Assessment of Lycopene and Levamisole in Management of Oral Lichen Planus – A Comparative Study

Pratibha[1,*], Kuldeep Singh Shekhawat[2], Deepak T.A[3], Chandni Srivastava[4]

[1]Senior Lecturer, Dept. of Oral Medicine & Radiology, Dr. B.R Ambedkar Institute of Dental Sciences & Hospital, Hari Om Nagar, New Bailey Road, West of Canal, Patna, Bihar - 801503
[2]Assistant Professor, Dept. of Public Health Dentistry, Srinivas Institute of Dental Sciences, Srinivas Nagar, Mukka, Surathkal, Mangaluru, Karnataka - 575021
[3]Professor, Dept. of Oral Medicine & Radiology, V.S Dental College and Hospital, V.V Puram, K.R Road, Bangalore, Karnataka - 560004
[4]Oral Pathologist, Samridhi Dental Hospital, Building No. C5, Kendriya Vihar, Kharghar, Navi Mumbai – 410210

***Corresponding Author**
E-mail: drpratibha144@gmail.com

Abstract

Objective: Oral Lichen Planus (OLP) is known to be persistent and resistant to treatment. Corticosteroids are the preferred mode of intervention in OLP, long courses of which have been shown to cause adverse effects. The goal of this study was to compare the safety and efficacy of Lycopene and of Levamisole in the management of Oral Lichen Planus.

Methods: 50 symptomatic OLP patients satisfying the inclusion criteria were randomly divided into two groups (A and B). Group A patients were administered lycopene 8mg / day in two divided doses for 8 weeks. Group B patients were administered levamisole 50mg in cyclic dosage i.e. thrice daily for 3 consecutive days followed by no drug for next four days; for 8 weeks. The patients were scored at baseline, 2 weeks, 4 weeks and 8 weeks using Visual Analog Scale (VAS) for symptoms and Tel-Aviv San Francisco (TASF) scale for overall response to treatment. Statistical analysis was performed using repeated measures of ANOVA, Z test and chi square test.

Results: Substantial reduction in pain and burning sensation was observed in both the groups at the end of treatment. A more potent therapeutic effect was observed in lycopene group. Specifically, 18 out of 25 (72%) patients in this group showed 50% or more improvement while 12 out of 25 (48%) patients showed 70-100% improvement. In levamisole group, 11 out of 25 (44 %) and 1 out of 25 patients showed 50% or more, and 70-100% improvement. No adverse effects were reported in either group.

Conclusion: When used as monotherapeutic agents, both lycopene and levamisole were found to be safe and effective alternatives for treatment of Oral Lichen Planus. Lycopene demonstrated a faster and more potent therapeutic effect compared to levamisole. The results of this research motivate further studies with larger sample size to evaluate these drugs in the treatment of OLP.

Key words: Lycopene, Levamisole, Oral lichen planus.

Access this article online	
Quick Response Code:	**Website:** www.innovativepublication.com
	DOI: 10.5958/2395-6194.2016.00002.3

Introduction

Oral Lichen Planus (OLP) is a chronic inflammatory mucocutaneous disease of the oral mucosa.[1] OLP is seen worldwide affecting approximately 1-2% of the population. It is mostly seen in the fifth to sixth decade of life and is twice more common in women than in men.[2] Erosive and atrophic forms of OLP are usually symptomatic.[1] OLP tends to be persistent and resistant to treatment.

The etiology of OLP has been extensively studied but has still not been understood completely. The disease appears to be a result of cell-mediated immune response involving abnormal functioning of T-lymphocytes.[3] Reports have also implicated increased oxidative stress and decreased antioxidant enzyme expression in the pathogenesis.[4] Various treatment regimens have been attempted to improve symptoms[6,8-10] but management remains challenging.

