

Review Article

Oral Submucous Fibrosis different treatment modalities and associated complications - A Review

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ABSTRACT:

Oral submucous fibrosis (OSMF) is a premalignant disorder which is most commonly associated with the chewing of areca nut (betel nut). Oral submucous fibrosis is diagnosed based on clinical symptoms and confirmed by histopathological report. Based on clinical symptoms and histopathology changes this condition is categorized in four stages. The initial presentation of OSMF is inflammation. Inflammation is followed by hypovascularity and fibrosis visible as blanching of the oral mucosa with a marble-like appearance. Blanching may be localized, diffuse, or reticular. In some cases, small vesicles may develop that rupture and form erosions. In the later advanced stage of OSMF, a fibrous band that restricts mouth opening (trismus) is characteristic. It causes further problems in oral hygiene, speech, mastication, and possibly swallowing. Development of fibrous bands in the lip leads to thickening and rubbery appearance. Management of this premalignant condition is mainly based on the level of disease. Most commonly favored line of treatment is Medical treatment (Non Surgical).

Keywords – Oral Submucous fibrosis, Premalignant condition, Oxitard, Aloe vera, Pentoxifylline, Spirulina.

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INTRODUCTION

Oral submucous fibrosis (OSMF) is a premalignant disorder which is most commonly associated with the chewing of areca nut (betel nut). The habit is mostly prevalent in South Asian populations. OSMF causes significant morbidity. If left untreated this condition can later transform into squamous cell carcinoma (SCC), which is also responsible for mortality. The combine use of areca nut and tobacco has led to a sharp increase in the frequency of OSMF.¹

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Based on clinical symptoms and histopathology changes this condition is categorized in four stages. The initial presentation of OSMF is inflammation. Inflammation is followed by hypovascularity and fibrosis visible as blanching of the oral mucosa with a marble-like appearance. Blanching may be localized, diffuse, or reticular. In some cases, small vesicles may develop that rupture and form erosions. In the later advanced stage of OSMF, a fibrous band is seen that restricts mouth opening (trismus). It causes further problems in oral hygiene, speech, mastication, and possibly swallowing. Development of fibrous bands in

the lip leads to thickening and rubbery appearance. It becomes difficult to retract or evert the lips, which transform the shape of lip into an elliptical shape.¹

About 5 million people in India have oral submucous fibrosis and recent data suggest a male predominance. Age group between second and third decade is commonly involved. Risk of malignant transformation ranges from 7% to 30%.² Oral submucous fibrosis [OSMF] is a high risk premalignant condition of oral cavity, pharynx and upper digestive tract, characterized by progressive inability to open the mouth and by inflammation and progressive fibrosis of the submucosal tissues.³ The most common symptom in advanced stage of OSMF is reduced mouth opening (trismus). The severity of trismus can be graded by measuring the interincisor opening or mouth opening. The mouth opening is categorized into stage I (less than 3 cm), stage II (2–3 cm), and stage III (less than 2 cm).⁴

⁶ In advanced stage it leads to the loss of puffed-out appearance of cheeks when a patient blows a whistle, fibrosis of tongue and mouth impairing tongue movement and leading to depapillation and blanching of mucosa. Etiology is multifactorial and most common factor for OSMF being arecanut. The factors responsible for fibrosis in areca nut are alkaloids, flavonoids and other trace elements like copper.⁷ Patients usually realize the seriousness of condition only after having burning sensation while having hot and spicy food. There is difficulty in mastication, speech, and swallowing and pain in throat and ears and loss of gestation in later stages as a result of fibrosis of mucosa both buccal and labial. In some studies it has been seen that patients with OSMF have difficulty in taste detection or better say OSMF leads to alteration in taste perception by tongue.⁸ Changes in these taste qualities may lead to altered food preferences and reduced appetite so it should be an important focus of attention in the treatment of patients in order to improve their nutritional status and the efficacy of the treatment.⁹

Management of OSMF

Management of this premalignant condition is mainly based on the level of disease. Most commonly favored line of treatment is Medical treatment (Non Surgical). Patient counseling is of utmost importance before starting any treatment. In early stages of this chronic precancerous condition medical management is the treatment of choice. A patient has to undergo dietary habit counseling followed by stopping the intake of arecanut, tobacco and spicy food. It is very important to see that patient's diet include proteins, vitamin D, E, B complex and micronutrients.

