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Original Article

Efficacy of Oral Lycopene in the Treatment of Oral Submucous Fibrosis

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Abstract

Introduction: Oral Submucous Fibrosis is a premalignant condition involving the oral cavity & pharynx. It predominantly occurs in the Indian subcontinent where the habit is more prevalent. The malignant potential and the origin of cancer were attributed to the generalized epithelial atrophy associated with OSMF. Carotenoids & lycopene has antioxidant activity which proved to be efficient in the management of premalignancy.

Materials and Methods: Study group comprised of 50 patients who were clinically and histopathologically diagnosed as oral submucous fibrosis. All the 50 patients with OSMF were supplemented with capsule Lycobig 5mg in BID dosage for 90 days along with mouth exercises and complete abstinence of oral chewing habits.

Results: The 50 OSMF subjects were divided into 3 clinical stages. In stage I with mouth opening of > 36 mm there were 6 (12%) subjects, stage II with mouth opening of 35-26 mm had 20 (40%) subjects, stage III with mouth opening of 25-15 mm had 24 (48%) subjects. Majority of our subjects were in clinical stage III. Majority subjects were in the age group of 21-30 years, 23 (46%). However statistically, there was no significant difference in age distribution among various clinical stages under study was observed (p=0.255; NS). The present study reported a statistically significant change in burning sensation score. Before treatment mean burning sensation score was 7.80±2.00 which became 2.98±2.737 after 90 days of treatment.

Aims and Objectives: The main of this study is to determine the effect of lycopene on the clinical stages of Oral Submucous Fibrosis and to determine the effect of lycopene in different age groups.

Key words: Carotenoids, Lycopene, Oral submucous fibrosis

INTRODUCTION

The mouth is the mirror of the body which reflects systemic diseases. Dental and medical practitioners encounter a wide spectrum of oral mucosal lesions in their day-to-day clinical practice. These mucosal lesions vary in nature from simple to life-threatening ones. Oral submucous fibrosis (OSMF) is one of the premalignant conditions involving the oral cavity and pharynx. It is a chronic, progressive, scarring disease that predominantly affects the people in India and South-east Asia.[1] The disease was first termed as Atrophia Idiopathica Mucosae Oris and was reported by Schwartz.[2] It predominantly occurs in the Indian subcontinent where the habit is more prevalent, so chewing of areca nut is an important factor in the etiology of OSMF.[3] Several factors such as chili consumption, nutritional deficiency, genetic susceptibility, autoimmunity, and collagen disorders have been suggested to be involved in the pathogenesis of this condition.[4] The malignant potential and the origin of cancer were attributed to the generalized epithelial atrophy associated with OSMF.[5]

Carotenoids are natural pigments synthesized by plants and are responsible for the colors of fruits and vegetables. Lycopene is the predominant carotenoid in the tomatoes and tomato products. Among dietary carotenoids lycopene is the most efficient quencher of singlet oxygen. This antioxidant activity is a potential mechanism by which lycopene may contribute to the prevention of a variety of cancers and other diseases.[6]

The present study offers a noninvasive and safe alternative or adjunct to conventional therapies and highlights

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the benefits of fresh fruits, vegetables, and nutritional supplements for both prevention and treatment of diseases.

MATERIALS AND METHODS

The study group comprised of 50 patients who were clinically and histopathologically diagnosed as OSMF. All the 50 patients with OSMF were supplemented with capsule Lycobig (Bestochem Pharmaceuticals Ltd) 5 mg in BID dosage for 90 days along with mouth exercises and complete abstinence of oral chewing habits.

Inclusion Criteria

The following criteria were included in the study:

- Patients who were physically healthy and well-oriented in time space and as a person
- A positive history of chewing arecanut or one of its commercial preparations
- Patients clinically and histopathologically diagnosed to be suffering from OSMF
- Patients who had symptoms i.e., pain burning sensation on eating normal/spicy foods and restricted mouth opening
- Patients not on any treatment for the same
- Patients who agreed to take medication supplied. Patients who agreed to follow up every 15 days for 90 days
- Patients who agreed for the biopsy and hematological examination.

Exclusion Criteria

The following criteria were excluded from the study:

- Patients with systemic diseases such as diabetes mellitus, hypertension, and bleeding disorders
- Patients with any other mucosal disease or any other skin disease which may be associated with oral lesions
- Patients with findings of any physical or mental abnormality, which would interfere with or be affected by the study procedure
- Patients with a known allergy or contraindication to study medications
- Patients with pericoronitis
- Patients with >15 mm mouth opening.

