COMPARATIVE STUDY OF THE EFFICACY OF LYCOPENE VERSUS PREDNISOLONE IN THE MANAGEMENT OF ORAL LICHEN PLANUS- A RANDOMIZED, DOUBLE BLIND CLINICAL TRIAL.

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ABSTRACT

Oral lichen planus (OLP) is a chronic inflammatory, immunologically mediated mucocutaneous disorder. Numerous topical and systemic therapies have been used in the treatment of OLP. Most of the current available treatments are palliative rather than curative. Corticosteroids are considered as the main treatment drugs. Unfortunately, some patients may develop refractory or resistance to corticosteroids therapy. This study aims to evaluate and compare the efficacy of lycopene and prednisolone in the management of OLP. This was a double-blind randomized comparative study in which clinically and histopathologically proven symptomatic OLP patients were enrolled and divided into two groups. Lycopene group received oral lycopene 4 mg/day (n=13) and prednisolone group received oral prednisolone 40 mg/day (n=15) for eight consecutive weeks. Assessments were made at baseline and after 2, 4, 6 and 8 weeks of treatment, based on the Numerical Rating Scale (NRS) and the Piboonniyom REU (Reticular, Erythematous and Ulceration) severity score. From the results obtained, the reduction of NRS burning sensation scores was statistically significant after two weeks of treatment in both groups. REU severity scores were decreased by 74% (p=0.005) and 91% (p=0.001) in lycopene and prednisolone groups respectively. Complete remission (EI=100%) of lesion was observed in two (15.4%) patients treated with lycopene and ten (66.7%) patients treated with prednisolone. However, the overall treatment response was
higher in the prednisolone group as compared to the lycopene group. In conclusions, prednisolone was found to be more effective than lycopene in the treatment of OLP.

KEYWORDS: Antioxidant, Lycopene, Oral lichen planus, Prednisolone.

INTRODUCTION
Oral lichen planus (OLP) is a common sub-acute, chronic inflammatory mucocutaneous disease of unknown aetiology with prevalence in general population ranging from 0.5-2.2%. The average age of disease presentation is between 30 and 60 years, and the disease is more common in female with a female to male ratio 1.4:1. Clinically, it is manifested as reticular, papular, plaque-like, erosive, atrophic and bullous forms. Atrophic and erosive lesions can cause symptoms ranging from a mild burning sensation to intense pain that interfere in speaking, eating and swallowing. Thus, symptomatic OLP patients often require treatment. Various treatments strategies have been used in the past, including topical or systemic corticosteroids, immunosuppressant’s, retinoid, phototherapy and surgery etc. However, most of the current available treatments are palliative rather than curative. Corticosteroids are considered as the main treatment drugs, which reduce inflammation, burning sensation and promote quick healing of lesions. Unfortunately, some patients are refractory and resistant to corticosteroids therapy. Therefore, the searching for new treatment modalities with fewer side effects, to reduce pain and eliminate lesions are considered necessary for OLP.

The exact aetiopathogenesis of OLP is unknown, however there are several factors such as genetic, infection, stress, trauma, autoimmune and psychology etc, are responsible for the aggravation of the disease. Several antigen-specific and non-specific inflammatory mechanisms are involved in its pathogenesis. Evidence points out that the disease is an immunological origin triggered by an unknown antigen which alters the basal keratinocytes, thereby activating auto-cytotoxic T lymphocytes. Activated T-cells release different kinds of cytokines such as interleukin (IL-2, IL-10, IL-4), interferon gamma (IFN-γ) and tumor necrosis factor (TNF-α), which promote chronic inflammation and apoptosis of oral epithelial cells. During this process, the inflammatory cells and keratinocytes generate various amounts of free radicals and reactive oxygen species (ROSs) that produce lipid peroxidation, proteins and nucleic acids oxidation in the surrounding cells. ROSs may damage the extracellular matrix and inhibit collagen and proteoglycan synthesis. The increase of oxidative stress, imbalance in antioxidant status and successful use of antioxidants (retinoids, lycopene) in
management of OLP suggest the role of oxidative stress in the pathogenesis of OLP.\cite{8,9} Recently, the significance of oxidative stress in different autoimmune and inflammation based diseases such as erosive lichen planus and psoriasis have been evaluated.\cite{8} Therefore, drugs with antioxidant and free radical scavenger properties may have important role in the management of OLP.

