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Lycopene and Intralesional Steroid Injections in the Management of Oral Submucous Fibrosis- A Comparative Study

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Abstract

Aim: To determine the efficacy of lycopene in the treatment of oral submucous fibrosis (OSF) and to compare it with intralesional triamcinolone acetonide injections.

Materials and Methods: 40 Grade II and Grade III OSF subjects who were diagnosed clinically were included in the study. These patients were divided into two groups A & B; each containing 20 subjects. Group A patients were given oral lycopene 16mg per day, 8mg in morning and 8mg at night. Group B received intralesional injections of 10mg/ml triamcinolone acetonoide mixed with lignocaine for 8 weeks biweekly. Evaluation of treatment effect was done on day 15, 30, 45 and 60 for improvement in mouth opening and reduction in burning sensation.

Results: All 40 patients were males. Mean improvement in mouth opening in Group A subjects was 1.30mm and in Group B was 1.8mm. Reduction in burning sensation in Group A was 3.10 and 3.8 in Group B on VAS. The p value (<0.001) was statistically significant. Conclusion: Lycopene in OSF patients results in substantial reduction in burning sensation with marginal improvement in mouth opening.

Introduction

In India, which is a part of Southeast Asia, areca nut and tobacco chewing in various forms is a frequent finding. These deleterious habits cause many lesions of oral mucosa including oral submucous fibrosis (OSF). OSF is a potentially malignant disease very commonly seen in Asian population.[1] OSF is an insidious, chronic disease affecting any part of the oral cavity and sometimes the pharynx.[2] The etiology, pathogenesis and treatment of OSF has been a controversial subject since it was first described by Schwartz as 'atropica idiopathica mucosae oris' in the year 1952.[3]

Various studies have shown that frequent consumption various forms of arecanut is the main causative factor for OSF.[4] Contents of arecanut activate excessive reactive oxygen species that damages the structure of cells, lipids, proteins, nucleic acids.[5]

Various treatment modalities tried over last two decades have been found to be providing only symptomatic and temporary relief. The management modalities applied so far includes supplements of iron, multivitamin therapy, pentoxifylline, intralesional steroid injections combined with hyaluronidase ,chylomicrons, human placental extracts and surgical fibrous bands excision and many others.[6]

Studies have shown that lycopene reduces hepatic fibrosis in rats and also it inhibits fibroblastic activity in humans in vitro[7]. Since it can inhibit fibroblastic activity its use in treatment of OSF was considered. Lycopene increases the mouth opening and reduces the burning sensation either singly or in combination with intralesional steroid injections. Hence this study aimed to determine the effectiveness of lycopene conservatively in the treatment of OSF and comparing it with intralesional injections of triamcinolone acetonide.

Materials and Methods

The study was conducted in Department of Oral Medicine and Radiology, Navodaya Dental college and Hospital, Raichur, Karnataka .40 OSF patients based on clinical findings were included in the study. Ethical clearance for the study was obtained from the Institutional Ethical Committee. Each patient was explained about the study. Instructions were given and written consent was taken from the patients. Patients consuming arecanut (in any form)who complained of burning sensation on eating hot and spicy food and with restricted mouth opening, patients ready to quit chewing arecanut/gutkha with or without tobacco and stop consuming spicy food and agree for treatment for the specified duration were included in the study. The exclusion criteria was patients suffering with any systemic diseases or conditions, pregnant women, OSF subjects with other precancerous lesions and conditions and subjects who had taken treatment for OSF in last 6 months. Patients were educated about the nature of the condition and its precancerous potential, and counselling and motivation of all the subjects under study was done to quit the habit of eating areca nut, tobacco or any other deleterious habit in any form. After history taking and clinical examination patients were divided into Group I, II, III and IV according Khanna J N and Andrade N N (1995) classification. Only patients falling under group II and group III were enrolled for the study. Group I cases were not taken because their mouth opening was not significantly reduced and Group IV cases were excluded because they had severe trismus (mouth opening less than 15mm) hence location of the site of injection would be difficult.

