

Management of oral submucous fibrosis: A Review

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Abstract

OSMF is a chronic disease of the oral cavity, which is more commonly found in the patients of south East Asia and is characterized by the build up of constricting bands of collagen in the buccal mucosa and adjacent structures. The precise cause is unknown but chewing of areca nut and its products, excess use of chilies and spices, poor nutrition, vitamin and iron deficiency have been suggested.

Treatment holds option of both non-surgical and surgical approach. Non-surgical management includes multivitamin supplements including lycopene and range of medicines (e.g. intra-lesional injections of steroids, hyaluronidase, human placental extracts, chymotrypsin, pentoxifylline, collagenase). Surgical intervention includes cutting of fibrous bands, which is used in more extreme cases. Heat therapy (thermodynamics) can also be used for resolving sub-mucous fibrosis.

Keywords: Atrophy Idiopathica, Hyaluronidase, Interferon Gamma, Aloe Vera, Pentoxifyllin, Chymotrypsin.

Introduction

Schwartz first described OSMF in 1952 and coined the term *atrophia idiopathica (trophica) mucosae oris*.⁽¹⁾ Several other descriptive terms have been coined by different authors from time to time including *idiopathic scleroderma of the mouth, idiopathic palatal fibrosis and sclerosing stomatitis*.⁽²⁻⁴⁾

Oral sub-mucous fibrosis is defined as an insidious chronic disease affecting any part of the oral cavity and sometimes the pharynx. Although occasionally preceded by and/or associated with vesicle formation, it is always associated with juxta-epithelial inflammatory reaction followed by fibro-elastic changes of the lamina propria with epithelial atrophy leading to stiffness of the oral mucosa and causing trismus and inability to eat.⁽⁵⁾

Oral sub-mucous fibrosis is a chronic and a well-recognized potentially malignant disorder associated with areca nut chewing, and is prevalent in south Asian population.⁽⁶⁾ Pathogenesis of OSMF is not yet established but is believed to be due to multifactorial causes, hence the treatment of oral sub mucous fibrosis postulates a major challenge for an oral medicine specialist. The purpose of this review is to highlight various treatment modalities for OSMF published in the previous literatures.

Treatment Options

Many researchers have elicited and worked upon, the existing etio-pathogenesis concerned with OSMF. The main symptoms of oral sub mucous fibrosis include burning sensation, difficulty to eat and trismus. The treatment of patients with OSMF depends on the degree of clinical involvement. Management of OSMF has been tried by both surgical and non-surgical approach.

1. **Conservative treatment** - Conservative treatment includes restriction of habits, nutritional or supportive therapy and oral physiotherapy.

a. **Restriction of habits** - The consumption of chilies, pan, areca nut, spices and commercially available, guthka, pan masala is increasing in India. Patient motivation to quit the habit in early stage of OSMF is an essential step of treatment, as it could possibly slow the progress of the disease.⁽⁷⁾

b. **Nutritional or supportive therapy** - Micronutrients and minerals such as vitamin A, B, C, D and E, iron, copper, calcium, zinc, magnesium, and selenium can efficiently diminish the oxidant levels. A low ingestion of fruits and vegetables is linked with an increased risk for pre-cancers and cancers.⁽⁷⁾

Ingestion of fruits and vegetables should be included in the regular diet since they deliver protection against the increased risk of cancer by raising levels of antioxidants.⁽⁷⁾ Lycopene is a carotenoid present in tomatoes has been revealed to have a number of effective antioxidant and anti-carcinogenic properties and has established intense benefits in precancerous lesions for instance leukoplakia.⁽⁷⁾

Polyphenols in green tea have considerable free radical scavenging activity and can protect cells from DNA damage caused by reactive oxygen species. It can also hinder tumor cell proliferation and induce apoptosis. Thus, many of the potential beneficial special effects of tea have been ascribed to the strong antioxidant activity of tea polyphenols.⁽⁷⁾

Various studies have been associated with the deficiency of iron both as a cause and consequence in etio-pathogenesis of OSMF. Thus, routine assessment of hemoglobin levels followed by iron supplements should be incorporated in the treatment plan.⁽⁷⁾

Immune milk has high-quality anti-inflammatory effect and contains a reasonable amount of vitamins such as A, B1, B2, B6, B12, C, pantothenic acid, nicotinic acid, folic acid, iron, copper and zinc. Presence of IgG antibody in immunized milk might restrain the inflammatory reaction and modulate cytokine assemblage in OSMF patients, which is foremost to significant improvement.⁽⁷⁾

