



MANAGEMENT OF ORAL SUBMUCOUS FIBROSIS: A REVIEW

Dental Science

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ABSTRACT

Oral submucous fibrosis (OSF) is a premalignant condition mainly associated with the practice of chewing betel quid containing areca nut, a habit common among South Asian people. It is characterized by inflammation, increased deposition of submucosal collagen and formation of fibrotic bands in the oral and paraoral tissues, which increasingly limit mouth opening.

The pathogenesis of the disease includes various factors like areca nut chewing, chillies, nutritional deficiencies and genetic processes. The management of OSF has been the subject of controversy ever since Schwartz first described the condition in 1952. Through this article, an attempt is made to update the numerous treatment modalities which can be used for patients suffering from OSMF.

KEYWORDS

Oral submucous fibrosis, treatment, areca nut

Oral submucous fibrosis (OSMF) is a potentially malignant disease that results in progressive juxtaepithelial fibrosis of the oral soft tissues, mainly occurring in the Indian subcontinent. It is a chronic, insidious, disabling disease involving oral mucosa, the oropharynx, and rarely, the larynx leading to loss of tissue mobility, marked rigidity and an eventual inability to open the mouth.^{1,2} The commonly involved site is buccal mucosa, followed by palate, retromolar region, faucial pillars and pharynx.³

There are multiple etiological factors associated with the initiation of oral submucous fibrosis. The most commonly etiologic agent being areca nut. It has an alkaloid and flavonoid component. The alkaloids namely arecoline, arecaine, guvacine, and guvacoline are present in areca nut, the most significant being arecoline which plays a crucial role in the pathogenesis of OSMF resulting in an increase in collagen production.^{4,5}

Numerous other factors include consumption of chilli, nutritional deficiency states, heredity susceptibility, autoimmunity, toxic levels of copper in food stuffs and masticatories, malnutrition resulting in low levels of serum proteins and collagen disorders have been suggested in the pathogenesis of this condition which causes production causing oral fibrosis. This causes production of free radicals and reactive oxygen species, leading to high rate of oxidation- peroxidation of polyunsaturated fatty acids.^{6,7}

OSMF is primarily seen in India, Bangladesh, Sri Lanka, Pakistan, Taiwan and China. In India most commonly affected regions are Bihar, Maharashtra, Gujarat and Madhya Pradesh.

Most frequently, younger generations are attracted because of commercially freeze dried areca nut products in various multicoloured eye catching pouches like gutkha and pan masala.⁸

Various biological pathways are involved for the increase in collagen synthesis or reduced collagen degradation is the possible mechanism in the development of the disease.

Under the effects of Ca (OH)₂, arecoline which is the main etiologic agent converts to arecaine causing fibroblastic proliferation.⁹

The stabilisation of the collagen structure is by flavanoids like tannins and catechins by inhibiting the cyclooxygenase pathway and by changing the cytoskeletal structure of Type 3 collagen to Type 1 collagen which is more resistant. This transformational change is due to increased expression of vimentin, an insoluble cytoskeletal protein in OSMF patients.^{10,11} The increase in collagen synthesis is due to activation of procollagen gene and lysyl oxidase activity and collagen degradation is inhibited by TIMP's (tissue inhibitor of matrix proteinases) gene and activation of plasminogen activator inhibitor (PAI) that prevents conversion of plasminogen to plasmin which plays a role in conversion of procollagenase to collagenase.¹²

Many treatment modalities have been proposed, allopathic, homeopathic, ayurvedic, surgical, physiotherapy etc. alone or in combination for the management of OSMF. The primary management for long term management is discontinuation of intake of areca nut, tobacco alcohol; increase the intake of fresh red fruits and green leafy vegetables. The present article aims to highlight various treatment modalities with their proposed mechanism of action in the management of Oral Submucous Fibrosis.

DRUG TREATMENT:

1. CORTICOSTEROIDS

These are immunosuppressive agents which decrease inflammation and collagen formation, thereby reducing the symptoms and lead to increased mouth opening. Steroids slow down the proliferation of fibroblasts thereby reducing the collagen fibres.^{13,14,15} They also play a vital role in increasing apoptosis of inflammatory cell, leading to palliative management in early cases of OSMF.¹⁶ Dexamethasone, methylprednisone and betamethasone are the synthetic drugs with glucocorticoid like effects.