Topical steroids, both topical and systemic, are commonly used as first line drugs in the treatment of OLP.[5] However, adverse effects such as insomnia, mood swings, fatigue, fluid retention etc. are common even with short courses of systemic steroids[6] Further, adverse effects such as bad taste and smell, nausea, dry mouth, sore throat, and candidiasis.[7] have also been reported with topical steroid use. Therapeutic interventions with lesser side effects are desirable, for which a variety of drugs have been investigated.[8-10] Additionally, potent alternative treatment strategies are also required for cases of OLP in patients for whom the use of steroids is not recommended.

Lycopene and Levamisole are two non-steroidal drugs which may hold promise for treating OLP. Lycopene is a structural acyclic isomer of b-carotene, a natural pigment synthesized by plants and microorganisms.[11] Acting as a potent antioxidant, lycopene may inactivate free radicals and attenuate free radical-

initiated oxidative reactions such as lipid peroxidation and DNA oxidative damage, thereby preventing tissue damage.[12] While these features have been demonstrated to benefit general health, few studies have investigated effect of lycopene in oral diseases.[9,13]

Levamisole is a synthetic phenylimidothiazole salt[14] classified as an immunomodulator. It enhances immune responsiveness by T-cell activation.[15] Levimisole may have promising therapeutic effects in OLP because the formation of subepithelial immune deposits is a characteristic histological feature of OLP.[16] The goal of this work was to compare the safety and efficacy of Lycopene and of Levamisole in the management of Oral Lichen Planus. This study was motivated by the need for a monotherapeutic agent as an alternative to steroids for the treatment of OLP.

Materials and Methods

This study group included 50 systemically healthy individuals who were diagnosed with OLP based on the clinical and histopathological criteria described by Gonzalez et. al.[17] Ethical clearance was obtained from the Ethical Committee of V. S. Dental College and Hospital, Bengaluru and informed consent was obtained from the participants of the study. The inclusion criteria for the study were as:

1. Histologically proven symptomatic OLP.
2. Age between 20 to 75 years
3. Ability to complete the present clinical trial.

Patients with proven or suspected hypersensitivity to lycopene and levamisole, those who had received therapy for OLP or other condition s within last 6 months preceding this study and pregnant and lactating females were excluded.

Patients were randomly allocated into two groups of 25 each – A (lycopene group) and B (levamisole group). Group A patients were administered lycopene 8mg / day in two divided doses for 8 consecutive weeks. Group B patients were administered levamisole 50mg in cyclic dosage i.e. thrice daily for 3 consecutive days followed by no drug for next 4 days; for 8 consecutive weeks. Patients were assessed at baseline, 2 weeks, 4 weeks and 8 weeks to evaluate response to medication. Symptoms such as pain and/or burning sensation were assessed using a Visual Analog Scale (VAS) of score 0 to 100 (score 0 being absolutely no burning sensation and score 100 being the most severe burning sensation felt). Clinical examination was performed at every review and overall response to treatment was recorded using the Tel Aviv- San Francisco Scale (TASF) 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.[18] Baseline CBC was performed for all the patients selected and was repeated after every month of treatment. Adverse effects, if any, were recorded. Statistical analysis was performed using repeated measures of ANOVA and Z test followed by chi square test for assessing safety and efficacy of the drugs, respectively.

Results

The participants in this study had an average age of 45.3 years. 16 participants were males and 34 were females. M:F ratio showed a slightly female predilection (0.47:1). 22 patients presented with reticular form of OLP, 20 with erosive, 6 with plaque-like and 1 each with papular and bullous forms. (see Table 1 for group wise distribution). Pre-treatment patient data was statistically analyzed and the difference between both groups were not statistically significant ($p>0.05$)

Figure 1 shows that a significant reduction in the mean scores for evaluating pain and burning sensation was observed in both the groups after treatment, with a more potent affect in group A (lycopene). Specifically in Group A, mean score at the end of 8 weeks had decreased from 53.6 ± 14.9 at baseline to 18.8 ± 15.6; a **64.9%** decrease in pain and burning sensation. In Group B (levamisole), at the end of 8 weeks of treatment the score showed a mean value of 39.6 ± 17.1 which represents **37.7%** decrease from baseline score of 63.6 ± 18 [Table 2].

