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RESEARCH ARTICLE

ROLE OF LYCOPENE AND COMBINATION OF LYCOPENE WITH MULTIVITAMINS IN THE TREATMENT OF ORAL SUBMUCOUS FIBROSIS PATIENTS – A COMPARATIVE STUDY

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ABSTRACT

Introduction: Oral Sub Mucous Fibrosis (OSMF) is the most common potentially malignant disorder found across India caused by chewing gutkha with tobacco. A number of studies have proven the use of antioxidants in the management of OSMF.

Aim: The aim of the present study was to compare the efficacy of antioxidants Lycopene and composition of carotenoids, lycopene, minerals and alpha lipoic acid in the treatments of OSMF patients.

Material and Method: 50 clinically diagnosed OSMF male patients were included in the study and were divided equally into two groups.

Group A –was administered with 8mg LYCOPENE capsuleorally with intralesional injection of dexamethasone (Dexona)and hyaluronidase (Hynidase)and GROUP B – with combination of carotenoids, lycopene, alpha lipoic acid and minerals (SM FIBRO) with intralesional injection of dexamethasone (dexona) and hyaluronidase (hynidase).

Both the groups were given intralesional injection every 10 days for 3 months. Different clinical parameters like mouth opening and burning sensation were evaluated every 10 days for 3months. ANOVA test and unpaired t test was done for statistical analysis.

Results: Group B patients showed improvement in degree of mouth opening, burning sensation, as well as elasticity of mucosa as compared to group A. Significant p value of <0.001 was noted on comparison between two Groups

Conclusion: Treatment modality of Group B was more effective in treating the patients with OSMF than group A. No side effects were seen in both the groups except some patients complained of pain during administration of intralesional injection.

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INTRODUCTION

OSMF is a common potentially malignant disorder found in India caused by chewing gutkha with tobacco and is characterized by progressive inability to open the mouth due to inflammation and progressive fibrosis of the sub mucosal tissues (Cox and Walker, 1996). Although thought to be multifactorial, various risk factors like areca nut chewing, chilli consumption, nutritional deficiency states, genetic susceptibility and collagen disorders have been suggested (Habie Thomas Samuel, 2015). It occurs when the synthesis of new collagen by myofibroblasts exceeds the rate at which it is degraded , such that the total amount of collagen increases over time (Borle and Borle, 1991).

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This leads to restricted mouth opening and burning sensation of the oral mucosa aggravated by spicy food. However, a more serious complication is the risk of developing oral malignancy that may be as high as 3-7.6% (Basu *et al*., 2015). Most important aspect of treatment is cessation of habit of chewing betel quid, areca nut, other local irritants, spicy and hot food, alcohol intake and smoking (Habie Thomas Samuel, 2015). Various modalities of treatment ranging from conservative treatment to surgical procedures have been attempted.Intra-lesional injections of steroids has been used in its treatment since quite long as a drug of choice.Other medical therapy include injection of placental extract, hyaluronidase, trypsin, collagenase, intralesional interferon-γ, oral zinc andpentoxiphylline. But there has been new interest in use of natural pigments in plants like lycopene, found to reverse the pathogenesis of OSMF (Habie Thomas Samuel, 2015).

Carotenoids have been known to decrease the incidence of oral premalignant lesions and cancer (Maserejian *et al*., 2007). Lycopene is a carotenoid in tomatoes (0.9-4.2 mg per 100 g) having high singlet oxygen quenching property. It has several potent anti-carcinogenic and anti-oxidant properties and has demonstrated profound benefits in precancerous lesions such as leukoplakia and OSMF (Gester, 1997). Hyaluronidase degrades the fibrous matrix promoting lysis of fibrous coagulum and activating specific plasmatic mechanism. Relief of symptoms of stiffness on oral cavity occurs through softening and diminishing fibrous tissue (Dr. Ramesh Ram Fry *et al*., 2014). The aim of the study was to compare the efficacy of antioxidants Lycopene and composition of Lycopene with multivitamins in the treatment of OSMF patients in two different groups. And objective of the study was to compare different clinical parameters like mouth opening and burning sensation in both the groups.