The study subjects were made to sit comfortably on a dental chair. Patients were examined under artificial illumination and the relevant data were entered into the proforma. The clinical examination was carried out following the method described by Kerr *et al.*[7] The patients personal history was recorded according to the different chewing habits such as pan, tobacco, and gutkha chewing, duration, and frequency of chewing. Symptoms such as burning sensation to normal food or spicy food and its duration, restricted mouth opening were noted. Extraorally clinical signs such as interincisal mouth opening were measured using Vernier caliper from the mesio-incisal angle of upper central incisor to the mesio-incisal angle of lower central incisor and recorded in millimeters. Intraorally, different sites were examined for blanching, consistency, and fibrous bands in the buccal mucosa.

Clinically subjects were grouped into four categories, according to the clinical staging of Khanna and Andrade.[2,8]

- Group I: Very early case - mouth opening >36 mm
- Group II: Early cases - mouth opening 26–35 mm
- Group III: Moderately advanced cases - mouth opening 15–25 mm
- Group IVa: Advanced cases - mouth opening 2–15 mm
- Group IVb: Advanced cases with premalignant changes and malignant transformation.

Table 1: Age and gender distribution

S. No.	Age group (years)	Gender				Total	
		Male		Female			
		No.	%	No.	%	No.	%
1.	≤20	5	11.9	0	0	5	10
2.	21–30	19	45.2	4	50.0	23	46
3.	31–40	12	28.6	2	25.0	14	28
4.	41–50	6	14.3	2	25.0	8	16
	Total	42	84	8	16	50	100

Table 2: Habits

Habits	No. of patients	Percentage
Gutkha+Pan+Tobacco	4	8.0
Gutkha+Pan	15	30.0
Gutkha+Tobacco	5	10.0
Gutkha alone	20	40.0
Pan alone	3	6.0
Pan+Tobacco	3	6.0
Total	50	100.0

Table 3: Signs and symptoms

S. No.	Clinical sign/symptom	No. of patients	Percentage
1.	Burning sensation normal food	9	18
2.	Burning sensation spicy food	42	84
3.	Restricted mouth opening	49	98

Table 4: Clinical staging

S. No.	Stage	No. of patients	Percentage
1.	I	6	12
2.	II	20	40
3.	III	24	48

RESULTS

The 50 subjects were in the age range of 17–50 years, with a mean age of 29.8 ± 8.7 years. Majority of patients were <30 years of age (56%).

Out of 50 subjects, 42 (84%) were males and 8 (16%) were females. Thus showing an extreme male predominance over females with a male-to-female ratio of 5.25:1 [Table 1]. Out of 50 subjects, Gutkha alone was the most prevalent adverse oral habit (40%) followed by Gutkha + Pan (30%), Gutkha + Tobacco (10%), Gutkha + Pan + Tobacco (8%) and Pan alone (6%), Pan + Tobacco (6%) [Table 2]. On clinical presentation, history of burning sensation on normal food was seen in 9 (18%) patients. The presence of burning sensation on spicy food intake was seen in 42 (84%) subjects. The mouth opening was restricted in 49 (98%) subjects [Table 3]. Majority of subjects were in clinical stage II 20 (40%) and stage III 24 (48%). There were 6 (12%) subjects in clinical stage I [Table 4].

Comparison of Burning Sensation Score before and after Treatment

Statistically significant change in burning sensation score visual analog scale was seen when post-treatment mean scores were compared with pre-treatment scores ($P < 0.001$). Before treatment, mean burning sensation score was 7.80 ± 2.00 which became 2.98 ± 2.737 after 90 days of treatment [Table 5].

Table 5: Comparison of burning sensation score before and after treatment

S. No.	Burning sensation	Mean	SD
1.	Before treatment	7.80	2.000
2.	After treatment	2.98	2.737
	Before treatment versus After treatment change in Burning sensation score	"t"=15.421; P<0.001	

Table 6: Comparison of mouth opening before and after treatment (mm)

S. No.	Mouth opening	Mean	SD
1.	Before treatment	26.42	6.11
2.	After treatment	28.58	6.828
	Before treatment versus After treatment change in mouth opening	t=5.742; P<0.001	

Table 7: Age and clinical staging

S. No.	Age group (years)	Clinical stage						Total	
		I		II		III			
		No.	%	No.	%	No.	%	No.	%
1.	≤20	0	0.0	3	15	2	8.3	5	10
2.	21–30	2	33.3	8	40	13	54.2	23	46
3.	31–40	4	66.7	4	20	6	25.0	14	28
4.	41–50	0	0.0	5	25	3	12.5	8	16
	Total	6	12	20	40	24	48	50	100

χ^2=7.775 (df=6); P=0.255 (NS)

Comparison of Mouth Opening before and after Treatment

Statistically significant change in mouth opening (mm) was seen when post-treatment mean was compared with pre-treatment scores ($P < 0.001$). Before treatment, mean mouth opening was 26.42 ± 6.11 mm which became 28.58 ± 6.828 mm after 90 days of treatment [Table 6].

