



COMPARATIVE STUDY OF CONVENTIONAL LOCAL STEROID INJECTIONS ONLY WITH MULTI-DRUGS THERAPY AND STEROID INJECTIONS IN ORAL SUBMUCOSAL FIBROSIS (OSMF).

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ABSTRACT

Oral submucous fibrosis (OSMF) is defined as the chronic inflammatory disease and progressive fibrosis with localized collagen disorder involving oral mucosa. There are multiple pathophysiological changes that occur in this disease. The aim of this study is to establish that multidrugs needed for effective conservative treatment in oral submucous fibrosis. A total number of 35 cases of OSMF managed in our ENT out patient department (OPD) over one year period (March 2010 to February 2011) were followed up until July 2011 and the results were analyzed retrospectively to find out any incidence of recurrence of this disease. All the cases received injection steroid and hyaluronidase with multivitamins (A, C and E in higher doses) for 10 weeks. At the end of treatment all the patients were relieved of burning sensation of mouth and got nearnormal mouth opening. The oral mucosa also changed from pale to pink. During follow-up no recurrence was detected. The study suggested that Vitamins A, C and E in higher doses are required to ensure best possible result apart from intralesional steroid and hyaluronidase as a standard conservative treatment protocol in oral submucous fibrosis.

KEYWORDS : Oral submucous fibrosis; angiogenesis; epithelialization; collagen synthesis.

INTRODUCTION

Oral submucous fibrosis (OSMF) is a chronic inflammatory disease with progressive fibrosis involving oral mucosa. The disease is characterized by blanching and stiffness of the oral mucosa, restricted mouth opening, burning sensation in the mouth, hypomobility of the soft palate and tongue, loss of gustatory sensation and seldom mild hearing loss due to blockage of eustachian tube. It is multifactorial and localized collagen disorder. There are complex pathophysiological changes producing reduced vascularity, and dense bundles and sheets of collagen immediately beneath the epithelium. The eventual thick band of hyalinized subepithelial collagen shows varying extension into submucosal tissues. There is a fibroelastic transformation of the juxtra-epithelial connective tissues. The epithelium is atrophic, with or without excess surface keratin and demonstrates intercellular edema.¹ It is precancerous disease^{1,2} with malignant transformation upto 3-7.6% of cases.¹ The widespread habit of chewing paan masala is a major risk factor of OSMF, especially in the younger age group.³

Various authors proved that OSMF patients have deficiency of beta-carotene, ascorbic acid, vitamin E, vitamin B complex and iron.^{1,4,5} Only conventional treatment of OSMF with steroid, hyaluronic acid and jaw dilatation exercise is not sufficient. So, Vitamin A, C and E to prevent fibrosis, angiogenesis at the avascular zone, increase of re-epithelialization at the atrophic epithelium and collagen synthesis. Borle et al⁶ reported that vitamin A 50000 IU once daily could cause symptomatic improvement. Maher R et al⁷ observed that multivitamin and multinieral supplementation causes significant improvement in signs and symptoms of OSMF.

The present study was undertaken to assess how the patient's signs and symptoms relieved and the changes appearing during conservative treatment in OSMF. The study was also aimed to establish the vitamins A, C and E is a must for effective conservative treatment along with steroid injection, hyaluronidase and jaw dilatation exercises in OSMF.

MATERIALS AND METHODS

The cases and controls were selected from the out patients department (OPD) of ENT, Calcutta National Medical College and Hospital, Kolkata, a tertiary health centre in Eastern India. Thirty five cases of OSMF were selected from ENT OPD.

All the patients received conservative treatment from March 2010 to February 2011 and the patients are kept in follow up till date. This study was approved by the ethical committee of Calcutta National Medical College and Hospital. The detailed history with special emphasis on habit of tobacco abuse, difficulty in mouth opening, burning sensation of mouth and changes of mouth cavity were noted. The history of the habit; especially with reference to the duration in years, the frequency of chews per day, and the preparation of areca nut used was recorded. The following parameters were used in the establishment of the diagnosis:-

1. A positive history of chewing of the areca nut or one of its commercial preparations.
2. Burning sensation on eating spicy foods.
3. Restricted mouth opening
4. Changes in the oral mucosa including the presence of palpable vertical fibrous bands, stiffness, and blanching.

