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# Efficacy of lycopene in the management of oral submucous fibrosis

Abhinav Kumar, BDS, MDS,[a] Anjana Bagewadi, BDS, MDS,[b] Vaishali Keluskar, BDS, MDS[c] and Mohitpal Singh, BDS, MDS[d] Karnataka, India
K.L.E.S.

***Objectives.*** To evaluate the efficacy of oral lycopene therapy in patients with oral submucous fibrosis and to compare these effects with a placebo.
***Study design.*** Fifty-eight patients with oral submucous fibrosis formed the population for the study and were randomly divided into 3 groups, evaluated weekly over a 2-month period. Patients of group A (n = 21) received 16 mg of lycopene, those of group B (n = 19) received 16 mg of lycopene along with biweekly intralesional steroid injections, and those of group C (n = 18) were given a placebo. Paired and unpaired *t* tests were used for statistical evaluation.
***Results.*** Mouth-opening values for the patients showed an average increase of 3.4 mm, 4.6 mm, and 0.0 mm for patients in groups A, B, and C, respectively. These values were statistically found to be highly significant.
***Conclusions.*** The observed effects suggest that lycopene can and should be used as a first line of therapy in the initial management of oral submucous fibrosis. **(Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007;103:207-13)**

Oral submucous fibrosis is a premalignant condition that has received considerable attention in the recent past because of its chronic debilitating and resistant nature. It is now strongly believed that there is a definite relation of the condition with the habit of areca nut chewing.[1-4] Areca nut has been deeply rooted in Indian culture and been used as a mouth-freshening agent that has had various symbolic roles throughout Indian history. The potential for malignant transformation in submucous fibrosis is considered high, and the disease affects persons of all ages and both sexes across the Indian subcontinent. Perhaps what is most disturbing about the condition is that it affects a number of adolescents as well.

[a]Assistant Professor, Department of Oral Medicine and Radiodiagnosis.
[b]Professor and Incharge HOD, Department of Oral Medicine and Radiodiagnosis.
[c]Professor, Department of Oral Medicine and Radiodiagnosis.
[d]Reader, Department of Oral Medicine and Radiodiagnosis.
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Carotenoids are natural pigments synthesized by plants and are responsible for the colors of fruits and vegetables. Lycopene is the carotenoid that gives tomato its bright red color, and it is one of the major carotenoids in Western diets. It accounts for 50% of the carotenoids in human serum.[5,6] It has been shown to have several potent anti-carcinogenic and antioxidant properties and has demonstrated profound benefits in precancerous lesions such as leukoplakia.[7] Lycopene exhibits the highest physical quenching rate constant with singlet oxygen.[8]

Tobacco chewing, smoking, and alcohol consumption have definite roles in the etiopathogenesis of oral cancers by generating increased reactive free radicals as well as by eliciting immunosuppression. Active oxygen species and reactive free radicals mediate phenotypic and genotypic alterations that lead mutations to neoplasia. A number of studies have proven that the management of premalignant lesions should include antioxidants along with the cessation of the habit.[7] Furthermore, lycopene has been found to inhibit hepatic fibrosis in rats as well as human fibroblast activity in vitro[9] suggesting its possible role in the management of oral submucous fibrosis. Micronutrient supplementation in the past has proved to be efficacious in the

management of oral submucous fibrosis.[10] It has also been suggested that a conservative approach to the correction of submucous fibrosis leads to improved results as compared with intralesional injections.[11] The purpose of this study was to determine the efficacy of lycopene as a conservative means in the management of oral submucous fibrosis.

## MATERIALS AND METHODS

Eighty-three patients who presented with signs and symptoms suggestive of oral submucous fibrosis were enrolled in the study. The following parameters were used in the establishment of the diagnosis and any 2 of 3 parameters were to be satisfied for inclusion in the study.

- A positive history of chewing of the areca nut or one of its commercial preparations, difficulty in swallowing and chewing, and burning sensation on eating spicy foods.
- Restricted mouth opening and changes in the oral mucous membrane including the presence of palpable vertical fibrous bands, stiffness, and blanching.
- Histopathological confirmation of oral submucous fibrosis by biopsy specimen.