Age and Clinical Staging

There were six patients in Stage I, out of these 2 (33.33%) were in age group 21–30 years while the remaining 4 (66.67%) were in age group 31–40 years. None of the patient of clinical Stage I was seen in age group <20 years or >40 years. Out of 20 patients in clinical Stage II, 8 (40%) were in age group 21–30 years, 5 (25%) were in age group 41–50 years and 4 (20%) were in age group 31–40 years. In clinical Stage III, out of 24 patients, 13 (54.2%) were in age group 21–30 years, 6 (25%) were in age group 31–40 years, 3 (12.5%) were in age group 41–50 years and the remaining 2 (8.3%) in age group <20 years. Statistically, there was no significant difference in age distribution among various clinical stages under study ($P = 0.255$; NS) [Table 7].

Correlation between Different Age Groups, Clinical Staging and Improvement in Burning Sensation

Stage I

- No statistically significant difference was seen between pre- and post-treatment values for either of the two age groups ($P > 0.05$). Although mean post-treatment burning sensation scores were lower as compared to pre-treatment values in both the age groups.

Stage II

- Post-treatment burning scores were significantly lower ($P < 0.05$) for all the age groups thus showing a significant improvement in post-treatment burning sensation following the treatment.

Stage III

- Post-treatment scores were significantly lower statistically for the age groups 21–30 years and 31–40 years. Although the post-treatment values of <20 years and 41–50 years were lower as compared to pre-treatment values, the change was not significant statistically ($P > 0.05$).
- For all age groups, the post-treatment mean burning sensation scores were significantly lower as compared to pre-treatment values [Table 8].

Table 8: Correlation between different age groups, clinical staging and improvement in burning sensation

S. No.	Age group (years)	Burning sensation (Mean±SD)						Total	
		Stage I		Stage II		Stage III			
		Pre	Post	Pre	Post	Pre	Post	Pre	Post
1.	<20	–	–	7.67±2.52	0.67±0.58*	7.50±0.71	1.50±2.12	7.60±1.82	1.00±1.22**
2.	21–30	9.40±1.41	4.50±4.95	6.63±1.92	1.63±1.30***	8.85±1.46	4.77±2.28***	8.09±1.91	3.65±2.60***
3.	31–40	5.25±2.06	0.75±5.25	8.75±2.50	3.25±2.75**	8.83±1.33	4.00±2.00**	7.79±2.42	2.86±3.42***
4.	41–50	–	–	7.40±1.67	2.20±1.79***	6.67±2.08	3.00±2.65	7.13±1.73	2.50±2.00***

Pre versus post: *P<0.05 – significant; **P<0.01 – highly significant; ***P<0.001 – very highly significant

Table 9: Correlation between different age groups, clinical staging and improvement in mouth opening

S. No.	Age group (years)	Mouth opening (Mean±SD)						Total	
		Stage I		Stage II		Stage III			
		Pre	Post	Pre	Post	Pre	Post	Pre	Post
1.	<20	–	–	24.67±6.11	28.00±4.58	20.00±1.41	21.00±2.83	22.80±5.07	25.20±5.22*
2.	21–30	37.00±0.00	40.00±2.828	29.13±3.441	32.38±4.78**	21.38±2.43	23.77±3.24**	24.48±5.63	27.17±6.81***
3.	31–40	37.25±0.500	37.00±2.31	29.50±1.73	32.75±2.87*	21.00±2.19	22.17±3.71	28.07±7.23	29.43±7.34*
4.	41–50	–	–	30.40±4.34	35.40±4.16*	21.00±2.00	22.00±1.73	26.88±5.96	30.38±7.67*

Pre versus post: *P<0.05 – significant; **P<0.01 – highly significant; ***P<0.001 – very highly significant

Correlation between Different Age Groups, Clinical Staging, and Improvement in Mouth Opening

Stage I

- No significant difference was seen between pre and post-treatment values for either of the two age groups ($P > 0.05$). Although mean post-treatment mouth-opening value was higher as compared to pre-treatment values in both the age groups.