Any 2 of above 4 parameters were to be satisfied for inclusion in the study.

INCLUSION CRITERIA:

Any 2 of 4 parameters in the age group 15 years to 65 years without any sex preference

A complete otorhinolaryngological examination was performed to rule out any hearing impairment, nasal tonality of voice and associated other disorders. Examination of oral cavity was done with special care. Severity of restricted mouth opening, blanching & wrinkles of oral mucosa, mobility of soft palate and tongue, blister of oral mucosa, fibrous bands in oral mucosa, mucosal petechiae, blotchy melanotic pigmentation, restriction of tongue protrusion were noted. Distance of jaw opening and tongue protrusion were measured with measuring scale. Each patient was informed about the condition and its precancerous potential. The patient was then advised to discontinue the use of areca nut in all preparations. All patients were advised to do jaw dilatation exercise three times daily at least 5 minutes duration each time for 10 weeks. Each of the patient was informed about the protocol and was given appropriate instructions after consenting to the necessary follow-up.

All the cases were randomized to receive treatment with inj. Steroid 40 mg with inj. Hyaluronic acid 1500 IU weekly in oral

mucosa with supplementation vitamin A 25,000 IU, vitamin C 500mg, vitamin E 200mg, daily for 10 weeks. No iron preparation or B complex supplementation done because no pallor was detected in any of 35 cases. A clinical examination was carried out at every recall visit and the findings were compared with those at the beginning of the treatment. Follow-up was done every monthly for 6 months after completed the 10 weeks treatment. The following parameters were recorded weekly over the duration of treatment:

Symptoms: Burning sensation, gustatory sensation, dryness and increase salivation were recorded at base line as present or absent, and at weekly intervals as persisting, reduced, or absent. These were recorded based on the patient response. The symptoms were graded on a 3-point severity rating scale. The recording was based on the patients reporting and physical examination.

Visual inspection: The involvement of the uvula was recorded as positive when it appeared as shrunken or deviated with or without blanching. Colour of oral mucosa (blanching), fibrous bands, wrinkle of oral mucosa, mucosal petechiae, blotchy melanotic pigmentation and visible vessels appeared (angiogenesis) were noted at base line as present or absent.

Mouth opening: This was assessed by the interincisal distance as measured from upper central incisor tooth to lower central incisor tooth. The measurement was made using scale and was recorded in millimeters. This was also recorded post-treatment at 6 month follow-up periods.

Palpatory findings: These were recorded as positive when a lack of suppleness and palpable fibrous bands or marked stiffness was evident for the areas of the right and left buccal mucosa, right and left vestibules, faucial pillars, soft palate, lips, and floor of mouth. An area of the mouth that could not be palpated because of reduced mouth opening was recorded as nonpalpable and was considered as positive.

Protrusion of tongue: The involvement of the tongue was recorded as positive when protrusion was restricted. The degree of protrusion was noted in units of mm from the incisal edge of the lower central incisor tooth. The distance from the mesial contact area of the lower central incisors to the tip of the protruded tongue was noted.

Statistical analysis: All quantified variables in the study that is mouth-opening measurements, age, duration and quantity of chews, were subjected to statistical analysis. All these values were analyzed for mean, standard deviation, errors, and range. Statistical comparison of pre-treatment and post-treatment jaw distance values were made with paired 't' test. P value set at 0.05 and was considered significant at <0.05, very significant at <0.01 and highly significant at <0.001.

RESULTS

The study was started in January 2010 and was completed in February 2011. In this study thirty eight OSMF patients were randomly selected. Three of them had lost to follow-up. The majority cases were males 78.13 % as compared to female 21.88%. Most of patients were in young age and <30 years of age. The patients belong to the age group ranging from 16 to 60 years.

All patients in the present study gave a positive history of areca nut chewing in the raw form or in a commercial preparation such as gutkha or pan masala. The most common form of areca nut used was found to be gutkha, with 86% patients. The median duration of habits in all patients was found to be 5 years. The frequency of chews per day varied between 1 and 15 per day, whereas a median frequency of

chews per day was found to be 6 in all patients.