MATERIALS AND METHODS

In a clinical comparative study done in 50 male subjects who were screened and diagnosed clinically having OSMF who reported in department of Oral medicine and Radiology at AMES Dental College and Hospital, Raichur, Karnataka, India. The patients aged between 18 - 55 years were included in the study. Detailed history including symptoms, habits of areca nut, gutkha, pan masala, smoking, and alcohol intake was taken. Patients who reported with the limited mouth opening and associated with blanched oral mucosa with palpable vertical fibrous bands were screened and those patients who were diagnosed clinically having OSMF were included in this study. Exclusion criteria were

- Severe psychiatric,
- Cardiac,
- Gastrointestinal or
- Metabolic disorders.

All patients were properly explained about the study and their written consent was taken. The ethical clearance was obtained from Institutional ethical committee. The cases were randomly divided into two groups irrespective of their socioeconomic status and grading of OSMF. The mean mouth opening in group A was 25.20 mm and in group B was 24.58 mm before treatment.

Group A –Lycopene (Lycostar) 8mg capsule (Mankind Pharmaceuticals)withintralesional injection of dexamethasone 4mg/ml and hyaluronidase 1500 IU and

Group B - Composition of carotenoids, lycopene, alpha lipoic acid ,vitamin E,and minerals (SM Fibro)(Indoco Remedies PVT Limited) with intralesional injection of dexamethasone and hyaluronidase. Group A was administered with 8mg lycopene (Lycostar) once daily and group B with lycopene, minerals, carotenoids, and alpha lipoic acid and vitamin E (SM FIBRO) once daily. Both the groups were given intralesionalinjections of Dexamethasone 4mg/ml and hyalurinidase 1500 IU every 10 days for 3 months. Different clinical parameters were evaluated every 10 days.The main parameters assessed were improvements in mouth opening as interincisal distance in mm and burning sensation by visual analog scale from 1 to 10. The data was entered in using computer software SPSS (Statistical package of social service) 20 and analysed using ANOVA test and unpaired t test.

RESULTS

50 male patients participated in present study 25 in each group A and group B. Age of patients ranged between 18 - 55 years (mean age 28.6 yrs).Average baseline mouth opening on day 1 in group A was 25.20mm (Table 1), whereas group B it was 24.58mm (Table 2). At the end of the study (day 90) mouth opening in group A was 29.35mm and 32.41mm in the group B.And this difference from day 1 to day 90 was highly significant ($p < 0.001$).

Table 1. Difference in Interincisal openingin millimeters (mm) within Group A at different time intervals using Repeated measures ANOVA

Time Interval	N	Mean	Standard Deviation	95% Confidence Interval		F	P
				Lower	Upper		
Day 1	25	25.2052	3.01083	23.962	26.448		
Day 10	25	25.7516	2.98775	24.518	26.985		
Day 20	25	26.2084	2.98376	24.977	27.440		
Day 30	25	26.6256	2.87380	25.439	27.812	193.486	<0.001
Day 40	25	27.0588	2.99431	25.823	28.295		
Day 50	25	27.5972	3.01660	26.352	28.842		
Day 60	25	28.1032	3.08823	26.828	29.378		
Day 70	25	28.4036	3.24693	27.063	29.744		
Day 80	25	28.8916	3.09878	27.612	30.171		
Day 90	25	29.3556	3.17407	28.045	30.666		

Table 2. Difference in Interincisal openingin millimeters (mm) within Group B at different time intervals using Repeated measures ANOVA

Time Interval	N	Mean	Standard Deviation	95% Confidence Interval		F	P
				Lower	Upper		
Day 1	25	24.5820	3.89872	22.973	26.191		
Day 10	25	25.3688	3.79562	23.802	26.936		
Day 20	25	26.2528	3.75649	24.702	27.803		
Day 30	25	27.2180	3.79956	25.650	28.786	331.771	<0.001
Day 40	25	28.1404	3.78633	26.577	29.703		
Day 50	25	29.0160	3.67128	27.501	30.531		
Day 60	25	29.6796	3.67834	28.161	31.198		
Day 70	25	30.4432	3.47648	29.008	31.878		
Day 80	25	31.4836	3.32693	30.110	32.857		
Day 90	25	32.4100	3.22491	31.079	33.741		

Table 3. Difference in Burning sensation within Group A at different time intervals using Repeated measures ANOVA

