

**LYCOPENE IN THE MANAGEMENT OF ORAL SUBMUCOUS FIBROSIS**

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**ABSTRACT**

**Background:** Oral Submucous Fibrosis is a potentially malignant disorder well known for its chronic and resistant nature. The conservative drug treatment that is currently available for this disorder is clearly inadequate. The aim of the study was to evaluate the efficacy of oral lycopene therapy when used in combination with conventional intralesional steroid therapy in the management of oral submucous fibrosis. **Methods:** Forty five patients with oral submucous fibrosis (grade III and IV) were included under the study and were randomly divided into 3 groups consisting of 15 cases each: Group A (oral lycopene 16 mg/day with biweekly intralesional steroids and hyaluronidase), Group B (oral antioxidant capsules with biweekly intralesional steroids and hyaluronidase) and Group C (biweekly intralesional steroids and hyaluronidase alone). Mouth opening and burning sensation were recorded from baseline to 6 weeks. Cases were followed up to 3 and 6 months. **Results:** There was significant increase in mouth opening among all the 3 groups. The results were statistically significant between Group A and C and Group B and C. **Conclusion:** Lycopene in combination with intralesional steroids and Hyaluronidase, is highly efficacious in improving the mouth opening and reducing other symptoms in patients with Oral Submucous Fibrosis. No side effects were reported with its usage.

**Keywords:** Submucous, anticarcinogenic, cyclooxygenase and lipoxygenase.

**INTRODUCTION**

Oral submucous fibrosis (OSF) is a potentially malignant disease that is insidious and chronic in nature affecting the entire oral cavity, sometimes extending to the pharynx. It has drawn considerable attention in recent past due to its high malignant potential and chronic debilitating and resistant nature. It is seen predominantly in people of Asian descent especially among Indian population [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 [2]. 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 [3]. The most alarming fact is that this habit is becoming increasingly popular among adolescents.

The ingredients of arecanut induce excessive reactive oxygen species which damages the cell structures, including lipids and membranes, proteins and nucleic acids. Moreover vitamin deficiency, iron deficiency anaemia, and malnutrition can derange the repair of the inflamed oral mucosa, leading to defective healing and the resulting atrophic oral mucosa is more susceptible to the effects of areca nut. Here comes the role of Antioxidant vitamins that stabilize and deactivate the free radicals before they attack cells 2.

One such type of antioxidant is Lycopene. Lycopene is a phytochemical, synthesized by plants (tomatoes) and microorganisms but not by animals. It is a powerful antioxidant and has a singlet-oxygen-quenching ability twice as high as that of beta-carotene and ten times higher than that of alpha-tocopherol 2. It is a potent anticarcinogenic and has demonstrated profound benefits in precancerous lesions like leukoplakia [4]. It has also been suggested that no single drug has provided complete relief of symptoms of OSF 2. So we decided to adopt a combination of drugs to treat OSF. The

aim of the study was to evaluate the efficacy of oral lycopene therapy when used in combination with conventional intralesional steroid therapy in the management of OSF.

**MATERIALS AND METHODS**

Totally 45 patients with signs and symptoms of OSF were recruited for the study from the Department of Oral Medicine and Radiology, Tamilnadu Government Dental College and Hospital, Chennai, India. The Institute's Ethical Committee approval was obtained. The patients were included under the study only after satisfying the following criteria:

- History of the habit of chewing arecanut or any of its commercial products.
- Burning sensation on eating spicy food.
- Restricted mouth opening with or without palpable vertical fibrous bands on the buccal mucosa with stiffness and blanching and without tongue involvement - Grade III and IV (Chandra et al [5])

Patients with histologically proven OSF turning into malignancy were excluded from the study. Informed consent was obtained from all the patients. They were then explained about the disease condition and its premalignant potential. The patients were then counselled to stop the habit of using arecanut in all its forms. Complete oral prophylaxis was done to improve the oral hygiene as well as to motivate the patient to stop the habit.