The patients were divided randomly in two groups; 20 in group A and 20 in group B

Group A: Subjects were given commercially available LYCORED capsules (Jagson Pharamaceuticals Ltd, India) containing lycopene (4000mcg) in the form of natural Lyco-o-Mato, zinc (7.5mg) as sulphate monohydrate, and selenium (35mcg) as monohydrated dioxide. Subjects were instructed to take 2 capsules of Lycored twice daily, making total 16mg dose of lycopene per day. Patients were instructed to take lycored capsules for 2 months.

Group B: Subjects were given intralesional injections of steroid KENACORT (Abbott Pharmaceuticals, India) containing triamcinolone acetonide 10 mg/ml and benzyl alcohol (preservative). It was mixed with 0.5 ml of Lignox 2%A (Indoco Remedies Ltd, India) containing Lignocaine hydrochloride 24.64 mg, adrenaline 0.0125 mg and preservative methylparaben 1mg. Injections were given in submucosally in multiple areas once a week for 2 months. A dose of 1.5 ml was given equally in all sites using insulin syringe under sterile precautions.

All the subjects were also advised do mouth opening exercise applying finger pressure after giving injections and taking capsules.

Improvement in mouth opening and reduction in burning sensation was assessed and recorded in the pro-forma for both the groups every 15 days for 2 months until treatment was completed. Comparison was done between same grades of patients of both the groups. Any adverse drug effects after treatment initiation were also evaluated.

The interincisal distance measured from the mesioincisal edge of the upper left central incisor tooth to the mesioincisal edge of the lower left central incisor tooth used as mouth opening measurement. Vernier caliper was used to record the mouth opening, in millimeters. Burning sensation was analysed using Visual Analog Scale (VAS) of 0-10, wherein 0 indicated no burning sensation and 10 indicated the intolerable burning sensation.

Statistical Analysis

Unpaired't' test was used to do the comparison between two groups. Mean and SD (standard deviation) was used to present the data. Comparison between two groups was done by using repeated measures of analysis of variance (ANOVA) test for both groups at five point data collection followed by Tukey-Kramer Multiple Comparisons Test to calculate the mean difference in burning sensation and mouth opening at different time points. A p-value less than 0.05 was considered as significant. Data analysis was done by using SPSS v16.0 software.

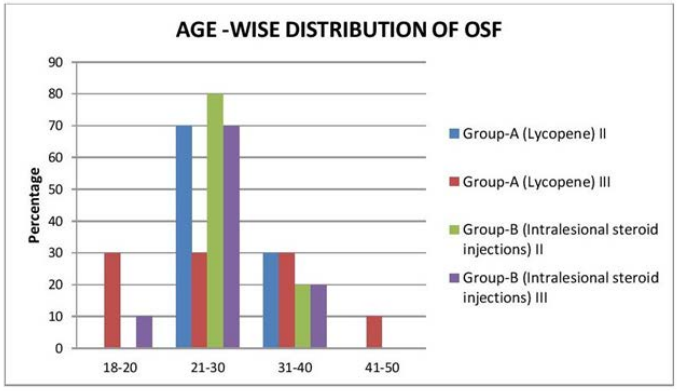
Results

All 40 subjects were males. Of 40; 25 subjects (62.5%) were between age group of 21-30 years (Table 1, Graph 1). All 40 subjects had habit of chewing gutkha in one or the other form; either only gutkha or gutkha with tobacco, cigarette or alcohol. Maximum number of subjects (65%) had the habit for less than 5 years and 35% for more than 5 years. 21 subjects (55%) had habit of chewing less than 5 gutkha sachets per day and 19 subjects (45%) more than 5 gutkha sachets per day. 35 (85%) of subjects had the habit of placing the quid in mouth for less than 15 min while 15 (15%) subjects kept the quid in mouth for more than 15 min.

