

Comparative efficacy of newer antioxidants spirulina and lycopene for the treatment of oral submucous fibrosis

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ABSTRACT

Context: Oral submucous fibrosis (OSMF) is a high-risk premalignant condition predominantly seen in the Indian subcontinent. The aim of the present study was to compare the efficacy of spirulina and lycopene in the management of OSMF. **Materials and Methods:** Sixty-eight subjects with clinico-pathologically diagnosed OSMF were included in the study which was conducted from March, 2013 to July, 2013. They were divided equally in two groups, Group A (spirulina group) and Group B (lycopene group). Group A was administered 500 mg spirulina in two divided doses for 3 months, and Group B was given 8 mg lycopene in two divided doses of 4 mg for 3 months. Evaluation for different clinical parameters was done 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:** The patients in both the groups showed improvement in all the parameters measured. Clinical improvements in mouth opening was significant in Group B ($P = 0.0006$), whereas ulcers/erosions/vesicles significantly ($P = 0.0001$) improved in the Group A. However, there was no significant improvement in pain associated with the lesion ($P = 0.004$) and burning sensation ($P = 0.005$) among the two groups. **Conclusion:** Lycopene can bring about significant clinical improvements in the symptoms like mouth opening, while spirulina can significantly improve ulcers/erosion/vesicles. Both the drugs also showed improvement in pain associated with the lesion and burning sensation. Thus, both the drugs appear to be promising for the treatment of OSMF.

Key words: Antioxidant, lycopene, oral submucous fibrosis, spirulina

INTRODUCTION

Oral submucous fibrosis (OSMF) is a potentially malignant disorder of the 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.^[1] Susrutha in ancient medicine described a condition similar to OSMF as "vidari," under the umbrella of mouth and throat diseases.^[2] In 1952, Schwartz described a condition of the oral mucosa as "atrophia idiopathica mucosa oris," with the term OSMF coined by

Joshi in 1953.^[3,4] Pindborg *et al.* defined the condition as "an insidious chronic disease affecting any part of the oral cavity and sometimes pharynx. 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."^[5] The etiology is believed to be multifactorial and the pathogenesis is not well known. The condition is associated primarily with the habit of areca nut and betel quid chewing, which is practiced predominately in the Indian subcontinent from a long time.^[1]

Treatment modalities have been advocated relieving the symptoms, but have not been successful so far. The first preventive measure should be in discontinuation of habit, and to maintain proper oral hygiene. The symptomatic medical treatment is predominantly aimed at improving mouth movements. Specific treatment includes

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administration of steroids, placental extracts, IFN gamma, pentoxifylline, lycopene, surgical excision, etc.^[6,7] The blue, green algae, spirulina is rich in carotenoids and other micronutrients possessing chemo preventive potential. It has been used to test the clinical activity in reversing the oral precancerous lesions like leukoplakia.^[8] Shetty *et al.* recently have evaluated the role of spirulina in the management of OSMF.^[9] 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 Kumar *et al.* and Karemore and Motwani.^[10,11] However, each treatment has its own limitations. The present study was carried out to compare the efficacy of these newer antioxidants in the management of OSMF.

MATERIALS AND METHODS

The present prospective study included 68 subjects with clinico-pathologically diagnosed OSMF reporting to the Department of Oral Medicine and Radiology. Patients of either sex with OSMF were included in the study, which was conducted from March, 2013 to July, 2013. 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 2 groups, Group A (spirulina group) and Group B (lycopene group). Group A was administered 500 mg spirulina in 2 divided doses for 3 months, and Group B was given 8 mg lycopene (Lycored™, Jagsonpal Pharmaceuticals, New Delhi) in 2 divided doses of 4 mg 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 using a vernier caliper. In edentulous patients, the inter ridge (alveolar) distance along the midline was measured.^[12] Three measurements were recorded consecutively, and the average value was calculated and recorded. Evaluation for presence, absence or reduction of other clinical parameters such as ulcers/erosions/vesicles, burning sensation and pain associated with the lesion was done at regular intervals of 1 month, 2 months and 3 months. The clinical parameters such as burning sensation, pain associated with the lesion, difficulty in swallowing and speech were evaluated by using a visual analog scale. The score of 0-1 was considered as absent, score in the range of 1-6 was considered as reduced and a score of 7-10 was evaluated as present. The data were 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 39 males and 29 females with a mean age of 30.9 ± 12.8 years. Sixty-two percent of the patients had habit of betel nut chewing, while 28% of the patients had tobacco chewing habit. Thirty-eight percent of the patients consumed spicy foods which were among the main causative factors for OSMF in the study population. Clinical improvements in mouth opening was significant in the Group B (*P* = 0.0006) [Table 1]. The effect of administration of spirulina in the Group A showed significant improvement in the ulcers/erosions/vesicles (*P* = 0.0001) [Table 2]. However, there was no significant improvement in pain associated with the lesion (*P* = 0.004) and burning sensation (*P* = 0.005) among the 2 groups [Tables 3 and 4]. There were no

