Review Article

JRAD Journal of Research and Advancement in Dentistry

J Res Adv Dent 2020;10:2s:109-116.

# Treatment Modalities for Oral Submucous Fibrosis: Review

**Jigar Joshi[1*] Dhaval N Mehta[2] Riddhi Goswami[3]**

[1]Reader, Department of Oral Medicine and Radiology, Narsinhbhai Patel Dental College and Hospital, Sankalchand Patel University, Visnagar, Gujarat, India.

[2]Professor and Head, Department of Oral Medicine and Radiology, Narsinhbhai Patel Dental College and Hospital, Sankalchand Patel University, Visnagar, Gujarat, India.

[3]PG Student, Department of Oral Medicine and Radiology, Narsinhbhai Patel Dental College and Hospital, Sankalchand Patel University, Visnagar, Gujarat, India.

## ABSTRACT

**Background**: One of the most common potentially malignant disorder, which is widely prevalent in the Indian subcontinent is Oral Submucous Fibrosis. This is an attempt to review the various available treatment modalities that aid in the prognosis of the condition and thereby improving the quality of life of the patient suffering from this condition.

**Keywords:** Fibrous bands, Oral Submucous Fibrosis, Treatment Modalities.

## INTRODUCTION

In ancient India, a renowned physician and surgeon named Sushrutha (600 BC), described a disease resembling Oral Submucous Fibrosis in his book named "Mouth & Throat disease" and called it as Vidhari.[1] It was first reported in 1952 by Schwartz among five Indian females from Kenya, and he designated the term 'atropica idiopathica mucosae oris' to this condition.[2] In 1953, Dr Joshi described this condition as 'submucous fibrosis'.[3,4] In India this condition was first described as "diffuse Oral submucous fibrosis" (Lal 1953), also described as idiopathic scleroderma of mouth (Su 1954), idiopathic palatal fibrosis (Rao 1962) and sclerosing stomatitis (Behl 1962). Pindborg & Sirsat four-decade ago were first to describe it as a premalignant condition .[5]

Oral Submucous Fibrosis (OSMF) is a potentially malignant disorder (PMD) and crippling condition of the oral mucosa, affecting mainly the South East Asian population especially those in the Indian subcontinent. It is a serious debilitating disease leading to fibrosis of the oral mucosa, trismus and difficulty in eating thus reducing the quality of life.[5,6]

OSMF is most commonly found in the age group of 20–40 years although it can occur in any decade.[5] This disease causes changes similar to those of systemic sclerosis (scleroderma) but is limited to oral tissues.[6] Recent epidemiological data indicate that the number of cases of OSMF has raised rapidly in India from an estimated 250,000 cases in 1980 to an estimated 5 million people in 2002.[5] Various authors had investigated the condition thoroughly and proposed several factors that play a role in the etiopathogenesis of this condition. Current evidence suggests that arecoline in the areca nut is the key factor in initiating the disease process.[7] The reasons for the rapid increase of the disease are reported to be due to an upsurge in the popularity of commercially prepared areca nut preparations like gutkha, khaini, pan masala, mawa, gudaku and others, which are increasingly being consumed by the people.[6,7]

Various treatment modalities, invasive &/or non-invasive are proposed for the management of OSMF. The noninvasive treatment regimens include dietary supplementation with iron, multivitamin supplements including Vitamin A or Vitamin B,

**Received:** Apr. 5, 2020: **Accepted**: Apr. 22, 2020

***Correspondence Dr. Jigar Joshi.**

Department of Oral Medicine and Radiology, Narsinhbhai Patel Dental College and Hospital, Sankalchand Patel University, Visnagar, Gujarat, India.

**Email: Not Disclosed**





pISSN 2278-0076

eISSN 2321-9270

lycopene - an extract of tomato, and a range of medicines (e.g. intralesional injection of steroids, hyaluronidase, human placenta extracts, chymotrypsin, Pentoxifylline and collagenase). Laser ablation and surgery, including the cutting of the fibrous bands of the jaw muscles and temporomandibular joint, are advised for more extreme cases.[7,8] This paper highlights a review of various treatment modalities for OSMF.