Table 1:

Age group	Group-A (Lycopene) %		Group-B (Triamcinolone acetonide) %		Total
	II	III	II	III	
18-20	0	3	0	1	4
21-30	7	3	8	7	25
31-40	3	3	2	2	10
41-50	0	1	0	0	1

GRAPH 1:



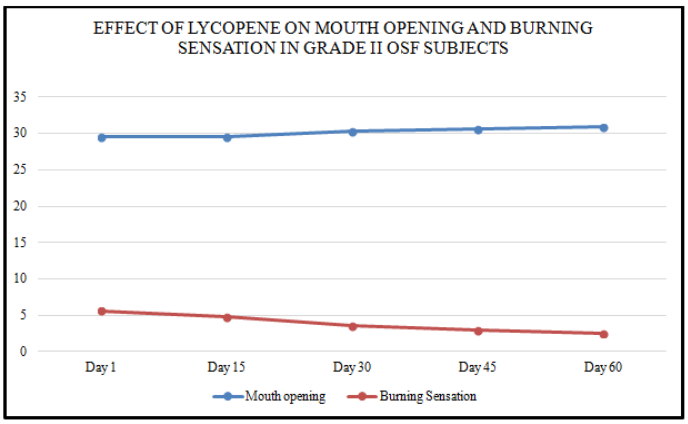
Effect of lycopene on mouth opening and burning sensation in grade II OSF subjects:

On day 1 the mean mouth opening was 29.6 ± 3.72 was and on day 60 it was 30.9 ±3.86. Mean improvement of 1.3 mm was noticed. On day 1 burning sensation was 5.6 ± 1.77 which reduced to 2.5 ± 0.85 on day 60. Statistically significant difference was found for both the parameters between day 1 and day 30, 45 and 60 ($p<0.001$) .No statistically significant difference between day 1 and day 15 ($p>0.05$) was seen (Table 2, Graph 2).

TABLE 2:

Day	1	15	30	45	60	F-value	p-value
Mouth opening	29.6 ± 3.72	29.6 ± 3.72	30.3 ± 3.62	30.6 ±3.68	30.9 ±3.86	37.64	P<0.0001
Burning sensation	5.6 ± 1.77	4.8 ± 1.87	3.5 ± 1.35	2.9 ± 0.99	2.5 ± 0.85	25.25	P<0.0001

GRAPH 2:



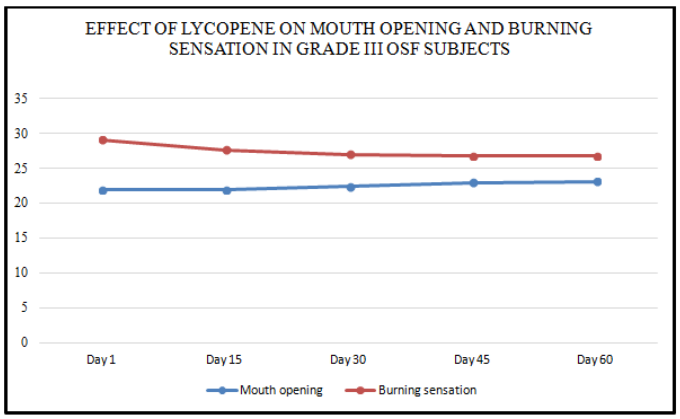
Effect of lycopene on mouth opening and burning sensation in grade III OSF subjects:

On day 1 the mean mouth opening was 21.9 ± 3.35 was and on day 60 it was 23.1 ±3.39. Mean improvement of 1.8 mm was found. It was noticed that the burning sensation was reduced from 7.2 ± 1.03 on day 1 to 3.7 ± 0.82 on day 60. Statistically significant difference was found for both the parameters between day 1 and day 30, 45 and 60 (p<0.001) .No statistically significant difference between day 1 and day 15 (p>0.05) was seen (Table 3, Graph 3)

TABLE 3:

Day	1	15	30	45	60	F-value	p-value
Mouth opening	21.9 ± 3.35	21.9 ±3.35	22.4 ±3.44	23.0 ±3.34	23.1 ±3.39	75.87	P<0.0001
Burning sensation	7.2 ± 1.03	5.8 ± 1.03	4.6 ± 0.84	3.8 ± 0.92	3.7 ± 0.82	133.30	P<0.0001