Following the establishment of the diagnosis, each patient was informed about the condition and its precancerous potential. The patient was then advised to discontinue the use of areca nut in all preparations. All patients underwent an oral prophylaxis procedure to remove extrinsic stains, whenever possible for the entire mouth and otherwise for the anterior teeth. This was done to motivate the patient toward recovery and to inform the investigator if the patient resumed the habit. Each patient was then randomly categorized by two investigators into one of the three groups in a double-blinded fashion. One investigator recorded variables and the other categorized the patients into study groups and dispensed LycoRed™ (Jagsonpal Pharmaceuticals Ltd., New Delhi, India ) capsules and placebo capsules, and gave intralesional steroid injections. The history of the habit, especially with reference to the duration in years, the frequency of chews per day, and the preparation of areca nut used was recorded. A clinical examination with pertinent findings was recorded. Each patient was informed about the protocol of the group and was given appropriate instructions after consenting to the necessary follow-up. The protocol used was approved by the institute's review board for research.

Patients of the first group (group A, n = 21) were given 16 mg of lycopene daily in 2 equally divided doses. Patients of the second group (group B, n = 19) were given 16 mg of lycopene daily in 2 equally divided doses and were given intralesional injections of betamethasone (2 1-mL ampules of 4 mg each) twice weekly. The patients of the third group (group C, n = 18) were given placebo capsules.

Lycopene used in the study was LycoRed™ 4 mg softgels, manufactured by Jagsonpal Pharmaceuticals Ltd., New Delhi, India, under license from LycoRed Natural Products Industries Ltd., Beer-Sheva, Israel, makers of natural lycopene, LYC-O-MATO®. Placebo used in the study was also manufactured for the trial by Jagsonpal Pharmaceuticals Ltd., New Delhi, and was supplied as bottled LycoRed™ capsules.

Patients were evaluated every week during the treatment period of 2 months. A clinical examination was carried out at every recall visit and the findings were compared with those at the beginning of the treatment. The following parameters were recorded weekly:

### Mouth opening

This was assessed as the interincisal distance as measured from the mesioincisal edge of the upper left central incisor tooth to the mesioincisal edge of the lower left central incisor tooth. The measurement was made using a geometric divider and scale and was recorded in millimeters. When the subject was edentulous, the opening between the upper and lower ridges was recorded using a bite block of modeling wax and was translated into millimeters. This was also recorded posttreatment at 3 and 6 month follow-up periods.

### Visual inspection

The involvement of the uvula was recorded as positive when it appeared as shrunken or deviated with or without blanching. The involvement of the tongue was recorded as positive when protrusion was restricted along with a history of the same given by the patient. The degree of protrusion was recorded in units of 5 mm from the incisal edge of the lower teeth. This was done by viewing the protruded tongue from the lateral aspect of the head and measuring the distance from the mesial contact area of the lower central incisors to the tip of the protruded tongue. When a value was found to lie in between units of 5 mm, it was adjusted to the higher limit. This was done to allow for the fine movements of the tip that did not permit an exact millimeter recording.

### Palpatory findings

These were recorded as positive when a lack of suppleness and palpable fibrous bands or marked stiffness was evident for the areas of the right and left buccal mucosa, right and left vestibules, faucial pillars, soft palate, lips, and floor of mouth. An area of the mouth that could not be palpated because of reduced

**Table I.** Number of patients in different age groups

| | *18-20 y* | *21-30 y* | *31-40 y* | *41-50 y* | *51-60 y* | *61-70 y* |
|---|---|---|---|---|---|---|
| Group A | 1 | 14 | 2 | 1 | 1 | 2 |
| Group B | 1 | 16 | 1 | 0 | 0 | 1 |
| Group C | 1 | 11 | 5 | 1 | 0 | 0 |

mouth opening was recorded as nonpalpable and was considered as positive.

### Burning sensation

This was recorded at baseline as present or absent, and at weekly intervals as persisting, reduced, or absent. It was recorded based on the patient's response.

All findings other than mouth opening, tongue protrusion, and symptoms (burning sensation) were graded by the examining investigator on a 3-point severity rating scale. This recording was based on the patient's reporting and physical examination. A change in this scale was considered a marker for improvement or deterioration in the condition of the affected area.