TREATMENT

A multitude of treatment modalities has been suggested for OSF. But none are found to be curative. More research has to be made in formulating a curative treatment regimen. The management of OSMF should be in combined form. The result of synergistic action is much better than single therapy.[8,9] The treatment of Patients with OSMF depends on the degree of clinical involvement. If the disease is detected at a very early stage, cessation of the habit is sufficient. Most patients with OSMF present with Moderate-to-Severe disease which is irreversible. [9]

Discontinuation of Habit & Counseling:

The Preventive measures should be in the form of Discontinuation of Habit, which can be encouraged through Education & Advocacy. Affected patients should be explained about the disease & its possible malignant potential. Thorough counselling should be given for de- addiction.[8]

Supportive Care: Vitamins, iron and mineral-rich diet should be advised to patients with OSMF. Intake of red tomatoes, fresh fruits and green leafy vegetables should be included in the regular diet. Intake of green tea should be included in the diet chart. Epigallocatechin-3-gallate, a component of green tea has also been demonstrated to inhibit oral cancer through the modulation of MMP-13.8,10

Antioxidants:

It is known that the process of carcinogenesis occurs by the generation of Reactive Oxygen Species, which act by initiating lipid peroxidation (LPO). Prevention against LPO mediated damage is done by antioxidants and it has also been reported that oral premalignant lesions can be successfully treated by antioxidant supplementation which led many clinicians to consider antioxidants in the treatment of OSMF. [7, 11]

Antioxidants neutralize highly reactive oxygen free radicals. Antioxidants are capable of stabilizing or deactivating free radical before they damage biomolecule. It includes Vitamin A, Vitamin C, Vitamin E, Carotenoids, trace elements like selenium, zinc, copper, manganese. [12] Micronutrients such as vitamins and minerals play an important role in normal human metabolism. Vitamin A plays an important role in maintaining normal growth and repair of epithelial tissues. Several studies conducted in the past observed that Vitamin A given at a concentration of 50,000 IU causes symptomatic improvement.[13,14]

Vitamin E has been also studied for its role in the treatment of OSMF. The efficacy of vitamin E was attributed to its antioxidant property. Reddi suggested that Vitamin E given concomitantly with the Hyalase and betamethasone was better than as compared with Hyalase and betamethasone alone. It works by preventing oxidation of essential cellular constituents, Protection against various drugs, metals & chemicals and acts as a scavenger of Free Radical. It may improve the survival of Erythrocytes.[15]

It is believed that Vitamin C reduces oedema between the collagen bundles and helps in regeneration of new collagen bundles with good approximation. In a study conducted by Singh et al., Vitamin C given in combination with placentrax and liver extract gave better results than the institution of vitamin C alone.[16] Several minerals also have been used as an adjunctive in the treatment of OSMF. Zinc plays an essential role in DNA synthesis and cell division. Zinc administered in combination with vitamin A gave good results. Apart from zinc, Magnesium also plays an essential role in many enzyme reactions and exerts stabilizing effects on excitable membranes.[8]

Lycopene:

It is used as the first line of therapy in the initial management of Oral Submucous Fibrosis. It is a carotenoid that gives the tomato its bright red colour; it accounts for 50% of the carotenoids in human serum. It is manufactured by the Lyc-O-Mato™ process and retains its natural proportions

with other compounds in the marketed pharmacological preparations. It exhibits the highest physical quenching rate constant with singlet oxygen. It has been shown to have several potent anti-carcinogenic and antioxidant properties and has demonstrated profound benefits in precancerous lesions.[17] Lycopene (16mg) advocated by Kumar provided a better response. A study conducted by Gupta et al., have advocated one tablet of antitoxin thrice daily for 6 weeks for improvement and amelioration of the symptoms.18 Also, it has been found to inhibit hepatic fibrosis in rats as well as human fibroblast activity in vitro. It also upregulates lymphocyte resistance to stress and suppress the inflammatory response.[8,17]

Spirulina:

It is the highest protein food- over 60% all digestible vegetable protein. It has the highest concentration of beta carotene, vitamin B-12, iron and trace minerals and the rare essential fatty acid. Spirulina is the richest Beta Carotene food with a full spectrum of ten mixed carotenoids. About half of them are orange carotenes (alpha, beta and gamma) and half are yellow xanthophylls. They work synergistically at different sites in our body to enhance antioxidant protection.[19,20]

Turmeric:

Turmeric has been found to inhibit many disease processes through their anti-inflammatory, antioxidant and anticancer properties. In addition, Curcuminoids isolated from turmeric has been found to have effective antioxidant, DNA- protectant and antimutagen action. It was observed that turmeric is given in any form, i.e., alcoholic extracts of turmeric, turmeric oil and turmeric oleoresin were all effective in decreasing the number of micronucleated cells (which are found to be increased in exfoliated oral mucosal cells and circulating lymphocytes of precancerous oral lesions) both in exfoliated oral mucosal cells and in circulating lymphocytes.

According to one study, the usage of turmeric oil daily for 3 months had a beneficial role in the treatment of OSMF. In addition, Deepa Das et al. found that turmeric dispensed in the form of curcumin and turmeric oil was effective in the treatment of OSMF which was evident by the positive changes observed in the histopathological examination after treatment along with the significant improvement in clinical signs and symptoms.[8]

Hastak et al. conducted In vitro study on the effect of alcoholic extracts of turmeric (TE), turmeric oil (TO) and turmeric oleoresin (TOR), on the incidence of micronuclei (Mn) in lymphocytes from normal healthy subjects. There was no associated increase in the number of Mn as compared with those found in untreated controls. All three compounds offered protection against benzo[a]pyrene induced increase in Mn in circulating lymphocytes. Patients suffering from submucous fibrosis were given a total oral dose of TO (600 mg TO mixed with 3 g TE/day), TOR (600 mg+3 g TE/day) and 3 g TE/day as a control for 3 months. It was observed that all three treatment modalities decreased the number of micronucleated cells both in exfoliated oral mucosal cells and in circulating lymphocytes. TOR was found to be more effective in reducing the number of Mn in oral mucosal cells.[21]

Milk:

Free milk contains a small amount of vitamin A, vitamin C, vitamin B1, Vitamin B2, Vitamin B 6, Vitamin B 12, Nicotinic acid, pantothenic acid, folic acid, iron, copper and zinc. Immune milk has anti-inflammatory components and modulates cytokine production.8 Tai et al., (2001) advocated 45 gms of immune milk powder twice a day, for 3 months and observed a regression of concomitant leukoplakia and erythroleukoplakia in addition to significant improvement in symptoms of OSMF.[14]

Aloe Vera: Compounds extracted from Aloe Vera have been used as an Immunostimulant that aids in fighting cancers in Cats and Dogs. Use of aloe vera for the treatment of OSMF is still under research.

Corticosteroids:

OSMF is always associated with the juxta-epithelial inflammatory response. The use of corticosteroids suppresses inflammatory response by their anti-inflammatory action. It prevents fibrosis by decreasing fibroblastic proliferation and deposition of collagen. Corticosteroids can be administered as a local injection (intralesional injection), topical

applications or in the form of mouth washes. Widely used preparations are dexamethasone, 4 mg biweekly injection, for a period of 10 weeks. Betamethasone (Betnesol) 0.5 mg mouthwash is given to relieve pain and burning sensation, for topical application triamcinolone 0.1% is given for relief of pain and burning sensation. Sinha and Jain have found that local injection of hydrocortisone 1.5 cc to be effective. Moreover, Kakar et al., found that injection of Dexamethasone (4 mg) and 1500 IU of hyaluronidase locally for 7 weeks gave superior results if it is followed by 3 weeks of hyaluronidase. [9,22]

Enzymes:

Experimental studies revealed that collagen altered in vivo is susceptible to fibrinolytic enzymes such as hyaluronidase, trypsin and elastase (Satyavathi, Sirsat, Year). Intralesional injection of Hyalase (Rallis India) used in the dose of 1500 IU and Chymotrypsin (Walter Bushnell India) 5000 IU are found to be effective. Hyaluronidase is known to break down hyaluronic acid, lower the viscosity of the intercellular cement substance and also decreases collagen formation. Fibrinolytic agents (Hyalase) were found to be acceptable by patients when it was dissolved in 2% lignocaine and used in the injection. Better results were obtained when a combination of steroids and a fibrinolytic agent was used vis-à-vis a single agent.[23] Collagenase and chymotrypsin are the enzymes that have shown good results in the treatment of OSMF. Collagenase is a lysosomal enzyme, Lin and Lin found that intralesional injection of collagenase resulted in significant improvement. Chymotrypsin, an endopeptidase is used as a proteolytic and anti-inflammatory agent in the treatment of OSMF. Gupta and Sharma (1988) injected Chymotrypsin (5000 IU), hyaluronidase (1500 IU) and dexamethasone (4 mg) twice weekly for 10 weeks submucosally and observed good results.[22]

Placental extract:

The action of the placental extract is essentially biogenic stimulation and its use is based on the tissue therapy method. According to this theory when animal and vegetable tissues are severed from the parent body and exposed to unfavourable conditions, but not mortal to their existence, undergo biogenic readjustment leading to the development of substance in the state of their survival. Such tissues or their extracts when implanted or injected into the body after the resistance of pathogenic factors stimulate metabolic or regenerative process thereby favouring recovery.

The injection placentrax is an aqueous extract of human placenta. The rationale for using Placental Extract (PE) in patients with OSMF derives from its proposed Anti-inflammatory effect, thereby preventing fibrosis by decreasing fibroelastic proliferation & deposition of collagen. It contains Nucleotides- Ribonucleic acid (RNA) & Adenosine Triphosphate (ATP), Enzymes- Alkaline & Acid Phosphatase, Glutamic oxaloacetic acid Transaminase, Glutamic acid, Pyruvic acid, Vitamins- vitamins E, B1, B2, B6, B12, Pantothenic acid, Biotin, PABA & Folic acid, choline, inositol. Amino- acid: alanine, asparagine, asparagine acid, cysteine, glycerine, histidine, leucine, lysine, phenylalanine, tryptopane, tyrosine, valine. Steroids: 17 ketosteroids, cholestrin, cholesterol. Fatty acids- Linolenic acid, Palmitic acid, Trace elements- Copper, Selenium & Magnesium. Dose- Intralesional Injection Of 2ml of PE solution can be given.[20] Ramanjaneyalu and Prabhakar Rao (1980) advocated 2 cc placentrax injection at weekly interval for 10 weeks. They have found it to be superior to Cortisone. Also, two cortisone resistant cases responded well to placentrax.[24] Furthermore Katharia et al., (1992)25 also carried out a study on 22 OSMF patients and injection of 2ml Placental extract (Inj. Placentrex) was given locally in the predetermined areas, once a week up to a total duration of one month. Effects were monitored in reducing the severity of the disease. The combination of dexamethasone, hyaluronidase and placental extract was found to give better results than with a single drug.

Interferon-gamma:

This plays a role in the treatment of patients with OSF because of its Immunoregulatory effect. IFN-gamma is a known Anti-Fibrotic Cytokine. Patients treated with an Intra-lesional injection of IFN-gamma experienced improvement of symptoms. IFN-gamma, through its effect of altering collagen synthesis, appears to be a key factor to the treatment of patients with OSF, and intra-lesional injections of the cytokine may have a significant therapeutic effect on OSMF (Haque, 2001). [13]

Table 1: Treatment modalities of OSMF.

