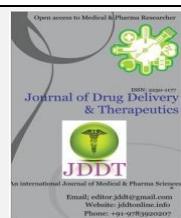


Available online on 15.05.2019 at <http://jddtonline.info>

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

© 2011-18, publisher and licensee JDDT, This is an Open Access article which permits unrestricted non-commercial use, provided the original work is properly cited



Open Access

Review Article

Oral Sub Mucous Fibrosis: A Review

Sonia T Sevlani*¹, Sheetal Gondkar¹, Ravindranath Saudagar²

¹ Department of Pharmaceutics, R.G. Sapkal College of Pharmacy, Anjaneri, Nashik-422213, Maharashtra, India

² Department of Pharmaceutical Chemistry, R. G. Sapkal College of Pharmacy, Anjaneri, Nashik-422213, Maharashtra, India

ABSTRACT

Oral Sub Mucous Fibrosis is a well-recognized clinical entity, known since the time of Sushruta. In the modern literature OSMF was first reported by Schwartz (1952), Joshi (1953) was the first person to describe this entity in India. Oral Sub Mucous Fibrosis (OSMF) is a potentially malignant disease that results in progressive juxtaepithelial fibrosis of the oral soft tissues, resulting in increasing loss of tissue mobility, marked rigidity and an eventual inability to open the mouth. The basic change is a fibroelastic transformation of the connective tissue in the lamina propria followed by vesicle formation. It is a well-known chronic insidious disease, precancerous condition, an autoimmune and collagen related disorder whose origin is multifactorial and is associated with chewing of betel quid. It is characterized by progressive hyalinization of the lamina propria. In the later stages the oral mucous membrane becomes very stiff and the patient suffers from trismus and hence difficulty in eating. Earlier OSMF had been confined to countries like India, Pakistan, Bangladesh, etc., but now it is being reported from western countries as well. Inspite of intensive research over the years, a single etiologic factor for OSMF cannot be pointed out with certainty. Patients suffering with OSMF are initially present with a blanched or marble-like pale mucosa, vesiculations and also show intolerance to hot and spicy food. The treatment of oral submucous fibrosis includes iron, multivitamins including lycopene, spirulina, pentoxifyline, colchicine local submucosal injections of steroids, hyaluronidase and chylomicrons, and surgical excision of the fibrous bands.

Keywords: Oral Sub Mucous Fibrosis, juxtaepithelial fibrosis, oral soft tissues, fibroelastic, lamina propria, collagen.

Article Info: Received 22 March 2019; Review Completed 09 May 2019; Accepted 12 May 2019; Available online 15 May 2019



Cite this article as:

Sevlani ST, Gondkar S, Saudagar R, Oral Sub Mucous Fibrosis: A Review, Journal of Drug Delivery and Therapeutics. 2019; 9(3):712-715 <http://dx.doi.org/10.22270/jddt.v9i3.2898>

*Address for Correspondence:

Sonia T Sevlani, Department of Pharmaceutics, R.G. Sapkal College of Pharmacy, Anjaneri, Nashik-422213, Maharashtra, India.

INTRODUCTION

Oral Sub Mucous Fibrosis is a very well-known clinical entity since the time of Sushruta. Schwartz (1952) was the first to report OSMF in modern literature, Joshi (1953) was the first person to describe this entity in India.¹ Oral Sub Mucous 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. OSMF results in an increasing loss of tissue mobility, marked rigidity and an eventual inability to open the mouth. The most commonly involved site is buccal mucosa, followed by palate, retromolar region, faucial pillars and pharynx.² The exact etiology of OSMF is still obscure, etiological factors are being mentioned such as genetic, autoimmune, nutritional and environmental. The pathogenic mechanism of developing OSMF with chewing areca nut is not clear, but it is associated with OSMF.³ A review in 2005 proposes that OSMF could be included under collagen metabolic disorders due to the imbalance in collagen production and breakdown. Elaborate pathways have been described on how there is an increase in collagen production as well as a pathway to explain decreased degradation of collagen thereby leading to an increased concentration of collagen in the tissues. Most of the current studies are concentrating on the role of areca nut and its constituents in the derangement of the extracellular matrix and collagen imbalance.⁴ The oral mucosa is involved symmetrically in most of the cases, buccal mucosa and lips are affected at an early stage although previously it was thought that the palate and the faucial pillars are involved first. The most common initial symptom is burning sensation of oral mucosa which is aggravated by spicy food. The