As per Tel Aviv San Francisco Scale, at the end of treatment 18 out of 25 (72%) patients in group A showed 50% or more improvement, with 12 out of 25 (48%) patients showing 70 - 100% relief in signs and symptoms and did not require further treatment. In group B, 11 out of 25 (44%) patients showed 50% or more improvement, only 1 out of 25 patients showed 70–100% relief in signs and symptoms and did not require further treatment. This difference was statistically significant ($p< 0.005$)

Higher mean TASF score was recorded at the end of 8 weeks of treatment in both groups [Figure 3] [Table 2]. However, the difference in mean was more statistically significant at the end of 2 weeks than at the end of treatment.[Table 3 & 4]. That is, patients in lycopene group showed significant response from the very beginning of therapy [Figure 2]. In comparison, Patients in levamisole group did not respond to initial therapy but the overall response to levamisole was statistically significant

Table 1: **Distribution of Clinical Forms of OLP**

Type of lesion	Group A	Group B	Total
1 – reticular	12	10	22
2 – erosive	09	11	20
3 – plaque like	02	04	06
4 – papular	01	0	01
5 – Bullous	01	0	01

Table 2: Mean descriptive statistics for Group A and Group B and the difference in their means.

	VAS			TASF		
	GROUP A Lycopene	**GROUP B Levamisole**	**Difference between Group A and Group B**	**Group A Lycopene**	**Group B Levamisole**	**Difference between Group A and Group B**
Baseline	53.6 ± 14.9	63.6 ± 18	***0.005***	-	-	
2 weeks	40.6 ± 13.7	60 ± 16.8	***0.000***	0.28 ± 0.45	0.88 ± 0.66	***0.001***
4 weeks	28.8 ± 16.7	51.6 ± 15.4	***0.000***	0.88 ± 0.6	1.6 ± 0.64	***0.000***
8 weeks	18.8 ± 15.6	39.6 ± 17.1	***0.000***	1.44 ± 0.65	2.24 ± 1.05	***0.004***

Table 3: Intragroup effects of lycopene
Pairwise Comparisons^

Measure: effect						
		a			95% Confidence Interval for Difference#	
(I) time	(J) time	Mean Difference (I-J)	Std. Error	Sig.[a]	Lower Bound	Upper Bound
1	2	13.000*	2.041	**.000**	7.131	18.869
	3	24.800*	3.422	**.000**	14.963	34.637
	4	34.800*	3.725	**.000**	24.091	45.509
2	1	-13.000*	2.041	**.000**	-18.869	-7.131
	3	11.800*	2.413	**.000**	4.862	18.738
	4	21.800*	2.782	**.000**	13.801	29.799
3	1	-24.800*	3.422	**.000**	-34.637	-14.963
	2	-11.800*	2.413	**.000**	-18.738	-4.862
	4	10.000*	1.708	**.000**	5.090	14.910
4	1	-34.800*	3.725	**.000**	-45.509	-24.091
	2	-21.800*	2.782	**.000**	-29.799	-13.801
	3	-10.000*	1.708	**.000**	-14.910	-5.090

Based on estimated marginal means*.
The mean difference is significant at the .05 level.
#. Adjustment for multiple comparisons: Bonferroni.
^. group = A(lycopene)