| Treatment | Treatment details |
|---|---|
| Micronutrients | Vitamin A, B complex, C, D |
| and minerals | and E, iron, copper, calcium, |
| | zinc, magnesium, selenium |
| | and others |
| Milk from | 45 g milk powder twice a |
| immunized cows | day for 3 months |
| Lycopene | 8 mg twice a day for 2 months |
| Pentoxyfilline | 400 mg 3 times a day for |
| | 7 months |
| Interferon gamma | Intralesional injection of |
| | interferon gamma (0.01– |
| | 10.0 U/mL) 3 times a day for |
| | 6 months |
| Steroids | Submucosal injections twice |
| | a week in multiple sites for |
| | 3 months |
| Steroids | Topical for 3 months |
| Hyalase + | — |
| dexamethasone | |
| Placental extracts | — |
| Turmeric | Alcoholic extracts of turmeric |
| | (3 g), turmeric oil (600 mg), turmeric oleoresin (600 mg) daily for 3 months |
| Chymotripsin, | Chymotripsin (5000 IU), |
| hyaluronidase and | hyaluronidase (1500 IU) and |
| dexamethasone | dexamethasone (4 mg), |
| | twice weekly submucosal |
| | injections for 10 weeks |

Vasodilator:

Occlusive blood vessels encountered in OSMF restrict nutrients and therapeutic substances from reaching the affected tissue, which may be one of the reasons for the unsatisfactory therapeutic effect of drug treatment of OSF. Thus vasodilators are used in the therapy of OSMF.[26]

Lai (1995) observed positive results while treating OSMF using buflomedial HCL (3 tablets of 450 mg each per day) and topical triamcinolone acetonide

0.1% on mucosal ulcers at bedtime. Buflomedial HCL (peripheral vasodilator) has been found to affect the tissues in diffuse fibrosis to a noticeable degree by the relief of local ischemic effect. [27]

Pentoxifylline is a methylxanthine derivative with vasodilating properties. It has an effect of increase mucosal vascularity. Improvement in OSMF is recorded with the help of pentoxyphylin in terms of improvement in mouth opening, tongue movement and decrease in fibrous bands. Rajendran (2006) administered as 400 mg thrice daily for a period of more than 12 months and observed improvement in symptoms of OSMF. Fibroblasts cultured in the presence of pentoxifylline produce twice as much collagenase activity and decreased amount of collagen, glycosaminoglycans and fibronectins. IL-1 induced fibroblast proliferation was inhibited by the addition of pentoxifylline.[7] Levamizole: Administration of immune-modulator which modifies both cellular and humoral immunity. Administration of Tab. Levamisole 50 mg results in a significant reduction in IgG, IgA and IgM.

Physiotherapy:

Oral Physiotherapy in the form of muscle stretching exercises for the mouth may be helpful to prevent further limitation of mouth movements. This includes blowing balloons, hot water gargling, forceful mouth opening with the help of sticks etc. This exercise put pressure on the fibrous bands. Forceful mouth opening has been tried with mouth gag & acrylic surgical screw. Also, Cox and Zoellner (2009) advocated five times daily physiotherapy by inter- positioning tongue spatulas between teeth and adding a new spatula every 5–10 days for 4 months and observed improved oral opening.[7,28]

Microwave diathermy:

Microwave diathermy (Low current is used 20 watts × 2450 cycles) is useful in some early or moderately advanced stages. It acts by Physio-Fibrinolysis of bands. Microwaves are quasi-optical and are applied by radiation. It, therefore, produces sharp localized deep heat without excessive heating of the skin and other subcutaneous tissues such as fat and is thus simple to apply with minimum discomfort.8 Gupta et al., (1980) advocated diathermy daily for 20 minutes at each site of lesion with 20 -25 watts of energy to produce comfortable warmth. Such 15 sittings were given to each patient and found valuable for the moderately advanced stage of OSMF.[29]

Other Therapies: Injection of Gold, Vitamin A & Collagenase, Vasodilator injection can be used in the management of OSMF. Chemotherapeutic agents like the topical application of Bleomycin can also be used in severe cases.[8]

Combined Therapy: With peripheral vasodilators (nylidrin hydrochloride), vitamin D, E & B complex, iodine, placental extract, local & systemic corticosteroids & physiotherapy claim a high success rate in oral submucous fibrosis management.[8]

Surgical Management:

Surgical treatment is indicated in patients with Severe Trismus and/or biopsy results revealing Dysplastic or Neoplastic changes. Surgical modalities that have been used include, Simple excision of the fibrous bands, Excision can result in contracture of the tissue and exacerbation of the condition. Split-thickness Skin Grafting following bilateral Temporalis Myotomy or Coronoidectomy. Trismus associated with OSMF may be due to changes in the Temporalis Tendon secondary to OSMF; therefore, skin grafts may relieve symptoms. Nasolabial Flaps and Lingual Pedicle Flaps, Surgery to create flaps is performed only in patients with OSMF in whom the tongue is not involved.[30]

Laser: CO2 laser surgery offers an advantage in Alleviating Functional restriction. ErCr:YSGG laser has utility in both hard and soft tissue procedures as the hydro-photonic process allows it to out-perform other conventional modalities in many ways. Choudhary et al. (2011), reported with pioneering effort in treating a moderate case of bilateral OSMF with Erbium Chromium Yttrium Scandium Gallium Garnet (ErCr:YSGG) laser showing promising result during follow-up.[8]

Cryosurgery:

It is the method of local destruction of tissue by freezing it in situ. Extreme cold is produced by liquid nitrogen or argon gas to destroy abnormal tissue. liquid sprays are better suited for the mucosal lesion. liquid nitrogen or argon gas is circulated through a hollow instrument called a

cryoprobe, which is placed in contact at the affected region. The operator uses an ultrasound or MRI to guide the cryoprobe and monitor the freezing of the cells, thus limiting damage to nearby healthy tissue. the frozen tissue thaws and is either naturally absorbed by the body, or it dissolves and forms a scab.[8]

POSSIBLE THERAPEUTIC INTERVENTIONS FOR OSF:

Some of the possible interventions suggested based on the pathway involved include (1) blocking the chronic inflammatory process by anti-inflammatory/immuno-modulatory drugs; (2) blocking TGF-b action by anti-TGF-b antibodies or peptide mimetics of soluble TGF-b receptors; (3) copper chelators like penicillamine to block LOX activity and prevent cross-linking; (4) other anti-LOX drugs that prevent its action; (5) collagenase activators like colchicine to promote collagen degradation. Probably a combinational therapy of the above-mentioned drugs thereby intervening at multiple points along the pathway might be useful for the successful treatment of Oral Submucous fibrosis.

## CONCLUSION

It appears quite clear that OSMF is a multifactorial disease, as is the case with oral cancer and most other precancerous lesions. This enigmatic condition needs awareness about the adverse effects of the use of areca nut and allied products. OSMF is considered among the high-risk PMD that progress into cancer. An atrophic mucosa is more likely to undergo malignant transformation and the rate of OSMF converting into malignancy is 4.5–7.6%. Thus there is a sustainable need for developing treatment modalities for OSMF to improving the quality of life of the patients suffering from the condition.

## CONFLICTS OF INTEREST

The authors declare they have no potential conflict of interests regarding this article.

## REFERENCES

1. Anand R, Pradhan R. Surgical management of submucous fibrosis. Ind J Dent Res 1994;1(4):3.

2. Patidar KA, Parwani RN, Wanjari SP. Correlation of salivary and serum IgG, IgA levels with total protein in oral submucous fibrosis. J Oral Sci 2011;53(1):97–102.

3. Pundir S, Saxena S, Aggrawal P. Oral submucous fibrosis disease with malignant potential – report of two cases. J Clin Exp Dent 2010;2(4):215–8.

4. Ahmad MS, Ali SA, Ali AS, Chaubey KK. Epidemiological and etiological study of oral submucous fibrosis among gutkha chewers of Patna, Bihar, India. J Indian Soc Pedod Prev Dent 2006 June;24(2):84–9.

5. More C B, Das S, Patel H, Adalja C, Kamatchi V, Venkatesh R, Proposed clinical classification for oral submucous fibrosis, Oral Oncology 48 (2012) 200–202.

6. More CB, Asrani M, Patel H, Adalja C. Oral submucous fibrosis-a hospital-based Retrospective study. J Pearldent 2010; 1(4):25–31.

7. Tadakamadla J, Kumar S Mamatha GP, Non-invasive management of Oral submucous fibrosis: a review, Journal of Oral Health Research, Volume 2, Issue 1, January 2011, 1-7.