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

Time interval	Spirulina	Lycopene	P value
Baseline	19.6±2.4	18.1±2.7	0.0006
1 month	20.9±2.9	21.5±2.1	
2 months	22.3±2.3	23.4±2.4	
3 months	23.7±2.4	26.5±2.6	

Table 2: Effect of spirulina and lycopene in reduction of ulcers/vesicles/erosions

Time interval	Spirulina			Lycopene		
	Present	Absent	Reduced	Present	Absent	Reduced
Baseline	33	1	-	31	3	-
1 month	24	6	4	26	5	3
2 months	18	10	6	20	8	6
3 months	10	17	7	14	13	7

Table 3: Effect of spirulina and lycopene on pain associated with lesion

Time interval	Spirulina			Lycopene		
	Present	Absent	Reduced	Present	Absent	Reduced
Baseline	30	4	-	32	2	-
1 month	23	6	5	24	4	6
2 months	16	10	8	17	9	8
3 months	11	16	7	10	16	8

Table 4: Effect of spirulina and lycopene on reduction of burning sensation

Time interval	Spirulina			Lycopene		
	Present	Absent	Reduced	Present	Absent	Reduced
Baseline	34	-	-	34	-	-
1 month	22	4	8	24	3	7
2 months	15	11	8	16	10	8
3 months	10	17	7	9	18	7

noticeable side effects of spirulina and lycopene. None of the patients withdrew from the study due to any reason. The patients were followed-up for a period of 2 months during which five patients from Group A and eight patients from Group B showed ulceration and burning sensation for a period of 7-10 days.

DISCUSSION

Oral submucous fibrosis is a precancerous condition of the oral cavity and oropharynx seen predominantly in the Indian subcontinent and Southeast Asian countries and is now globally considered an Indian disease. The condition is preceded by burning sensation of the oral mucosa, ulceration and pain. OSMF is characterized by blanching and depigmentation of the oral mucosa, reduced movement and depapillation of tongue, and progressive reduction of mouth opening.^[13,14] Nasal twang due to fibrosis of nasopharynx and hearing impairment due to stenosis of eustachian tube may be seen in advanced stages of the condition.

The overall prevalence rate in India is believed to be about 0.2-0.5% and the prevalence by gender varying from 0.2% to 2.3% in males and 1.2-4.57% in females.^[15,16] It is considered to have a high degree of malignant potential, which ranges between 2.3% and 7.6%.^[17] Various factors such as, ingestion of chilies, genetic susceptibility, nutritional deficiencies, altered salivary constituents, autoimmunity and collagen disorders may be involved in the pathogenesis of OSMF.^[15] The most common etiological factor is areca nut and its products. The ingredients of areca nut induce excessive reactive oxygen species, which damages the cell structures. Accompanied with this, vitamin deficiency, iron deficiency anemia, and poor nutrition can disturb the repair of the inflamed oral mucosa, leading to poor healing. This results in atrophic oral mucosa, which becomes more susceptible to the effects of areca nut. The antioxidant vitamins are thus employed to stabilize and deactivate the free radicals before they attack cells.^[6]

Majority of OSMF patients present with irreversible moderate-to-severe condition. It may be associated with oral leukoplakia and other potentially malignant disorders or with squamous cell carcinoma. 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.^[16,18] The pathology is suggested to

develop within the epithelium due to intraoral trauma and various other irrational factors and poor oral hygiene.^[19]