Table 4: Intragroup effects of levamisole
Pairwise Comparisons^

Measure: effect						
		a			95% Confidence Interval for Difference#	
(I) time	(J) time	Mean Difference (I-J)	Std. Error	Sig. a	Lower Bound	Upper Bound
1	2	3.600	1.514	.155	-.754	7.954
	3	12.000*	1.915	**.000**	6.495	17.505
	4	24.000*	2.082	**.000**	18.015	29.985
2	1	-3.600	1.514	.155	-7.954	.754
	3	8.400*	1.973	**.002**	2.727	14.073
	4	20.400*	1.778	**.000**	15.289	25.511
3	1	-12.000*	1.915	**.000**	-17.505	-6.495
	2	-8.400*	1.973	**.002**	-14.073	-2.727
	4	12.000*	2.582	**.001**	4.577	19.423
4	1	-24.000*	2.082	**.000**	-29.985	-18.015
	2	-20.400*	1.778	**.000**	-25.511	-15.289
	3	-12.000*	2.582	**.001**	-19.423	-4.577

Based on estimated marginal means
#. Adjustment for multiple comparisons: Bonferroni.
*. The mean difference is significant at the .05 level.
^. group = B (levamisole)

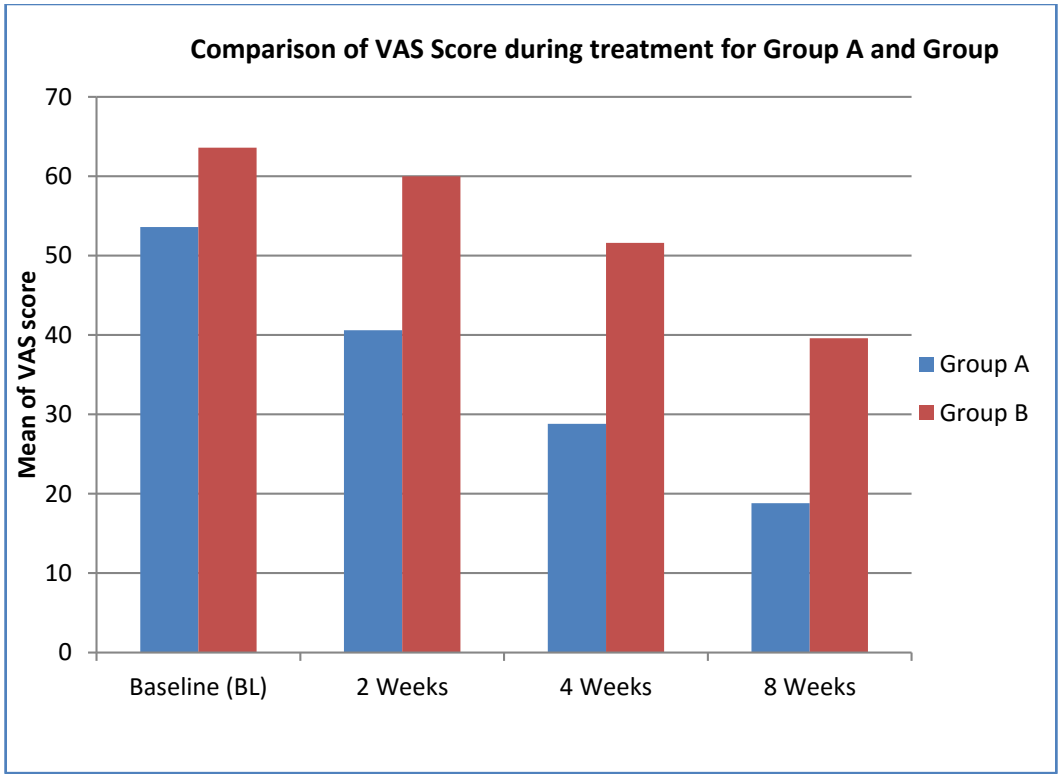

Fig. 1: A comparison of VAS scores of groups A and B at every review. The mean scores decreased for each group over time.