GRAPH 3:



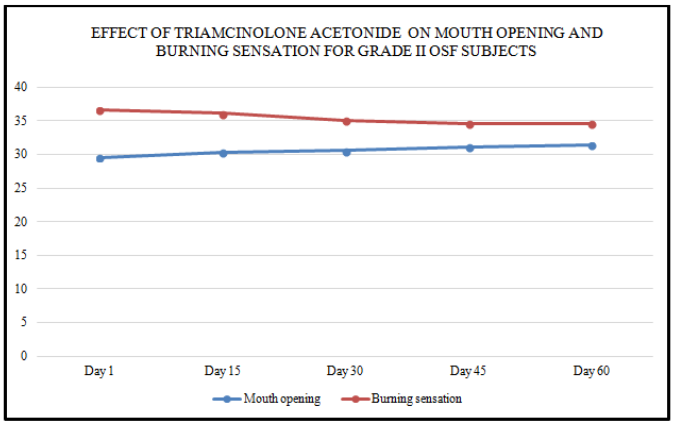
Effect of triamcinolone acetonide on mouth opening and burning sensation in grade II OSF subjects:

Mean mouth opening on day 1 was 29.6 ± 3.47 was and on day 60 was 31.4 ±3.24. Mean improvement of 1.8 mm was noted. Reduction in burning sensation from 7.0 ± 1.05 on day 1 to 3.2 ± 1.23 on day 60 was found. Statistically significant difference was found between day 1, day 15, 30, 45 and 60 (p<0.001) for both the parameters. (Table 4, Graph 4)

TABLE 4:

Day	1	15	30	45	60	F-value	p-value
Mouth opening	29.6 ± 3.47	30.3 ±3.54	30.6 ±3.47	31.1 ±3.39	31.4 ±3.24	18.18	P<0.0001
Burning sensation	7.0 ± 1.05	5.8 ±	4.5 ± 1.51	3.5 ± 1.35	3.2 ± 1.23	38.49	P<0.0001

GRAPH 4:



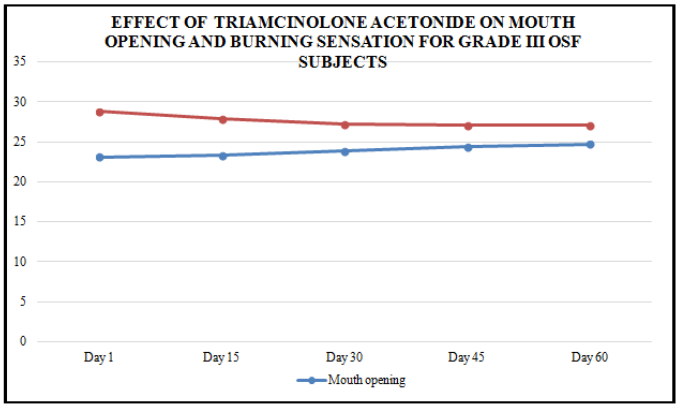
Effect of triamcinolone acetonide on mouth opening and burning sensation in grade III OSF subjects:

On day 1 and day 60 the mean mouth opening was 23.1 ± 1.66 was and 24.75 ± 1.75 respectively. 1.65 mm was the mean improvement. Burning sensation reduced from 5.7 ± 2.54 on day 1 to 2.4 ± 1.07 on day 60. Statistically significant difference was found between day 1, day 15, 30, 45 and 60 (p<0.001) for both the parameters. (Table 5, Graph 5).