Stage II

- Post-treatment mean mouth opening was higher in all the age groups thus showing an improvement in post-treatment mouth opening. The improvement was also statistically significant for all the age groups except age group <20 years.

Stage III

- Post-treatment mean mouth opening was higher in all the age groups thus showing an improvement in post-treatment mouth opening. However, the improvement was statistically significant for the age group 21–30 years only.

For all age groups, the post-treatment mean mouth opening was significantly higher as compared to pre-treatment values [Table 9].

Clinical Staging versus Improvement in Burning Sensation

Maximum improvement was seen in Stage I as compared to Stage II and Stage III however it was not significant statistically. There was a significant difference when improvement in stage II was compared with stage III [Table 10].

Clinical Staging versus Improvement in Mouth Opening

Maximum improvement was seen in Stage II as compared to Stage I and Stage III. However, none of the comparisons revealed a significant difference between groups [Table 11].

DISCUSSION

OSMF is a chronic progressive and irreversible disease affecting the oral, oropharyngeal and sometimes esophageal mucosa.[9] An ideal treatment is one which provides no morbidity, reverses the changes in the mucosa to normal and cures OSMF. Treatment needs coupled with cessation of oral habits and daily mouth exercises to manage the early and advanced cases. Lycopene is a very potent antioxidant[10] present mainly in tomato and tomato products.[11] It has been shown to inhibit the premalignant and malignant tumor cell growth.[12] It has also shown potent benefits in leukoplakia, lichen planus and OSMF.

In the present study, the 50 subjects were in the age range of 17–50 years with a mean age of 29.8 years. This is comparable to mean age of 29.1 years specified by Sinor *et al.*,[13] 32 years reported by Haider *et al.*,[14] 28 years by Kumar *et al.*,[15] 28.8 years by Hazarey *et al.*[16] Among the 50 OSMF subjects, 42 (84%) were males and 8 (16%) were female patients, thus showing an extreme male predominance over female with the ratio of 5.25:1. A similar male predominance was reported by Ahmad *et al.*[17] who found male to female ratio was 2.7: 1., Hazarey *et al.*[16] as 4.9:1, Ramadass *et al.*[18] as 3:1, Raina *et al.*[19] as 3.3:1, Tupkari *et al.*[20] as 11.6:1.

Table 10: Clinical staging versus improvement in burning sensation

S. No.	Clinical stage	Mean	SD
1.	Stage I (*n*=6)	92.64	121.74
2.	Stage II (*n*=20)	75.21	19.60
3.	Stage III (*n*=24)	52.74	25.39
	Stage I versus II	t=0.643; *P*=0.526	
	Stage I versus III	t=1.551; *P*=0.132	
	Stage II versus III	t=3.223; *P*=0.002	

Table 11: Clinical staging versus improvement in mouth opening

S. No.	Clinical stage	Mean	SD
1.	Stage I (*n*=5)	2.24	7.13
2.	Stage II (*n*=20)	10.15	11.49
3.	Stage III (*n*=24)	8.37	9.28
	Stage I versus II	t=1.584; *P*=0.126	
	Stage I versus III	t=1.502; *P*=0.144	
	Stage II versus III	t=0.569; *P*=0.572	

In our study, it was observed that OSMF patients were taking different preparations of arecanut; however, out of 50 subjects, Gutkha alone was the most prevalent adverse oral habit (40%), similar findings reported by Ahmad *et al*.,[17] Sinor *et al*.,[13] Shah and Sharma[21] found that most of their subjects had the habit of chewing gutkha which is in accordance with our study.

The present study regarded gutkha as a possible prime etiological factor for OSMF. The habit forming process of gutkha chewers is due to tobacco and areca nut, which if consumed for longer duration and frequencies is responsible for causing addiction, leading to OSMF.

In the present study, burning sensation on normal food was seen in 9 patients (18%), burning sensation on spicy food intake was seen in 42 (84%) subjects. The similar percentage is quoted by Raina *et al*.[19] in 95% of subjects, by Afroz *et al*.[9] in 74.1% and intolerance to spicy foods in 60.4% of subjects. The mouth opening was restricted in 49 (98%) subjects which is comparable to 97.02% of Tupkari *et al*.[20] When the fibrous bands are laid down submucosally, the blood supply to the epithelium will be compromised resulting in epithelial atrophy and increased permeability of the epithelium to the irritants. Furthermore, there could be ulceration and atrophy of the papillae of the tongue. All these factors contribute to burning sensation. In normal individuals mouth opening ranges from 35 to 55 mm. In the present study, 49 (98%) patients had restricted mouth opening. The 50 OSMF subjects were divided into three clinical stages proposed by Khanna and Andrade In stage I with mouth opening of >36 mm there were 6 (12%) subjects, which was in contrast to 3 (3%) subjects reported by Khanna and Andrade[8] in Stage II with mouth opening of 35–26 mm there were 20 (40%) subjects, as compared to 22 (22%) subjects by Khanna and Andrade[8] the Stage III with mouth opening of 25–15 mm were 24 (48%) subjects, as compared to 42 (42%) subjects by Khanna and Andrade.[8] Majority of subjects were in clinical stage II (40%) and III (48%). There were 6 (12%) subjects in clinical staging I.

