

TREATMENT OF ORAL SUBMUCOUS FIBROSIS WITH LYCOPENE, BETA-CAROTENE, ZINC, SELENIUM, COPPER, ALPHA-LIPOIC ACID, AND ALPHA-TOCOPHERYL ACETATE

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ABSTRACT

This study was carried out to examine the efficacy of multi-drug therapy with the combination of lycopene, betacarotene, zinc, selenium, copper, alpha-lipoic acid, and alpha-tocopheryl acetate in the management of oral submucous fibrosis. 46 patients with OSMF were divided into three categories; group 1 (inter-incisal opening >35 mm), group 2 (inter-incisal opening 25 to 35 mm), and group 3 (inter-incisal opening 15 to 25 mm). Inter-incisal distance and burning sensation (scored using the visual analogue scale) were recorded preoperatively and at the 2nd month of drug therapy. All data were statistically analyzed using SPSS software. Comparison within the three groups for change in inter-incisal distance and burning sensation after drug therapy was studied by paired t-test. Intergroup comparison of inter-incisal distance and burning sensation was done by one-way ANOVA with Tukey's post hoc test for pairwise comparison. The mean age of patients included in the study was 29.71 years, with a male to female ratio of 8:1. The mean increase in mouth opening was 1.3, 3.9, and 2.4 mm while decrease in burning sensation was 1.42, 2.46, and 1.86 for groups 1, 2, and 3, respectively (which was statistically significant). Intergroup comparison showed a statistically significant increase in mouth opening and reeducation of burning sensation between groups 1 and 2, as well as groups 2 and 3. Multidrug therapy was effective in improving burning sensation symptoms and mouth opening in OSMF patients. The combination therapy was most effective in patients with early-stage OSMF (mouth opening between 25 to 35 mm).

Key words: Trismus, Oral submucous fibrosis, Mouth opening, Burning sensation.

Introduction

Oral submucous fibrosis (OSMF) is a precancerous condition which predominantly affect the Indian subcontinent population. Schwartz in 1952, documented oral fibrosing disease in 5 Indian women from Kenya and used the term "atrophica idiopathica mucosa oris" for the same [1]. In 1953, Joshi coined the termed oral submucous fibrosis [2]. Various nomenclatures have been put forward for OSMF, and include areca nut induced oral fibrosis, areca nut chewer's syndrome, gutkha syndrome, and asian sideropenic dysphagia [3]. Although it can be seen in any age group, the highest prevalence of OSMF is seen between 30-40 years of age [4]. Common symptoms of OSMF include burning sensation of the oral cavity when consuming spicy food, blisters on the palate, recurrent ulcerations, defective gustatory sensation, generalized inflammation of the oral mucosa, and oral dryness. Clinical presentation of the condition shows significant blanching and fibrosis of the oral mucosa that ultimately leads to rigidity and gradual inability to open mouth. Severe cases may also lead to fibrosis of esophageal and pharyngeal mucosa, significant functional morbidity, and hearing impairment [5].

Although multiple causative agents are implicated to cause OSMF, the main etiologic factor triggering OSMF is areca nut chewing, which is commonly observed in the Indian subcontinent. Various mechanisms have been proposed for the etiopathogenesis of OSMF including; stabilization of collagen structure by tannins and catechin due to decrease in collagenase secretion, large amounts of collagen production during prolonged exposure to areca nut, deficiency in collagen phagocytosis, increased collagen cross-linking, formation of stable collagen by fibroblasts, and deficiencies in vitamins and micronutrients [6].

Etiopathogenesis of OSMF is variable and multifactorial. Similarly, various treatment approaches have been used for its management. The management options for OSMF depend on the severity of the condition and include pharmacological approach, surgical management, physiotherapy, or a combination of the above. Several categories of drugs have been used to treat OSMF with varying success rates. Medical management of OSMF includes steroids (dexamethasone, betamethasone, hydrocortisone), enzymes (collagenase, hyaluronidase, chymotrypsin), cardiovascular drugs (pentoxifylline, buflomedil, nyldrin), antioxidants (carotene, vitamin E, lycopene), vitamins (A, B, & C), and microelements (zinc, copper, magnesium) [7-14]. This study

was carried out to examine the efficacy of multi-drug therapy with combination of lycopene, betacarotene, zinc, selenium, copper, alpha lipoic acid, alpha tocopheryl acetate in management of OSMF.