Lycopene is a most efficient singlet oxygen quenching carotenoid, which exerts its potent antioxidant activities by physical and chemical quenching of reactive free radicals.\cite{6} In literature, lycopene has profound benefits in various oral mucosal lesions such as oral submucous fibrosis, leukoplakia, OLP and periodontal diseases.\cite{6,10,11,12} The main purpose of the study was to evaluate and compare the efficacy of lycopene with prednisolone in the management of OLP. This study was motivated by the need for a monotherapeutic agent with a minimal or no reported adverse effects and act as a safe effective alternative to steroids for long-term use in treatment of OLP.

**MATERIALS AND METHODS**

Patients with age above 18 years and clinically symptomatic (associated with burning sensation or pain) OLP patients were recruited for this double-blind randomized comparative study from the Department of Oral Medicine and Radiology, College of Dental surgery, B. P. Koirala Institute of Health Sciences (BPKIHS). The Institutional Ethical Review Board (IERB) approval was obtained (IERB no: 636/069/070) and registered on ClinicalTrials.gov: NCT02587117. Patients with lichenoid reactions, any other mucosal diseases, pregnant, breast feeding, systemic disease/s (diabetes, hypertension, active peptic ulcer), serious or recurrent infection, HIV, and with the habit of gutkha, betel nut, pan, lime, smoking, and tobacco chewing were excluded from the study. Patients receiving any kind of systemic or local drugs treatment for the same or treatment likely to modify their OLP such as systemic steroids, antifungals, immunosuppressant's, anti-oxidant, were asked to discontinue their medication for a minimum of four weeks before entering the study. No concomitant intake of medication and alcohol were permitted. Each patient was explained about the disease condition and its precancerous potential, which were helped the patient to reduce the psychological stress. Patient was advised to perform complete oral prophylaxis. Written informed consent was obtained.
Each patient was evaluated by a single blinded oral medicine specialist, who recorded demographic data, previous treatment compliance, clinical history (to exclude lichenoid reaction with drugs, restoration or other dental materials) and performed clinical examination to record lesion number, types, size (in cm\(^2\)) and site of involvement in oral mucosa. Baseline investigations were performed to rule out any systemic, renal or hepatic disease, when suspected. The most representative site of lesions was selected and punch biopsy was performed under local anaesthesia. Biopsy specimen was submitted to the central pathology department of the BPKIHS for histopathological examination. Clinically and histopathologically diagnosed OLP patients were randomized (Figure 1) by using computer generated numbers (Microsoft Excel Computer Software 2010) as follows-

**Fig 1: Flow diagram of OLP patient enrolment, randomization, intervention and follow-up.**

Lycopene group patients received oral lycopene capsules 2 mg (LycoRedTM, Jagsonpal Pharmaceuticals Ltd., New Delhi, India) two capsule/day (total dose was 4 mg) and prednisolone group patients received oral prednisolone capsules 20mg (Wysolone, Wyeth India) two capsule per day (total dose was 40 mg) in morning for eight consecutive weeks of treatment. Then the prednisolone dose was tapered to 30 mg/day for two weeks, then to 20
mg/day for next two weeks and finally to 10 mg/day for the last two weeks. Patients were referred to a trained pharmacist to collect their assigned medication according to their unique drug code number. Both drugs were made identical in appearance along with unique drug code (101, 102, 103…………..128) to mask the identity of drugs.