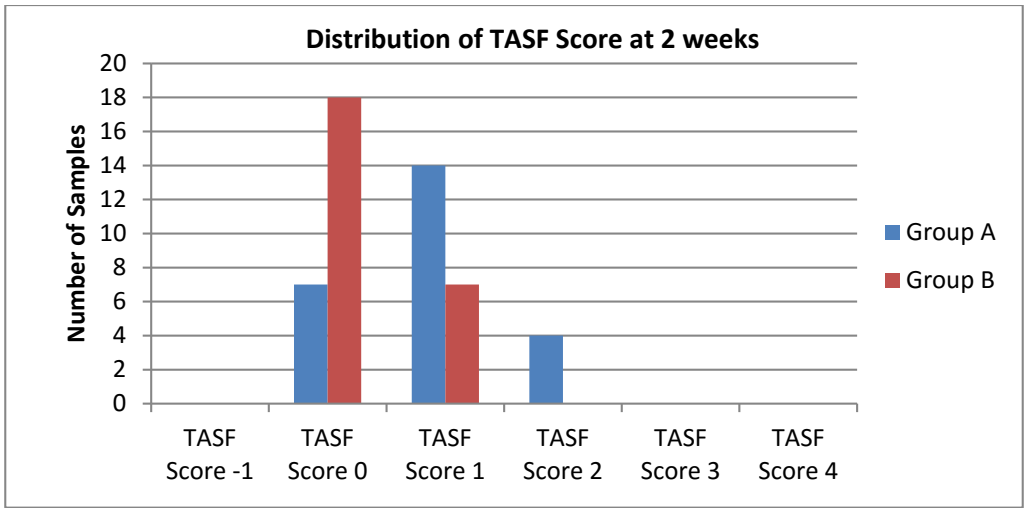

Fig 2: The overall treatment response observed after 2 week of therapy. A greater number of group A participants scored higher on the TASF scale.

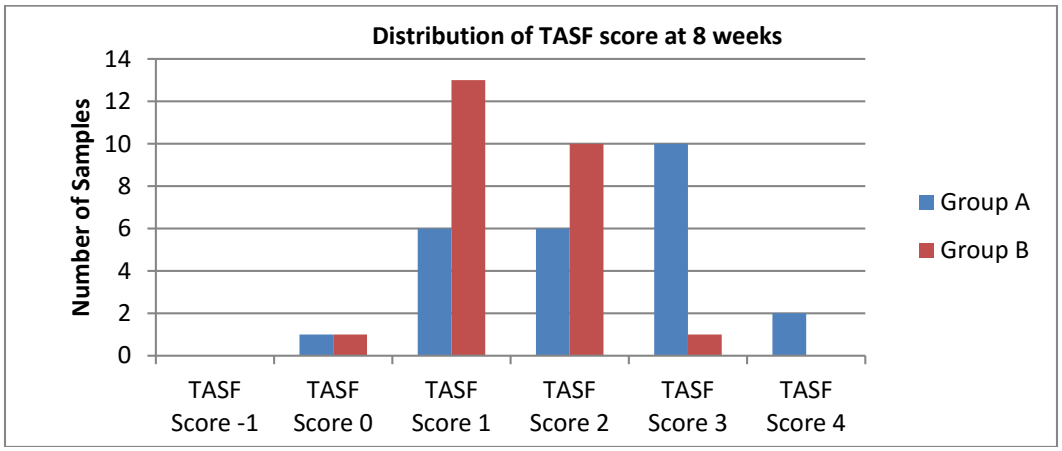

Fig. 3: The overall treatment response at the end of 8 weeks of therapy. Both group A and group B patients scored higher on the scale than at the beginning of treatment.