Many studies have found the use of intralesional steroids as highly effective.¹⁷⁻²⁰

Current concept is based upon the use of intralesional steroids injected in the fibrotic bands biweekly over a period of 6-8 weeks along with mouth opening physiotherapy exercises.²¹

2. ENZYMES

Lin et al,²² conducted a study to assess the efficacy of collagenase in the management of OSMF and it was seen that collagenase treatment not only resulted in a significant improvement of oral opening, but patients also led to striking reduction in sensitivity to spices, sour, cold, and heat.

Hyaluronidase is a fibrinolytic enzyme. It helps in the breakdown of hyaluronic acid, which lowers viscosity of the intercellular cement substance; it also decreases collagen formation with dosage of 1500 IU biweekly for 10 weeks. Various studies have used different regimens of intralesional injections in patients, 4mg dexamethasone biweekly; 1500 IU of hyaluronidase with 1cc of lignocaine biweekly; 4mg of dexamethasone and 1500 IU of hyaluronidase; 2cc placentex biweekly and found out that combination of dexamethasone and hyaluronidase for seven weeks gave maximum improvement.^{23,24}

Chymotrypsin, an endopeptidase, hydrolyzes ester and peptide bonds and is also used as a proteolytic and anti-inflammatory agent in the treatment of OSMF.²⁵

D Gupta & S C Sharma has reported successful treatment of oral submucous fibrosis with local injections of chymotrypsin, hyaluronidase, and dexamethasone.²⁶

Placentex is an extract of human placenta containing nucleotides,

enzymes, steroids, vitamins and amino acids. It acts by biogenic stimulation. It is injected into the body after resistance to pathogenic factors and stimulates the metabolic or regenerative processes. Studies have reported beneficial effects of weekly administration of injection placentrex in the management of Oral Submucous fibrosis.²⁷⁻²⁹

3. VITAMINS AND MINERALS

Tobacco and areca nut chewing elicit immunosuppression by generating high free radical levels. The free radicals mediate phenotypic and gene alterations leading to mutations (neoplastic effect). The use of antioxidants can reduce oxidative damage by scavenging free radicals.

OSMF is also correlated with impaired nutritional status; hence, various investigators have supplemented the patients with multiple micronutrients which include zinc, vitamin A, B, C, iron, folic acid, copper, calcium and manganese.

Dhariwal et al.³⁰ investigated the role of zinc acetate along with vitamin A and the results showed an increased mouth opening and reduction in burning sensation.

According to **Gurprasad et al.**³¹ the level of serum Vitamin C and Iron was found to be significantly decreased in OSMF patients and recommended therapeutic substitution of vitamin C and Iron in the management of OSMF.

β-carotene / Vitamin A- β-carotene scavenges free radical species that retards the development of cancer cells.³² A study conducted by **Gupta et al.**³³ revealed decrease in the plasma beta carotene and vitamin E levels in patients with OSMF.

Lycopene- Selvam and Dyanand suggested a combination of lycopene with intralesional steroids and hyaluronidase to be highly efficacious in reducing the symptoms and mouth opening of OSMF patients.³⁴ **Karemore, Motwani and Sunderraj S et al.** also found that lycopene was highly efficacious in relieving sign and symptoms of OSMF.³⁵⁻³⁸

Patil et al.³⁹ compared the use of lycopene and spirulina and found that the use of lycopene increases mouth opening whereas spirulina healed ulcers, erosions and vesicles.

According to **Kumar et al.** Lycopene 8 mg with Vitamin E is highly effective treatment for OSMF patients.⁴⁰

4. INTERFERON GAMMA

Interferon gamma possess immuno-regulatory and anti-fibrotic cytokine effect leading to alteration of collagen synthesis causing down regulation of collagen synthesis. In vivo studies of intra-lesional injection of 0.01- 10.0U/ml 3 times a day for 6 months showed improvement of symptoms.^{41,42}

5. IMMUNIZED MILK

It was found that cow's milk which is immunized with human intestinal bacteria (immune milk) contains an anti-inflammatory component that may repress the inflammatory reaction and modulate cytokine production. A study showed the effect of oral administration of milk from cows immunized with human intestinal bacteria in OSF. It has been seen that 45 grams of immune milk powder given twice a day for 3 months resulted in significant improvement in intolerance to spicy foods in 80% and increase in inter incisal distance in 69.2% patients.⁴³

6. PENTOXYPHYLLINE

Pentoxifylline increases red cell deformability, leukocyte chemotaxis, antithrombin and anti-plasmin activities.