The most commonly affected area was faucial pillars 98.5% and least commonly involved area was the lips 3.12%. Other involved areas in descending order were buccal mucosa right side 96.1%, buccal mucosa left side 95.9%, hard palate 90.4%, soft palate 78.6%, floor of mouth 67.6%, uvula 15.6% and tongue 12.48%.

All the patients who reported to the study complained of a burning sensation on eating spicy foods that was not present before the development of OSMF. All the patients in this study reported a complete relief from burning sensation with in two weeks of instituting therapy.

There were no reported of side-effects or intolerance to these multidrugs. Some of the cases were complaints oral pain and due to secondary infection and were treated successfully with antibiotic and antiseptic mouth wash.

DISCUSSION

Therapeutic benefit of a disease depends on many factors. The main offender of that disease should be avoided first. Any deficiency of micronutrients should be supplemented initially. The pathophysiological changes should be prevented as main treatment protocol. The drugs should be added to reverse the abnormal anatomy and physiology of the body occurred as a result of the disease process.

Anuradha CD and Devi CS⁴ showed that there was an increase in the globulin fraction of protein and hence a decreased A/G ratio in OSMF patients. There was a significant increase in total protein levels possibly due to the increase in globulin fractions and other serum proteins. Ascorbate and iron levels decreased perhaps because of their utilization in collagen synthesis. The total tissue collagen content increased significantly in patients with advanced disease. Soma et al⁵ reported that beta-carotene was decreased in all grades of OSMF cases and vitamin E level was showed to be decreased in grade II and III OSMF cases but not in grade I cases. However, mean vitamin E level was found to be decreased as compared to healthy control. The possibility of ROS (Reactive Oxygen Species) playing a part in aetiopathogenesis of the disease also exist. Administration of nutrient antioxidants may have protecting effect with clinical improvement of OSMF. So in this study we want to show vitamin A, C and E supplementation is essential for OSMF and the results corroborate this.

Borle et al⁶ reported that vitamin A 50,000 I U once daily could cause symptomatic improvement of OSMF. In this current study vitamin A and C supplementation fulfilled the excess need of collagen synthesis and vitamin A reversed the atrophic epithelium into healthy epithelial tissue by promoting differentiation and maintaining structural integrity of epithelial tissue.

Maher R et al⁷ noted a combination of micronutrients (vitamin A, B complex, C, D & E) and minerals (iron, calcium, copper, zinc magnesium and others) supplementation showed significant improvement in intolerance to spicy food, burning sensation, and mouth opening. Similar significant improvement found in this current study. OSMF with conventional inj. steroid and hyaluronidase and jaw dilatation still is valid. Steroid inj. prevents fibrosis and hyaluronidase hydrolyze hyaluronic acid, a polysaccharide found in the tissue which facilitating absorption and diffusion. It acts via hypodermolysis.^{1,12} Along with this treatment, OSMF patients had supplemented with vitamin A, C, and E. Most probably, in this study better result observed due to this supplementation of multivitamin.

Damian M. Bailey et al¹¹ observed that vitamin C

supplementation increased peripheral concentration of LH, total creatine phosphokinase (CPK) and VEGF protein during reperfusion in surgical ischemic zone. These findings suggested that ascorbate prophylaxis may have promoted iron-induced oxidative lipid damage via a Fenton-type reaction initiated during the ischemic phase of surgery. The subsequent release of LH into the systemic circulation may have catalyzed formation of second generation radicals implicated in the regulation of vascular permeability and angiogenesis. Most probably, in this study vitamin C produced angiogenesis in avascular oral mucosa and reversed vascularity in OSMF which was seen in oral mucosa during follow-up treatment. Moreover, OSMF patients were found vitamin C deficient.^{4,5} Hence, this vitamin supplementation was appropriate and the current study treatment outcome also showed good results. Most probably, in this study change of color in mucosa and appearing of new vessels (angiogenesis) were observed due to vitamin C. This finding was also supported by Bailey et al[6].

