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Comparing the Efficacy of Intralesional Triamcinolone Acetonide and Hyaluronidase with Placental Extract in Oral Submucous Fibrosis Cases: An Original Research

Mazen Ahmad Almasri
Dept of Oral Maxillofacial Surgery, Faculty of Dentistry, King Abdulaziz University, India

Kannan Venugopal
Consultant Oral and Maxillofacial Surgeon, Kollam Kerala, India

Keshini M. P
Coorg Institute of Dental Sciences, Coorg, Karnataka, India

Meghali Diwaker
Consultant oral and maxillofacial surgeon, Goa, India

Amrita Das
Department of Periodontology and Implantology, Dr. Hsrsm Dental College, Hingoli. Maharashtra, India

Vijay Kumar Yadav
Dept. of Oral Medicine and Radiology, Hazaribag College of Dental Sciences and Hospital, Hazaribag, Jharkhand, India

Shilpi Bhattacharya
Consultant Prosthodontist & Implantologist, Clove Dental, Visakhapatnam, AP, India

***Abstract*---**Intralesional infiltrations with placental extract and triamcinolone with hyaluronidase are equally effective in treating trismus of OSMF. No difference in treatment efficacy was seen in placental extract group or with triamcinolone with hyaluronidase group. Oral submucous fibrosis is a widely prevalent oral mucosal lesion in Indian population and considering its premalignant potential and severe clinical manifestations many studies are done by many authors regarding various aspects of this condition such as etiology pathogenesis and treatment. Arecoline of Areca catechu is mostly

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***Corresponding author**: Almasri, M. A.; Email: malmasri@kau.edu.sa*
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attributed as the causative factors in addition to pan and tobacco in different combinations. In our study a random allocation of 120 patients was done equally into two groups. Group 1 received 4 ml of placental extract injection intralesionally at weekly interval for 12 weeks and Group 2 received combination of triamcinolone acetonide(10 mg/ml) + hyaluronidase (1,500 IU) at weekly intervals for 12 weeks. Treatment outcome was evaluated on the basis of improvement in trismus, oral mucosal pattern and reduction in burning sensation.

***Keywords*---**hyaluronidase injection, oral submucous fibrosis, placental extract injection, triamcinolone acetonide, trismus.

Introduction

Oral submucous fibrosis (OSMF) is a chronic insidious premalignant condition of the oral mucosa. It is an insidious, chronic change in fibroelasticity, characterized by a burning sensation in the oral cavity, blanching and stiffening of the oral mucosa and oropharynx and trismus. Schwartz coined the term atrophica idiopathica mucosa oris to describe an oral fibrosing disease as he discovered in five Indian women from Kenya. It is clinically and histopathologically characterized diffusely blanched mucosa, presence of fibrous bands, depapillated tongue, erosions in the mucosa, where the patients chiefly complains of burning mouth and inability to take spicy food. Juxtaepithelial inflammatory reaction, fibroelastic changes in the lamina propria and epithelial atrophy leading to stiffness of oral mucosa, trismus and inability to eat. It is a precancerous condition common in the Indian subcontinent. The incidence varies from 0.2 to 0.5% in India with a higher percentage being found in southern areas. The exact etiology is still obscure, but many factors, such as betel nut, tobacco, smoking, pan masala and chillies, have been thought to be contributory. If untreated, the risk of malignant change in advanced cases of OSMF is relatively high. The clinical diagnosis is done on the basis of (a) difficulty to take hot and spicy foods, (b) difficulty in opening mouth, (c) inability to protrude the tongue, (d) blanching of oral mucosa, (e) reduced elasticity and mobility of tissues (f) presence of fibrous bands on palpation. Treatment includes intralesional injections of placental extract which act as biogenic stimulant and use is based on the tissue therapy method. Also used are intralesional corticosteroid injections with hyaluronidase.