Its positive and efficacious role has been seen by studies conducted by **Patil S and Jaychandran et al.**^{44,45}

Several other studies have claimed that pentoxifylline could be used as an adjunct therapy in the routine management of oral submucous fibrosis.^{46,47,48}

7. LASERS

Study conducted by **S.Gupta et al.**, showed that lasers can provide an alternative and better means for surgical fibrotomy, relieving trismus in moderate OSMF as they have faster healing and minimal surgical

site scarring and relapse.⁴⁹ Similar effects are also seen in other studies.⁵⁰

8. NATUROPATHY

In a study conducted by **Patel et al.**⁵⁶ 24 OSMF patients were subjected to *Koshthashuddhi* (mild purgation) and *Shodhana Nasya* (errhine therapy); *Pratisarana* (external application) with *Madhupippalyadi Yoga, Kavala* (gargling) with *Ksheerabala Taila* and internally *Rasayana Yoga* were given for 2 months and were followed for 1 month. For the first 3 days, *Erandabhrishtha Haritaki*⁵⁷ powder 5–10 g was taken with luke warm water at bed time for *Koshthashuddhi* (mild purgation), which was then followed by *Shadabindu Taila Nasya* (errhine therapy),⁵⁸ 4–8 drops in each nostril for 5 days.

Following this, *Pratisarana* (external application) was done, *Kavala* (gargling) and *Rasayana Yoga* were administered twice a day simultaneously for 60 days.

The study showed this ayurvedic treatment modality is effective in the management of OSMF without any adverse effect as well as having sustained relief in follow-up.

SESAME OIL PULLING

Oil pulling means swishing of the oil in the mouth that can be performed by using sesame oil, coconut oil and sunflower oil.⁵⁹ Sesame oil contains three ligans (sesamin, sesamol and sesaminol) which contain Vitamin E and polyunsaturated fatty acids. In addition, linoleic acid and oleic acid are also major components of sesame oil that possess antioxidative properties that reduce lipid peroxidation by diminishing the free radical injury to tissues.⁶⁰ The beneficial effects of oil pulling was seen by **Khera et al** that showed increase in mouth opening, tongue protrusion, improved gingival index and reduction in VAS Scale.⁶¹

TULSI:

According to Ayurveda, the use of Tulsi (*Ocimum sanctum* Linn) enhances immunity and metabolic functions. It helps in reducing inflammation by inhibiting the inflammation-causing enzymes.⁶² Studies have shown that by using 1 gm tulsi and 1 gm turmeric mixed in glycerine base, highly significant improvement was seen in VAS scale of the.^{63,64,65}

ALOE VERA:

Aloe vera is an emollient resin and a mannoprotein containing many amino acids, called 'wound healing hormones'.⁶⁶ The polysaccharides in the gel of the leaves has anti-inflammatory, immunomodulatory, antioxidant and wound-healing properties.^{67,68}

Various studies have shown beneficial effects of aloe vera in management of submucous fibrosis.^{69,70}

SPIRULINA:

Spirulina is a source of proteins, carotenoids and possess antioxidant property with high amount of beta carotene and superoxide dismutase so it can be effectively used in treatment of OSMF.⁷¹

CURCUMIN:

Turmeric (*Curcuma longa* Linn) is made into a yellow powder with a bitter yet sweet taste possessing anti-inflammatory properties leading to suppression of cellular transformation, proliferation and metastasis by downregulating tumor necrosis factor (TNF)-induced NF-κB activation and NF-κB-dependent reporter gene expression.^{72,73}

Several studies have shown that curcumin holds good promise in the treatment of OSF in future.⁷⁴⁻⁷⁷ A comparison of various formulations of curcumin (tablets, capsules and oil) was assessed in a study and it was seen oil showed better results in the reduction of burning sensation, whereas capsules showed good improvement in the score of mouth opening and tongue protrusion stating that turmeric in all forms is a better treatment modality in improving signs and symptoms of OSMF.⁷⁸

9. PHYSIOTHERAPY

The earliest signs of OSMF are blanching of the oral mucosa followed by development of fibrous bands in the areas such as buccal mucosa, palate, posterior larynx, lips and tongue leading to difficulty in mouth opening most prominent feature of OSMF.

For regaining the tissue elasticity, studies have been conducted to use physiotherapy as an allied treatment option.