8. Taneja L, Nagpal A, Vohra P, Arya V, Oral submucous Fibrosis: An oral physician approach, Journal of Innovative Dentistry, Vol 1, Issue 3, Sept-December 2011.

9. Chole RH et al. Review of drug treatment of oral submucous fibrosis, Oral Oncology 48 (2012) 393–398.

10. Lavina T, Anjana B and Vaishali K. Haemoglobin levels in patients with oral submucous fibrosis, JIAOMR 2007, 19:02,329–333.

11. Garewal HS. Response of oral leukoplakia to beta carotene. J Clin Oncol. 1990;8, 1717-20.

12. Maher R et al, Evaluation of multiple micronutrient supplementation in the management of oral submucous fibrosis in Karachi, Pakistan. Nutr Cancer. 1997; 27:41-7.

13. Haque MF, Meghji S, Nazir R and Harris M, Interferon gamma may reverse oral submucous fibrosis. J Oral Pathol Med Jan 2001, 30: 12 -21.

14. Tai YS, Liu BY, Wang J.T., Sun A. , Kwan H. W. and Chiang C.P. Oral administration of milk from cows immunised with human intestinal bacteria leads to significant improvements of symptoms and signs in patients with oral submucous fibrosis . J Oral Pathol Med 2001, 30: 618 -25

15. Reddi R. Oral Submucous Fibrosis - A recent trend in its treatment. JIAOMR.1993; 4: 7-8.

16. Singh N, Singh J, Singh U. Oral Sub Mucous Fibrosis. A New Approach to treatment with combined therapy. J Indian Dent Assoc. 1996; 67: 168-70.

17. 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.

18. Gupta S, Reddy MVR, Harinath BC. Role of oxidative stress and antioxidants in aetiopathogenesis and management of oral submucous fibrosis. Indian J Clin Biochem. 2004; 19: 138-41.

19. Textbook of Oral Medicine & Radiology, Ghom A, Chapter Premalignant lesion.

20. More C, Thakkar K. Oral submucous fibrosis-An insight. J Pearldent 2010;1(3).

21. Das A, Balan A, Sreelatha KT, Comparative Study of the Efficacy of Curcumin and Turmeric Oil as Chemopreventive Agents in Oral Submucous Fibrosis: A Clinical and Histopathological Evaluation, Journal of Indian Academy of Oral Medicine and Radiology, April-June 2010;22(2):88-92

22. Gupta D, Sharma SC. Oral submucous fibrosis – A new treatment regimen. J Oral Maxillofac Surg 1988; 46: 830–3.

23. Kakar PK, Puri RK and Venkatachalam VP. Oral submucous fibrosis- treatment with hyalase J Laryngol Otol 1985, 99 :57 -59

24. Ramanjaneyulu P, Prabhakar R. Submucous Fibrosis: New Treatment. J Indian Dent Assoc.1980; 52: 379-80.

25. Katharia SK, Singh SP, Kulshreshtha VK. The effects of placental extract in management of oral submucous fibrosis. Indian J Pharmac. 1992; 24: 181-3.

26. Jing Hu, Xiaowen Jiang. Drug Treatment of Oral Submucous Fibrosis: A Review of the Literature. J Oral Maxillofac Surg. 2009;67:1510-5.

27. Lai DR, Chen HR, Lin LM, Huang YL, Tsai CC. Clinical evaluation of different treatment methods for oral submucous fibrosis. A 10-year experience with 150 cases. J Oral Pathol Med. 1995;24:402-6.

28. Cox S, Zoellner H. Physiotherapeutic treatment improves oral opening in oral submucous fibrosis. J Oral Pathol Med. 2009;38:220-6.

29. Gupta DS, Gupta MK, Golhar BL. Oral submucous fibrosis-Clinical study and management by physiofibrolysis (MWD). J Indian Dent Assoc. 1980; 52:375-8.

30. Sunil M K, Oral Submucous fibrosis: A Review, BFUDJ, Volume 1, number 1, July, 2010, 30-34.