TABLE 5:

DAY 1	1	15	30	45	60	F-value	p-value
Mouth opening	23.1± 166	23.3± 164	23 .85 ± 175	24.75 ± 175	24.75 ± 175	64.46	P<0.0001
Burning sensation	5.7± 2.54	4.6± 2. 12	3.4 ± 1.77	2.7 ± 1.25	2.4± 107	25.16	P<0.0001

GRAPH 5:



Discussion

In India and Southeast Asia OSF is a widespread premalignant condition. It is one of the most poorly understood and unsatisfactorily treated diseases. Worldwide estimates have shown that this disease is more confined in India and Southeast Asia[2]. Prevalence ranging from 0.7% to 6.42% has been found and high prevalence of this condition has been seen in younger group.[8-12]

Various clinical, epidemiological and animal experimental studies have proved arecanut/gutkha chewing as a main etiological factor in causation of OSF.[13,14]

Lycopene an antioxidant, is a carotenoid, major source of it in humans are tomatoes and its products. It is anticarcinogenic and is used in the management of various cancers. It has a preventive effect in many chronic diseases owing to its antioxidant properties. Potential malignant diseases of oral cavity like leukoplakia also show improvement when managed with lycopene. Since the malignant transformation potential of OSF is about 2.3 to 7.6%[2] , the antioxidant properties of lycopene can be beneficial in reducing its advancement to carcinoma.[3]

25(62.5%) subjects in our study were in the age group of 21-30 years and 10 (25%) subjects between 31-40 years. Earlier the disease was reported in the age group of 50-59 years.[2] Study by Kalbande etal have also found the age range of the OSF patients between 20-49 years with peak incidence of the condition between 21-30 years.[15] In another study by Hazarey et al which was done on 1000 OSF subjects the patients the age was found between 27 to 35 years[8]. Also Sharma etal found 98(42.06%) subjects of 230 OSF belonged to 15 to 24 years of age group[12].

All 40 patients were males in our study. The results of our study correlate with other studies[8-12] where male predominance was found. The M:F ratio was found as 4.9:1 by Hazarey etal[8], 4.3:1by Sharma etal[12] . Limited sample size could be the reason of no female subjects in our study.

We noticed in our study that all 40(100%) patients had habit of chewing gutkha in one or other form. Arecanut/gutkha chewing habit is a common causative factor of OSF.[13,14] According to study by Ariyawardhana et al the only causative factor for OSF is betel nut chewing .Tobacco chewing/smoking and alcohol consumption have no interactive effect in the causation of OSF.[16] Ranganathan et al study has also stated that all arecanut products cause OSF and panmasala (arecaquid + additives) carries higher risk.[17]

Arecanut and arecanut products are addictive and psychoactive in nature.[18] (The psychoactive nature of arecanut is contributed to binding of arecoline to GABA receptors in brain).[19] . It is additionally detailed that as the frequency expands the dependency increases likewise as the dependence builds, the frequency increases[20]. In the present study burning sensation was present in 100% (40) of the patients. Also all 40 subjects had difficulty in mouth opening with blanching of oral mucosa and palpable fibrous bands. In a cross-sectional study of 1000 OSF

patients by Hazarey et al 90.8% had inability to open the mouth.[8] Also Sudhakar et al study of 45 OSF subjects all (100%) patients complained of restricted mouth opening and burning sensation.[10] Even Lai et al study of 150 OSF subjects reported that many of their subjects had either hypersensitivity to spicy foods and other irritants and severe mouth opening reduction[21]. In present study also we have found that reduced mouth opening and burning sensation were the chief complaint of all the subjects. It was also observed that only these two parameters made the patient to seek treatment. Patients were neither aware nor worried about all other symptoms of OSMF such as blanching of mucosa, deviated uvula, restricted movements of soft palate or tongue or reduced puffing of cheeks.