The patients were then randomly divided into three groups (A, B and C) consisting of 15 cases each. Group A patients were given oral Lycopene capsules 16 mg (Lycostar®, Mankind Pharma Ltd., New Delhi, India), one capsule/day along with bi-weekly intralesional injections of Dexamethasone 1.5 ml & Hyaluronidase 1500 IU mixed with lignocaine. Lycostar contains Lycopene 5000 µg along with various micronutrients. Group B patients were given oral antioxidant capsules (Multivitamin A-Z soft capsules, PrimePharm, Shanghai, China), one capsule/day along with bi-weekly intralesional injections of Dexamethasone 1.5 ml & Hyaluronidase 1500 IU mixed with lignocaine. Group C patients were given bi-weekly intralesional injections of Dexamethasone 1.5 ml & Hyaluronidase 1500 IU with lignocaine alone without any other oral supplements.

Patients were evaluated every week during the treatment period of 6 weeks. The following parameters were recorded during each week:

**Burning sensation**

It was recorded at baseline before the start of the treatment and at the end of every week for a period of 6 weeks during treatment using Visual Analog Scale (VAS) for pain. It was scored from 0 to 10 purely based on patient's response (Score 0: no pain; Score 10: severe pain).

**Mouth opening**

Mouth opening was assessed by measuring the interincisal distance from the mesioincisal edge of the maxillary right central incisor to the mesioincisal edge of the mandibular right central incisor using vernier callipers. If either of the teeth were missing, their left side counterpart was used for measurement. Mouth opening was recorded at baseline before the start of the treatment and subsequently at the end of every week for 6 weeks during treatment period. It was also recorded post treatment at 3 and 6 month follow-up period.

**Table 1: Shows Age Distribution of Patients**

Groups	18-20 Y	21-30 Y	31-40 Y	41-50Y
Group A	2	11	1	1
Group B	0	9	5	1
Group C	0	7	7	1

**Habits**

All the patients included under the study had the habit of chewing arecanut either in the pure form or in the form of gutkha, pan masala or mawa. The most common form of areca nut used was Gutkha (64.4%). 29 out of 45 patients were using it. The median duration of habits was 5 yrs (range: 1 to 15years). The median frequency of chews per day was 5 times (range: 1 to 20 times).

**Burning sensation**

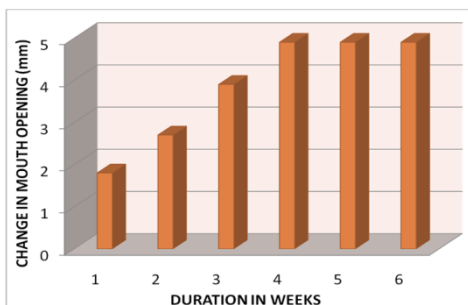
The mean VAS scores at baseline before start of treatment among patients in group A, B and C were 7.5, 7 and 7.5 respectively. All the patients in Group A, B and C reported complete relief of burning sensation (score 0) within 3 weeks of the start of treatment.

**Mouth opening**

**Change in mouth opening among Group A**

The average increase in mouth opening from baseline (before treatment) to week 6 was  $4.9 \pm 2.5$  mm. When the average mouth opening values from week 1 to 6 were compared with the baseline value, the results were found to be statistically significant ('p' value: < 0.0001, 0.001, 0.001, 0.001, 0.001 and 0.001 respectively). (Fig.1)

A bar chart demonstrating average change in mouth opening during treatment period in Group A.



