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Original Article

A Multinutrient Approach to Treating Oral Submucous Fibrosis: Lycopene, Beta-Carotene, Zinc, Selenium, Copper, Alpha-Lipoic Acid, and Alpha-Tocopheryl Acetate

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ABSTRACT

Alpha-lipoic acid, beta-carotene, zinc, selenium, copper, lycopene, and alpha-tocopheryl acetate were all used in this study to investigate the effectiveness of multi-drug therapy in the treatment of oral submucous fibrosis. Group 1 included 46 patients with OSMF (inter-incisal opening > 35 mm), group 2 included 25-35 mm, and group 3 included 15-25 mm. Inter-incisal distance and burning sensation (as measured by the visual analogue scale) were determined before surgery and during the second month of medication therapy. SPSS software was used to statistically analyze all of the data. A paired t-test was used to compare the three groups' changes in inter-incisal distance and burning sensation following medication therapy. Tukey's post hoc test was used for pairwise comparisons, and a one-way ANOVA was used to compare inter-incisal distance and burning sensation between groups. The study's subjects had an average age of 29.71 years and an 8:1 male-to-female ratio. For groups 1, 2, and 3, the mean increase in mouth opening was 1.3, 3.9, and 2.4 mm, while the mean decrease in burning sensation was 1.42, 2.46, and 1.86 mm (both statistically significant). Comparisons of groups 1 and 2, as well as groups 2 and 3, revealed a statistically significant increase in mouth opening and reeducation of burning sensation. OSMF patients' mouth opening and burning sensation symptoms improved with multidrug therapy. The patients with early-stage OSMF (mouth opening between 25 and 35 mm) responded well to the combined therapy.

Keywords: Trismus, Oral submucous fibrosis, Mouth opening, Burning sensation

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Introduction

A precancerous condition that primarily affects people from the Indian subcontinent is oral submucous fibrosis (OSMF). Schwartz used the term "atrophica idiopathica mucosa oris" to describe the oral fibrosing disease he observed in five Indian women from Kenya in 1952 [1]. Joshi first used the phrase "oral submucous fibrosis" in 1953 [2]. Several names have been proposed for OSMF, such as Asian sideropenic dysphagia, gutkha syndrome, areca nut chewer syndrome, and areca nut-induced oral fibrosis [3]. OSMF is most common in people between the ages of 30 and 40, while it can occur in any age range [4]. When eating spicy food, the oral cavity may burn. Other common symptoms of OSMF include blisters on the palate, frequent ulcers, impaired gustatory perception, widespread inflammation of the oral mucosa, and dry mouth. The condition's clinical manifestation includes severe oral mucosal blanching

and fibrosis, which eventually results in rigidity and a progressive inability to open the mouth. In severe cases, hearing loss, substantial functional morbidity, and fibrosis of the pharyngeal and esophageal mucosa may also result [5].

Chewing areca nuts, which is a typical practice in the Indian subcontinent, is the primary etiologic factor that causes OSMF, even though several causative agents have been identified. The etiopathogenesis of OSMF has been attributed to several mechanisms, such as the stabilization of collagen structure by tannins and catechins as a result of decreased collagenase secretion, high levels of collagen production during extended areca nut exposure, a lack of collagen phagocytosis, increased collagen cross-linking, fibroblasts' formation of stable collagen, and vitamin and micronutrient deficiencies [6].

OSMF has a complex and varied etiopathogenesis. Similarly, many treatment approaches have been used to manage it. Physiotherapy, medication, surgery, or a combination of these are the available treatment options for OSMF, depending on the severity of the problem. Various pharmacological categories have been used to treat OSMF, with varied degrees of success. Cardiovascular medications (pentoxifylline, buflomedil, nylidrin), enzymes (collagenase, hyaluronidase, chymotrypsin), antioxidants (carotene, vitamin E, lycopene), vitamins (A, B, and C), and microelements (zinc, copper, magnesium) are all part of the medical management of OSMF [7–14]. To manage OSMF, this study looked at the effectiveness of multi-drug therapy using lycopene, beta-carotene, zinc, selenium, copper, alpha lipoic acid, and alpha-tocopheryl acetate.

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 a 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 in the study were further grouped into three categories:

- Group 1 (Very early stage): Characterized by a 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 25-35 mm) with pale buccal mucosa with moderate degrees of fibrosis.
- Group 3 (Moderately advanced stage): Presenting with trismus (inter-incisal opening ranging from 15-25 mm). The buccal mucosa appears 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 the mesio-incisal point angle of the upper right central incisor tooth to the 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 (10 mg), 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 in 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 were expressed as mean ± 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 tests, a P-value < 0.05 was considered statistically significant. The analysis of data was performed using SPSS version 19.