All the measurements and evaluations were performed at baseline and after 2, 4, 6 and 8 weeks of treatment by a single oral medicine specialist. Patients, investigator and outcomes assessor were blinded to the treatment assignment. During each appointment, intensity of burning sensation was measured by using standard self-response Numerical Rating Scale (NRS). It was scored from 0 to 10 purely based on patient’s response (Score 0: no oral discomfort; Score 10: extreme oral discomfort). On each appointment, clinical examination was performed to record the severity of the individual lesion by using Piboonniyom REU\textsuperscript{[13]} (Reticular, Erythematous and Ulceration) severity score, which is based on the presence of reticular, atrophic, erosive-ulcerative areas of the lesion(s). Individual lesion was scored as follows (Table 1):

\begin{table}
\centering
\begin{tabular}{|l|l|}
\hline
Reticular/Hyperkeratotic areas & 0= no white striations  \\
& 1= presence of white striations or keratotic papules  \\
\hline
Erythematous/Atrophic areas & 0= no lesion  \\
& 1= lesions < 1 cm\textsuperscript{2}  \\
& 2= lesions from 1 to 3 cm\textsuperscript{2}  \\
& 3= lesions > 3 cm\textsuperscript{2}  \\
\hline
Ulceration areas & 0= no lesion  \\
& 1= lesions < 1 cm\textsuperscript{2}  \\
& 2= lesions from 1 to 3 cm\textsuperscript{2}  \\
& 3= lesions > 3 cm\textsuperscript{2}  \\
\hline
\end{tabular}
\caption{Piboonniyom REU\textsuperscript{[13]} (Reticular, Erythematous and Ulceration) severity score and Efficacy Indices\textsuperscript{[14]} (EI) based on the change in REU severity score}
\end{table}

\textbf{Efficacy Index (EI)} = \frac{[\text{before treatment total REU severity score} - \text{after treatment total REU severity score}]}{\text{before treatment total REU severity score}} \times 100\%

- Complete remission- \(\text{EI} = 100\%\) (complete disappearance of lesions)
- Marked improvement- \(75\% \leq \text{EI} < 100\%\) (75 to 99.9\% reduction of lesion severity)
- Moderate improvement- \(25\% \leq \text{EI} < 75\%\) (25 to 74.9\% reduction of lesion severity)
- Mild improvement- \(0.1\% \leq \text{EI} < 25\%\) (0.1 to 24.9\% reduction of lesion severity)
- No improvement- \(\text{EI} = 0\%\)
- Disease worsening = negative EI

For each of the three clinical signs, a score was derived by summation of the scores of all areas: reticular score =\(\Sigma R\), erythematous score = \(\Sigma E\) and ulceration score = \(\Sigma U\). Reticular, erythematous and ulceration score of individual lesion was multiplied by weighted score 1.0,
1.5 and 2.0 respectively, that give rise to total weighted score. The difference in total weighted scores between baseline and after treatment numerically expressed the clinical and symptomatic improvement. The lesion size was determined by using transparent grid calibrated to 1mm$^2$ and University of North Carolina-15 periodontal probe (UNC-15). Maximum size of the lesion was the distance between two opposite largest outside edges of the lesion. Two measurements were multiplied (length x width) to represent the cross-sectional area of the lesion. The Efficacy Indices$^{[14]}$ (EI) of the lycopene and prednisolone treatments was calculated on the basis of change in REU severity score of lesions (Table 1). After completion of treatment, all patients were re-examined by another consultant (unblinded) to further taper the dose of prednisolone and to treat the patients with incomplete remission of lesions. Data were analysed using mean, median, standard deviation, independent sample t-test, Mann–Whitney U test and Wilcoxon Singed Ranks test. Values of P < 0.05 and confidence interval 95% were considered statistically significant.

RESULTS
A total of 28 patients (10 male and 18 female) with a female predilection (female: male = 1.8:1) and the age range from 20 to 65 years were evaluated for the treatment response. In a few patients, reticular, erythematous and ulceration lesions coexisted in the same. The baseline characteristics of OLP patients are presented in Table 2.