Non surgical treatment

Conventional therapies in the treatment of OSMF are empirical and symptomatic in nature. The major targets of treatment can be summarized as:

- Anti-inflammatory
- Oxygen radical-scavenging
- Antifibrotic.¹

Conventional therapies include Intralesional Injections of corticosteroids, placental extracts, hyaluronidase, physiotherapy and surgery.¹⁰ These present therapies have inconsistent outcome with several side effects. Corticosteroids are immunosuppressive agents which are believed to decrease inflammation and collagen formation, thereby reducing the symptoms and resulting in increased mouth opening. They have been found to produce side effects like severe adrenal insufficiency, edema, osteonecrosis, osteoporosis, myopathies, peptic ulcers, hypocalcemia, euphoria, psychosis, ocular complications and myasthenia.¹¹

Levamisole modifies both cellular and humoral immunity. The anti-inflammatory effects and its ability to modulate inflammatory cytokines reduces burning sensation but several side effects have been noted like nausea, vomiting, diarrhoea, mouth sores, loss of appetite, stomach pain, change in taste and smell, muscle aches, fatigue, dizziness, headache and skin rash.¹²

Interferon gamma (IFN-gamma) has anti-fibrotic effect. When given in a dosage of 50 µg (0.25 ml) intralesionally twice a week over 8 weeks, recombinant human INF-γ showed improvement in both mouth opening and burning sensation. Adverse effects included aching muscles, diarrhoea, fever and chills, headache, nausea or vomiting, skin rash, unusual tiredness.¹³

There is no specific treatment for oral submucous fibrosis, it's just the combination of drugs based on the symptoms. Therefore, the search for an effective treatment modality still continues. Many natural plants extracts, synthetic drugs, etc have been introduced and tried for the management of OSMF. One such plant is aloe vera which promotes wound healing, and also has anti-inflammatory, immunomodulatory, and antioxidant properties.¹⁴ Aloe vera is a nannoprotein containing many amino acids known as 'wound healing hormones'. The polysaccharides contained in the gel of the leaves, promote wound healing, and have anti-inflammatory, immunomodulatory, antioxidant properties and gastro protective properties. Further, sterols in the Aloe vera have strong ability to inhibit inflammation similar to the action of cortisone without any side effects.¹⁵

Oxitard is another herbal antioxidant formulation containing the extracts of *Mangifera indica*, *Withania somnifera*, *Daucus carota*, *Glycyrrhiza glabra*, *Vitis vinifera*, powders of *Embllica officinalis* and *Yashada bhasma*; and oils of *Triticum sativum*. *Mangifera indica* is shown to have antibiotic, anti-asthmatic, antiseptic, antiviral, hypotensive, anti-emetic properties. *Withania*

somnifera provides overall health and wellness with its anti-stress, anti-anxiety, anti-inflammatory, anti-convulsive and anti-arthritis properties. *Daucus carota* acts as a good antiseptic as it is a rich source of vitamin A. *Glycyrrhiza glabra* normalizes the hoarseness in voice and has immunomodulatory and anti-inflammatory properties. *Vitis vinifera* have anti-inflammatory, astringent and an effect to curb the burning sensation. *Embolica officinalis* is a rich source of vitamin C and is a potent antibiotic. *Yashada bhasma* contains zinc which plays a significant role in protein synthesis, cell division and wound healing. *Triticum sativum* is a rich source of minerals and has an antioxidant property.¹⁶

A Comparative study was conducted to compare the efficacy of herbal antioxidants oxitard and aloe vera in the treatment of oral submucous fibrosis, and it was found that overall assessment of symptoms like mouth opening, tongue protrusion, difficulty in swallowing and speech and pain associated with the lesion showed that oxitard capsules can bring about significant clinical improvements than aloe vera gel in the treatment of OSMF.¹⁷

Pentoxifylline is a methylxanthine derivative which has vasodilating property. It decreases inflammatory mediators, increase production of PGE2 and PGI2 by vascular epithelium and maintain cellular integrity and homeostasis after acute injury. These features are pertinent in treating intermittent claudication caused due to arterial occlusion and hence found to be effective in treating OSMF.^{18,19} In a study it was administered for three months which showed statistically highly significant results. However, Rajendran et al., found significant results with mouth opening and burning sensation although results with tongue protrusion were not significant.¹⁸

Spirulina is blue green algae with rich natural source of proteins, carotenoids and other micronutrients.^{20,21} It has been primarily assessed in treating leukoplakia with promising results. The chemopreventive capacity to reverse precancerous lesions of spirulina is attributed to the antioxidant property with high amount of beta carotene and superoxide dismutase.^{20,22,23}

