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Review Article

# Various medical and surgical treatment modalities in oral submucous fibrosis: A review of literature

**Ashish Singh[1], Nitin Jaggi[1], Nikhil Purohit[1], Vizarat Ali Syed[1,*]**

[1] *Dept. of Oral and Maxillofacial Surgery, Maharana Pratap College of Dentistry & Research Centre, Gwalior, Madhya Pradesh, India*

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ABSTRACT

Oral submucous fibrosis is a chronic debilitating disease and a premalignant condition of the oral cavity. It is characterized by inflammation and progressive fibrosis of the submucousal tissue. The various aetiological factors are areca nut, capsaicin in chillies, micronutrients deficiency of iron, zinc essential vitamins and genetic predisposition. Through this article an attempt is made to include various treatment modalities related to oral submucous fibrosis.



## 1. Introduction

Oral submucous fibrosis (OSF/OSMF) was first illustrated by Schwartz in 1952 as 'idiopathic tropica mucosa oris'.[1] Later on in 1953 Joshi has given the present term 'oral sumucous fibrosis'[2] and Pindborg et al., found a prevalence of 0.2-0.5% in India.[3] In a recent study it was found that the prevalence of OSMF in India has increased from0.03% to 6.42%.[4] Pindborg et al. in 1966, defined it as "an insidious chronic disease affecting any part of the oral cavity and sometimes the pharynx; occasionally preceded by and/or associated with vesicle formation, it is always associated with juxtraepithelial inflammatory reaction followed by a fibro elastic changes of the lamina propria, with epithelial atrophy leading to stiffness of the oral mucosa causing trismus and inability to eat".[5]

## 2. Aetiopathogenesis

When the disease was first describe in 1952, it was classified as an idiopathic disorder.[1] Oral submucous fibrosis can transform into oral cancer, and particularly squamous cell carcinoma, at a rate in the range of 7% to 13%.[6] The factors that have been discussed as possible aetiological factors to date are areca nut, capsaicin in chillies, micronutrients deficiency of iron, zinc and essential vitamins. In addition to these factors there is possibility of a gentic predisposition of some individuals to develop OSF.[6]

Previous studies on the pathogenesis of OSF have suggested that the occurance may be due to:

1. Stimulation of fibroblast proliferation and collagen synthesis by areca nut alkaloids.[7]
2. Clonal selection of fibroblast with a high amount of collagen production during the long term exposure to areca nut ingredients.[8]
3. By stabilization of collagen structure by catechin and tannins from the areca nut.[9]
4. By decreased secretion of collagenase.[10]
5. By production of collagen with a more stable structure (collagen type I trimer) by fibroblast.[11]
6. And by an increase in collagen crosslinkage as caused by upregulation of lysyl oxidase.[12]
7. Deficiency in collagen phagocytosis.[13]
8. Effect of fibrogenic cytokines secreted by activated macrophages and T lymphocytes on fibroblasts.[14]

* *Corresponding author.*
*E-mail address*: syedvizaratali92@gmail.com (V. A. Syed).

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**Table 1:**

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|---|---|---|---|---|
| **Grade - I** | | | | |
| **Clinical** | **Functional** | **Histopathological** | **Treatment** | **Prognosis** |
| Involvement of less than one-third of the oral cavity, Mild blanching, burning sensation, recurrent ulceration, Stomatitis and dryness of mouth. | Mouth opening up to 35 mm | Stage of inflammation- Fine edematous collagen, congested blood vessels, Abundant neutrophils along with lymphocytes with myxomatous changes in subepithelial, connective tissue layer of epithelium. | Cessation of habit, nutritional supplement, antioxidants, topical steroid ointment. | Excellent |
| **Grade - II** | | | | |
| **Clinical** | **Functional** | **Histopathological** | **Treatment** | **Prognosis** |
| Involvement of one-third to two-third of the oral cavity, blanching of oral mucosa with mottled and marble like appearance, fibrotic bands palpable and involvement of soft palate and premolar area. | Mouth opening 25-35 mm, cheek flexibility reduced by 33%. | Stage of hyalinization- Juxtraepithelial collagen hyalinazation with lymphocytes, eosinophils. Dilated and congested blood vessels. Less fibroblastic activity. Granulation changes in muscle layer with reduced inflammatory cells in subepithelial layer. | Habit cessation, nutritional supplement, intralesional injection of placental axtracts, hyaluronidase, steroid therapy, physiotherapy. | Good. Recurrent rate is low. |
| **Grade - III** | | | | |
| **Clinical** | **Functional** | **Histopathological** | **Treatment** | **Prognosis** |
| Involvement of greater than two-third of the oral cavity. Severe blanching, Broad thick fibrous palpable bands at cheeks and lips and rigid mucosa, depapillated tongue and restricted tongue movement and shrunken bud like uvula. Floor of the mouth involvement and lymphadenopathy. | Mouth opening 15-25 mm, cheek flexibility reduced by 66% | Stage of fibrosis- Complete collagen hyalinization without fibroblast and edema. Obliterated blood vessels, plasma cells and lymphocytes are present. Extensive fibrosis with hyalinization from subepithelial to superficial muscle layers with atrophic, degenerative changes | Surgical treatment including band excision and reconstruction with Buccal Fat Pad or split thickness graft bilateral temporalis myotomy and coronoidectomy. | Fair. Recurrence rate is high. |
| **Grade - IV** | | | | |
| Clinical | Functional | Histopathological | Treatment | Prognosis |
| Leukoplakia changes, erythroplakia ulcerating and suspicious malignant lesion. | Mouth opening <15 mm or nil | Stage of malignant- Transformation: Erythroplakia changes into squamous cell carcinoma. | Surgical treatment and biopsy of suspicious lesion. | Poor, malignant transformation. |