Materials and Methods

The study was conducted in the Department of Oral and Maxillofacial Surgery after due approval from the institutional ethical committee. Both female and male patients referred to the department from October 2018 to September 2019, diagnosed with OSMF, and willing to participate in the study and follow-up were included. Patients with history of chewing areca nut or commercial preparations containing areca nut, difficulty in chewing/swallowing and burning sensation when consuming spicy food, restricted mouth opening, and changes in oral-mucosa including the presentation of palpable fibrous bands, blanching, stiffness, and histopathologically confirmed OSMF by biopsy were included in the study. Advanced cases of OSMF (with mouth opening <15 mm) were referred for surgical management. Patients with the presence of ulcero-proliferative neoplastic lesions and not willing to quit the habit were excluded from the study. The patients enrolled for the study were further grouped into three categories:

- Group 1 (Very early stage): Characterized by burning sensation and normal mouth opening is normal (inter-incisal opening more than 35 mm).
- Group 2 (Early stage): Presenting with limitation of mouth opening (inter-incisal opening of 25 to 35 mm) with pale buccal mucosa with moderate degrees of fibrosis.
- Group 3 (Moderately advanced stage): Presenting with trismus (inter-incisal opening ranging from 15 to 25 mm). The buccal mucosa appearing pale with vertical fibrous bands in buccal mucosa evident on palpation.

The history of habit in terms of duration, frequency of chews/day, and type of areca nut preparation were recorded. Subsequently, patients were advised to discontinue using areca nut in all forms. Oral prophylaxis was done to remove extrinsic stains on the teeth. This was performed to motivate them towards recovery. It also informed the investigator if the patient resumed the habit. They were grouped based on

the stage of the disease. Pre-treatment value (baseline) of mouth opening was evaluated as the inter-incisal distance measured in millimeters from mesio-incisal point angle of upper right central incisor tooth to mesio-incisal point angle of the lower right central incisor tooth. Similarly, the visual analogue scale was used to determine the baseline value of oral cavity burning sensation (with values from 0 to 10; 0 being no burning sensation and 10 being the most severe burning sensation). Subsequently, participants were dispensed capsules containing lycopene (5mg), Betacarotene (10mg), selenium (75 mcg), zinc sulfate (27.45 mg), copper (1 mg), alpha-lipoic acid (50 mg), and alpha-tocopheryl (10 IU). The capsules were prescribed two times daily for 2 months. Patients were kept on bi-weekly follow-up. The patients were evaluated at the 2nd month for burning sensation of the oral cavity and mouth opening following the same pre-treatment parametric scales.

Statistical analysis

All the data were entered into Microsoft excel 2010 and the descriptive statistics for age was expressed as mean \pm standard deviation (SD) for each group. The mean age among the three groups and the difference between genders were compared by one-way ANOVA and chi-square tests, respectively. Comparison within the three groups for change in inter-incisal distance and burning sensation after drug therapy was studied by paired t-test. Intergroup comparison of inter-incisal distance and burning sensation was done by one-way ANOVA with Tukey's post hoc test for pairwise comparison. For all the above tests p value <0.05 was considered statistically significant. The analysis of data was performed using SPSS (v.19).

Results and Discussion

A total of 46 patients diagnosed with OSMF were enrolled in the study. The total number of patients in group 1 (very early stage), group 2 (early stage), and group 3 (moderately advanced stage) were 18, 13, and 15, respectively. The mean age of the patients in groups 1, 2, and 3 were 29.27, 31, and 29.13 years, respectively. The disease was predominantly seen in males, with 41 males and 5 females reporting with OSMF. The M:F ratio was 8:1. There was no statistically significant difference among the 3 groups with relation to age and gender (**Table 1**).