Vitamin A promotes differentiation and maintains structural integrity of epithelial tissue all over the body. It also promotes mucus secretion, inhibits keratinization and improves resistance to infection. Physiological amount of vitamin A appears to be required for proper antibody response, normal antibody response, normal lymphocyte proliferation and killer cell function. Vitamin C is essential for formation and stabilization of collagen triple helix. It directly stimulates collagen synthesis and is very important for maintenance of intercellular connective tissue.¹² These vitamins supplementation helped in OSMF patients in two ways: 1) to fulfill the deficiency of those vitamins. 2) to produce normal mucosa. The treatment outcome of this study also showed similar results.

Vitamin A was administered through oral route at a dose of 250 IU/kg of body weight per day. The results were evaluated by morphometry, histology and autoradiography. Several alterations were observed by Koussoulakos et al [9] after 7 to 14 days of treatment in the wound epidermis: a) reversal of keratinization, b) decrease in the incorporation of the tritiated thymidine, c) increased mitotic activity in the stratum germinativum and in the middle layer of the epithelial cells, as well. Demetriou et al [10] suggested that vitamin A and retinoic acid enhance collagen synthesis and fibroblast as well as cell morphologic differentiations which are major steps of wound healing. In this current study vitamin A probably, reversed to normal epithelium in oral mucosa by this noble mechanism of this vitamin.

Various clinical research and experiment suggested that vitamin A and C have probably great role of wound healing and tissue repair by increasing collagen turnover and re-epithelialization. K D Tripathi [8] shared similar views. In this current study we found that OSMF patients got reversed normal oral mucosa with this conservative multidrugs and supplementation of vitamins as treatment regime.

CONCLUSION

It is multifactorial disease with multivitamin and multimineral deficiency. Hence, supplementation of all these vitamins and minerals are one of the major steps of treatment and should be used in the initial management of OSMF. Moreover, there is chronic and complex pathophysiological changes in oral mucosa. Therefore, multidrugs treatment needs to prevent all these changes and to reverse its normal physiological functions. The result of this current study suggested multidrugs including supplementation of specific vitamins to ensure the best conservative treatment protocol of OSMF.

Table I: Disappearing of symptoms during treatment in OSMF patients.

Serial no.	Symptoms	Complete disappear
1.	Burning sensation of mouth	3 weeks
2.	Nasal intonation of voice	4 weeks
3.	Dryness of mouth/ increase salivation	5 weeks
4.	Difficulty in swallowing	6 weeks
5.	Impairment of mouth movement	6 weeks
6.	Loss of gustatory sensation	8 weeks

Table II: Mouth opening improvement after treatment at the end 10 week and 6 months of follow-up OSMF patients.

Group	Mouth opening (mm)	Mouth opening (mm)	Mouth opening (mm)
	Pre-treatment (average mm)	Post-treatment (average mm)	6th months of follow-up
GrI (45mm)	46	48	50
GrII (20-44mm)	34	46	50
GrIII (20mm)	19	45	48
GrIV	37	39	20

TableII shows GrI- Mouth opening \geq 45mm before start treatment.

GrII-Mouth opening 20-44mm before start treatment

GrIII -Mouth opening \leq 20mm before start treatment

GrIV- Control group only conventional steroid inj. received and post treatment improvement not statistical significant (=6.54 d.f=3 p=0.088).

Table III: Tongue protrusion improvement after treatment at the end 10 week and 6th month of OSMF patients.

Group	Tongue protrusion	Tongue protrusion	Tongue protrusion
	Pre-treatment	Post-treatment	At 6 th month of follow-up
GrI(45mm)	20mm	32mm	34mm
GrII(20-44mm)	15mm	31mm	34mm
GrIII(20mm)	10mm	30mm	34mm
GrIV	170mm	22mm	10mm

Table III shows post treatment tongue protrusion improvement not statistical significant ($\chi^2=4.13$ d.f=3 p=0.24738)

Table IV: Clinical response after 10 wks of treatment

	GrI & GrII	GrIII & GrIV
Complete response-100%	21	6
Partial and stable response-	3	12

Table IV shows clinical response with conservative treatment highly statistically significance ($\chi^2=10.89$ p=0.0009663, d.f=1)

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