Treatment modalities have been advocated for relieving the symptoms, but with no significant success. The first step of preventive measure should be in advising the patient to discontinue the habit of betel nut chewing, tobacco, spicy foods and chilies, which can be encouraged through education, counseling and advocacy. Medical treatment is symptomatic and predominantly aimed at improving mouth movements, with each treatment having its own limitations. According to Canniff and Harvey the medical management of OSMF is both empirical and unsatisfactory.^[17] According to Maher *et al.* multiple minerals and micronutrients showed significant improvement in mouth opening of 41% of the patients.^[20] Whereas, Borle and Borle. showed an improvement in symptoms of OSMF but insignificant improvement in mouth opening with Vitamin A.^[21] Sudarshan *et al.* have shown significant improvement in the mouth opening with aloe vera.^[22] Singh *et al.* have shown significant improvement in mouth opening, hyperkeratosis, pain in mouth and size of the lesion with oxitard capsules.^[7] Rajendran *et al.* found significant results with mouth opening and burning sensation with pentoxifylline, although results with tongue protrusion were not significant.^[23] Shetty *et al.* recently have shown that spirulina can bring about significant improvement in mouth opening and tongue protrusion in the management of OSMF.^[9] Lycopene has also showed significant improvement in mouth opening in the study by Karemore and Motwani.^[11] The present study is the first to compare the efficacy of the 2 newer antioxidants spirulina and lycopene in the improvement of clinical parameters such as, mouth opening, ulcers/erosions/vesicles, pain associated with the lesion and burning sensation.

Spirulina is a microalgae with rich natural source of proteins, carotenoids and other micronutrients and used in daily diet of African and American natives. It contains phenolic acid, tocopherols, and beta-carotene which are known to exhibit antioxidant properties.^[9] Spirulina has been used for the treatment of several oral mucosal lesions with successful results. It has been primarily assessed in treating leukoplakia with promising results.^[8] However, its effects on OSMF are not well-documented.

Lycopene is a major carotenoid obtained from tomato with potent anticancer activity.^[24] The antioxidant properties of lycopene are thought to be primarily involved in its preventive effects in chronic diseases and many types of cancers including potentially oral 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.^[25] 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.^[11]

There was a significant improvement in mouth opening in patients who were given lycopene soft gel orally than those who were given spirulina ($P = 0.0006$). Similarly, Karemore and Motwani, Kumar *et al.* observed significant improvement in mouth opening in the lycopene group.^[10,11] However, the spirulina group showed significant improvement in the ulcers/erosions/vesicles ($P = 0.0001$). Both the groups showed improvement in burning sensation and pain associated with the lesion, but this was not statistically significant ($P > 0.0001$). The relief from burning sensation in patients treated with spirulina is probably due to beta-carotene, phenolic acid, tocopherols, and various micronutrients present in spirulina.^[26] Administration of beta-carotene systemically and topically improves the epithelial integrity and also induces redifferentiation of dysplastic epithelium.^[27] There were no noticeable side-effects of spirulina and lycopene similar to the findings of Shetty *et al.* and Karemore and Motwani.^[9,11]

The results of the present study show that the spirulina significantly improves ulcers/erosions/vesicles, while lycopene significantly improved mouth opening. Both the drugs were equally effective in improving the pain and burning sensation of the patients. Thus, both the drugs can be thought to bring about equal positive outcomes for the patients with OSMF. A larger sample size, with a longer period of treatment follow-up, and a multi-institutional double-blind prospective study for assessment of effects of both the drugs is recommended to draw further conclusion on their utility in the treatment of OSMF.

CONCLUSION

Treatment of OSMF has been a challenge ever since its discovery. Newer drugs have been constantly evolving for the management of this complex disease. The results of the present study showed that both spirulina and lycopene were found to be equally effective in the management of OSMF. Quitting of the habit alone as an intervention may have a significantly greater effect, on the symptoms of OSMF. Hence, intervention studies and public health campaigns at the community level must be encouraged, as they may prove to be the best way of controlling OSMF.

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