Comparative study of the efficacy of lycopene and aloe vera in the treatment of oral submucous fibrosis

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ABSTRACT

Background and Aim: Oral submucous fibrosis (OSMF) is a high-risk premalignant condition largely seen in the Indian subcontinent. A number of studies have proven the use of antioxidants in the management of OSMF. Therefore, the aim of the present study was to compare the efficacy of two antioxidants, lycopene and aloe vera in the management of OSMF. **Material and Methods:** One hundred and twenty clinicopathologically diagnosed OSMF patients, were included in the study. They were divided equally into, Group A (lycopene group) and Group B (aloe vera group). Group A was administered 8mg lycopene in two divided doses of 4mg daily and Group B was given5mg aloe vera gel to be applied topically thrice daily for 3 months. Different clinical parameters were evaluated at regular intervals and data was analyzed using the Student's paired *t*-test and Chi-square test. $P < 0.001$ was considered to be statistically significant. **Results:** Clinical improvements in mouth opening and tongue protrusion were significant in Group A ($P < 0.001$). Subjective symptoms of burning sensation ($P = 0.007$), pain associated with the lesion ($P = 0.005$), and difficulty in swallowing and speech ($P = 0.003$) improved in both the groups, but were insignificant. There was a mild to moderate decrease in the size of the lesion. **Conclusion:** The present study concludes that though, there is no definitive treatment for the condition; however, lycopene can bring about significant clinical improvements in the symptoms like mouth opening and tongue protrusion when compared to aloe vera. Both the drugs appear to be promising in the treatment of OSMF.

Key words: Aloe vera, antioxidants, lycopene, oral submucous fibrosis

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INTRODUCTION

Oral submucous fibrosis (OSMF) is defined by Pindborg and Sirsatas an insidious chronic disease affecting any part of the oral cavity and sometimes pharynx.[1] Although occasionally preceded by and/or associated with vesicle formation, it is always associated with juxtaepithelial inflammatory reaction followed by fibroelastic changes in the lamina propria, with epithelial atrophy leading to stiffness of the oral mucosa causing trismus and difficulty in eating. It is a potentially malignant disorder of oral cavity, pharynx, and upper digestive tract; characterized by progressive inability to open the mouth and by inflammation and progressive fibrosis of the submucosal tissues.[2] Susrutha in ancient medicine described a condition similar to OSMF as "vidari", under the umbrella of mouth and throat diseases.[3] In 1952, Schwartz described a condition of the oral mucosa as "atrophia idiopathica mucosa oris", with the term OSMF coined by Joshiin 1953.[4,5] The pathogenesis of the disease is not well known, but the etiology is believed to be multifactorial. The condition is widely regarded to be associated with areca nut alkaloids and tannins, which play a major role in the etiology of OSMF. The habit of betel quid chewing is practiced predominantly in the Indian subcontinent from a long time.[2] The flavanoids contained in areca nut are thought to have some direct effect on the collagen metabolism. Alkaloids result in the accumulation of collagen.[6]

Various epidemiological studies have indicated a substantial decrease in precancerous and cancerous lesions with the

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increase in the dose of antioxidants. Oxitard capsules have been successfully tried in the treatment of OSMF by Singh *et al*.[8] Lycopene has also been proved to be the most potent radical scavenger in various studies. It has been tried in the treatment of leukoplakia and also in OSMF by Singh *et al*., and Karemore and Motwani.[8,9] Also a preliminary study has been carried out to compare the efficacy of aloe vera and antioxidants.[10] No studies have been done till date to compare the efficacy of lycopene and aloe vera in the treatment of OSMF. Hence, the present study was carried out to evaluate and compare the efficacy of lycopene and aloe vera for the management of OSMF.

