ORIGINAL RESEARCH

EFFICACY OF LYCOPENE IN COMBINATION WITH VITAMIN E IN MANAGEMENT OF ORAL SUBMUCOUS FIBROSIS - A CLINICAL PROSPECTIVE STUDY

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ABSTRACT:
Background: Oral submucous fibrosis is a precancerous condition with 7-12% malignant potential rate. Present study was conducted with aim to elucidate the role of lycopene in treatment of oral submucous fibrosis. Material and methods: The study group included 72 patients with OSMF. Out of 72, 24 patients were given lycopene, other 24 with lycopene + Vitamin E and remaining 24 were on placebo drug. Lycopene group patients received 8 mg Lycored TM per day in two divided doses of 4 mg each, second group with LYC-O-MATO soft gels while placebo group patients received placebo tablet twice a day. Patients were examined for changes in mouth opening and other clinical symptoms of OSMF during three months. Results: Lycopene in combination with vitamin E was found to be significantly efficacious in the improving signs and symptoms of OSMF. It was effective in reducing the objective signs of OSMF as demonstrated by the improved maximal mouth opening, and reduction in burning sensation, erosion/ ulceration. Conclusion: Lycopene in combination with vitamin E is a highly efficacious drug in the management of oral submucous fibrosis which is proven to be as safe and reliable treatment method.
Key words – Lycopene, Oral submucous fibrosis, Precancerous condition, Vitamin E.

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INTRODUCTION:

Oral cancer is a progressive disease known to involve a series of recognizable stages called 'the multistep process of tumorogenesis'. Tobacco use, in any form, is implicated as an important risk factor in the development of oral cancer. In the long incubation period between the initiation of carcinogenic tobacco habits and the development of invasive oral cancer, well-defined precancerous or premalignant lesions/conditions occur. Oral submucous fibrosis (OSMF) is a chronic, debilitating, premalignant condition affecting all ages and both sexes in the Indian subcontinent. Although thought to be multifactorial, various risk factors like areca nut chewing, chilli consumption, nutritional deficiency states, genetic susceptibility and collagen disorders have been suggested. It is a chronic condition characterised by mucosal rigidity of varying intensity due to fibro-elastic transformation of juxta-epithelial layer. Predominantly Type I collagen with variable amounts of other types of collagen constitute fibrosis.[1] A variety of etiologic factors including capsaicin, betel nut alkaloids, hypersensitivity, autoimmunity, genetic predisposition and chronic iron and vitamin B-complex deficiency have been suggested by various authors, the most common of which is chewing areca nut. Excessive use of areca nut may cause fibrosis due to increased synthesis of collagen and induce the production of free radicals and reactive oxygen species, which are responsible for high rate of oxidation/peroxidation of polyunsaturated fatty acids which affect essential constituents of cell membrane and might be

involved in tumorigenesis. Arecanut chewing is deep rooted in Indian culture and has been used as a mouth freshening agent that has various symbolic roles throughout Indian history. The most alarming fact is that this habit is becoming increasingly popular among adolescents.[2] Various modalities of treatment ranging from conservative treatment to surgical procedures have been attempted. Intra-lesional injections of steroids has been used in its treatment since quite long as a drug of choice. But there has been new interest in use of natural pigments in plants like lycopene, found to reverse the pathogenesis of OSMF.[3] Lycopene, a carotenoid found in tomato products, prevents oxidation of low density lipoprotein (LDL) cholesterol and reduces the risk of developing atherosclerosis and coronary heart disease. The daily consumption of tomato products provides at least 40 mg of lycopene which was enough to lower low density lipoprotein (LDL) oxidation. High LDL oxidation is associated with increased risk of atherosclerosis and coronary heart disease. This lycopene level can be achieved by drinking just two glasses of tomato juice a day. Research shows that lycopene in tomatoes can be absorbed more efficiently by the body if processed into tomato juice, sauce, paste and ketchup.[4] It is a powerful antioxidant and has a singlet-oxygen-quenching ability twice as high as that of betacarotene and ten times higher than that of alpha-tocopherol. It is a potent anticarcinogenic and has demonstrated profound benefits in precancerous lesions and conditions. Vitamin E also known as tocopherol have antioxidant properties whose major function is to prevent peroxidation of unsaturated fatty acids. Lycopene has been successfully tried in management of leukoplakia and few studies have been conducted in recent time in lieu of treatment of oral submucous fibrosis.[5]

So, this study had been conducted to elucidate the role of lycopene in combination with vitamin E in management oral submucous fibrosis.