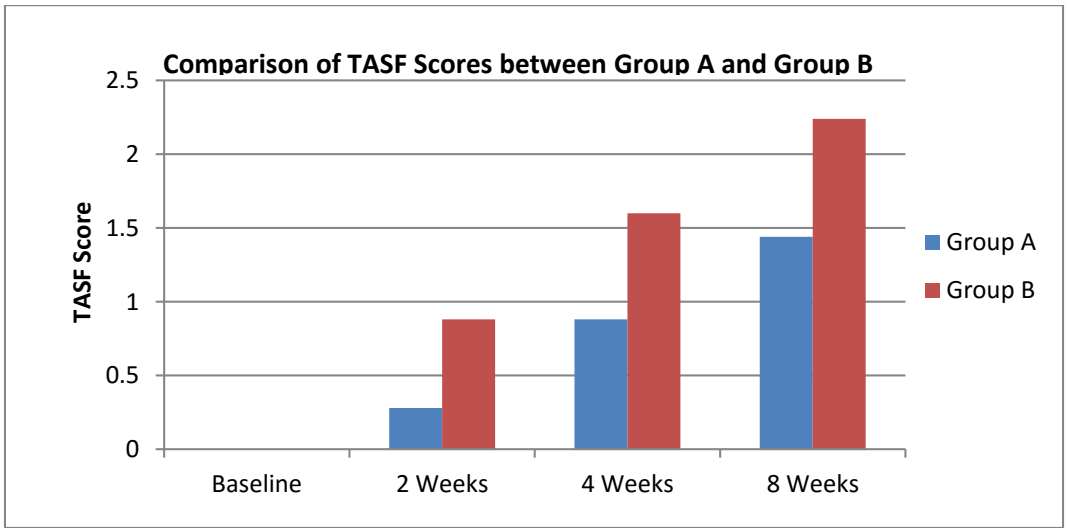

Fig. 4: The comparison of overall treatment response between both groups; a greater number of group A patients scored higher on the scale.

Discussion

Oral Lichen Planus(OLP) is a chronic condition which substantially degrades the quality of life of the patient. Several cases prove refractory to treatment. Several treatments have been reported in literature with varying degrees of success.[8-10,17]

The goal of this work was to compare the safety and efficacy of Lycopene and of Levamisole in the management of Oral Lichen Planus. Lycopene exerts its antioxidant activity by physical and chemical quenching of free radicals.[11,12] It has shown to be effective in the management of oral leukoplakia and oral submucous fibrosis and to play a role in the chemoprevention of oral cancer.[13,14] However, its role in the management or prevention of OLP has been investigated by few studies.[9] Lycopene may be effective in OLP because significantly decreased levels of antioxidants have been reported in patients with atrophic and erosive OLP.[4] Further, by virtue of its antioxidant and anticancer properties, it may be useful in the prevention of malignant transformation.

Levamisole is a levisomer of tetramisole 2,3,5,6-tetrahydro- 6-phenylimidazole [2,1-6] thiazolemono-hydrochloride),. It is a synthetic phenylimidothiazole salt and has been used as a broad spectrum anti-helminthic drug since 1966.[15] In 1978, Renoux et al.[16] reported that levamisole increased cellular immunity. In 1990, the FDA approved levamisole for many autoimmune and inflammatory diseases and it is now classified as an immunomodulator drug. It enhances immune responsiveness by T-cell activation. Levamisole may have a protective or curative effect on diseases characterized by formation of immune complexes. It has been confirmed that formation of subepithelial immune deposits is a histological feature of OLP.[17]

The dose regimen of 8 mg/day of lycopene employed in the present study was derived from a previous study that used lycopene in oral leukoplakia with effective results.[14] The duration of 8 weeks was chosen because OLP is a chronic condition. This duration is consistent with previously reported studies performed to treat OLP that employs other drugs. Levamisole is typically recommended for intermittent use because some studies report agranulocytosis as a side effect of continuous administration. In our study, intermittent cyclic dosage of levamisole(150mg thrice weekly in divided doses) was chosen due to safety considerations. No patients in levamisole group reported any adverse effects.

In this study, the most common forms of OLP were found to be reticular and erosive, which are most commonly described as having the most severe symptoms and refractory.[1] Lycopene group reported lowering in burning sensation at 2 weeks which indicates that lycopene probably has an earlier therapeutic onset than levamisole. Although there was significant reduction in the mean scores for evaluating pain and burning sensation in both the groups after 8 weeks of treatment, this reduction was more in lycopene group (64.3%) as compared to the levamisole group (37.7%). The more potent therapeutic effect observed in the former is significant enough to be attributed to the drug.