Table 1. Table showing gender distribution between the three groups

Category	Type	Group1 Count (%)	Group2 Count (%)	Group3 Count (%)	P-value (Chi-Square)	Category	Group1 (Mean \pm SD)	Group2 (Mean \pm SD)	Group3 (Mean \pm SD)	P-value (ANOVA)
Gender	M	16 (89%)	12 (92%)	13 (87%)	0.8911	Age	29.27 \pm	31 \pm	29.13 \pm	0.7284
	F	2 (11%)	1 (8%)	2 (13%)						

All patients had a habit of areca nut chewing either in the form of betel nut or as commercially available products (gutka) for a period ranging from 2 years to 20 years. The frequency of chew varied from 1 to 10 packs per day.

An increase in mouth opening was observed in all patients at the 2nd-month follow-up after the multidrug therapy. The mean interincisal distance in group 1 was 36.6 mm pre-operatively, which increased to 38 mm at the 2nd-month

follow-up. In groups 2 and 3, the preoperative mean value of interincisal distance increased from 28.30 mm and 17.8 mm to 32.23 mm and 20.2 mm at the 2nd-month follow-up. The mean increase in mouth opening in groups 1, 2, and 3 was 1.3, 3.9, and 2.4 mm, respectively, which was significant (p-value; paired t-test 0.00018, <0.00001, and 0.00002) (**Table**

2). Evaluation of burning sensation showed a decrease in VAS scores in all groups. The difference in VAS scores for burning sensation before and after multidrug therapy was 1.42, 2.46, and 1.86 for groups 1, 2, and 3, respectively, which was significant (p-value; paired t-test <0.00001) (**Table 3**).

Table 2. The pre- and post-intervention mouth opening within each group.

Group (n)	Pre-intervention Score (Mean ± SD)	Post-intervention Score (Mean ± SD)	Mean difference	t-value	P-value (Paired 't' Test)
Group 1 (18)	36.6 ± 1.08	38 ± 1.08	1.4	4.760	0.00018
Group 2 (13)	28.30 ± 2.01	32.23 ± 2.61	3.93	8.063	0.00001
Group 3 (15)	17.8 ± 3.40	20.2 ± 4.45	2.4	6.186	0.00002

Table 3. The pre- and post-intervention burning sensation (VAS score) within each group.

Group (n)	Pre-intervention Score (Mean ± SD)	Post-intervention Score (Mean ± SD)	Mean difference	t Value	p Value (Paired 't' Test)
Group 1 (18)	2.25 ± 0.70	0.83 ± 0.70	1.42	-12.718	<0.00001
Group 2 (13)	6.30 ± 1.10	3.84 ± 1.28	2.46	-13.442	<0.00001
Group 3 (15)	7.86 ± 1.50	6 ± 1.69	1.86	-11.297	<0.00001

The difference of pre- and post-drug therapy interincisal distance and burning sensation (VAS score) among the three groups was evaluated by one-way ANOVA with Tukey’s post hoc test for paired comparison. For interincisal distance and burning sensation scores, the p-value corresponding to

the F-statistic of one-way ANOVA was <0.05, showing that one or more treatments were significantly different (**Table 4**). Tukey’s post hoc test was subsequently done to identify which pair of treatments were significantly different from each other (**Tables 4 and 5**).

Table 4. Comparison of mean difference of interincisal distance among the three followed by intergroup comparison.

Group (N)	Mean difference of interincisal distance (Mean ± SD)	P-value ANOVA (F)	Tukeys' Post Hoc Test For Intergroup comparison		
			Group 1 and 2 Tukey Q statistic (P-value) inference	Group 1 and 3 Tukey Q statistic (P-value) inference	Group 2 and 3 Tukey Q statistic (P-value) inference
Group 1 (18)	1.4333 ± 1.1882	0.000084 (11.764)	6.8597 (0.0010053) Significant	6.8597 (0.0010053) In-significant	3.8751 (0.0237135) Significant
Group 2 (13)	3.9231 ± 1.7541				
Group 3 (15)	2.4000 ± 1.5024				

Table 5. Comparison of mean difference of burning sensation scores among the three groups followed by intergroup comparison.