**Figure 1: It Shows Changes in Mouth Opening in Group A**

**Change in mouth opening among Group B**

The average increase in mouth opening from baseline (before treatment) to week 6 was  $4.3 \pm 0.8$  mm. The results were statistically significant when the average mouth opening values from week 1 to 6

**Statistical analysis**

Mean and Standard Deviation were estimated for each study group. Normality of the data was tested in each group by using Kolmogorov Smirnov test. Mean values were compared between different study groups by using Kruskal-Wallis One Way ANOVA followed by Mann-Whitney U-Test after adjusting the p-values for multiple comparison by using Bonferroni Correction method. Mean values were compared between different time points within the same group by using Wilcoxon Signed Rank Sum Test. In the present study,  $p < 0.05$  was considered as the level of significance.

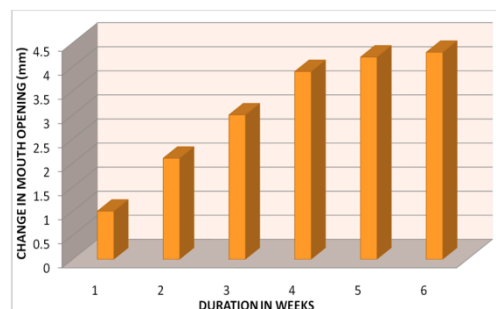
**RESULTS**

**Age and sex distribution**

All the patients fall within the age range of 18 to 49 years with maximum number of patients in the age group of 21 to 30 years. Eleven patients in group A, nine patients in group B and 7 patients in group C were in this age group (Table 1). All the 45 patients were male.

were compared with the baseline value ('p' value: < 0.0001, < 0.0001, 0.001, 0.001, < 0.0001 and 0.001 respectively). (Fig.2)

A bar chart demonstrating average change in mouth opening during treatment period in Group B.

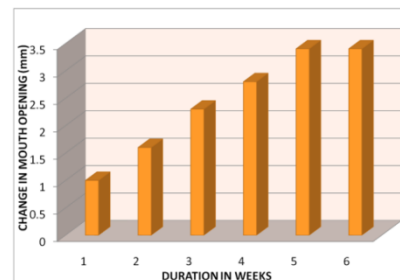


**Figure 2: It Shows Changes in Mouth Opening in Group B**

**Change in mouth opening among Group C**

The average increase in mouth opening from baseline (before treatment) to week 6 was  $3.4 \pm 0.5$  mm. When the average mouth opening values from week 1 to 6 were compared with the baseline value, the results were found to be statistically significant ('p' value: < 0.0001, < 0.0001, < 0.0001, < 0.0001, < 0.0001 and < 0.0001 respectively). (Fig.3)

A bar chart demonstrating average change in mouth opening during treatment period in Group C.



**Figure 3: It Shows Changes in Mouth Opening in Group C**

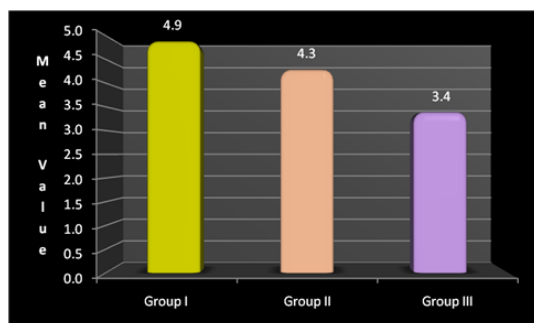
### Intergroup comparison in mouth opening

When the average mouth opening values between baseline and week 6 was compared among all the three groups (A, B and C), there was

**TABLE 2: SHOWS INTERGROUP COMPARISON IN MOUTH OPENING BETWEEN BASELINE AND WEEK 6**

Time points compared	Group	Mean $\pm$ S.D.	Overall p-value	Significant Groups
Week 0 to Week 6	A	4.9 $\pm$ 2.5	<0.0001 (Sig.)	A vs. C
	B	4.3 $\pm$ 0.8		B vs. C
	C	3.4 $\pm$ 0.5		

A bar chart demonstrating average change in mouth opening from baseline to week 6 among Group A, B and C.



**Figure 4: It Shows Intergroup Comparison in Mouth Opening**

### Adverse effects

No adverse effects were reported during the treatment period as well as during follow-up.