MATERIALS AND METHODS

The present prospective study included 120 subjects with clinicopathologically diagnosed OSMF reporting to the Department of Oral Medicine and Radiology. Patients of either sex with OSMF were included in the study. Those with any evidence of severe psychiatric, cardiac, gastrointestinal or metabolic disorders, and pregnancy and lactation were excluded from the study. Ethical clearance was obtained from the Institutional Ethical Committee. A written informed consent was obtained from the patients prior to the inclusion in the study. Detailed family and medical history with a history of associated habits and the course of the disease was recorded. A thorough clinical examination was carried out and relevant findings were recorded. The subjects were randomly divided equally in two groups, Group A (lycopene group) and Group B (aloe vera group). Group A was administered 8 mg lycopene (Lycored™, Jagsonpal Pharmaceuticals, New Delhi) in two divided doses of 4 mg for 3 months and Group B was given 5 mg aloe vera gel (Sheetal Lab, Surat) to be applied topically thrice daily for 3 months. Mouth opening was measured by measuring the distance between the center of incisal edges of maxillary central incisors and mandibular central incisor at maximum opened mouth. In edentulous patients, the inter ridge (alveolar) distance along the midline was measured.[11] Three measurements were recorded consecutively and the average value was calculated and recorded. Tongue protrusion was measured as distance between lower central incisor and tip of the tongue on protrusion.[11] Evaluation for presence, absence, or reduction of other clinical parameters such as burning sensation, pain associated with the lesion, difficulty in swallowing and speech, and variation in the size of the lesion was done at regular intervals of 1, 2, and 3 months. The clinical parameters such as burning sensation, pain associated with the lesion, and difficulty in swallowing and speech were evaluated by using a visual analog scale (VAS). The score of 0–1 was considered as absent, score of 2–6 was considered as reduced, and a score of 7–10 was evaluated as present. The data was entered using computer software SPSS 12.0 (SPSS Inc, Chicago, USA) and analyzed using the Student's paired *t*-test and Chi-square test. $P < 0.001$ was considered to be statistically significant.

RESULTS

There were 64 males and 56 females with a mean age of 31.6 ± 12.7 years. Fifty-six percent of the patients had habit of betel nut chewing, while 26% of the patients had tobacco chewing habit, and 40% of the patients consumed spicy foods which were among the main causative factors for OSMF in the study population. Clinical improvements in mouth opening and tongue protrusion were significant in Group A ($P < 0.001$) [Tables 1 and 2]. The effect of administration of both the antioxidants showed improvement in the subjective symptoms of burning sensation ($P = 0.007$), pain associated with the lesion ($P = 0.005$), and difficulty in swallowing and speech ($P = 0.003$); but were insignificant when compared [Tables 3-6]. There was a mild to moderate decrease in the size of the lesion. Seventeen patients of Group A and 15 patients from Group B showed a severe degree of change in the size of the lesion, that is, a decrease of > 2.5 cm. Twenty-three patients from Group A and 20 patients from Group B showed a moderate (1.5–2.5 cm) change in the size of the lesion at the end of the study. Sixteen patients from Group A and 19 patients from Group B showed a mild (0–1.5 cm) change in the size of the lesion. However, four patients from Group A and six patients from Group B showed no change in the lesion size over the study period. There were no reported side effects of lycopene. However, few patients reported nausea in the early visits, which was well tolerated. None of the patients withdrew from the study due to any reason.

Table 1: Effect of lycopene and aloe vera in improving mouth opening (mean values in mm)

	Lycopene	Aloe vera	*P*
Baseline	18.2±2.1	17.7±2.2	<0.001
After 1 month	20.2±2.2	18.6±1.8	
After 2 months	22.4±2.5	20.4±2.0	
After 3 months	25.9±2.3	22.1±1.9	

Table 2: Effect of lycopene and aloe vera in improving tongue protrusion (mean values in mm)

	Lycopene	Aloe vera	*P*
Baseline	9.8±2.1	9.2±2.0	<0.001
After 1 month	10.3±1.9	9.9±1.8	
After 2 months	15.7±2.2	12.4±2.1	
After 3 months	19.1±1.9	16.1±2.2	

Table 3: Effect of lycopene and aloe vera on pain associated with pain

	Lycopene			Aloe vera		
	Present	Absent	Reduced	Present	Absent	Reduced
Baseline	59	1	-	59	1	-
After 1 month	53	3	4	51	5	4
After 2 months	35	11	14	40	9	11
After 3 months	24	25	11	30	21	9

Table 4: Effect of lycopene and aloe vera on difficulty in swallowing

	Lycopene			Aloe vera		
	Present	Absent	Reduced	Present	Absent	Reduced
Baseline	58	2	-	59	1	-
After 1 month	50	4	6	52	4	4
After 2 months	36	11	13	41	10	9
After 3 months	23	25	12	26	21	13

Table 5: Effect of lycopene and aloe vera on difficulty in speech

	Lycopene			Aloe vera		
	Present	Absent	Reduced	Present	Absent	Reduced
Baseline	57	3	-	58	2	-
After 1 month	41	9	10	45	7	8
After 2 months	32	19	9	34	16	10
After 3 months	18	28	14	23	27	10