Materials and Method

This is a comparative case series analysis study of 120 OSMF patients managed under two different treatment groups done during the study period of 2 years from January 2017 to January 2019. The study clearance was obtained. 120 patients, both males and females, were randomly allocated into two groups of 60 each, i.e. group 1 (n = 60) and group 2 (n = 60). All patients in the present study are arecanut, betel quid, gutkha and tobacco chewers in various combination. Diagnosis of OSMF were done on clinical criteria. Lesions suggestive of other diseases clinically were excluded from the study. SPSS 17 program were used to analyze the data. The selected patients included both males and females of all age groups and socioeconomic status. There were 75 males and 45 females in our

study. The average age was 25.4 years in group 1 and 30.2 years in group 2. Most of the patients were young manual laborers who easily had access to gutkha (flavored arecanut with tobacco) cheaply.

Apart from the baseline investigations mouth opening, color and burning sensation of the oral mucosa were recorded in both groups before and after infiltration of 4 ml placental extract in group 1 and triamcinolone acetonide (10 mg/ml) + hyaluronidase (1500 IU) in group 2. Intralesional injections were given in the soft palate and in the fibrous bands formed anterior to anterior pillars (at multiple sites bilaterally). The mouth opening was recorded using a graduated vernier gauge to measure the distance between the upper and lower central incisal edges at maximal unaided mouth opening. Interincisanal diameter of 40 mm and above was considered as normal mouth opening score (grade 0, no trismus), 30 to 39 mm (grade 1, trismus), 20 to 29 mm (grade 2, trismus), 10 to 19 mm (grade 3, trismus) and 0 to 9 mm (grade 4, trismus). The color of oral mucosa was assessed in natural light and scored as normal pink (0), red or deep pink Increased burning sensation of mouth to chilies or spicy foods is graded according to the severity of burning as; no burning sensation (0), minimal burning sensation (1), moderate burning sensation (2) and severe burning sensation (3). The infiltrations were done submucosally 1 ml on each side of the palate and pillars. The infiltrations were done every week in both groups and the three parameters IID, color of oral mucosa and burning sensation noted.

Table 1
Groups 1 and 2

GROUP 1	PLACENTAL EXTRACT	4 ml	
GROUP 2	TRIAMCINOLONE AND	10 mg/ml	
	HYALURONIDASE	1500 IU	P< 0.05

Results

The average IID improved from 16.266 to 35.9 mm in group 2 and from 15.83 to 33.8 mm in group 1 after 12 weeks of treatment. A significant improvement were seen in both the groups in all the three parameters. The difference in mouth opening score at 12 weeks were significant with group 2 patients showing better results compared to group 1. The difference of scores in improvement of burning sensation and oral mucosal pattern at 12th week were not significant when groups 1 and 2 were compared. Most of the patients in group 1 and 2 had relief from grade 3 to grade 1 trismus after 12 weeks of treatment. Significant reduction in burning sensation was seen from the 3rd week itself in both groups. Color of the oral mucosa improved from blanched white to normal pink in most of the cases. No reactions to the injections or complications were seen in both study groups. All the patients were given multivitamins, iron folic acid tablets and antioxidants after 12 weeks. No analgesics were given. Pearson's Chi-square test was used to test significance of the results in the two groups and the values were tabulated using Levene's test for equality of variances. Overall intralesional triamacinolone acetonide and hyaluronidase is better than placental extract in treating trismus of OSMF but give equal results when parameters of burning sensation and improvement in oral mucosal color is concerned.

Discussion

Oral submucous fibrosis is a widely prevalent oral mucosal lesion in Indian population and considering its premalignant potential and severe clinical manifestations many studies are done by many authors regarding various aspects of this condition such as etiology pathogenesis and treatment. Arecoline of Areca catechu is mostly attributed as the causative factors in addition to pan and tobacco in different combinations. Arecoline, an active alkaloid found in betel nuts, stimulates fibroblasts to increase production of collagen. Arecoline was found to elevate the mRNA and protein expression of cystatin C, a non glycosylated basic protein consistently up regulated in a variety of fibrotic diseases, in a dose-dependent manner in persons with OSMF. Arecoline is an inhibitor of metalloproteinases and a stimulator of tissue inhibitor of metalloproteinases, thus decreasing the overall breakdown of tissue collagen.