The overall treatment response [Figure 4] assessed by Tel Aviv San Francisco Scale showed significant percentage of patients in lycopene group demostrated 50% or more improvement, notably 48% patients showing 70 - 100% relief in signs and symptoms and did not require further treatment. In the levamisole group, 44% patients showed 50% or more improvement. However, only 1 patient showed 70–100% relief in signs and symptoms and did not require further treatment. The difference in the mean percentage improvement was statistically highly significant.

The results of this study, therefore, indicated that lycopene was more effective in controlling the signs and symptoms of OLP. Although the percentage of patients benefitted is clearly higher in the lycopene group, the difference in mean was more statistically significant at the end of 2 weeks than at the end of 8 weeks of treatment. In other words, the treatment effect of levamisole might be less potent and slower than that of lycopene, but in the long term, levamisole monotherapy was also shown to be effective for the treatment of OLP. In our knowledge, a comparative assessment of efficacy of Lycopene and Levamisole has never been reported in literature.

The adverse effects associated with corticosteroids used in the treatment of OLP represent a major clinical problem.[5-7] Several other clinical trials with other drugs like retinoids etc. in OLP patients have reported adverse effects[8,10]. Levamisole was associated with agarulocytosis in some studies. [19,20] However, this rare side effect was observed only in patients with HLA-B27 positivity and in conditions requiring extremely long term therapy like Rheumetoid arthiritis. Tai et al[21] reported a case of itching as side effect in a study of levamisole in OLP, but in our study none of the patients in levamisole group reported any side effects. Lycopene is a safe drug with no reported adverse effects.[22] Our findings were consistent with the safety profile of Lycopene - none of the patients from lycopene group in our study reported any adverse effects. Further, none of the patients reported recurrence of lesions in our study, although the study period was limited.

While the results of this study are promising, it should be interpreted in the light of its limitations. However, there are still some problems which require further investigation. First, this study provides limited insights into the mechanisms involved in the therapeutic effects of lycopene and levamisole in OLP. Further studies should be performed to gain mechanistic insights into the therapeutic effects of these

drugs, which will help establish appropriate drug dosage and effective treatment regimen. Second, the commercial availability of levamisole in the dosage required was found to be a major problem. The cyclic dosage recommended also results in decreased patient compliance. More research proving the effectiveness of this drug in oral diseases is needed to make it widely available in the future. Similarly, an exclusive lycopene formulation is not yet available. For example, the drug used in this study also included Vitamin A, α-tocopherol, zinc and selenium, which are known to have antioxidant properties. It is unclear that apparent reductions in disease risk result whether from the other constituents or from lycopene alone.

Lastly, the limited sample size and short follow up period in this study necessitate more elaborate clinical trials to further investigate the potential use of lycopene and levamisole in management of Oral Lichen Planus.

Conclusion

The results of this study showed that both lycopene and levamisole are effective and safe alternatives to steroids for OLP. Lycopene produced relief from symptoms within the first week of treatment and a significant improvement in signs and symptoms by the end of 2 months. While no immediate change in symptoms was observed after initial therapy with levamisole, a significant therapeutic effect was observed after two months of treatment. A more potent effect was observed with use of lycopene than levamisole. No adverse effects were seen with the use of either drug in the entire duration of this study. The results of this study motivate continued investigation of Lycopene and Levamisole in management of OLP with larger sample size and longer follow-up periods.

Conflict of Interest: The authors declare no conflict of interest.