### Table 2. Baseline characteristics of OLP patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Lycopene (n=13)</th>
<th>Prednisolone (n=15)</th>
<th>Total (n=28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex: Male : Female (n)</td>
<td>7 : 6</td>
<td>3 : 12</td>
<td>10 : 18</td>
</tr>
<tr>
<td>Age (years)</td>
<td>41.69±13.97</td>
<td>48.07±12.27</td>
<td>45.11±13.24</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>58.23±9.94</td>
<td>60.13±6.36</td>
<td>59.25±8.11</td>
</tr>
<tr>
<td>Site of OLP (n, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buccal mucosa</td>
<td>13 (100%)</td>
<td>15 (100%)</td>
<td>28 (100%)</td>
</tr>
<tr>
<td>Gingiva</td>
<td>6 (46.15%)</td>
<td>5 (33.34%)</td>
<td>11 (39.28%)</td>
</tr>
<tr>
<td>Lip</td>
<td>2 (15.38%)</td>
<td>7 (46.67%)</td>
<td>9 (32.14%)</td>
</tr>
<tr>
<td>Tongue</td>
<td>3 (23.07%)</td>
<td>5 (33.34%)</td>
<td>8 (28.57%)</td>
</tr>
<tr>
<td>Hard palate</td>
<td>1 (7.69%)</td>
<td>1 (6.67%)</td>
<td>2 (7.14%)</td>
</tr>
<tr>
<td>Duration of lesions (months)</td>
<td>13.38±13.52</td>
<td>7.13±6.46</td>
<td>10.04±10.63</td>
</tr>
<tr>
<td>Type of lesions (n, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reticular/plaque type</td>
<td>13 (100%)</td>
<td>14 (93.34%)</td>
<td>27 (96.42%)</td>
</tr>
<tr>
<td>Erythematous/Atrophic</td>
<td>6 (46.15%)</td>
<td>6 (40.00%)</td>
<td>12 (42.85%)</td>
</tr>
<tr>
<td>Erosive/ulcerative</td>
<td>4 (30.78%)</td>
<td>5 (33.34%)</td>
<td>9 (32.14%)</td>
</tr>
<tr>
<td>Past treatment taken(n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (only Topical)</td>
<td>11</td>
<td>12</td>
<td>23</td>
</tr>
<tr>
<td>No</td>
<td>2</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Baseline NRS burning sensation</td>
<td>3.69±1.75 (4)</td>
<td>3.60±2.03 (3)</td>
<td>3.64±1.87 (4)</td>
</tr>
</tbody>
</table>
There were not statistically significant differences between groups with respect to age, sex, duration of lesions and type or site of OLP. Baseline NRS burning sensation score (P=0.851) and baseline REU severity score (P=0.641) were not statistically significant difference in between groups (Table 2).

In both lycopene and prednisolone groups, reduction of mean NRS burning sensation scores was statistically significant after two weeks of treatment with more reduction in the prednisolone group than that of the lycopene group (Table 3). However, the mean NRS burning sensation score reduction was not statistically significant (Figure 2) in between the groups. Reduction of the REU severity score was statistically significant after six weeks (p=0.011) of treatment with lycopene and after four weeks (p=0.005) of treatment with prednisolone (Table 3). This mean REU severity score reduction in between groups was statistically significant (p =0.004) only after eight weeks of treatment (Figure 3).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lycopene (n=13)</th>
<th>Prednisolone (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean± SD (Median)</td>
<td>Mean difference and % reduction from baseline</td>
</tr>
<tr>
<td>NRS burning sensation scores</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>3.69±1.75 (4)</td>
<td>-</td>
</tr>
<tr>
<td>Week 2</td>
<td>2.77±1.59 (2)</td>
<td>0.92±1.32 (25%)</td>
</tr>
<tr>
<td>Week 4</td>
<td>2.00±1.53 (1)</td>
<td>1.69±1.38 (46%)</td>
</tr>
<tr>
<td>Week 6</td>
<td>0.77±0.93 (1)</td>
<td>2.92±1.71 (79%)</td>
</tr>
<tr>
<td>Week 8</td>
<td>0.23±0.44 (0)</td>
<td>3.46±1.56 (94%)</td>
</tr>
<tr>
<td>REU severity scores</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>8.23±5.85 (6.5)</td>
<td>-</td>
</tr>
<tr>
<td>Week 2</td>
<td>7.69±5.72 (6)</td>
<td>0.54±1.66 (7%)</td>
</tr>
<tr>
<td>Week 4</td>
<td>6.27±4.82 (6)</td>
<td>1.96±2.42 (24%)</td>
</tr>
<tr>
<td>Week 6</td>
<td>3.73±3.15 (2)</td>
<td>4.50±3.35 (55%)</td>
</tr>
<tr>
<td>Week 8</td>
<td>2.15±1.68 (2)</td>
<td>6.08±4.52 (74%)</td>
</tr>
</tbody>
</table>