Time Interval	N	Mean	Standard Deviation	95% Confidence Interval		F	P
				Lower	Upper		
Day 1	25	7.1640	.95998	6.768	7.560		
Day 10	25	6.1520	.94918	5.760	6.544		
Day 20	25	5.3600	1.11093	4.901	5.819		
Day 30	25	4.6000	1.08397	4.153	5.047	26.346	<0.001
Day 40	25	3.9160	1.18028	3.429	4.403		
Day 50	25	3.2320	1.18944	2.741	3.723		
Day 60	25	2.5800	1.18110	2.092	3.068		
Day 70	25	3.2080	6.49185	.528	5.888		
Day 80	25	1.4200	.99373	1.010	1.830		
Day 90	25	.8840	.71629	.588	1.180		

Table 4. Difference in Burning sensation within Group B at different time intervals using Repeated measures ANOVA

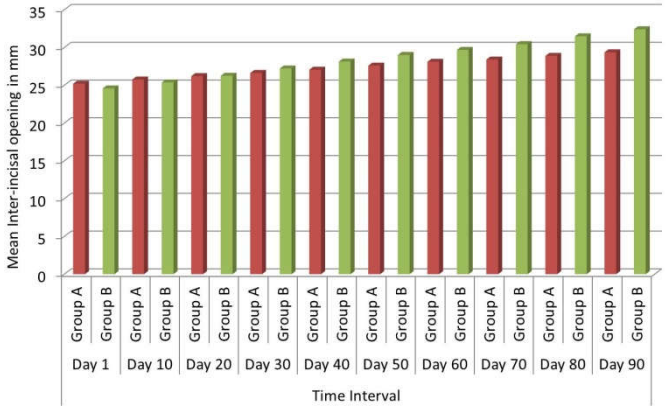
Time Interval	N	Mean	Standard Deviation	95% Confidence Interval		F	P
				Lower	Upper		
Day 1	25	6.4720	1.10360	6.016	6.928		
Day 10	25	5.2160	1.18978	4.725	5.707		
Day 20	025	4.3160	1.21576	3.814	4.818		
Day 30	25	3.3080	1.24161	2.795	3.821	432.265	<0.001
Day 40	25	2.6600	1.10905	2.202	3.118		
Day 50	25	1.9560	1.02676	1.532	2.380		
Day 60	25	1.2840	.67062	1.007	1.561		
Day 70	25	.7240	.47634	.527	.921		
Day 80	25	.3320	.25120	.228	.436		
Day 90	25	.2020	.12288	.151	.253		

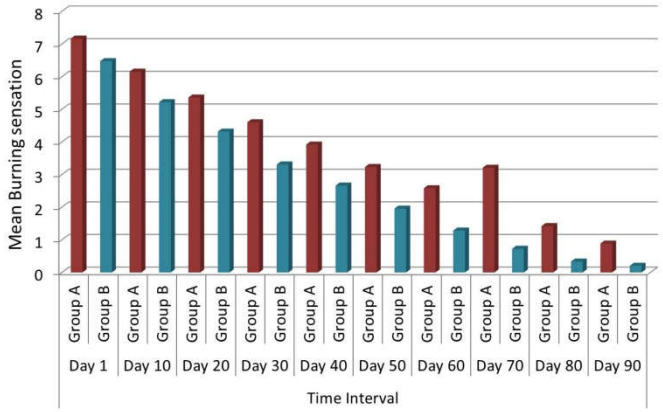
Table 5. Difference in Interincisal opening in millimeters (mm) between Group A and Group B at different time intervals using Unpaired T test

Time Interval	Groups	Mean	Standard Deviation	Mean Difference	95% Confidence Interval for Difference		T	P
					Lower	Upper		
Day 1	Group A	25.2052	3.01083	.62320	-1.35766	2.60406	.633	.530
	Group B	24.5820	3.89872					
Day 10	Group A	25.7516	2.98775	.38280	-1.55966	2.32526	.396	.694
	Group B	25.3688	3.79562					
Day 20	Group A	26.2084	2.98376	-.04440	-1.97352	1.88472	-.046	.963
	Group B	26.2528	3.75649					
Day 30	Group A	26.6256	2.87380	-.59240	-2.50812	1.32332	-.622	.537
	Group B	27.2180	3.79956					
Day 40	Group A	27.0588	2.99431	-1.08160	-3.02276	.85956	-1.120	.268
	Group B	28.1404	3.78633					
Day 50	Group A	27.5972	3.01660	-1.41880	-3.32957	.49197	-1.493	.142
	Group B	29.0160	3.67128					
Day 60	Group A	28.1032	3.08823	-1.57640	-3.50775	.35495	-1.641	.107
	Group B	29.6796	3.67834					
Day 70	Group A	28.4036	3.24693	-2.03960	-3.95249	-.12671	-2.144	.037
	Group B	30.4432	3.47648					
Day 80	Group A	28.8916	3.09878	-2.59200	-4.42028	-.76372	-2.851	.006
	Group B	31.4836	3.32693					
Day 90	Group A	29.3556	3.17407		-4.87398	-1.2348		
	Group B	32.4100	3.22491	-3.05440			-3.375	.001