which arecoline is the most potent agent and plays a major role in the pathogenesis of OSMF by causing an abnormal increase in collagen production.^[2] The exact etiology of OSMF is still obscure, etiological factors are being mentioned such as genetic, autoimmune, nutritional and environmental. The pathogenic mechanism of developing OSMF with chewing areca nut is not clear, but it is associated with OSMF.³ A review in 2005 proposes that OSMF could be included under collagen metabolic disorders due to the imbalance in collagen production and breakdown. Elaborate pathways have been described on how there is an increase in collagen production as well as a pathway to explain decreased degradation of collagen thereby leading to an increased concentration of collagen in the tissues. Most of the current studies are concentrating on the role of areca nut and its constituents in the derangement of the extracellular matrix and collagen imbalance.⁴ The oral mucosa is involved symmetrically in most of the cases, buccal mucosa and lips are affected at an early stage although previously it was thought that the palate and the faucial pillars are involved first. The most common initial symptom is burning sensation of oral mucosa which is aggravated by spicy food. The

periods of exacerbation manifested as vesiculation, ulceration, pigmentation changes, dryness of mouth, depapillation of tongue. Gingiva become fibrotic, depigmented with loss of stippling. As the disease progresses gradual stiffening of oral mucosa with tough and leathery consistency associated with fibrous bands in the buccal mucosa which run in a vertical direction involving the tissue around the pterygomandibular raphae that causes varying degrees of difficulty in mouth opening. In severe labial involvement, the opening of the mouth is altered to an elliptical shape. Similarly when soft palate is involved it appears as a heavy curtain is hanging from the hard palate and uvula become shrunken which appears as bud shape. In severe cases of fibrosis involving tongue and buccal mucosa causes difficulty in eating, blowing, whistling and sucking. In advanced cases involvement of oesophagus and eustachian tube leads to difficulty in swallowing food, referred pain to ears and deafness and nasal voice have been noticed.⁵

A few reasons proposed for the increased incidence of OSMF in India:⁴

- The low cost, easy availability, attractive packaging, and aggressive marketing have led to a substantial increase in the number of people initiating this habit and getting addicted to it.
- Advertisements portray consumption of these products as confidence boosters or a status symbol giving it a midas touch.
- Advertisements also portray these products as breath fresheners thereby attracting a larger audience.
- In India areca nut is deeply rooted in the cultural/religious beliefs of the people, it is considered sacred so is distributed to people during occasions like marriages, etc., and hence people chewing it is not uncommon nor is it objectionable.
- Due to minimal symptoms in the early stages there could be a lower reporting of the incidence of OSMF also a lack of awareness regarding the same.
- Multiple pregnancies combined with poor nutritional status of women can act as a promoting factor in the presence of habits.

SYMPTOMS

The symptoms and signs depend on the progression of the lesions and on the number of affected sites. More than one oral site is involved in most cases. OSF has been reported to occur commonly in conjunction with other diseases, such as leukoplakia and lichen planus. In advanced lesion, the fibrosis extends from the subepithelial lamina propria through the entire submucosa to the muscle layer. Thick inextensible vertical fibrous bands appear in the cheeks, faucial pillars, and encircle the lips. Narrowing of the oral aperture caused by circular fibrous bands in the lips is not only disfiguring, but also limits oral access, leading eventually to malnutrition and poor oral hygiene.⁵ The symptoms and signs are limited mouth opening, dryness, burning sensation, absent gustatory sensation, difficulty in chewing and swallowing and ulceration and vesication of mucous membrane.²

Etiopathogenesis⁴

A single etiologic factor for OSMF cannot be pointed out with certainty, rather several causative factors have been proposed. According to a review in 1989, the etiologic factors can be conveniently divided into initiators and promoters of OSMF. The initiators for OSMF include – chillies, areca nut, tobacco, and streptococcal infection, on the other hand the promoters include – anemia (iron deficiency), vitamin deficiencies (B complex and folate), malnutrition (protein), and immunologic derangements. In 1995 Murti *et al.* emphasized the role of areca nut as the etiologic agent for OSMF.

A review in 2005 proposes that OSMF could be included under collagen metabolic disorders due to the imbalance in collagen production and breakdown. Elaborate pathways have been described on how there is an increase in collagen production as well as a pathway to explain decreased degradation of collagen thereby leading to an increased concentration of collagen in the tissues. Most of the current studies are concentrating on the role of areca nut and its constituents in the derangement of the extracellular matrix and collagen imbalance.

Tilakaratne *et al.* in 2006 proposed various pathogenetic mechanisms like areca alkaloids causing fibroblast proliferation and increased collagen synthesis, stabilization of collagen structure by tannins and catechins, copper content in arecanut and its contribution in fibrosis, upregulation of cyclo-oxygenase-2, role of fibrogenic cytokines, genetic polymorphisms predisposing to OSF, inhibition of collagen phagocytosis, stabilization of extracellular matrix, and role of collagen-related genes.