Source of Support: Nil

References

1. Alan Motto do Canto, Helena Muller, Ronaldo Rodrigues de Freitas, Paulo Sergio da Silva Santos. Oral lichen planus(OLP): clinical and complementary diagnosis. An Bras Dermatol. 2010;85(5):669-75
2. M. Carrozzo, R. Thorpe. Oral lichen planus: a review. Minerva Stomatol 2009;58:519-37
3. Lavanya N, Jayanthi P, Umadevi K Rao, Ranganathan K.Oral lichen planus: An update on pathogenesis and treatment JOMFP 2011;15: 2:127-32
4. Ergun S, Troşala SC, Warnakulasuriya S, Özel S, Önal AE, Ofluoğlu D, Güven Y, Tanyeri H. Evaluation of oxidative stress and antioxidant profile in patients with oral lichen planus. J Oral Pathol Med.2011;40(4)286-93.
5. Lodi G, Scully C, Carrozzo M, Griffiths M, Sugerman PB, Kobkan Thongprasom. Current controversies in oral lichen planus: Report of an international consensus meeting. Part 2.Clinical management and malignant transformation. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2005;100:164-78
6. Thongprasom K, Dhanuthai K. Steroids in the treatment of lichen planus: a review. J. Oral Sci 2008;50(4)377-85.
7. Jainkittivong A, Kuvatanasuchati J, Pipattanagovit, Sinheng W. Candida in oral lichen planus patients undergoing topical steroid therapy. Oral Surg Oral Med Oral Pathol Oral Radiol Endod2007;104:61-66.
8. Gorsky M,Raviv M. Efficacy of etretinate (Tigason) in symptomatic oral lichen planus.Oral Surg Oral Med Oral Pathol 1992; 73(1)52-55
9. Sawarn N, Shashikanth C, Sawarn S, Jirge V, Chaitanya NC, Pinkapani R. Lycopene in the management of oral lichen planus: a placebo controlled study. Indian J Dent Res 2011;22:639-43
10. Lu SY, Chen WJ, Eng HL. Dramatic response to levamisole and low-dose prednisolone in 23 patients with oral lichen planus: a 6-year prospective follow-up study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1995;80:705-709.
11. Clinton SK. Lycopene: Chemistry, Biology, and Implications for Human Health and Disease; Nutrition Rev 1990;56:2:35-52
12. Lu R, Dan H, Wu R, Meng W, Liu N, Jin X et al. Lycopene: features and potential significance in the oral cancer and precancerous lesions;J Oral Pathol Med 2011,40: 361–368
13. Kumar A, Bagewadi A, Keluskar V, Singh M. Efficacy of lycopene in the management of oral submucous fibrosis; Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007;103: 207–13.
14. Singh M, Krishanappa R, Bagewadi A, Keluskar V. Efficacy of oral lycopene in the treatment of oral leukoplakia; Oral Oncol 2004;40:591-6.
15. Janssen PA.The levamisole story.Prog Drug Res1976;Vol 20:347-83
16. Renoux G, Renoux M, Teller MN, McMahon S, Guillaumin JM. Potentiation of T-cell mediated immunity by levamisole. Clin. Exp. Immunol 1976; 25: 288-96.
17. Francisca Fernández-González, Rocío Vázquez-Álvarez, Dolores Reboiras-López, Pilar Gándara-Vila, Abel García-García, José-Manuel Gándara-Rey. Histopathological findings in oral lichen planus and their correlation with the clinical manifestations; Med Oral Patol Oral Cir Bucal. 2011 Aug 1;16 (5):e641-6.
18. Rosenthal M, Trabert U, Muller W. The effect of levamisole on peripheral blood lymphocyte subpopulations in patients with rheumatoid arthritis and ankylosing spondylitis; Clin Exp Immunol 1976;25:493 496.
19. Scott J, Dieppe PA, Huskisson EC. Continuous and intermittent levamisole. A controlled trial; Ann Rheu Dis 1978; 37:259-261.
20. Tai HW, Park SY, Kim BS, Seo PH. Park,SR. Levamisole Monotherapy for Oral Lichen Planus; Ann Dermatol 2009, 21:3:250-25
21. Trumbo PR. Are there adverse effects of lycopene exposure? J Nutr 2005; 135: 2060S 1S.