Table 6. Difference in Burning sensation between Group A and Group B at different time intervals using Unpaired T test

Time Interval	Groups	Mean	Standard Deviation	Mean Difference	95% Confidence Interval for Difference		T	P
					Lower	Upper		
Day 1	Group A	7.1640	.95998	.69200	.10381	1.28019	2.365	.022
	Group B	6.4720	1.10360					
Day 10	Group A	6.1520	.94918	.93600	.32396	1.54804	3.075	.003
	Group B	5.2160	1.18978					
Day 20	Group A	5.3600	1.11093	1.04400	.38174	1.70626	3.170	.003
	Group B	4.3160	1.21576					
Day 30	Group A	4.6000	1.08397	1.29200	.62921	1.95479	3.919	.000
	Group B	3.3080	1.24161					
Day 40	Group A	3.9160	1.18028	1.25600	.60472	1.90728	3.878	.000
	Group B	2.6600	1.10905					
Day 50	Group A	3.2320	1.18944	1.27600	.64414	1.90786	4.060	.000
	Group B	1.9560	1.02676					
Day 60	Group A	2.5800	1.18110	1.29600	.74983	1.84217	4.771	.000
	Group B	1.2840	.67062					
Day 70	Group A	3.2080	6.49185	2.48400	-.13357	5.10157	1.908	.062
	Group B	.7240	.47634					
Day 80	Group A	1.4200	.99373	1.08800	.67582	1.50018	5.307	.000
	Group B	.3320	.25120					
Day 90	Group A	.8840	.71629		.38975	.97425	4.692	.000
	Group B	.2020	.12288	.68200				





Mean increase in mouth opening was 4.15mm in group A and 7.82mm in group B.The mean difference in interincisal opening between group A and group B on day 1 was 0.62mm where as at the end of the study it was 3.05mm.(Table-5) The mean baseline VAS score of burning sensation 7.16 in group A and 6.47 in group B. The mean scores at the end of the study were 0.88 and 0.20 in group A and group B respectively, with the mean decrease in burning sensation of 6.28 in group A and 6.27 in group B. (Table-3 and 4). The mean difference in burning sensation in between group A and B on day 1 was 0.69 and day 90 was 0.68.(Table-6) It was highly significant ($p<0.001$). No patients in any group showed local or systemic side effects due to the treatment. However, maximum improvement in mouth opening and decrease in burning sensation was recorded in the group B where a combination of steroid and lycopene and minerals were given to the patients.

DISCUSSION

Oral submucous fibrosis (OSMF) is an insidious, chronic disease affecting any part of the oral cavity, and sometimes pharynx. Although occasionally preceded and/or associated with vesicle formation, and always associated with ajuxtraepithelial inflammatory reaction followed by fibroelastic change of the lamina propria, with epithelial atrophy leading to stiffness of the mucosa and causing inability to open the mouth and difficulty ineating (Pindborg and Sirsat, 1966). It is a potentially malignant condition of the oral cavity and oropharynx which is predominantly seen in the Indian subcontinent and Southeast Asian countries and is now globally considered as an Indian disease (Santoshpatil *et al*., 2015). 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 (Yoithapprabhunath *et al*., 2013).

Fig. 1. Mouth opening assessment before treatment (pretreatment) -18mm

It is considered to have a high degree of malignant potential, which ranges between 2.3 and 7.6% (Canniff and Harvey, 1981). The precancerous nature of OSMF has been proved by higher occurrence of OSMF in oral squamous cell carcinoma patients (Dayal, Reddy and Anuradha Bhat, 2000). The disease has a complex pathophysiology, and various factors such as, ingestion of chillies, nutritional deficiencies, genetic susceptibility, altered salivary constituents, autoimmunity, and collagen disorders may be involved in the disease aetiology (Khan *et al*., 2012). Areca nut and related products are the most common etiological factors. Arecanut includes arecoline, arecaidine and tannins which stimulate fibroblast proliferation and dysregulate collagen synthesis. Intra-lesional steroids benefit by immunosuppression and inhibition of fibroblast proliferation and collagen synthesis (Manas Gupta *et al*., 2015).