Angadi *et al.* in 2011 restated that areca nut by far is the most probable etiologic agent for OSMF.

CLASSIFICATION OF OSMF:

➤ Clinical staging

- Stage 1 (S1) – Stomatitis and/or blanching of oral mucosa
- Stage 2 (S2) – Presence of palpable fibrous bands in buccal mucosa and/or oropharynx, with/without stomatitis
- Stage 3 (S3) – Presence of palpable fibrous bands in buccal mucosa and/or oropharynx, and in any other parts of oral cavity, with/without stomatitis
- Stage 4 (S4) (a) – Any one of the above stage along with other potentially malignant disorders e.g. oral leukoplakia, oral erythroplakia, etc.
- Stage 4 (S4) (b) – Any one of the above stage along with oral carcinoma.

➤ Functional staging

- M1. Inter incisal mouth opening is up to or > 35 mm
- M2. Inter incisal mouth opening between 25 mm and 35 mm
- M3. Inter incisal mouth opening between 15 mm and 25 mm
- M4. Inter incisal mouth opening < 15 mm.



Figure 1: Mouth opening before treatment measured by vernier caliper.²



Figure 2: Mouth opening after the treatment measured by vernier caliper.²

TREATMENT

Behavioural therapy: Counselling against continuing the habit is an essential step in the treatment of any disease. Interventions have showed that basic strategies such as short films, personal communication and showing photographs of harmful effects can be significantly effective in deterring people from starting or continuing the tobacco habit.^{7,8}

Steroids: The steroids act by inhibiting generation of inflammatory factors and increasing the apoptosis of inflammatory cells^[9,10,11]. Although steroids are one of the most often used drugs for OSMF clinicians should be alert to avoid any complications such as one reported of central serous chorioretinopathy following a 2 month treatment with a combination of triamcinolone, hyaluronidase and placenctrix.¹²

Enzymes:

Collagenase – It acts by lysing fibrogen, increasing vascular circulation and epithelial regeneration

Hyaluronidase – It depolymerises hyaluronic acid thereby lowering the viscosity of intercellular cementing substance.

These enzymes provide good results when combined with steroids.^{10,11}

Nutritional supplements: Vitamin A plays an important role in maintaining the normal growth and repair of epithelial tissues.

Hence a novel treatment modality has been proposed recently by a few authors,¹³ which involves supplementation with zinc acetate 50 mg three times daily and Vit A 25,000 IU once daily.^{10,11}

Antioxidants: Lycopene is a phytochemical, synthesized by plants (tomatoes) and microorganisms. Lycopene is a powerful antioxidant and has a singlet-oxygen-quenching ability twice as high as that of beta-carotene and ten times higher than that of alpha-tocopherol.^{11,14,15}

Systemic drugs: (Cardiovascular)

Pentoxifylline is a tri-substituted methylxanthine derivative, which leads to decrease in red cell and platelet aggregation, granulocyte adhesion, fibrinogen levels, and lowers whole blood viscosity. But the major deterrents of pentoxifylline are its side effects related to gastrointestinal tract and central nervous system.

Buflomedil is a vasoactive agent which claims to exert beneficial effects on the microcirculation.

Nylidrin is a sympathomimetic agent which is chemically related to the epinephrine ephedrine series, it produces vasodilation of the arterioles of skeletal muscles.^{10,16,17}

Immune milk: Immune milk is, milk from cows immunized with human intestinal bacteria. Proposed anti-inflammatory activity is by modulation of cytokines. Only one study showed the effect of oral administration of milk from cows immunized with human intestinal bacteria in OSMF. Forty-five grams of immune milk powder twice a day for 3 months resulted in significant improvement in intolerance to spicy foods in 80% and increase in interincisor distance in 69.2% patients.¹¹

Interferon gamma: IFN gamma is a known anti-fibrotic cytokine. In an open uncontrolled study intra-lesional interferon gamma treatment resulted in reduced burning sensation, increased suppleness of the buccal mucosa and improvement in the mouth opening by 42% in OSMF patients.¹¹

Ayurvedic therapy: Oxitard formulation contains the extracts of *Magnifera indica*, *Withania somnifera*, *Daucus carota*, *Glycyrrhiza glabra*, *Vitis vinifera*, *Syzygium aromaticum*, powders of *Emblica officinalis* and *Yashada bhasma*; and oils of *Triticum sativum*. The role of chilies being an important factor in disease progression, this drug does have efficacy to address that issue. One study by Singh et al., used Oxitard capsule in 48 cases, in patients having difficulty in mouth opening and pain a dose of two capsules twice daily for a period of 3 months was standardized; they concluded that there was significant increase in mouth opening along with decrease in pain in the mouth.¹⁸

Stem cell therapy for oral submucosal fibrosis^{19,20}

In the recent studies scientists proved that intralesional injection of autologous bone marrow stem cells is a safe and

very effective way of treating oral sub mucosal fibrosis. It has been shown that autologous bone marrow stem cell injections induces angiogenesis in the area of lesion which in turn decreases the extent of fibrosis thereby leading to significant increase in mouth opening.