### Statistical analysis

All quantified variables in the study, that is, mouth-opening measurements, age, duration and quantity of chews, were subjected to statistical analysis. All these values were analyzed for mean (or median as applicable), standard deviation, errors, and range. The unpaired *t* test was used for evaluation of statistical significance of mouth-opening values between groups. The paired *t* test was used for evaluation of statistical significance of mouth-opening values between weeks in the same group.

*P* value was set at .05 and was considered very significant at $<.01$ and highly significant at $<.001$.

## RESULTS

### Age and sex distribution

Fifty-eight patients completed the trial and 25 were lost to follow-up. The 58 patients who completed the trial all were male, and they had an age range of 18 to 70 years with a median age of 28 years. The median age distribution of patients in groups A, B, and C was 28 years, 26 years, and 29 years, respectively. Fourteen patients in group A, 16 patients in group B, and 11 patients in group C were in the age group of 21 to 30 years (see Table I).

### Habits

All patients in the present study gave a positive history of areca nut chewing in the raw form, as a quid or in a commercial preparation such as gutkha or pan masala.

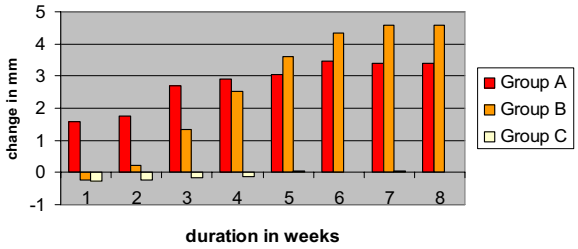


Fig. 1. A column chart demonstrating the average change in mouth opening over the duration of treatment.

The most common form of areca nut used was found to be gutkha, with 89.66% (52 of 58) patients using it this way.

The median duration of habits in all patients was found to be 7 years (ranging from 1 to 25 years).

The median duration of habits in individual groups A, B, and C was 8 years, 6 years, and 8 years, respectively.

The frequency of chews per day varied between 1 and 20 per day, whereas a median frequency of chews per day was found to be 6.5 in all patients. In the study groups (Group A + Group B) it was 8. Individually in groups A, B, and C it was 8, 8, and 5.5, respectively.

### Statistical analysis

The comparison of these findings either singly or in combination could not be related to the severity of mouth opening as judged by the interincisal distance. No statistically significant correlation was found.

### Mouth opening

*Pretreatment.* The average mouth opening in Group A was 31.76 mm ± 10.14 mm (range 13-45 mm). The average mouth opening in Group B was 25.41 mm ± 6.83 mm (range 17-39 mm). The average mouth opening in Group C was 30.61 mm ± 7.55 mm (range 14-45 mm). These values did not statistically differ sufficiently to be significant (groups A vs B, $P = 1.91$; B vs C, $P = 1.61$; A vs C, $P = 1.81$).

*Posttreatment.* The average mouth opening in Group A was 35.14 mm ± 10.87 mm (range 13-47 mm). The average mouth opening in Group B was 30.00 mm ± 7.87 mm (range 17-43 mm). The average mouth opening in Group C was 30.67 mm ± 7.89 mm (range 14-47 mm). The mouth-opening values were found to be stable at the posttreatment 3-month and 6-month follow-up periods.

*Change in mouth opening and statistical analysis-* (see Fig. 1)

GROUP A. The improvement in mouth opening recorded, when compared with the initial mouth opening,

was statistically found to be very significant ($P < .01$) in the first week and significant ($P < .05$) in the second week, and it attained highly significant values ($P < .001$) in the third week, after which it remained highly significant until the completion of the treatment.

When comparisons were made between individual weeks and the end result, the changes were found to lose significance from the fourth to the eighth week. The average improvement in mouth opening of Group A patients was 3.4 mm.

GROUP B. The improvement in mouth opening recorded, when compared with the initial mouth opening was statistically found to be not significant ($P > .05$) in the first and second weeks and significant ($P < .05$) in the third week, and it attained highly significant values ($P < .001$) in the fourth week, after which it remained highly significant until the completion of the treatment.