A study was conducted to assess the efficacy of spirulina and pentoxifylline and also to compare them in treatment of oral submucous fibrosis. It was found that both the drugs are effective in treatment of OSMF with results of Spirulina proved to be superior than pentoxifylline as no side effects were observed. Also it was superior in reducing burning sensation and hence can be advised in OSMF patients suffering from severe subjective symptoms.²⁴

In many cases, combined drug treatment is performed, although controlled clinical trials are completely lacking. In other patients, depending on severity of

disease, physical therapy and/or surgery is added to drug therapy.²⁵

Patients mostly get benefit from physical therapy in conjunction with drug treatment. The more advanced OSMF is, the more limited the efficacy of pharmacological treatment. Patients may benefit from surgery or laser surgery in such situations.²⁶

A 6-week course of intralesional injections of 4 mg dexamethasone/mL and 1,500 U hyaluronidase twice weekly improved trismus and other clinical parameters associated with fibrosis. In addition, autofluorescence of the affected mucosa normalized for collagen and nicotinamide adenine dinucleotide (reduced form) spectra.²⁶

A combination of micronutrients and minerals was evaluated in a single-arm study. Significant improvement in symptoms was observed after 1–3 years of treatment. The interincisor distance was stable in 49% of patients and improved in 41%, and leukoplakia regressed.²⁷

Till date there is no specific treatment for this condition and it requires large clinical trial to come to any one specific line of treatment.

Surgical treatment

The surgical treatment of this condition involves excision of the fibrotic bands and interpositional grafts to retain the increased oral opening. Various procedures and graft material have been utilized with differing success rates. Surgical management of OSMF has involved excision of the fibrotic bands either by the scalpel or using a laser, with or without the use of interpositional grafts to maintain the oral opening.

The surgical treatment protocols based on literature can be divided into the following steps:

1. Excision of fibrotic bands with scalpel or using lasers.
2. Coverage of the mucosal defect using flaps, grafts and collagen membranes.
3. Adjunctive procedures intraoperatively included coronoideotomies and masticatory muscle myotomies.
4. Post operative oral physiotherapy, dietary supplementation and other medications.

There are different methods for primary excision of the bands. Earlier use of scalpel was the most common then came the use of lasers for primary excision. The most common lasers used were the ErYCCG laser²⁸, KTP 532^{29,30}, and the diode lasers^{31,32}. The choice of lasers seems to have been determined by their availability in the surgical unit rather than a scientific selection. Laser excision seemed to have been carried out in limited areas of fibrosis and only in cases related to the buccal mucosa. Reports of use of lasers in other oral sites were not forthcoming. Apart from standard postoperative

physiotherapy, no secondary procedures were used in conjunction with lasers. The efficacy of laser excision was rated as good, excellent, with follow ups extending to a maximum of 6 months only.

Conservative Adjunctive Surgical Procedures:

Detachment of the coronoid process from its temporalis muscle attachment (coronoidotomy) or intentional sectioning of the coronoid process with or without detachment of the muscle (coronoidectomy) was the most common procedure described in adjunct to primary excision of the bands.³² The use of this procedure was found to be popular even in cases where interpositional grafts were placed.

Interpositional Grafts (Flap):

Use of interpositional grafts in areas of band excision have been the most populous methods of surgical intervention in OSMF. The grafts used in the studies have been divided, for purposes of discussion, into local flaps and distant flaps. Local flaps imply donor sites in the head and neck region transposed to the oral cavity by pedicle attachments. Distant flaps include free flaps with arteriovenous anastomoses from donor sites in the arm and thigh.³³

Complications associated with Oral Submucous Fibrosis:

As the name signifies Oral submucous fibrosis is a premalignant condition affecting any part of oral mucosa. These diseases can occur intraorally, but also in the descending parts of the gastrointestinal tract, like esophagus or liver. Malnutrition and hepatitis virus infection are independent risk factors.³⁴

This premalignant condition can be seen associated with following complications:

OSMF is always associated with stained teeth and gingiva. In many cases it has been seen that this premalignant condition is associated with some white patches also that is Leukoplakia, and sometimes red patches that is erythroplakia. Erythroplakia has highest malignant transformation capacity. OSMF also leads to impairment in mouth opening, speaking and swallowing, stomatitis, Dysphagia, Odynophgia, Esophageal involvement. Use of arecanuts, cigarette smoking leads to depapillation of tongue, which is an initial symptom of development of OSMF. This depapillation of tongue leads to alteration in taste perception and loss of appetite. Taste alteration is an alarm which tells about this beginning of this condition. Last and the most dangerous complication associated with OSMF is development of Squamous cell carcinoma.

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