A similar study was conducted by Pratihha et al.,\(^14\) who assessed the effect of lycopene 8 mg/day for 8 consecutive weeks in 25 patients using the Tel Aviv San Francisco Scale. She observed that two (8%) patients had complete remission of lesions (score 4 = 90–100% remission of sign and symptoms), and the remaining patients (n = 23, 92%) had partial remission of lesions. The results of our study were more or less similar to the Pratihha et al.,\(^14\) study. Similarly, a double-blinded, placebo controlled study was conducted by Saawarn et al.,\(^6\) using lycopene at a dose of 8mg/day for 8 consecutive weeks in 15 patients. The overall treatment response was evaluated by using Tel Aviv-San Francisco scale. They showed 7 (46.6%) patients had complete remission of lesions (Score 4 →90-100% remission of sign and symptoms), and 8 (53.4%) patients had partial remission of OLP lesions at the end of treatment. The beneficial effect of lycopene was observed in a higher percentage of patients in Saawarn et al.,\(^6\) study as compared to our study. The difference in findings may be possibly attributed to the difference in patient selection, the severity of disease presenting at the time of treatment, and the patient response factors.

In another study by Arbabi-Kalati et al.,\(^21\), conducted on 30 patients, using topical corticosteroid along with 15 mg of systemic lycopene daily for 1 month. They reported the reduction of Thongprasom disease scores 4.1 ± 1 at baseline to 1.7 ± 1.2 at the end of treatment. The percentage change of the disease scores was 58.54%, which was more or less similar to our study (69%) finding. However, Arbabi-Kalati et al.,\(^21\) used both topical corticosteroids and systemic lycopene simultaneously, and the beneficial effect of lycopene alone becomes unclear.

Previously, many non-pharmaceutical products with proven antioxidant properties have been evaluated for the treatment of OLP lesions. Results have shown that partial to complete remission of OLP lesions with purslane (Portulaca oleracea) was 83% (n = 20, treatment period 6 months), A. vera (Aloe barbadensis) was 78% (n = 23, treatment period 3 months), and topical application of turmeric (curcumin) was 100% (n = 10, treatment period 3 months).\(^{5,7,13}\) The results of these antioxidants were more or less similar to lycopene in our study, which produced 100% partial to complete remission of OLP lesions (n = 13, treatment period two months) in shorter treatment duration.

Long-term clinical presentation of a reticular form of OLP lesions has some chance of conversion into atrophic or erosive forms.\(^5\) Atrophic or erosive forms of lesions are often symptomatic and produce discomfort to the patients. Therefore, the complete remission of reticular forms of lesions in two patients in our study was considered as a significant result.

In our study, capsule LycoRed was given to the patients which contains antioxidants such as Vitamin A, α-tocopherol, zinc, and selenium apart from lycopene. These might have produced synergistic action to lycopene, increasing free radical scavenging capacity. By considering the chronicity of the disease and the need for long-term treatment, lycopene can be recommended as a good treatment option with minimal adverse effects. However, this study was conducted on a small study population, over a limited time; any strong conclusions cannot be derived. Further studies on a large scale with long-term follow-up are recommended to investigate the potential use of lycopene in the effective management of OLP lesions.

Conclusion
The result of the present study was encouraging. In contrast to other management modalities for OLP, lycopene offers a safe, efficacious, and reliable treatment that yields a significant improvement in the signs and symptoms of the patients, which may be due to its antioxidant and anti-inflammatory activity. Therefore, lycopene can be recommended as a good treatment option in the prevention and management of OLP lesions.

References
Kushwaha, et al. Lycopene in the treatment of oral lichen planus