Results and Discussion

The study included 46 participants who had been diagnosed with OSMF. There were 18, 13, and 15 patients in total in groups 1 (very early stage), 2 (early stage), and 3 (moderately advanced stage). Patients in groups 1, 2, and 3 had respective mean ages of 29.27, 31 years, and 29.13 years. 41 men and 5 women reported having OSMF, indicating that the condition was more common in men. The ratio of M to F was 8:1. Regarding age and gender, there were no statistically significant differences between the three groups **(Table 1)**.

Table 1. Gender distribution between the three groups

Category	Type	Group 1 count (%)	Group 2 count (%)	Group 3 count (%)	P-value (Chi-Square)	Category	Group 1 Mean	Group 2 Mean	Group 3 Mean	P-value (ANOVA)
Gender	M	16 (89%)	12 (92%)	13 (87%)	0.8911	Age	29.27	31	29.13	0.7284
	F	2 (11%)	1 (8%)	2 (13%)						

All of the patients chewed areca nuts for 2-20 years, either as betel nuts or as commercially accessible products (gutka). The chewing frequency ranged from one to ten packs daily.

At the second-month follow-up following the multidrug medication, all patients showed an increase in mouth opening. Before surgery, group 1's mean interincisal distance was 36.6 mm; at the 2-month follow-up, it had grown to 38 mm. At the 2-month follow-up, the preoperative mean interincisal distance values in groups 2 and 3 rose from 28.30 mm and 17.8 mm to 32.23 mm and 20.2 mm. Groups 1, 2, and 3 experienced substantial increases in mouth opening, with mean increases of 1.3, 3.9, and 2.4 mm, respectively (P-value; paired t-test = 0.00018, < 0.00001, and 0.00002) **(Table 2)**. All groups' VAS values decreased when the burning sensation was evaluated. Before and during multidrug therapy, groups 1, 2, and 3 had burning sensation VAS values of 1.42, 2.46, and 1.86, respectively. This difference 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

One-way ANOVA with Tukey's post hoc test for paired comparison was used to assess the differences in interincisal distance and burning sensation (VAS score) between the three groups before and after medication therapy. The P-value for the one-way ANOVA's F-statistic for interincisal distance and burning sensation ratings was less than 0.05, indicating that at least one treatment was substantially different **(Table 4)**. To determine which pair of treatments were substantially different from one another, Tukey's post hoc test was next used **(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)	The 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				

The increase in mouth opening between groups 1 and 2 and groups 2 and 3 was statistically different, according to an intergroup comparison (P-values = 0.0058 and 0.0395, respectively). However, the difference between groups 1 and 3 was not statistically significant (P-value = 0.766) **(Table 4)**. A statistically significant difference in the decrease in burning sensation between groups 1 and 2 and groups 2 and 3 was also observed in the intergroup comparison (P-values = 0.0013 and 0.0306, respectively). However, the difference between groups 1 and 3 was not statistically significant (P-value = 0.766) **(Table 5)**.

The main characteristics of OSMF, a chronic, incapacitating illness, are inflammation and increasing fibrosis of the oral submucosal tissues. An irreversible, progressive, debilitating collagen metabolic illness caused by chronic chewing of areca nuts and their preparations, OSMF affects the oral mucosa and occasionally the oesophagus and pharynx, resulting in functional morbidity and mucosal stiffness as well as a possible risk of malignant transformation, according to More and Rao [3]." According to a survey conducted in 2004, India has the highest oral cancer registry in the world, with 75,000–80,000 cases recorded annually, and OSMF was one of the main risk factors [15]. Compared to other Asians, Indians, both inside and outside of India, have the highest prevalence of OSMF. Of these, the rural population makes up around 0.4% [16]. Chewing areca nuts is currently thought to be the main etiologic cause causing OSMF. Additional factors include hereditary vulnerability, collagen problems, autoimmune, dietary deficiencies, and excessive chilli consumption [17]. The etiopathogenesis of OMSF is complex. Numerous explanations have been put up, such as the overproduction of collagen brought on by prolonged exposure to areca nuts. While areca nut tannins and catechin block collagenases to decrease collagen degradation, areca nut alkaloids promote fibroblast proliferation. These substances' combined effects result in fibrosis and histological changes in the oral mucosa [18]. Forty-six OSMF cases were enrolled in this investigation. With an 8:1 male-to-female ratio, the sickness was most common in men. According to the literature, the male tendency for OSMF varies, ranging from 6:1 to 42:1 [4, 19]. The social habit of chewing

areca nuts, which is prevalent among males in India and other Southeast Asian nations, is linked to the high prevalence in males. Despite reports of OSMF in children as young as ten, individuals in their second and third decades of life are most commonly affected [20]. With a range of 21–45 years, the mean age of the cases in the current study across all three groups was 29.71 years. It's interesting to note that, with a mean age of 39, the impacted females belonged to the older age range of 32–45 years. The results were comparable to those of Punnya *et al.* [21].