Among the steroids, dexamethasone was selected for the study as it has better local potency, longer duration of action and lesser systemic side effects (Basu *et al*., 2015). Lycopene is a carbon acyclic carotenoid and exhibits the highest physical quenching rate constant with singlet oxygen (Kumar *et al*., 2007).

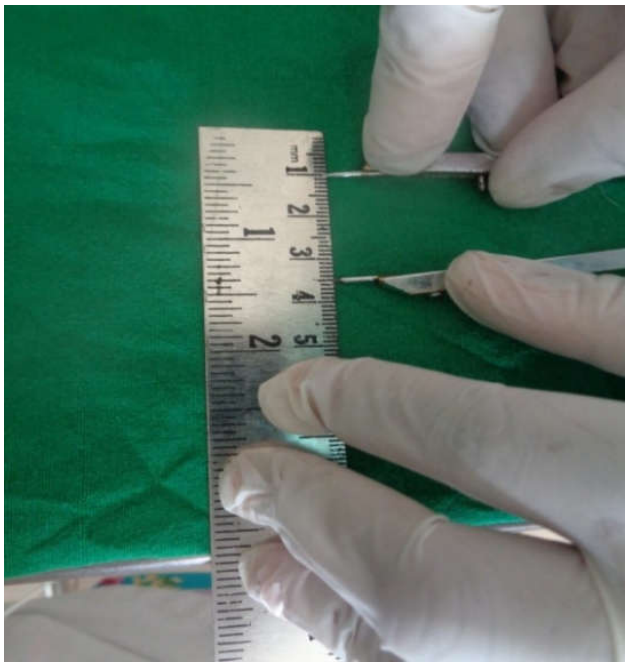


Fig. 2. Mouth opening assessment after treatment (post treatment) -25mm

The present study compared the efficacy of the two antioxidants with intralesional injection and in the improvement of various clinical parameters such as mouth opening, burning sensation, difficulty in swallowing, pain associated with the lesionand tongue protrusion. There was significant difference between Group A and Group B. Group B patients showed an average improvement of 7.5 – 8 mm where as in group A showed minimal improvement of 4 mm. The change in mouth opening was considered highly significant in group B than in Group A. Canniff *et al* reported in 1986 that the management of oral submucous fibrosis purely by means of intralesional steroids has been repoted be widely unsatisfactory with minimal impairment of opening. The improvement seen in our study was with thethe combination of lycopene and multivitamins with dexamethasone 4mg/ml and hylaurinidase 1500 IU showed highly significant improvement (Canniff and Harvey, 1981). Kumar *et al* evaluated efficacy of oral lycopene in patients with OSMF and compared these effects with placebo.Patients receiving lycopene showed an average increase of 3.4 mm in mouth opening and patients receiving a combination of steroids and lycopene showed 4.6mm increase but in our study maximum improvement of mouth opening 7-8 mm seen in group B whichis highly significant (Kumar *et al*., 2007). Kakar *et al* reported that patients treated with hyaluronidase showed quick improvement in symptoms but a combination of dexamethasone gave better and long term results (Karkar *et al*., 1985). Similar in our study there was quick improvement in group B showed highly significant improvement. According to Rehana Maher *et al*, multiple micronutrients and minerals showed significant improvement in symptoms with 41% cases showing some improvement in mouth opening (Maher *et al*., 1997), contrary to which RM Borle and SR Borle showed improvement in symptoms of oral submucous fibrosis with vitamin A but not in mouth opening (Borle and Borle, 1991). But in our study with group B showed highly significant improvement in mouth opening, reduced burning sensation and elasticity of mucosa. Our study reveals that lycopene in combination with multivitamins with intralesional injections steroids and hyalurinidase is highly effective in improving mouth opening and burning sensation. This study comprised of smaller sample size, hence further studies are required with larger sample size to make data more statistically significant.

Conclusion

Combination of intralesional injections with lycopene, beta-carotene, selenium, zincsulphate, copper, alphalipoic acid and alpha tecopheryl acetate therapy has great benefits in alleviating the symptoms of OSMF patients and can be tried out as a first line treatment in selected patients suffering from the disease.

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