Group (N)	Mean difference of burning sensation scores (Mean ± SD)	P-value ANOVA (F)	Tukeys' Post Hoc Test For Intergroup comparison		
			Group 1 and 2 Tukey Q statistic (P-value) inference	Group 1 and 3 Tukey Q statistic (P-value) inference	Group 2 and 3 Tukey Q statistic (P-value) inference
Group 1 (18)	1.42 ± 0.1354	0.000084 (11.764)	6.8597 (0.0010053) Significant	6.8597 (0.0010053) In-significant	3.8751 (0.0237135) Significant
Group 2 (13)	2.46 ± 0.1831				
Group 3 (15)	1.86 ± 0.1652				

Intergroup comparison showed a statistically significant difference in the increase in mouth opening between groups 1 and 2 and groups 2 and 3 (p-values of 0.0058 and 0.0395, respectively). While this difference was not statistically significant between groups 1 and 3 (p-value = 0.766) (**Table 4**). Similarly, the intergroup comparison showed a statistically significant difference in reduction in burning sensation between groups 1 and 2 and groups 2 and 3 (p-values 0.0013 and 0.0306, respectively). While this difference was statistically insignificant between groups 1 and 3 (p-value = 0.766) (**Table 5**).

OSMF is a chronic debilitating condition that is predominantly characterized by progressive fibrosis and inflammation of the oral submucosal tissues. More and Rao defined OSMF as “an irreversible, progressive, debilitating collagen metabolic illness due to chronic chewing of areca nut and its preparations; that affects oral mucosa and sometimes the oesophagus and pharynx, which leads to functional morbidity and stiffness of the mucosa; and a potential risk of malignant transformation [3].” A review in 2004 reported that India ranked number one with highest registries of oral cancer worldwide with 75,000-80,000 cases reported each year, with OSMF being one of the major predisposing condition [15]. Prevalence of OSMF is highest among Indians living in and outside India compared to other Asians. Among these, about 0.4% account for the rural population [16]. Currently areca nut chewing is considered as the major etiologic factor responsible for OSMF. Other factors such as excessive consumption of chili, nutritional deficiency, autoimmunity, collagen disorders, and genetic susceptibility are involved [17]. Etiopathogenesis of OSMF is multifactorial. Various mechanisms are suggested, including excess collagen production due to long-term exposure to areca nut. Areca nut contains alkaloids that increase fibroblast proliferation whereas tannins and catechin in areca nut reduce collagen degradation through the inhibition of collagenases. The combined effects of these compounds contribute to the histological alterations in the oral mucosa and cause fibrosis [18]. In this study, 46 OSMF cases were enrolled for the study. The disease was predominantly seen in males, with a male to female ratio of 8:1. Literature reports varying male predisposition for OSMF, from as high as 42:1 to 6:1 [4, 19]. The high incidence in males is related to the social practice of areca nut chewing common in the male population in India and south-east Asian countries. Although OSMF has been reported as early as in 10 years old children, it most frequently affects adults in the 2nd and 3rd decade of life [20]. In the present study, the mean age of cases included in all the three groups together was 29.71 years, with a range of 21-45 years. Interestingly, females affected were in a higher age group of 32-45 years, with a mean of 39 years. The findings were similar to Punnya *et al.* [21].