- c. **Oral physiotherapy** - Physiotherapy in OSMF can be in the form of physical exercise regimen and splints or other devices. Muscle stretching exercises intended for the mouth may be supportive to avoid further limitation of mouth movements. This is considered to put pressure on fibrous bands. Forceful mouth opening have been tried with mouth gag and acrylic surgical screw.⁽⁷⁾
- d. **Microwave diathermy** - Heat therapy acts by fibrinolysis of bands. Microwave diathermy selectively heats only juxta-epithelial connective tissue and limiting the area to be treated. Thus, it is easy to apply with minimum discomfort.⁽⁷⁾

Medical Treatment

Treatment includes intra-lesional injection of steroids, placentex and fibrinolytic agents. Medical treatment is symptomatic and intended at improving movements.

- a. **Steroids** - Steroids are well recognized to act as immunosuppressive agents causing inhibition of inflammation found in OSMF lesions, thus reducing this fibro-collagenous condition. In addition, steroids can slow down the proliferation of fibroblasts and thus reducing the number of collagen fibers.⁽⁷⁾
Sub-mucosal intra-lesional injections weekly or topical application of steroids in patients with moderate OSMF may help to avoid additional damage. Steroid ointment applied topically may be helpful in ulcers and painful oral mucosa. A local injection of hydrocortisone 1.5 cc is found to be efficient.⁽⁷⁾
- b. **Hyaluronidase** - *In vitro* studies, suggest that hyaluronidase attacks quickly on collagen from OSMF patients than on normal collagen. Hyaluronidase degrades the hyaluronic acid matrix, lowers the thickness of intracellular cemental substances as well as activating definite plasmatic mechanisms. As a result, it causes softening and diminishing of fibrous tissue.⁽¹³⁾ Kakar *et al.* found that injection of 1500 IU of hyaluronidase and dexamethasone (4 mg) locally for 7 weeks gave superior results if it was followed by 3 weeks of hyaluronidase injections.⁽⁷⁾
- c. **Collagenase** - Reduced content of functional collagenase observed in OSMF patients is one of the mechanisms accountable for collagen accumulation. Lin and Lin found that intra-lesional

collagenase injections not only results in a noteworthy improvement of mouth opening, but also experience a striking decline in hypersensitivity to spices, cold, and heat which helps to re-establish eating function.⁽⁷⁾

- d. **Placental extracts**- The injection placentex is an aqueous extort of human placenta containing nucleotides, enzymes, amino acids, steroids and vitamins. It acts by "biogenic stimulation". Filatov mainly due to the method of "tissue therapy" introduced its use in 1933. Such tissues or their extracts, implanted or injected into the body after conflict to pathogenic factors, stimulate the metabolic or regenerative processes, thereby favoring recovery.⁽⁷⁾
- e. **Chymotrypsin**: Chymotrypsin is an endopeptidase enzyme that can execute proteolysis.⁽⁸⁾

Interferon (IFN)-gamma

IFN-gamma plays a significant role in the treatment of OSMF for the reason that it has immunoregulatory effect. Haque *et al.* studied that IFN-gamma is a known anti-fibrotic cytokine, effect of which was considered on collagen synthesis by arecoline stimulated OSMF fibroblast. This clinical trial of IFN-gamma intra-lesional injections gave major progress in mouth opening.⁽⁹⁾

Aloe vera

Aloe vera foliage, extract and resin present anti-microbial, anti-inflammatory and healing properties. Sudarshan *et al.* has carried out a preliminary study to contrast the efficacy of *A. vera* with antioxidants in the treatment for OSMF. Results of this study showed that *A. vera* response is enhanced in all the parameters evaluated and responded in all the clinico - histopathological stages chiefly in patients with mild-stage clinically and early-stage histo-pathologically. Use of *A. vera* also showed decline in burning sensation, improvement in mouth opening and cheek flexibility. It was concluded that *A. vera* group reduces the burning sensation and recovers mouth opening thus enhancing patient's quality of life.⁽¹⁰⁾

Turmeric

Curcumin (diferuloylmethane) found in turmeric, a natural yellow pigment exhibits anti-oxidant, anti-inflammatory and anti-cancer properties. Turmeric oil and turmeric oleoresin together offers defense against DNA damage. As such, it may fulfill two roles in the putative treatment of OSMF, both as an anti-inflammatory agent and as a chemo-preventive agent. It also provides a base for a simple, safe, acceptable and cost effective interference for earlier stages of OSMF. Rai *et al.* also conducted a study using curcumin in the treatment of oral precancerous lesions. 25 patients of OSMF were included and these patients were cured by curcumin. As there was an increase in local and

systemic antioxidant status.⁽¹¹⁾

Pentoxifylline therapy

Pentoxifylline is a methylxanthine derivative that produces dose-related effects. It can act in following possible ways:

1. Microcirculation is progressed and platelet aggregation as well as granulocyte adhesion is reduced.
2. Leukocyte deformability is amplified and as well as slows down neutrophil adhesion and activation. It has anti-thrombin, anti-plasmin, and fibrinolytic activity.
3. It can cause degranulation of neutrophils, increases natural killer cell activity and inhibits T-cell and B-cell activation.
4. It can maintain cellular integrity and homeostasis following acute injury.
5. This drug can also reduce the symptoms in patients with OSMF, in addition to its function in improving the vascularity.⁽⁷⁾

Rajendren *et al.* used pentoxifylline as an accessory drug in OSMF treatment and after 7 months trial and 6-12 months follow-up, the patients showed progress in signs and symptoms as compared to controls.⁽⁷⁾

Surgery

It is the technique of choice in patients with limited mouth opening and/or biopsy showing dysplastic or neoplastic changes.⁽¹²⁾ It includes:

1. Fibrotomy
2. Fibrotomy with grafts
3. Laser treatment
4. Mononuclear Stem Cell Therapy

Fibrotomy- The surgical treatment involves excision of fibrous bands and forceful mouth opening resulting in a raw wound surface. Relapse is common complication that occurs after surgical release of the oral trismus caused by OSMF.⁽¹²⁾

Fibrotomy with grafts- Initially surgeons aimed at surgical elimination of the fibrotic bands which showed further scar formation and recurrence of trismus, to prevent which, they started using various interpositional graft materials. The principle behind is incision (incorrectly termed as excision) or surgical release of fibrous bands followed by forceful opening of the mouth (widening of the incised tissue or region), and covering of surgical defects using various flaps or synthetic biological material.⁽¹²⁾

Extra-oral flaps- Split thickness skin graft.

- Superficial temporal fascia pedicled flap.
- Nasolabial flap.
- Platysma myocutaneous muscle flap.

Intraoral flaps - Tongue flap

- Palatal island flap

- Buccal fat pad

Microvascular free flaps - Radial forearm free flap

- Anterolateral thigh flap

Alloplasts - Collagen membrane

- Artificial dermis

Laser treatment: Lasers offer oral surgeons with a new modality for treating OSMF. The erbium chromium yttrium scandium gallium garnet (Er Cr: YSGG) laser has a wavelength of 2780 nm, well absorbed by water and is used on oral soft tissue without creating thermal damage. The overall advantage of laser surgery include a somewhat bloodless operative field and thus outstanding visibility, reduced need for local anesthesia, less probability of bacterial infection, reduced mechanical tissue trauma, fewer sutures, quicker healing, reduced post-operative edema, scarring and tissue shrinkage. Chaudhary *et al.*, highlights the attempt in treating a moderate case of bilateral OSMF with Er Cr: YSGG laser showed a better end result during follow-up.⁽¹⁴⁾

Mononuclear Stem Cell Therapy: Sankaranarayanan *et al.* (2013) conducted a study to assess the effectiveness of stem cell therapy in the treatment of OSMF by evaluating the improvement in function and to assess the sustainability of the result with 5 years follow-up. Out of seven patients, three were treated with stem cells obtained by Ficoll method and four patients were treated with stem cells obtained by point of care delivery system. Post-treatment improvement in the clinical presentation was assessed and confirmed by histo-pathological features. The range of follow-up of cases was from 6 months to 5 years. Reduction in blanching, improved elasticity of mucosa, decrease in burning sensation while consuming spicy food, increase in mouth opening was observed. The above results were found to be sustained in the follow-up period.⁽¹³⁾

Conclusion

This review of the literature for treatment of OSMF yields a spectrum of treatment modalities to manage OSMF. Numerous treatment modalities that have been implicated to cure the disease are the use of corticosteroids, hyaluronidase, placentrix, IFN, and microwave diathermy, etc. Surgical treatment is also considered by incision of fibrotic tissues and covering the defect with grafts. Though, till date, there is no single method, which can be used as the definitive treatment modality for OSMF. Recent literature proves that the combination of drugs produce effective results in the management of this disease. A more extensive clinical trials involving a greater number of cases and including more parameters are necessary to come to a final conclusion about a particular modality in the management of OSMF.

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