### DISCUSSION

Oral submucous fibrosis is well known for its chronic and resistant nature. The conservative drug treatment that is currently available for OSF is clearly inadequate. No single drug has provided complete relief of symptoms of OSF 2; this has led to the use of combination of drugs to treat the condition.

Lycopene is a major carotenoid found in tomato which has potent anticancer activity in many types of cancer 6. The antioxidant properties of lycopene are thought to be primarily involved in its preventive effects in chronic diseases. It also has potent benefits in oral potentially malignant lesions like leukoplakia 4. Because of its high number of conjugated dienes, lycopene is one of the most potent antioxidants, with a singlet-oxygen-quenching ability twice as high as that of  $\beta$ -carotene and 10 times higher than that of  $\alpha$ -tocopherol 7. The antioxidant potential has been ranked as follows: lycopene >  $\alpha$ -tocopherol >  $\alpha$ -carotene >  $\beta$ -cryptoxanthin > zeaxanthin =  $\beta$ -carotene > lutein [8]. OSF is well known for its high rate of malignant transformation which is about 2.3 to 7.6% 2. In this regard, the antioxidant properties of lycopene may be of great benefit by withholding its progression to carcinoma.

In our study, all the patients were males (100%). It clearly demonstrates male predominance of the condition. This was in accordance with the study conducted by Ranganathan et al which recorded a male to female ratio of 9.9:1 among OSF patients [9]. Maximum number of patients (27 out of 45 patients; 60%) in our study fell under the age group of 21 to 30 years which was similar to the findings of Maher et al who reported that 70% of males with OSF were below 30 years of age [10]. When considering the habit of chewing arecanut, most of the patients in our study chewed Gutkha (64.4%). OSF was more prevalent among Gutkha chewers than the other forms of arecanut. The study conducted by Bathi et al was also in agreement with this fact [11].

In OSF grades I and II, the mouth opening of the patients are not affected. The efficacy of lycopene and other antioxidants is similar in early stages of OSF when mouth opening is normal 2. But the

statistically significant change between Group A and Group C, and Group B and Group C ('p' value: < 0.0001). (see table 2, Fig.4) There was no change in the mouth opening at 3 and 6 months.

difference arises only when restriction in mouth opening sets in. Also Kumar et al suggests that severe cases of OSF are poor responders to lycopene 3. So in our study, we included patients only with grade III and IV OSF. The improvement in mouth opening from baseline (before start of treatment) to week 6 was statistically significant among all the three study groups A, B and C.

When intergroup comparisons were made with regard to mouth opening, there was significant difference between Group A (lycopene with intralesional steroids) and C (intralesional steroids alone) as well as Group B (antioxidants with intralesional steroids) and C (intralesional steroids alone) ('p' value < 0.0001). But even though Group A (lycopene with intralesional steroids) showed greater improvement in mouth opening (34.9  $\pm$  5.6) than Group B (antioxidants with intralesional steroids) (32.2  $\pm$  6.7), the results of Group A and B did not differ enough to be statistically significant ('p' > 0.05).

This clearly indicates that lycopene is more efficacious than other antioxidants when used in combination with intralesional steroids to treat OSF. The improvement in mouth opening observed in our study can be attributed to two reasons: 1. Lycopene exerts its anti-inflammatory action by increasing the lymphocyte resistance to stress [12], inhibition of pivotal pro-inflammatory mediators, such as the reduction of reactive oxygen species, the inhibition of synthesis and release of pro-inflammatory cytokines, changes in the expression of cyclooxygenase and lipoxygenase, modifications of eicosanoid synthesis, and modulation of signal transduction pathways, including that of the inducible nitric oxide synthase [13]. 2. Lycopene has been shown to inhibit hepatic fibrogenesis in LET rats by Kitade et al [14]. A similar action may be expected in OSF.