When comparisons were made between the individual weeks and the end result the changes were found to lose significance from the sixth to eighth week. The average improvement in mouth opening of Group B patients was 4.6 mm.

GROUP C. There was no improvement in the mouth opening values of these patients.

### Areas affected (see Table II)

Among the 58 patients who completed the trial, the most commonly affected areas were found to be the faucial pillars: 94.8% (n = 55); the vestibule and buccal mucosa of right side: 91.4% (n = 53); buccal mucosa of left side: 86.2% (n = 50); soft palate: 82.8% (n = 48); uvula: 72.4% (n = 42); floor of mouth: 70.7% (n = 41); and tongue: 67.2% (n = 39). The least commonly involved area was the lips: 39.7% (n = 23).

### Improvement of areas (see Table III)

The proportion of subjects showing improvements in various regions of the mouth were:

*Buccal mucosa of left side (1).* A 37.5% improvement was shown in Group A, a 38.89% improvement in Group B, and a 6.25% improvement in Group C.

*Buccal mucosa of right side (2).* A 33.33% improvement was shown in Group A, a 36.84% improvement in Group B, and a 12.5% improvement in Group C.

*Tongue (3).* A 70% improvement was shown in Group A, a 60% improvement in Group B, and no improvement in Group C.

*Faucial pillars (4).* No improvement was shown in any of the 3 groups.

*Soft palate (5).* A 7.14% improvement was shown in Group A, and no improvement in Groups B and C.

*Uvula (6).* No improvement was shown in any of the 3 groups.

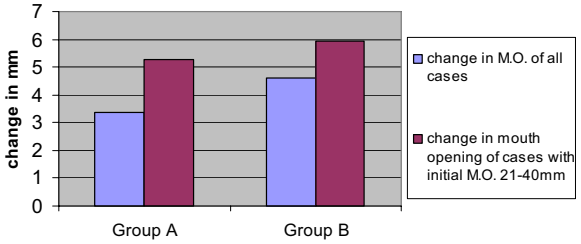


Fig. 2. A column chart demonstrating the effect of selectively including cases with initial mouth-opening values between 21 mm and 40 mm (*M.O.,* mouth opening).

*Lips (7).* A 50% improvement was shown in Group A, and no improvement in Groups B and C.

*Vestibule (8).* A 5.26% improvement was shown in Group B, and no improvement in Groups A and C.

*Floor of mouth (9).* A 9.09% improvement was shown in Group A, a 20% improvement in Group B, and no improvement in Group C.

### Symptoms

All patients who reported to the study complained of a burning sensation on eating spicy foods that was not present before the development of submucous fibrosis.

All patients in the study groups (Group A + Group B) also reported a complete relief from burning sensation within 2 weeks of instituting therapy. One patient reported a relapse of burning sensation every time he stopped taking lycopene. On further evaluation, however, the same patient also gave a history of excessive consumption of chilies that were added to his food regularly. Upon reduction of chilies intake, he was free of burning sensation.

Among placebo (Group C) patients only one patient reported relief of burning sensation.

### Side effects or intolerance

There were no reported instances of side effects or intolerance to lycopene. Only one patient in Group A reported the development of severe burning sensation and oral ulcers one week after beginning therapy. However, he was able to tolerate the drug following the cessation of drug for one week and had no further complaints and reported amelioration of symptoms. These burning sensations were not attributed to lycopene.

## DISCUSSION

Lycopene is a powerful antioxidant obtained from tomatoes. It is manufactured by the Lyc-O-Mato™ process and retains its natural proportions with other compounds in the marketed pharmacological prepara-