## 3. Classification

The following classification system given by Passi D et al.[15] in 2017, which includes all the parameter/component of OSF such as clinical features, histopathological features, functional component, treatment part, and prognosis. (Table 1)

## 4. Management

OSMF is well known for its chronic nature. Being categorize into premalignant condition, no conservative treatment till date has given complete resolution of the disease. Various treatment modalities are available to treat this condition which includes medical, surgical and physiotherapy.

### *4.1. Medical management*

#### *4.1.1. Hyluronidase, dexamethasone and placental extract*

Kakar et al. in 1985 in his study, a total of 96 patients with Oral Submucous Fibrosis have received four regimens of treatment— local dexamethasone, local hyaluronidase. Local combination of dexamethasone and hyaluronidase, and local placental extract. The group of patients receiving hyaluronidase alone showed quicker improvement in symptoms although its combination with dexamethasone gave somewhat better longer-term results.[16] Katharia SK. 1992, includes 22 patients in which inj. Placenta extract 2ml was given locally. There was significant improvement in mouth opening, color of oral mucosa, burning sensation, and reduction of fibrous band.[17]

#### *4.1.2. Nylidrine hydrochloride*

Sharma et al. 1987, in 56 cases use nylidrine hydrochloride in tablet form 6mg for 3-8 weeks along with conventional medical management with the success rate 62.07%.[18]

#### *4.1.3. Triamcinolone acetonide*

Khanna J.N. in 1995, a series of 100 patients is presented. Very early and early cases were treated by local injection of triamicinolone acetonide (40 mg), while advanced cases were treated by surgical intervention. Those patients who responded favorably revealed improvement in the clinical picture, and experienced an increase in mouth opening and regression of recurrent stomatitis, ulceration, and burning sensation.[19]

#### *4.1.4. Turmeric (TE), Turmeric Oil (TO) and Turmeric Oleoresin (TOR)*

Hastak K. in 1997, studied patients suffering from OSMF were given total dose of TO (600mg TO mixed with 3 g TE/day), TOR (600 mg + 3g TE/day) and 3 g TE/day as a control for 3 months. It was observed that all three treatment modalities decreses the number of micronucleated cells, so offered protection against benzo[a]pyrene induced increase in micronuclei in circulating lymphocytes and it is an excellent scavenger of free radical and also offer protection against DNA damage.[20]

#### *4.1.5. Interferone gamma*

Haque et al., with intralesional IFN-g treatment showed improvement in the patients mouth opening from an inter-incisal distance before treatment of 21±7 mm, to 30±7 mm immediately after treatment and 30±8 mm 6-months later, giving a net gain of 8±4 mm (42%) (range 4–15 mm).[21]

#### *4.1.6. Immunized milk*

Tai et al in his study includes 26 OSF patients who received immune milk treatment (45 g of immune milk powder twice a day) for 3 months. He found that the interincisor distance was significantly improved (>3 mm of the baseline measurement) in 18 of the 26 (69.2%) OSF patients.[22]

#### *4.1.7. Anti TGF beta drugs*

Rajlalitha P. studied the effect of TGF β, which is an important cytokine thought to play a key role in development of OSMF. Its effects can be counteracted by use of anti-TGF β drugs in the form of commercial antibodies or peptide mimetics.[23]