Table 6: Effect of lycopene and aloe vera on burning sensation

	Lycopene			Aloe vera		
	Present	Absent	Reduced	Present	Absent	Reduced
Baseline	60	-	-	60	-	-
After 1 month	48	3	9	47	4	9
After 2 months	30	12	18	32	14	14
After 3 months	7	32	21	9	29	22

DISCUSSION

OSMF is a potentially malignant, precancerous condition of the oral cavity and oropharynx which is predominantly seen in the Indian subcontinent and Southeast Asian countries and is now globally considered an Indian disease. The overall prevalence rate in India is believed to be about 0.2–0.5% and prevalence by gender varying from 0.2 to 2.3% in males and 1.2 to 4.57% in females.[12,13] It is considered to have a high degree of malignant potential, which ranges between 2.3 and 7.6%.[14] The precancerous nature of OSMF has been proved by higher occurrence of OSMF in oral squamous cell carcinoma patients, histological diagnosis of cancer without any clinical suspicion in OSMF, high frequency of epithelial dysplasia, and higher prevalence of leukoplakia among OSMF. The debate over the initiation of malignancy in OSMF due to epithelium or due to connective tissue is still unanswered.[13,15] However, it has been suggested that the pathology develops within the epithelium due to intraoral trauma and various factors such as, irritation from jagged teeth, sharp overhanging restoration, ill-fitting dentures, jacket crowns, prolong use of tobacco, and poor oral hygiene.[11,16]

The disease has a complex pathophysiology, and various factors such as, ingestion of chilies, nutritional deficiencies, genetic susceptibility, altered salivary constituents, autoimmunity, and collagen disorders may be involved in the disease etiology.[12] Areca nut and related products are the most common etiological factor. Burning sensation of the oral mucosa, ulceration, and pain precede the condition. The disease is characterized by blanching of the oral mucosa, reduced movement and depapillation of tongue, progressive reduction of mouth opening, and depigmentation of oral mucosa.[17,18] Advanced stages may be characterized by nasal twang due to fibrosis of nasopharynx and hearing impairment due to stenosis of Eustachian tube. Most of the patients present with irreversible moderate-to-severe condition. The changes of OSMF are limited to oral tissues and similar to those of scleroderma. It may be associated with oral leukoplakia and other potentially malignant disorders or with malignancy such as squamous cell carcinoma.[17]

Many therapeutic and surgical treatment modalities have been advocated for relieving the symptoms, but no definitive treatment is currently acceptable. The first step of preventive measure should be to advise the patient for the discontinuation of the habit, through education, counseling, and advocacy. Medical treatment includes various drugs such as, steroids, placental extracts, interferon (IFN) γ, lycopene, pentoxifylline, surgical excision, laser removal, etc., These have proved to be symptomatic, with their own limitations and are predominantly aimed at improving mouth movements. Caniif *et al*., have stated that the medical management of OSMF is both empirical and unsatisfactory.[14] Rehana *et al*., have shown significant improvement in mouth opening of 41% of the patients with multiple minerals and micronutrients.[19] Whereas, Borle and Borle showed improvement in symptoms of OSMF, but

insignificant improvement in mouth opening with vitamin A.[20] Lycopene has also showed significant improvement in mouth opening in the study conducted by Karemore and Motwani and Singh *et al*., have shown significant improvement in mouth opening, hyperkeratosis, pain in mouth, and size of the lesion with the administration of oxitard capsules.[8,9] Sudarshan *et al*., have shown significant improvement in the mouth opening with aloe vera.[10] No studies have been done till date to compare the effectiveness of lycopene and aloe vera in the treatment of OSMF. Hence, the present study compared the efficacy of the two antioxidants lycopene and aloe vera in the improvement of various clinical parameters such as, mouth opening, difficulty in swallowing, speech, pain associated with the lesion, tongue protrusion, and burning sensation.

Lycopene is a major carotenoid obtained from tomato with potent anticancer activity due to its preventive effects in chronic diseases.[21] It also has potent benefits in oral potentially malignant lesions like leukoplakia. 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 β-carotene and 10 times higher than that of α-tocopherol.[22] New findings have reported the anticancer activity of lycopene is due to the upregulation of connexin 43 and stimulation of gap junctional communication that does not involve its role as an antioxidant.[9]

Aloe vera is a mannoprotein containing many amino acids known as 'wound healing hormones'. The polysaccharides contained in the gel of the leaves, promote wound healing and have anti-inflammatory, immunomodulatory, antioxidant, and gastro-protective properties. Further, sterols in aloe vera have strong ability to inhibit inflammation similar to the action of cortisone without any side effects. It can be found easily and is of low cost in India.[10]