**Table II.** Involvement of areas (number of cases)

| | *Buccal mucosa of left side* | *Buccal mucosa of right side* | *Tongue* | *Faucial pillars* | *Soft palate* | *Uvula* | *Lips* | *Vestibule* | *Floor of mouth* |
|---|---|---|---|---|---|---|---|---|---|
| Group A | 16 | 18 | 10 | 18 | 14 | 12 | 6 | 16 | 11 |
| Group B | 18 | 19 | 15 | 19 | 19 | 18 | 7 | 19 | 15 |
| Group C | 16 | 16 | 14 | 18 | 15 | 12 | 10 | 18 | 15 |

tions.[12] It has been shown to inhibit various types of cancers and has been shown to have potent benefits in oral premalignant lesions such as leukoplakia, where it has been shown to modulate dysplastic changes.[7] This study evaluated the efficacy of lycopene in the management of oral submucous fibrosis. All patients in the present study were males (100%), although 3 females too had reported with this condition initially. Another study by Lai et al., in which the authors treated 150 patients (145 males and 5 females), has also shown a 96.67% male predilection for the condition, which was similar to our study.[13] Most of the patients were 21 to 30 years of age (70.69%), a finding that concurred with that of Maher et al., who reported that 70% of males with submucous fibrosis were <30 years of age.[3] In another study conducted in 1991 by Borle and Borle in 326 patients, the majority of patients also were <30 years of age.[11] All patients in the present study gave a history of areca nut chewing. Nut chewing was also found by Canniff et al. in their article on the pathogenesis and management of oral submucous fibrosis back in 1986.[4] The attributable risk (AR) for chewing areca nut products as compared with no chewing habits in a population studied by Maher et al. was found to be 98.6%.[3] Our findings agree with this association.

The average improvement in mouth opening in Group A (only lycopene) increased by 3.4 mm, but some individual case patients did show maximum improvements of 5 mm, 6 mm, and 9 mm. The change in mouth opening was considered highly significant statistically ($P < .001$), and evaluation on a weekly basis showed the changes maintained this high significance from the third week onward.

Group B patients (lycopene and intralesional steroids) showed an average improvement of 4.6 mm, although some individual case patients showed maximum improvements of 7 mm and 8 mm. One patient showed a 3-mm reduction in mouth opening. The change was again considered highly significant statistically ($P < .001$), and weekly evaluation revealed this high significance to be maintained from the fourth week onward.

The management of oral submucous fibrosis purely by means of intralesional steroids has been reported to be widely unsatisfactory and was deemed useful only for patients with minimal impairment of opening by Canniff et al in 1986.[4] The improvement seen in our study therefore must be attributed to the combination of lycopene with steroids that may exert its action synergistically.

Canniff et al. in 1986 described submucous fibrosis as a chronic progressive scarring disease of the oral cavity and oropharynx.[4] In a micronutrient supplementation study on oral submucous fibrosis in Pakistan, Maher et al.[10] reported findings that indicated that as the mouth opening decreases, the likelihood of improvement also decreases. This means for example, that a patient with submucous fibrosis with a mouth opening in the range of 15 mm is less likely to respond to treatment than a patient with mouth opening in the range of 25 mm. This is a characteristic, peculiar to the condition of submucous fibrosis, and was also found in our study. In the present study, it was found that patients with mouth opening <20 mm at initial presentation showed no improvement in Group A (3 cases) and an average of 1.4 mm of improvement in Group B (5 cases), suggesting that these patients may be poor responders.

It also logically follows that mouth opening cannot be used as a tool for the evaluation of improvement in submucous fibrosis when mouth opening is minimally or not impaired. The maxillofacial surgery clinic in Zurich accepts 36 mm to 38 mm incisal distance as the healthy adult minimum opening.[14] Therefore to obtain a more "realistic" value of mouth-opening improvement, patients with mouth opening <20 mm and >40 mm were excluded, and mouth-opening averages were calculated. It was found that Group A patients then had a significant average improvement of 5.25 mm ± 3.25 mm ($P < .05$) that was similar to Group B patients with a very significant average improvement of 5.92 mm ± 1.51 mm ($P < .01$) (see Fig. 2).

When intergroup comparisons were made, the results of Group A and Group B did not differ enough to be statistically significant ($P > .05$). However, when the results of Group A (lycopene) were compared with Group C (placebo), the change was highly significant ($P < .001$). Similarly, Group B (lycopene and intralesional steroids) yielded highly significant results ($P < .001$) compared with Group C (placebo).