The present study depicts that out of 6 (12%) patients in Stage I, 2 patients (33.33%) were in the age group of 21–30 years, 4 patients (66.67%) were in the age group of 31–40 years. None of the patients of clinical Stage I were seen in age group <20 years or >40 years. In clinical Stage II out of 20 patients (40%), 8 patients (40%) were in the age group of 21–30 years, 5 patients (25%) were in the age group of 41–50 years and 4 patients (20%) were in the age group of 31–40 years. In clinical Stage III, out of 24 patients (48%), 13 patients (54.2%) were in the age group of 21–30 years, 6 patients (25%) were in the age group of 31–40 years, 3 patients (12.5%) were in the age group of 41–50 years and the remaining 2 patients (8.3%) were in the age group of <20 years. Statistically, there was no significant difference in the age distribution among various clinical stages under study ($P = 0.255$; NS).

In the present study, the mean burning sensation score before treatment was 7.80 ± 2.00 which became 2.98 ± 2.737 ($P < 0.001$) highly significant after 90 days of treatment. Similar studies have been quoted which supports the beneficial role of various antioxidants in OSMF by Lai *et al*.[22] as 88% improvement. In the present study in Stage I OSMF patients, no significant difference was seen between pre- and post-treatment values for either of the two age groups ($P > 0.05$).

In Stage II OSMF patients, the post-treatment burning sensation scores were significantly lower ($P < 0.05$) for all the age groups, particularly in age group between 21 and 30 years and 41–50 years thus showing a very highly significant ($P < 0.001$) improvement in post-treatment burning sensation score following the treatment.

In Stage III OSMF patients, the post-treatment burning sensation scores were significantly lower statistically for the age groups between 21 and 30 years and 31–40 years. Although the post-treatment values of <20 years and between 41 and 50 years were lower as compared to pre-treatment values, the change was not significant statistically ($P > 0.05$).

However, maximum improvement was observed in Stage I with 92.64% as compared to Stage II with 75.21% and Stage III with 52.74%; however, it was not significant statistically. There was a significant difference when improvement in Stage II was compared with Stage III.

In the present study, the mean mouth opening was 26.42 ± 6.11 mm which became 28.58 ± 6.828 mm after 90 days of treatment. The change in the mouth opening was considered very highly significant ($P < 0.001$). Kumar *et al.* (2006)[15] also observed an improvement of 5.25 ± 3.25 mm with an average gain of 3.4 mm, Raina *et al.*[19] reported improvement in mouth opening from 16 + 0.7 to 24 + 0.3 mm.

In Stage I, OSMF patients in the age group of 21–30 and 31–40 years showed no significant difference between pre- and post-treatment values ($P > 0.05$), although mean post-treatment mouth opening was higher as compared to pre-treatment values in both the age groups. In Stage II OSMF patients, the post-treatment mean mouth opening was higher in all the age groups thus showing an improvement in the post-treatment mouth opening, was also statistically significant for all the age groups except age group <20 years which is in accordance with Kumar *et al.*[15] In Stage III, OSMF patient's improvement was statistically significant for the age group between 21 and 30 years only. In the present study, maximum improvement in the mouth opening was seen in Stage II and is in accordance with Kumar *et al.*[24] who also advocated the beneficial effects of antioxidants in Stage II, as compared to in Stage I and Stage III.

CONCLUSION

OSMF is a disease with high degree of morbidity. It also carries a significant mortality rate of oral cancer. As no effective surgical and medical treatment is presently available for this clinical condition, but administration of nutrient antioxidants has proven to have a protecting effect at an early stage and with a significant clinical improvement in OSMF.[23] Oral Lycopene was seen to be efficacious, safe, and non-invasive treatment modality for OSMF. It was proven to yield significant improvement in signs and symptoms of the disease. Hence, a long-term follow-up study of the patients to fix the dose and duration of therapy is necessary to validate the use of such therapy in OSMF cases and prevent malignant transformation.

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