We believe that lycopene when combined with intralesional steroids offer more benefit than when used alone. Our view is also supported by Chole et al 2. But it was contradicting with the findings of Kumar et al who stated that the results were better when lycopene is used alone 3. In our study, the greater improvement in mouth opening when lycopene was combined with intralesional steroids may be attributed to the synergistic effect obtained when both the drugs were used together.

Our study clearly demonstrates that Lycopene in combination with intralesional steroids and Hyaluronidase, is highly efficacious in improving the mouth opening and reducing other symptoms in patients with Oral Submucous Fibrosis. No side effects were reported with its usage; hence it proves to be a completely safe drug when compared with the other treatment options available for oral submucous fibrosis. It can be prescribed either alone as a first-line drug in early stages of the disease or in combination with intralesional steroids in moderate stages of OSF. Further studies with larger sample size should be undertaken to substantiate its efficacy in the management of oral submucous fibrosis and to demonstrate the probable mechanisms through which it exerts its action.

### REFERENCES

1. Akbar M. Oral submucous fibrosis – a clinical study. J Indian Dent Acad 1976; 48: 365-73.
2. Revant H. Chole, Shailesh M. Gondivkar, Amol R. Gadbaal, Swati Balsaraf, Sudesh Chaudhary, Snehal V. Dhore et al. Review of drug treatment for oral submucous fibrosis. Oral Oncol 2012; 48: 393-8.

3. Kumar A, Begawadi 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.
4. Singh M, Krishanappa R, Bagewadi A, Keluskar V. Efficacy of oral lycopene in the treatment of oral leukoplakia. *Oral Oncol* 2004; 40: 591-6.
5. Chandra GDS, Rameshwar DS, Iqbal A. Treatment modalities in Oral submucous fibrosis: how they stand today? Study of 600 cases. *Indian Journal of Oral and Maxillofacial surgery* 1992; 7: 43-7.
6. Teodoro AJ, Oliveira FL, Martins NB, Maia GA, Martucci RB, Borojevic R. Effect of lycopene on cell viability and cell cycle progression in human cancer cell lines. *Cancer Cell Int.* 2012 Aug 6; 12(1): 36. [Epub ahead of print]
7. Palozza P, Catalano A, Simone R, Cittadini A. Lycopene as a guardian of redox signalling. *Acta Biochim Pol.* 2012; 59(1): 21-5.
8. Stahl W, Junghans A, De Boer B, Driomina ES, Briviba K, Sies H. Carotenoid mixtures protect multilamellar liposomes against oxidative damage: synergistic effects of lycopene and lutein. *FEBS Lett* 1998; 427: 305-8.
9. Ranganathan K, Devi Mu, Joshua E, Kirankumar K, Saraswathi TR. Oral submucous fibrosis: a case-control study in Chennai, South India. *J Oral Pathol Med.* 2004; 33(5): 274-7.
10. Maher R, Lee AJ, Warnakulasuriya KA, Lewis JA, Johnson NW. Role of areca nut in the causation of oral submucous fibrosis: a case-control study in Pakistan. *J Oral Pathol Med.* 1994; 23(2): 65-9.
11. Bathi RJ, Parveen S, Burde K. The role of gutka chewing in oral submucous fibrosis: a case-control study. *Quintessence Int.* 2009; 40(6): e19-25.
12. Heber D, Lu Q-Y. Overview of mechanisms of action of lycopene. *Exp Biol Med* 2002; 227: 920-3.
13. Palozza P, Parrone N, Catalano A, Simone R. Tomato lycopene and inflammatory cascade: basic interactions and clinical implications. *Curr Med Chem.* 2010; 17(23): 2547-63.
14. Kitade Y, Watanabe S, Masaki T, Nishioka M, Nishino H. Inhibition of liver fibrosis in LEC rats by a carotenoid, lycopene, or an herbal medicine, Sho-saiko-to. *Hepatol Res.* 2002; 22(3): 196-205.