REFERENCES

1. Kakar PK, Puri RK, Venkatachalam VP, Oral Submucous Fibrosis—treatment with hyalase ,The Journal of Laryngology & Otology, 1985; 99(1): 57-60
2. Chole R.H, Patil R, Drug Treatment of Oral Sub Mucous Fibrosis – A Review, International Journal of Contemporary Medical Research, 2016; 3(40).
3. Agrawal A, Kaushal Y, Vaidya S, Shrivastava K, Medical management of oral submucous fibrosis, International Journal of Otorhinolaryngology and Head and Neck Surgery 2017; 3(3):628-631
4. Hebbar PB, Sheshaprasad R, Gurudath S, Pai A, Sujatha D, Oral Sub Mucous Fibrosis in India: Are we progressing?? Indian Journal of Cancer • July 2014
5. Gupta M, Mishra P, Shrivastava K, Singh N, Singh P, A Review Oral Submucous Fibrosis- Current Concepts of Aetiology & its Management , 2015; 1(1).
6. Lai DR, Chen HR, Lin LM, Huang YL , Tsai CC, Clinical evaluation of different treatment methods for oral submucous fibrosis. A 10-yearexperience with 150 cases. Journal of Oral Pathology and Medicine 1995: 24:402-6
7. Anantha N, Nandakumar A, Vishwanath N, Venkatesh T, Pallad YG, Manjunath P, et al. Efficacy of an anti-tobacco community education program in India. Cancer Causes Control 1995; 6:119-29.
8. Warnakulasuriya S. Squamous cell carcinoma and precursor lesions: Prevention. Periodontol 2000; 2011:57:38-50.
9. Kerr AR, Warnakulasuriya S, Mighell AJ, Dietrich T, Nasser M, Rimal J, et al. A systematic review of medical interventions for oral submucous fibrosis and future research opportunities. Oral Dis 2011;17:42-57
10. Jiang X, Hu J. Drug treatment of oral submucous fibrosis: A review of the literature. J Oral Maxillofac Surg 2009; 67:1510-5.
11. Chole RH, Gondivkar SM, Gadball AR, Balsaraf S, Chaudhary S, Dhore SV, et al. Review of drug treatment of oral submucous fibrosis. Oral Oncol 2012; 48:393-8.
12. Kar IB, Sethi AK. A rare ocular complication following treatment of oral submucous fibrosis with steroids. Natl J Maxillofac Surg 2011; 2:93-5.
13. Mukherjee S, Ray JG, Chaudhuri K. Zinc and vitamin A as a low cost management of oral submucous fibrosis: Comment on Chole RH et al. "Review of drug treatment of oral submucous fibrosis. Oral Oncol 2012; 48:e27-8.
14. Kumar A, Bagewadi A, Keluskar V, Singh M. Efficacy of lycopene in the management of oral submucous fibrosis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007; 103:207-13.
15. Kerr AR. Efficacy of oral lycopene in the management of oral submucous fibrosis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007; 103:214-5.
16. Rajendran R, Rani V, Shaikh S. Pentoxifylline therapy: A new adjunct in the treatment of oral submucous fibrosis. Indian J Dent Res 2006; 17:190-8.
17. Sharma JK, Gupta AK, Mukhija RD, Nigam P. Clinical experience with the use of peripheral vasodilator in oral disorders. Int J Oral Maxillofac Surg 1987; 16:695-9.
18. Routray S, Motgi AS, Sunkavalli A. Comment on "Chole RH et al. Review of drug treatment of oral submucous fibrosis. Oral Oncol 2012; 48: e13-4.
19. Sankaranarayanan S, Ramachandran CR, Manjunath S, Murugan P et.al,(June 2008). Autologous Bone Marrow stem cells for treatment of Oral Sub-Mucous Fibrosis - a case report. Sixth Annual Meeting of International Society for Stem Cell Research (ISSCR). Philadelphia.
20. Abraham S, Sankaranarayanan S, Padmanaban J, Baskar S et.al (June 2008). Autologous Bone Marrow Stem Cells in Oral Submucous Fibrosis – Our experience in three cases with six months follow-up. 8th Annual Meeting of Japanese Society of Regenerative Medicine. 68. Tokyo, Japan. pp. 233-55.