In our study in group A subjects who received lycopene it was found that the mean difference in increase in mouth opening did not show statistically significant difference ($p>0.05$) between day 1 and day 15. However when the comparison was made between day 1 with day 30, day 45 and day 60 statistically significant difference ($p<0.05$) was observed. It was observed that the mean improvement in mouth opening was 1.3mm .Mean improvement in burning sensation was 3.10. The results of our study are in contrast to that of Kumar et al wherein OSF subjects receiving 16 mg of lycopene daily for 2 months showed mean improvement in mouth opening of 3.4 mm.[4] In another study of 96 patients by Karemore et al, 46 patients receiving 8 mg lycopene per day for 3 months, have shown improvement in mouth opening by 5.65 mm in 69.5% of subjects with significant reduction in other symptoms.[22] The results of our study correlate with the studies of Gowda BBK et al done on 12 OSF patients where patients received 2 mg lycopene twice for 3 months and it was observed that mouth opening had improved by only 1-3 mm, whereas burning sensation was completely reduced.[6] Sunderraj et al tudy observed that subjects receiving lycopene responded with improvement in burning sensation reduction with only 1-3mm increase in mouth opening[23].

Group B subjects who received triamcinolone acetonide (TA) showed showed statistically significant difference ($p<0.05$) in mouth opening improvement between day 1 and day 15 and even on day 30, 45, 60. The mean improvement in mouth opening was 1.8mm and burning sensation reduced from mean±SD of 7.0 ± 1.05 to 3.2 ± 1.23, the mean improvement being 3.80.

The results of our study correlate with Jiang et al study wherein 40 subjects receiving triamcinolone acetonide showed mean improvement in mouth opening of 2.00± 1.21 mm.[24] But Selvam et al observed mean improvement in mouth opening of 3.4±0.5 mm after giving intralesional steroids.[6]

Kumar et al study observed that subjects taking triamcinolone acetonide with lycopene showed mean improvement in mouth opening (MO) of 4.6 mm whereas subjects receiving lycopene only showed improvement of 3.4 mm.[4] Anil G et al also showed that subjects receiving lycopene and intralesional steroids showed a improvement in MO of 4.0=9± 2.5.[25] Lai etal in a study of 150 OSF subjects of which 25 received 10mg/ml of triamcinolone acetonide with placebo for 2 months it was observed that the mean increase in mouth opening in these patients was 6.28±1.94 mm.[21] Hence these studies opine that combination therapy works more efficiently in the management of clinical symptoms of OSF rather than single therapy.

Reduction in burning sensation in the present study is in correlation with other studies. However the improvement in mouth opening was less as compared to other studies. This can be due to use of single drug i.e only

triamcinolone acetonide without combining with any other drug as mentioned earlier. Whereas in other studies[24,26,27] it is observed that triamcinolone is combined with other drugs like lycopene, hyaluronidase, salvionolic acid B. The result variation could also be due to limited sample size taken in our study; that is 40 subjects.

In an review done by Warnakalasuriya and Ross Kerr[28] that focuses on multiple treatment options tried for this irreversible disease, it has been concluded that no single therapy can be recommended for the treatment of OSMF. The only best factor that can help to reduce the diseases burden is stoppage of arecanut eating habit.

In an another extensive review[29] the authors have mentioned that none of the interventions reported till date have shown oral health related improvement in life style of OSMF cases. Reduced burning sensation and improvement in mouth opening has been achieved with some interventions but there are no long term follow-ups. Also this review stresses to initiate a low-cost research plan for future clinical trials in this field especially in those regions of the world where OSMF is more prevalent.

Conclusion

Compared with previous observations of effect of lycopene on reducing the symptoms in OSF patients, the present study showed that lycopene doesn't help improve mouth opening but significant reduction in burning sensation is found. However the changes were non-significant when compared to intralesional injections of triamcinolone acetonide.

Hence within the limitations of the study it may be concluded that lycopene can effectively reduce burning sensation which one of the significant complaint of OSF patients. But when compared to intralesional steroid injections of triamcinolone acetonide it is not effective in improving the mouth opening. Hence using lycopene as a substitute to triamcinolone acetonide would be inappropriate. Further studies with a larger sample size with longer follow up period in different stages of OSF subjects are required.

From the observations of the present study we conclude that lycopene when combined with habit cessation/ physical therapy like mouth opening exercises in OSF patients results in substantial reduction in burning sensation with more or less no Improvement In Trismus.

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