#### *4.1.8. Collagenase*

Lin H-J et al., studied the effect of 1ml of collagenase (1% solution) mixed with 1ml of xylocaine. The collagenase treatment not only resulted in a significant improvement of oral opening, but patients also experienced a striking reduction in hypersensitivity to spices, sour, cold, and heat which helped restore eating function.[24]

#### *4.1.9. Lycopene*

Kumar et al. in his study, were given 16 mg of lycopene daily in 2 equally divided doses and were given intralesional injections of betamethasone (2, 1-mL ampules of 4 mg each) twice weekly. He found average increase in mouth opening of patients about 4.6mm.[25]

#### *4.1.10. Levamisole and beta carotene*

Jirge et al. With levamisole 50 mg three times daily for three alternate weeks Reported 7.1% improvement in mouth opening which further increased to 10.7% in subsequent months. ß carotene: is an important precursor of vitamin A.Use of commercial antioxidant capsules containing ß carotene 2 capsules daily for six weeks demonstrated 6.7% increase in mouth opening; however, this was static and no further improvement was noticed in subsequent months.[26]

#### *4.1.11. Chymotrypsin, vitamins and minerals*

Chymotrypsin: an endopeptidase, hydrolyzes ester and peptide bonds. It was used as proteolytic and

antiinflammatory agent in the treatment of OSMF.[27] Vitamins and minerals: Vitamins and microelements are essential in the normal metabolism of organisms. Some studies regarded deficiencies in vitamins and minerals as promoting the initiation and development of OSMF.

#### *4.1.12. Pentoxyfilline and spirulina*

Bhavana S. includes 40 patients, with 20 patients in pentoxyfilline and 20 patients in spirulina group. Spirulina was used for the first time for treatment of Oral submucous fibrosis (OSMF) and it proved to be superior than pentoxyfilline as no side effects were observed.[28]

#### *4.1.13. Aloe vera*

Sarwar A. in a study found that the group receiving aloe vera had a significant improvement in most symptoms of OSMF compared with the nonealoe vera group, in both the medicinal and surgical categories. Aloe vera gel was effective as an adjuvant in treatment of OSMF.[29]

#### *4.1.14. Colchicine*

Krishnamoorthy B. study includes 50 patients were manage by medical approach. Patients who are receiving tablet colchicine orally, 0.5 mg twice daily shows early reduction in the burning sensation. There was also a significant improvement in the mouth opening and in the movement of the tongue.[30]

#### *4.1.15. Stem cell therapy*

Sankarnarayanan et al. Have demonstrated the effectiveness of stem cell treatment in OSMF patients and found reduction in blanching, improved suppleness of the mucosa, decrease in the burning sensation while consuming spicy food, significant increase in the mouth opening.[31]

#### *4.1.16. Oral stent*

Le PV et al., has suggested the use of an oral stent as a treatment adjunct to surgery should be considered especially when the surgical technique is prone to relapse.[32]

### *4.2. Surgical management*

#### *4.2.1. Surgical resection of fibrotic bands and split thickness skin graft*

Excision of fibrous bands; This is effective at increasing oral opening but requires aggressive and sustained physiotherapy to get a good outcome Adequate surgical release often results in bilateral buccal soft tissue defects which tend to contract and shrink if left to heal by secondary intention. Thus, the resulting soft tissue defect requires resurfacing with well-vascularized tissue of adequate dimensions.[33] Yen D.J.C. in 1982, suggested that those patients who are treated by cutting of fibrotic bands showed only further scar formation and recurrence of trismus. Patients who received 0.016 inch split thickness grafts showed satisfactory results, with a decrease in trismus and preservation of elasticity of the graft.[34]

#### *4.2.2. Nasiolabial flap*

Kavarana et al. in 1987, have been used bilateral full thickness naso-labial flaps successfully in three patients to give long-term relief of the severe trismus caused by oral submucous fibrosis. The flaps are set into defects created by incision of the oral mucosa.[35] Borle R.M. in 2008, evaluated the use of extended nasolabial flaps and coronoidectomy in the management of 47 patients with histologically confirmed oral submucous fibrosis. Their interincisal opening improved significantly from a mean of 14mm (range 3–23) to a mean of 41mm (range 23–55). The main disadvantage being the extraoral scars.[36]

#### *4.2.3. Tongue flap*

Tepan M. G. et al. in 1986, included 25 patients for study and shows good results without any complication.[37] Golhar S. et al. in 1987, included 21 patients with maximum followup of 3 year with preoperative mouth opening less than 1.5 cm. The results are excellent with post operative mouth opening obtained was in the range of 2-4 cm.[38]