*Wilcoxon Signed Rank Test: significant (p<0.05).
Fig. 2 Inter group comparison of NRS burning sensation scores. *Mann Whitney U test: significant (p<0.05).

Fig. 3 Inter group comparison of REU severity scores. *Mann Whitney U test: significant (p<0.05).

Fig 4: Various degrees of improvement based on efficacy indices (EI) rank scales.
As a result of eight weeks of treatment, complete remission (EI=100%) of lesion(s) was observed in two (15.4%) patients in the lycopene group and ten (66.7%) patients in the prednisolone group (Figure 4). OLP lesion(s) worsening in either group was not observed. Common adverse events reported in lycopene group were flatulent (n=9, 69.2%) and nausea (n=4, 30.8%) whereas in prednisolone group, puffiness of face (n=13, 86.7%), mild headache (n=10, 66.7%), dizziness (n=8, 53.3%) and epigastric distress (n=6, 40%) were noted. None of the symptomatic adverse events led to the discontinuation of the drugs.

DISCUSSION

There are contrasting opinions about the mainstay treatment of OLP patients. Some authors advocate systemic corticosteroid therapy is the most effective, whereas others advocate the topical use of high potent corticosteroid. Additionally, numerous other immunosuppressant agents have been employed. But none of them are free from adverse effects and to prevent recurrence of the lesions. Corticosteroid remains the first line treatment for OLP because of decreasing T-cell mediated immune activity and thereby modulating the immune functions. Systemic steroids are reserved for widespread lesions and the lesions that are resistant or unresponsive to topical steroid therapy.

The chronic inflammatory nature of OLP generates various amounts of free radicals and reactive oxygen species (ROSs) that also involved in its aetiopathogenesis. Therefore, drug with antioxidant and anti-inflammatory properties may exert beneficial effects in OLP. A natural potent antioxidant lycopene has a highly unsaturated conjugated Dienes, which exerts antioxidant activity by inactivating free radicals and by attenuating free radicals-initiated oxidative reactions. It scavenges singlet oxygen (O$_2^*$), nitrogen dioxide (NO$_2^*$), thiyl (RS$^*$), hydrogen peroxide (H$_2$O$_2^*$) and sulphonyl (RSO$_2^*$) radicals. Its singlet-oxygen-quenching ability is twice as high as that of β-carotene and ten times higher than that of α-tocopherol. It protects biological molecules including lipids, lipoproteins, proteins and DNA from oxidative damage. Lycopene expresses anti-inflammatory activity (a) by scavenging singlet oxygen and peroxyl radical, (b) by up-regulating lymphocyte resistance to stress, (c) by reducing IL-4 and TNF-α production and (d) by increasing IgG production. It also regulates gene function, gap-junction communication, hormone and immune modulation, anti-proliferation and pro differentiation activities.