Till date, no treatment protocol has been formulated to restore the mouth opening to normal; however, an improvement of a few millimeters has been observed. The present study showed improvement in both the groups at the end of the study. The present study showed a 27.9% improvement in group A and 25% in Group B. This was not in line with the findings of Sudarshan *et al*., who showed an improvement of 20% in the patients who were given aloe vera, whereas those who were given antioxidants, showed an improvement of only 9%, which was lower than the findings of the present study.[10] Karemore and Motwani showed an improvement of 69.56% which was much higher than the findings of the present study.[9] Alam *et al*., also showed significant improvement with aloe vera in a recent study, similar to the findings of the present study. They administered aloe vera to patients who were treated medicinally with submucosal injection of hyaluronidase and dexamethasone and also to surgically treated patients over a period of 6 months.[23] Tongue protrusion also showed improvement in both the groups, but Group A showed more significant improvements ($P < 0.001$). Sudarshan *et al*., showed an improvement of 8.8% in the aloe vera group, while the antioxidant group showed 4.25% improvement in the tongue protrusion, in contrast to 43.4% improvement in the aloe vera group in the present study.[10] Group A showed an improvement of 50.5% in the tongue protrusion.

Both the groups showed improvement in the burning sensation at the end of the study. However, the results when compared were statistically not significant ($P = 0.007$). Sudarshan *et al*., showed an improvement of 80% in burning sensation in the aloe vera group; whereas, 65.7% patients in the antioxidant group showed improvement in burning sensation.[10] This difference was statistically significant ($P = 0.008$), in contrast to the findings of the present study. Karemore and Motwani also showed a significant improvement in the tolerance to spicy foods and burning sensation with lycopene.[9] They showed that 31 patients of the total 46 patients were relieved of burning sensation due to spicy foods at the end of the study period. However, 32 patients in the present study were relieved of burning sensation and 21 patients reported reduction in the same at the exit. Only seven patients in the lycopene group and nine patients in the aloe vera group had persistent burning sensation at the end of the study. Biweekly submucosal injection for a period of 10 weeks with dexamethasone (4 mg), hyaluronidase (1,500 IU), and placental extracts (2 ml) also showed similar results with 82, 82, and 51%reduction in burning sensation, respectively.[24]

The effect of administration of both the antioxidants showed improvement in the subjective symptoms of pain associated with the lesion ($P = 0.005$) and difficulty in swallowing and speech ($P = 0.003$), but were insignificant when compared. Twenty-five patients in Group A and 21 patients from Group B showed complete absence of pain at the end of the study. Twenty-three patients in Group A and 26 patients in Group B had persistent difficulty in swallowing at the exit. Whereas, 18 patients who were administered lycopene and 23 patients who were given aloe vera gel had difficulty in speech. There was a mild to moderate decrease in the size of the lesion. 17 patients of Group A and 15 patients from Group B showed a severe degree of change in the size of the lesion, that is, a decrease

of > 2.5 cm. Twenty-three patients from Group A and 20 patients from Group B showed a moderate (1.5–2.5 cm) change in the size of the lesion at the end of the study. Sixteen patients from Group A and 19 patients from Group B showed a mild (0–1.5 cm) change in the size of the lesion. However, four patients from Group A and six patients from Group B showed no change in the lesion size over the study period.

There were improvements in both the groups, but significant improvements were observed in Group A. The carotenoid lycopene found in tomatoes offers a noninvasive treatment modality for OSMF due to its antiproliferative, anti-inflammatory, and antioxidant activity. The sterols in aloe have strong anti-inflammatory properties, similar to cortisone, without any of the side effects. The fact that aloe works similar to aspirin in blocking prostaglandin effects, still remains to be proven. Aloe vera can be applied topically, is easily available, safe to use, cost-effective, noninvasive, and effective treatment modality for OSMF. A larger study with larger sample size and longer follow-up period is encouraged to get more accuracy in the efficacy of the antioxidants. Discontinuation of the habit alone as an intervention may have a significantly greater effect, in the OSMF patients. Thus, encouragement should be given to intervention studies and public health campaigns at the community level for controlling OSMF.

CONCLUSION

Lycopene was seen to be more efficacious in improving mouth opening and tongue protrusion in OSMF patients proving to be more reliable treatment modality. However, improvements were observed in burning sensation, difficulty in swallowing and speech, and pain associated with the lesion. It therefore can be used as a more promising first-line drug than aloe vera for the successful management for OSMF and also as a control for the disease progression.

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