#### *4.2.4. Palatal island flap*

Khannna J.N. et al. in 1995, technique of utilizing bilateral palatal island flap to cover the exposed area, in combination with bilateral temporalis myotomy and coronoidectomy, was performed. On average, the mean maximal opening was found to range from 34 to 45 mm postoperatively over a period of 4 years. This is a considerable improvement over a preoperative mean maximal opening of 3-25 mm. The donor areas healed well. Rejection or necrosis of the flap was not seen.[39]

#### *4.2.5. Artificial dermis*

The first collagen-based bilayer membrane was developed by Yannas et al.[40] Omural S. et al., in 1997, uses the membrane similar to the one which is developed by Yannas et al[40] but has been modified in antigenecity as well as in chemical and physical structure of the collagen sponge. The membrane was placed on oral mucosal defects of five patients after operations for cancer. In all cases the postoperative course was unremarkable and the repair was effective.[41] Chen et al. examined a total of 125 sites repaired with artificial dermis in 84 patients. He concluded that an artificial dermis may be an alterative to a split-thickness skin graft for patients with oral mucosal defects after removal of premalignant lesions.[42]

#### *4.2.6. Superficial temporal fascia flap*

In a study by Mokal N.J. et al., preoperative mouth opening was 0–5 mm. Inter incisor distance of 45 mm was achieved

intra operatively on release of mucosa, masseter origin and temporalis insertion. All patients had complete survival of flap and full take of the skin graft.[43]

#### *4.2.7. Radial forearm flap*

Lee J T et al. In his study, A total of 10 patients with advanced oral submucous fibrosis were surgically treated. Preoperative mouth opening was mean 2.3 mm. The intraoperative mouth opening was mean 16 mm after submucous release, and mean 35.5 mm after further release via myotomy and coronoidotomy. The postoperative mouth opening was mean 28.2 mm after a mean of 21 months' follow-up, and the mean increase was 25.9 mm.[44]

#### *4.2.8. Anterolateral thigh flap*

Wei-chen C. has report two cases who received successful reconstruction using bipaddled ALT perforator flaps.[45]

#### *4.2.9. Buccal fat pad*

Sharma R. et al.[46] and Kothari M.C. et al.[47] suggested by there study that BFP is reliable for the treatment of OSMF.[46]In a study by Mehrotra D. et al., a total of 100 patients of oral submucous fibrosis were included and randomly allocated to different surgical groups, 25 patients per group. After excision of fibrous bands, group I had buccal fat pad graft, group II had tongue flap, group III had nasolabial fold flap, and group IV had split skin graft for correction of mucosal defect created after incising the fibrous bands. She concluded that buccal fat pad rotation is superior to other procedures, because it offers ease of surgery, can be performed under local anesthesia as a day care procedure, shows little postoperative morbidity, and has good patient acceptance, and there appear to be no contraindications to its use.[48]

#### *4.2.10. Laser*

Talsania R.[49] Arpit S[50]and Utkarsh L.[51]in there study suggested diode laser is less expensive and effective in OSMF.Zainab C. includes a case series of 16 cases of moderate OSMF treated with Erbium Chromium Yttrium Scandium Gallium Garnet (ErCr:YSGG) laser fibrotomy under local anesthesia in combination with cessation of habits, topical steroids, lycopene and oral physiotherapy is presented. The mean increase in mouth opening achieved at 1 year was 17.5 mm.[52] Alper S. suggested that ErCr:YSGG laser is superior in compare to diode laser.[52]

### *4.3. Physiotherapy*

Stephan C. studied effect of physiotherapy in Nepali patients for 4 months and found that it improves oral opening but not oral pain.[53] Nidhi in her study found that significant improvement was observed in patients with physiotherapy after a period of 4 weeks.[54] Vijayakumar M. studied ultrasound therapy effect in 21 individuals with 3 month followup period. He found that the mean improvement in mouth opening was 6.26 mm.[55]

## 5. Conclusion

OSMF is mainly a disease in Indian subcontinent. Possible aetiological factors to date are areca nut, capsaicin in chillies, micronutrients deficiency of iron, zinc and essential vitamins. From the time the fist diagnosis and treatment given, till this date there is no complete success has achieved. Reason for this may be the unpredictable etiology, immune response or immune status of individual patient. Thus there is need to educate people regarding the condition in early stage before its too late. Every treatment, medicinal or surgical has its pro and cons.

## 6. Source of Funding

None.

## 7. Conflict of Interest

The authors declare that there is no conflict of interest.

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## Author biography

**Ashish Singh,** Professor

**Nitin Jaggi,** Professor and HOD

**Nikhil Purohit,** Reader

**Vizarat Ali Syed,** PG Student

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