- a. According to **Vijaykumar**,⁷⁹ physiotherapy interventions can be used in the management of OSMF by improving their mouth opening and reducing their intensity of burning sensation.
- b. **Chaitanya et al**,⁸⁰ made a novel intraoral appliance—"Nallan C-H" can be used for treating inoperable trismus in palliative care setting.
- c. **Taneja et al**⁸¹ used Hister's jaw exerciser in order to increase the active mouth opening in severe cases of OSMF and showed promising results.
- d. **Microwave diathermy** (Low current is used 20 watts × 2450 cycles) is useful in some early or moderately advanced stages and acts by physiofibrinolysis of bands. Microwave diathermy seems superior to short wave, because selective heating of juxta epithelial connective tissue is possible, thereby limiting the area treated.
- e. **Ultrasound** has a role in deep heating modality. It causes selective rising of the temperature in accumulated areas.⁸²
- f. **Cryosurgery**- It is the method of locally destroying the abnormal tissue by freezing it in situ and applying liquid nitrogen or argon gas.⁸³

10. SURGICAL TREATMENT

In patients with severe trismus, surgical intervention is done which includes simple excision of fibrotic bands with reconstruction using buccal fat pad and split thickness graft along with temporalis myotomy and coronoidectomy. The surgery is performed under general anaesthesia. The intubation is difficult due to restricted mouth opening. Endotracheal intubation under deep inhalational anaesthesia or using muscle relaxants with regional block is preferred. Fiber-optic guided intubation techniques have also been used.⁸³

S.No	DRUG	MECHANISM OF ACTION
1.	CORTICOSTEROIDS	Induce decrease inflammation and collagen formation, thereby reducing the symptoms and lead to increased mouth opening. Slow down the proliferation of fibroblasts thereby reducing the collagen fibres
2.	ENZYMES - Collagenase - Hyaluronidase - Chymotrypsin - Placentrix	Breakdown of hyaluronic acid, thereby lowering the viscosity of the intercellular cement substance Anti inflammatory action Biogenic stimulation. Activation of procollagen gene and lysyl oxidase activity and collagen degradation is inhibited by TIMP's (tissue inhibitor of matrix proteinases) gene.
3.	VITAMNS & MINERALS - Zinc - Vitamin A, C, E - Iron - Carotene - Spirulina - Lycopene	They act by reducing oxidative damage by scavenging free radicals. Possess anti oxidant property.
4.	INTERFERON GAMMA	Possess immuno-regulatory effect and has anti-fibrotic cytokine effect and hence its major role in altering collagen synthesis
5.	IMMUNIZED MILK	Possess anti-inflammatory action that repress the inflammatory reaction and modulate cytokine production leading to decreased inflammatory response.
6.	PENTOXIPHYLLINE	Increases red cell deformability, leukocyte chemotaxis, antithrombin and anti- plasmin activities and has fibrinolytic activity
7.	LASERS	Photo-thermal action results in disruption of the tissue, using sufficient deposition of heat to vaporize the tissue. Disruption of the tissues causes breakdown of the collagen fibres.

8.	AYURVEDIC TREATMENT - Oil pulling - Tulsi - Aloe Vera - Spirulina - Curcumin	Possess antioxidative properties that reduce lipid peroxidation by diminishing the free radical injury to tissues Acts by reducing inflammation by inhibiting the inflammation-causing enzymes Possess anti-inflammatory, immunomodulatory, antioxidant and wound-healing properties. Antioxidant property with high amount of beta carotene and superoxide dismutase. Anti-inflammatory agent leading to suppression of cellular transformation, proliferation and metastasis by downregulating tumor necrosis factor (TNF)-induced NF-κB activation and NF-κB-dependent reporter gene expression
9.	PHYSIOTHERAPY	Help in increasing the elasticity of the fibrosed areas.
10.	SURGERY	Excision of fibrous bands and reconstruction of the resultant defects using skin grafts and local, regional and distant flaps such as oral mucosal flaps, myomucosal island flaps, tongue flaps, local muscular flaps like temporalis or temporalis fascia transfer and buccal fat pad.

CONCLUSION

OSMF is a premalignant condition and is a paradox to the oral medicine experts because its high recurrence rate despite treatment therapies.

This Article aims to enlighten of the recent treatment modalities of OSMF for improving the management of OSMF according to its various stages.

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