MATERIALS AND METHODS

This was a clinical prospective study conducted between March 2015 and July 2015 on total of 90 patients, who visited the Department of Oral Medicine and Radiology, Vyas Dental College & Hospital, Jodhpur, Rajasthan, India, were selected for the study, where oral submucous fibrosis was confirmed both clinically and histologically. Of these, 72 patients successfully completed the trial and reported for follow-up. Ethical approval was obtained from relevant ethical committee prior to study commencement. The aim and purpose of the study was explained to each patient thoroughly and written consent was obtained. Also the habits like tobacco chewing and ethanol usage were assessed on each visit and the patients were encouraged to discontinue the same. These 72 patients were randomly categorized (irrespective of the size and severity of the lesions) in two groups:

Group A (Lycopene Group): Twenty-four patients were treated with 8 mg of lycopene in two equally divided doses. The product used in the study was softgel Lycored TM, Jagsonpal Pharmaceuticals, New Delhi

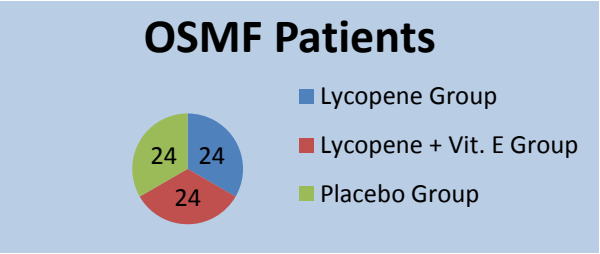
Group B (Lycopene + Vit. E Group): Twenty-four patients were treated with 8 mg of lycopene + vitamin E (400 I.U.) + selenium (200 mcg) in two equally divided doses. The product used in the study was LYC-O-MATO soft gels, manufactured by Mano pharmaceuticals, Chennai, India.

Group C (Placebo Group): Twenty four patients were given placebo capsules once daily.

Patients were evaluated every 15 days during the treatment period of three months and were further followed up for two months. The main parameters assessed were improvements in mouth opening as inter-incisor distance in mm and burning sensation by visual analog scale (VAS) from 1 to 10. The two parameters were recorded weekly for 2 months. One-way ANOVA followed by post hoc Tukey's test for group-wise comparisons were used. During each visit, the patients were examined for Presence or absence of erythematous areas/ulceration/erosions, Burning sensation and mouth opening.

RESULTS:

All the patients (100%) had habit of chewing areca nut or gutkha. Results showed that there was significant improvement in mouth opening in patients subjected to lycopene as compared to placebo group. (Table 1, 2 and 3) Patients also showed reduction in burning sensation and erythematous/ ulceration/ erosions. (Table 4 and 5)



Graph 1: Distribution of oral submucous fibrosis patients in three groups.

Table 1: Improvement of mouth opening in consecutive weeks in different groups

Group	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8
A	24.80	25.60	25.80	26.25	28.5	30.6	31.40	32.20	32.60
B	24.60	26.20	26.80	27.20	28.85	32.65	32.80	33.20	33.60
C	25.10	25.20	25.60	25.80	26.20	26.5	26.60	26.80	27.10

Table 2: Maximum mouth opening

	Lycopene group No. of patients (%)	Lycopene + Vit. E group No. of patients (%)	Placebo group No. of patients (%)
Baseline	24 (100)	24 (100)	24 (100)
Improvement at exit	18 (75)	20 (83.33)	4 (16.67)
No Improvement at exit	6 (25)	4 (16.67)	20 (83.33)

Table 3: Comparison of mouth opening (post-treatment) for lycopene and placebo group

Characteristics	Lycopene group	Lycopene + Vit. E group	Placebo group
Mean ±SD	5.38 ± 2.45	6.28 ± 2.45	1.08±0.25
P value		P< 0.05	

Table 4: Burning sensation at exit in both the groups. (Percentage in parentheses)

Out of 24 patients	Lycopene group		Lycopene + Vit. E group		Placebo group	
	Present	Absent	Present	Absent	Present	Absent
Exit	4(16.67)	20 (83.33)	2(8.33)	22(91.66)	8 (33.33)	16 (66.67)
Chi square value					$\chi 2$ =1.69 Significant P<0.05	