The most common complaint by a majority of individuals suffering from OSMF is the oral cavity burning sensation

that generally aggravates the consumption of spicy food. The condition may affect any part of the oral cavity and may also involve the esophagus and pharynx depending on the severity. There are different intensities of characteristic mucosal rigidity due to fibroelastic transformation of the juxtaepithelial layer that progressively results in trismus. In cases of tongue involvement, protrusion is restricted. Many classification systems have been documented in literature each having their own pros and cons [22]. In general, OMFS can be categorized into early, moderate, and severe stages depending on their clinical presentation. Early OMFS is characterized by stomatitis and vesiculation with minimum difficulty in mouth opening. Moderate cases present with blanching, fibrosis, and reduced mouth opening, whereas severe cases involve sequelae of OSMF, leukoplakia, erythroplakia, as well as hearing and speech difficulty [4]. Patients in the current study were grouped according to the functional grading system given in 2017 by Passi *et al.* [23].

Treating OSMF depends on the severity of clinical presentation. In cases of early detection of the condition, cessation of the habit is followed by nutritional supplements including; proteins, vitamin D, E, and B complex, and micronutrients [24]. Moderate-to-severe cases are irreversible and their treatment is primarily symptomatic and aims at improving the mouth opening and relieve the burning sensation. With newer evolved concepts in managing OSMF, pharmacological drugs have gained popularity. Antioxidants, micronutrients, intralesional injections of corticosteroids, hyaluronidase, aloe vera, and placental extracts have been reportedly used in treating OSMF [24]. Intralesional injections of corticosteroids, either alone or in combination with hyaluronidase and placental extracts have been most frequently used for the management of OSMF [25]. Steroid injections are given submucosal, beneath the fibrotic bands across the oral mucosa at weekly intervals for 4 to 8 weeks [24]. Intralesional injections for management of OSMF require patient compliance.

Oral therapy using antioxidants like alpha lipoic acid and lycopene has been used as the first-line drug for OSMF. Lycopene has antioxidant, anti-inflammatory, and antiproliferative action. It prevents the damage caused by reactive free radicals to cells and their components [26]. In recent years novel oral drug therapies for OSMF have included; zinc acetate tablets for 4 months, 50 mg (8 hourly for 2-3 months), and vitamin A (25,000 IU once daily) [18]. Other drugs like salvianolic acid B, turmeric, colchicine, immunomodulatory drug levamisole, vasodilator pentoxifylline, spirulina, interferon gamma, herbal antioxidants and aloe-vera have shown promising result [7, 27, 28].

Various drugs act by varying mechanisms to relieve the symptoms of OSMF. Thus, this study was performed to assess the role of oral multi-drug therapy using lycopene, beta-carotene, zinc, selenium, copper, alpha-lipoic acid, and

alpha-tocopheryl acetate for the management of OSMF. Lycopene, alpha-lipoic acid, and beta-carotene are strong anti-oxidant [24]. Alpha tocopheryl acetate has anticancer properties [29]. Trace elements like zinc, selenium, copper are essential for various cellular functions [30]. Zinc enhances immunity by increasing the function of cell mediating innate immunity, NKs, and neutrophils. It also increases cytokine production, macrophages, thereby aiding in phagocytosis and intercellular killing [31]. In this study multidrug combination therapy was administered to patients with very early (mouth opening >35 mm), early (mouth opening between 25-35mm), and moderately advanced stage of OSMF (mouth opening between 15-25mm). An increased mouth opening and reduced burning sensation were reported in all OSMF groups. Maximum improvement in mouth opening and relief from burning sensation was reported in cases with early-stage OSMF (group 2), which was statistically superior when compared with group 1 (very early stage) and group 2 (moderately advanced stage).

Conclusion

Oral multidrug therapy using a combination of lycopene, beta-carotene, zinc, selenium, copper, alpha-lipoic acid, alpha-tocopheryl acetate was effective in the improvement of burning sensation symptoms and mouth opening in OSMF patients. The combination therapy was most effective in patients with early-stage OSMF (mouth opening between 25 to 35 mm).

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Ethics statement: The study was conducted after approval (KIMSDU/IEC/04/201) from the institutional ethical committee of Krishna Institute of Medical Sciences Deemed to be University (KIMSDU/IEC/04/201).

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