In this study, partial to complete remission of lesions was observed in all patients. NRS burning sensation scores were statistically highly significant decreased in lycopene (94%,
p=0.001) and in prednisolone (98%, p=0.001) groups after eight weeks of treatment. REU severity scores were decreased by 74% (p=0.005) and 91% (p=0.001) in lycopene and prednisolone groups respectively. However, better results in all the parameters were observed in the prednisolone group than that of the lycopene group.

Our rationale for dose selection (lycopene 4 mg/day, prednisolone 40 mg/day) was based on the previous studies. Initial high dose of prednisolone 40 to 80 mg in the morning followed by tapering of the dose of 5-10 mg per 1-2 weeks of interval is effective for treatment of OLP.\[^{5,17,18}\] The dose of lycopene 4-8 mg/day for 2 to 32 weeks (most of the studies used 8 weeks of medication) is very effective for the treatment of oral leukoplakia, OLP and oral periodontal disease as well as reversal of dysplastic changes and hyperkeratosis.\[^{6,10,11}\] Daily intake of 3.7 –7 mg may be sufficient to maintain circulating levels of lycopene at levels sufficient to combat oxidative stress, to reduce lipid peroxidation, to decrease inflammation and TNF-α production\[^{19,20,21,22}\] and the subject with low baseline lycopene levels respond better to low doses of lycopene than the subjects with elevated baseline levels of lycopene.\[^{15}\] Single oral dose administration is possible because the half-life of lycopene is 2–3 days.\[^{23}\] Therefore, we decided to select initial high dose of 40 mg/day prednisolone for two weeks and then tapering of the doses and 4 mg/day of lycopene for a period of eight weeks.

Carbone M et al\[^{24}\] found 40.9% (n=9) of patient with complete remission and 50% (n=11) patients with partial remission of OLP lesion in initial two months of treatment with prednisolone 50 mg/day along with tapered doses. In our study, complete remission was observed in 66.7% (n=10) and partial remission in 33.4% (n=5) of patients after eight weeks of treatment with prednisolone 40 mg/day along with tapered doses, which was more or less similar to the results reported by Carbone M et al.\[^{24}\] A double blind placebo controlled randomized clinical trial conducted by Saawar N et al\[^{6}\] a significant reduction in burning sensation (84%, P=0.001) was observed with lycopene at the doses of 8mg/day for eight consecutive weeks of treatment. Comparing this result with our study, burning sensation was reduced by 94% (p=0.001) with 4 mg per day of lycopene at the end of eight weeks of treatment. Even at the low dose of lycopene the beneficial effect was observed.

Both lycopene and Prednisolone demonstrated a prominent and impressive clinical response in controlling symptoms related to OLP. The resolution of reticular lesion in our study can be regarded as a significant result. The reticular form of lesion may transform into atrophic or erosive form and atrophic and erosive forms of lesion have the increased risk of malignant
transformation (up to 0.2-2%) as compared to another forms.\textsuperscript{[25,26]} Therefore, it may be presumed that lycopene and prednisolone may decrease the risk of malignant transformation in OLP.

Further, the drug used in this 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 study had some limitations. The study was performed in a small series of patients at a single medical centre and was precluded the opportunity to assess for relapse of disease. Further studies are recommended on a larger sample size to obtain valid power along with multi-centre design with a longer follow-up period to evaluate the relapse rate.

\textbf{ACKNOWLEDGEMENT}
I acknowledge our faculty member Dr. Iccha Kumar Maharjan, Associate Professor, CODS, BPKIHS for his support and proper management of patients after withdraw from clinical trial. I thanks to the entire participant patients for their encouraging involvement and cooperation for the completion of this study.

\textbf{CONCLUSION}
Our results are encouraging as it confirmed that treatment with prednisolone was more effective in pain relief, resolution of lesions and was more cost effective. An effective clinical response was obtained after treatment with lycopene along with good patient acceptance and fewer acceptable side effects. Therefore, lycopene can be used as an alternative treatment of OLP but it cannot be considered as the first drug of choice.

\textbf{REFERENCES}