Table 5: Improvement of Burning sensation in Lycopene group Placebo group

Group	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8
A	10	9.6	8.4	7.6	6.2	5.4	3.2	2.1	0.4
B	10	9.6	8.2	7.4	5.80	5.20	3.0	1.60	0.10
C	10	9.8	9.6	9.4	8.8	8.6	8.4	7.8	7.6

Table 6: Erythematous areas/ulcerations/erosions at exit in Lycopene and Placebo group

	Lycopene group		Lycopene + Vit. E group		Placebo group	
Out of 24 patients	Present	Absent	Present	Absent	Present	Absent
Exit	4	20	2	22	8	16
Chi square value					$\chi 2$ =1.79 Significant P<0.05	

DISCUSSION

This is study was conducted to evaluate the efficacy of lycopene in combination with vitamin E to manage Oral submucous fibrosis. OSMF was defined by Schwartz as 'a chronic disease affecting any part of the oral cavity and sometimes the pharynx, associated with juxta-epithelial inflammatory reaction followed by a fibro-elastic change of the lamina propria leading to stiffness of oral mucosa and causing trismus. Although various risk factors are implicated, most important factor is areca nut chewing in various forms such as gutkha, pan masala etc.[6]

Present study revealed that all the patients have positive history of areca nut chewing in the raw form, as a quid or in a commercial preparation such as gutkha or pan masala which has proven to be a major causative agent for oral submucous fibrosis.

According to J P Caniff [7], medical management of oral submucous fibrosis is both empirical and unsatisfactory, while treatment with vitamins was ineffective in improving trismus as stated by Lai DR et al[8].

Gupta S et al[9] in 2004 and L Aravindh et al[10] in 2012 observed that there is significant reduction of vitamin E in OSMF patients which in turn reflects the significant increase of oxidative stress in the progression of Oral sub mucous fibrosis to Oral cancer. Considering existing data, a newer antioxidant like lycopene in combination with Vitamin E with more potent properties is tried in the present study.

Present study showed significant improvement in symptoms of oral submucous fibrosis in placebo group with cessation of habit only, which reinforces the literature published about stoppage of habit as the first line of treatment.[11]

Till date, no treatment protocol has been formulated to restore the mouth opening to normal; however, gross improvement has been observed. Present study showed significant improvement in mouth opening (83.33%) in OSMF patients subjected to lycopene + Vit. E treatment as compared to with only lycopene (75%) and placebo group. Similar results have also been obtained by Karemore et al[12] who observed improved mouth opening of 69.56% with lycopene group, whereas Maher R et al[13] showed lesser percentage (41%) using multiple micronutrients. But we did not find any study in reviewed literature which has used the combination of Vit. E with lycopene.

Although the underlying mechanism which leads to trismus in OSMF patients is still poorly understood, the main cause may be fibrosis and fibrous band formation in the oral mucosa. Patients who had longer history of OSMF had a lesser improvement in mouth opening than patients who had short-term disease. Present study showed that patients who stopped their habit recently showed significant improvement in mouth opening as compared to patients who complained of decreased mouth opening and had stopped chewing betel nut three-four years back. These findings suggested that there may be a synergistic effect of lycopene and cessation of the habit in bringing about the improvement in mouth opening.

Present study showed better tolerance to spicy food and burning sensation alongwith absence of erythematous areas or ulceration or erosions in lycopene with Vit E group as compare to lycopene and placebo group.

91.66%of subjects of group B have shown significant improvement in burning sensation as compared to group A (83.33%) and placebo group having 66.67%. Definite reduction in the burning sensation and an increase in the mouth opening were noted with oral lycopene in the study by Kumar et al.[14] and Gowda B et al[15]. also found encouraging results with lycopene therapy and added that long term maintenance therapy may be needed to have an impact on oral cavity cancer incidence. Present study showed a significant improvement in mouth opening, burning sensation and erosions/ ulcers with a combination of Vitamin E and lycopene.

CONCLUSION:

Lycopene is an efficacious drug and when it is used in combination with vitamin E it is proven to be more potent, safe and reliable method to treat oral submucous fibrosis in contrast to other management modalities, which offers a non invasive option that yields significant improvements in the symptoms as well as objective signs of the condition.

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