The majority of people with OSMF most frequently complain of a burning feeling in their mouth, which becomes worse when they eat spicy foods. Depending on how severe the illness is, it can affect any area of the oral cavity as well as the oesophagus and throat. The fibroelastic alteration of the juxtaepithelial layer causes varying degrees of distinctive mucosal rigidity, which eventually leads to trismus. The protrusion is reduced when the tongue is involved. Numerous classification schemes, each with advantages and disadvantages, have been recorded in the literature [22]. Based on their clinical presentation, OMFS can often be divided into three stages: early, moderate, and severe. Stomatitis and vesiculation with little difficulty opening the mouth are characteristics of early OMFS. Blanching, fibrosis, and decreased mouth opening are the symptoms of moderate instances; leukoplakia, erythroplakia, and hearing and speech difficulties are the symptoms of severe cases [4]. The functional grading method developed by Passi *et al*. [23] was used to group the patients in the current investigation.

The severity of the clinical presentation determines how OSMF is treated. When the problem is discovered early, nutritional supplements such as proteins, vitamin D, E, and B complex, and micronutrients are taken once the habit is broken [24]. Treatment for moderate-to-severe instances is mostly symptomatic and attempts to improve mouth opening and reduce burning. These cases are permanent. Pharmacological medications have become more common as a result of more advanced ideas for treating OSMF. OSMF has reportedly been treated with antioxidants, micronutrients, hyaluronidase, aloe vera, placental extracts, and intralesional injections of corticosteroids [24]. The most common treatment for OSMF has been intralesional injections of corticosteroids, either by itself or in conjunction with placental extracts and hyaluronidase [25]. For four to eight weeks, weekly submucosal steroid injections are administered over the oral mucosa, beneath the fibrotic bands [24]. Intralesional injections for the management of OSMF require patient compliance.

For OSMF, oral treatment with antioxidants such as lycopene and alpha lipoic acid has been the first-line treatment. Lycopene possesses anti-inflammatory, anti-proliferative, and antioxidant properties. It protects cells and their components from the harm that reactive free radicals can inflict [26]. Zinc acetate tablets for four months, 50 mg taken eight hours a day for two to three months, and vitamin A (25,000 IU once daily) are examples of new oral medication treatments for OSMF that have been developed recently [18]. Other medications that have demonstrated encouraging results include salvianolic acid B, turmeric, colchicine, levamisole, an immunomodulatory medicine, pentoxifylline, a vasodilator, spirulina, interferon-gamma, herbal antioxidants, and aloe vera [7, 27, 28].

Different medications relieve OSMF symptoms in different ways. Therefore, the purpose of this study was to evaluate the potential of oral multi-drug therapy for the treatment of OSMF by using lycopene, beta-carotene, zinc, selenium, copper, alpha-lipoic acid, and alpha-tocopheryl acetate. Strong antioxidants include beta-carotene, lycopene, and alpha-lipoic acid [24]. The anticancer effects of alpha-tocopheryl acetate [29]. Numerous cellular processes depend on trace metals like copper, zinc, and selenium [30]. Zinc improves immunity by boosting the activity of neutrophils, NKs, and cells that mediate innate immunity. Additionally, it boosts macrophages and cytokine secretion, which helps with phagocytosis and intercellular death [31]. Patients with very early (mouth opening > 35 mm), early (mouth opening between 25 and 35 mm), and moderately advanced (mouth opening between 15 and 25 mm) stages of OSMF were treated with multidrug combination treatment in this study. All OSMF groups reported a decrease in burning sensation and an increase in mouth opening. When compared to groups 1 (very early stage) and 2 (moderately advanced stage), the early-stage OSMF cases (group 2) showed the greatest improvement in mouth opening and alleviation from burning sensation.

Conclusion

OSMF patients' burning sensation symptoms and mouth opening were effectively alleviated by oral multidrug therapy that included lycopene, beta-carotene, zinc, selenium, copper, alpha-lipoic acid, and alpha-tocopheryl acetate. In patients with early-stage OSMF (mouth opening between 25 and 35 mm), the combination therapy was most successful.

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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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