**Table III.** Improvement of areas (number of cases)

| | *Buccal mucosa of left side* | *Buccal mucosa of right side* | *Tongue* | *Faucial pillars* | *Soft palate* | *Uvula* | *Lips* | *Vestibule* | *Floor of mouth* |
|---|---|---|---|---|---|---|---|---|---|
| Group A | 6 | 6 | 7 | 0 | 1 | 0 | 3 | 0 | 1 |
| Group B | 7 | 7 | 9 | 0 | 0 | 0 | 0 | 1 | 3 |
| Group C | 1 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

These results indicate that lycopene either singly or in combination with intralesional steroids is, indeed, efficacious in improving the mouth opening in patients with submucous fibrosis and in reducing associated symptoms. The precise reason for this efficacy may be because of two reasons:

- Lycopene has been shown to inhibit hepatic fibrogenesis in LEC rats by Kitade et al.[9] and may exert a similar inhibition on abnormal fibroblasts in submucous fibrosis. This would also be in concurrence with another study on oral submucous fibrosis performed by Haque et al,[15] who reported a positive result in submucous fibrosis cases with a therapeutic modality used for liver fibrosis.
- Lycopene also upregulates lymphocyte resistance to stress and suppresses the inflammatory response.[16]

The statistics also implied that although the combination of lycopene and intralesional steroids conferred greater benefits in mouth opening, the use of only lycopene demonstrated improvement in mouth opening sooner. This effect was seen by the third week of treatment with a plateau reached at the fourth week, as opposed to lycopene with steroids that provided its maximum benefits by the fifth week, with the effects reaching a plateau at 6 weeks. This may be explained by a poorer tissue perfusion (because of interstitial spaces being blocked by steroid) in those patients in whom intralesional steroids were also given. Lycopene in these patients would therefore be available to the target tissues after a "delay." The better results seen in this group may be attributed to the synergistic action of lycopene with steroids, both of which have been known to modulate the inflammatory response.[16]

The tongue was the area of the mouth where maximal improvement was seen in both study groups (A and B). It was also an area that was involved with less frequency compared with other areas of the mouth in all groups. This may be attributed to the tongue being a highly vascular organ, so drug perfusion might be better and also the presence of specialized keratinized mucosa on the dorsum could play a role in limiting the areca nut toxins (see Tables II and III).

Lycopene was also useful in effectively reducing the burning sensation associated with submucous fibrosis, and this result was achieved within 2 weeks in all patients in groups A and B and one patient in group C. There were no associated side effects with the use of lycopene.

There were a number of limitations to this study. Twenty-five subjects initially enrolled in the study were lost to follow-up. The vast majority of subjects were from backward socioeconomic groups, most with no formal education and several for whom it was their first dental visit. Not surprisingly, for most of these patients a restricted mouth opening was not the presenting complaint. These are persons who view a hospital with some degree of suspicion and skepticism, as they are more accustomed to home remedies and traditional treatments. Restriction in mouth opening and burning sensation for many does not warrant attention, as they concern themselves only with severe pain and disability. A lot of "bearable" pain in these patients is never attended to. For the same reason, a visual analog scale could not be used to assess burning sensation. Many of them are likely to have continued with the chewing habit, or to have switched to a nontobacco-related areca nut habit that would not stain teeth, thereby removing any sign that the investigators could find of their persistence with the habit.

## CONCLUSION

A positive clinical response was seen in both study groups in this study when compared with placebo. Lycopene was seen to be efficacious as a safe, reliable drug in the management of oral submucous fibrosis. In contrast to other management modalities for submucous fibrosis, it offers a noninvasive option that yields significant improvements in the symptoms as well as objective signs of the condition. It should therefore be used as a first-line drug that would further the motivation and compliance of patients with this debilitating condition. Further trials in this regard should be carried out to investigate the probable mechanisms by which lycopene exerts this beneficial effect as well as the effects of supplementation with other dosages and use over other time frames.

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*Reprint requests:*

Dr Abhinav Kumar
Department of Oral Medicine and Radiodiagnosis
Institute of Dental Studies and Technologies
Delhi - Meerut Road, N.H. 58
Kadrabad, Modinagar 201201
UP - India
abhinavmathur@yahoo.com