Keratinocyte growth factor-1, insulin-like growth factor-1 and IL-6 expression, which have all been implicated in tissue fibrogenesis, were also significantly up regulated in persons with OSMF due to areca quid chewing and arecoline may be responsible for their enhanced expression. Flavanoid, catechin and tannin in betel nuts cause collagen fibers to cross-link, making them less susceptible to collagenase degradation. This results in increased fibrosis by causing both increased collagen production and decreased collagen breakdown. OSMF remains active even after cessation of the chewing habit, suggesting that components of the arecanut initiate OSMF and then affect gene expression in the fibroblasts, which then produce greater amounts of normal collagen. Chewing areca quid may also activate NF-kappa-B expression, thereby stimulating collagen fibroblasts and leading to further fibrosis. Arecanuts have a high copper content and chewing areca-nuts for 5 to 30 minutes significantly increases soluble copper levels in oral fluids. This increased level of soluble copper supports the hypothesis that copper acts as an initiating factor in OSMF by stimulating fibrogenesis through up regulation of copper-dependent lysyl oxidase activity. Other factors attributed are immunological, nutritional, allergy, viral and candidal infections.

The disease initially presents as burning sensation in oral cavity. It is clinically divided into three stages. In stage 1 there is stomatitis, erythematous mucosa, vesicles, mucosal ulcers, melanotic mucosal pigmentation and mucosal petechiae. In stage 2, fibrosis occurs in ruptured vesicles and ulcers when they heal. There is blanching of oral mucosa. Vertical and circular palpable fibrotic bands are seen in buccal mucosa. Specific findings include trismus, stiff and small tongue, blanched and leathery floor of mouth, fibrotic and depigmented gingiva, rubbery soft palate with decreased mobility, blanched and atrophic tonsils, shrunken band-like uvula and sinking of cheek not commensurate with age or nutritional status. In stage 3, there are sequelae in the form of leukoplakia in about 25% of cases, speech and hearing deficits because of involvement of tongue, palate and eustachian tubes. Treatment protocol for OSMF is not standardized. Most important aspect of medical treatment is quitting chewing betel quid, arecanut, other local irritants, spicy and hot food, alcohol and smoking.

The various modalities of treatments include: Intralesional corticosteroid injections with hyaluronidase, intralesional injections of placental extract,

systemic administration of corticosteroids, lycopene, pentoxifyline therapy and surgical excision of fibrous bands is being tried with various degrees of success. Placental extract contains growth factors and anti-inflammatory agents and also antiplatelet activity. The action of placenta extract is essentially biogenic stimulation and use is based on the tissue therapy method. According to this theory when animal and vegetable tissues are severed from the parent body and exposed to unfavorable conditions, but not mortal to their existence, undergo biogenic readjustment leading to development of substance in the state of their survival to ensure their vitality biogenic stimulators.

Such tissues or their extract when implanted or injected into the body after resistance of pathogenic factors stimulates metabolic or regenerative process thereby favoring recovery. Triamcinolone acetonide suppresses immune system by reducing activity and volume of lymphatic system. It heals inflammatory mucosal lesions that are responsive to steroids. Decreases inflammation by suppressing the migration of polymorphonuclear leukocytes and by reversing capillary permeability. It is a better corticosteroid for intralesional injection as it has better local potency, longer duration of action and lesser systemic absorption. Hyaluronidase is an enzyme which reduces the viscosity of ground substance, thus making the tissues more permeable to injected corticosteroid triamcinolone acetonide. It stimulates hydrolysis of hyaluronic acid, one of the chief ingredients of tissue cement, which offers resistance to diffusion of liquids through tissues. It facilitates distribution and absorption of locally injected substances. It also promotes resorption of excess fluids and extravasated blood in the tissues.

Conclusion

Intralesional infiltrations with placental extract and triamcinolone with hyaluronidase are equally effective in treating trismus of OSMF. No difference in treatment efficacy was seen in placental extract group or with triamcinolone with hyaluronidase group. But placental extract injections are cost-effective. No side effects were seen in both study groups.

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