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VARIOUS TREATMENT MODALITIES IN ORAL SUBMUCOUS FIBROSIS: A REVIEW OF LITERATURE

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ABSTRACT:
Oral submucous fibrosis is a persistent, pre-cancerous condition of the oral mucosa, which is related with betel quid chewing habit. OSMF is strongly connected with the risk of oral cancer. Hence, it is very important to treat and manage OSMF in early stages. The purpose of this review was to highlight various treatment modalities for OSMF with little emphasis on clinical and histopathological features of OSMF. Various types of treatment modalities include conservative methods, medical management, and invasive methods like surgical elimination of the fibrotic bands and combined therapy. Our review of the literature for treatment of OSMF yielded a spectrum of treatment modalities to manage OSMF. Recent literature proves that the combination of drugs produces effective results in the management of OSMF. However, a more extensive clinical trial is necessary to come to a final conclusion about a particular treatment modality in managing OSMF.

INTRODUCTION:

Oral submucous fibrosis was first described by Schwartz in 1952 in modern literature. Whereas, it was described by shushruta for the very first time in Indian Medical Literature. Schwartz coined the term 'Idiopathictropica mucosa oris'[1]. Term Oral submucous fibrosis was given later by Joshi in 1953.[2] Prevalence of OSMF in Indian subcontinent was found to be 0.2-0.5% by Pindborg et al. and a recent study showed that it had increased from 0.03% to 6.42%[3]. OSMF is

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mainly seen in countries like India, Bangladesh, Sri Lanka, Pakistan, Taiwan, and China[4]. It is more common in younger generation due to advent of commercially freeze dried areca nut products.

Pindborg and Sirsat defined it as "one of an insidious, chronic disease that affects any part of the oral cavity and sometimes the pharynx. Although occasionally preceded by, or associated with, formation of vesicles, it is always associated with juxtaepithelial inflammatory reaction followed by fibroelastic change of the lamina propria and epithelial atrophy that leads to stiffness of the oral mucosa and causes trismus and as inability to eat." WHO defined it as "a generalized pathological state of the oral mucosa associated with significantly increased risk of cancer."

High morbidity in OSMF pertains to its progressive inability to open the mouth which results in nutritional deficiencies and significant mortality rate is because it can transform into oral cancer, particularly squamous cell carcinoma, at a rate of 7.6%[5].

As an initial symptom patient complains of burning sensation while eating hot and spicy foods. Clinically the disease is marked by remission and relapses of vesicles, ulcer formation, blanching and pigmentation of oral mucosa, altered salivary flow, de-papillation of tongue, oral mucosa getting stiffed, progressive difficulty in mouth opening along with difficulty in phonation[6].

AETIOPATHOGENESIS:

Initially in 1952 it was considered as an idiopathic disorder. Later, various studies indicated that it had a multifactorial originwhich was associated with consumption of areca nut[7]. Local irritants including tobacco, cigarette, smoke, betel nut and pan chewing, chillies plays are associated with the pathogenesis of the disease. However, areca nut quid is considered to have a prime role in etiology of OSMF. Areca nut contains high copper content and so saliva of areca nut chewers will have high amount of soluble copper. In OSMF patients,lysyl oxidase remains unregulated which is a copper depending enzyme that plays a vital role in collagen synthesis and its cross linking will lead to OSMF.

Arecoline, which is a constituent of areca nut is responsible for fibroblastic proliferation and synthesis of collagen. Constituents like tannins and catechin are responsible for stabilizing the collagen fibrils which renders them resistant to degradation by collagenase. Capsaicin, which is active extract from chillies is also proved to be responsible.

Studies in the past have suggested that occurrence pertains to:

1. By fibroblast proliferation and synthesis of collagen by areca nut alkaloids[8]
2. Clonal section of fibroblast showing high amount of collagen production due to long term exposure to areca nut ingredients[9].
3. By reduced secretion of collagenase[10]
4. Reduced collagen phagocytosis[11]
5. By stabilization of collagen structure from the areca nut[12].
6. Effect of fibrogenic cytokines secreted by activated macrophages and T lymphocytes on fibroblasts[13].

CLINICAL FEATURES:

Angadi et al. outlined that patient having habits with duration of 2-5 years were more likely to develop OSMF. Mostly affected area was posterior one-third of the oral cavity[14]. Highest occurrence of habits was in the range of 5-6 times/day (42.5%) while many patients also had a frequency >10 times/day.

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The window between commencement of chewing habit and advance of clinical symptoms of OSMF varies widely that may range from a few months to several decades depending on type of areca nut consumed. Burning sensation, blanched oral mucosa, ulcer formation, reduced salivary flow. During the later stages, oral mucosa becomes stiff due to presence of the fibrous bands on the buccal mucosa, tongue, lips, soft palate which would limit mouth opening that would hamper mastication, speech and swallowing[15].

Progression of these bands in the lips would make the lip bulky and would make the retraction or eversion hard. Tongue will be depapillated on the tip and lateral margins along with blanching or fibrosis of ventral mucosa. Shrunken uvula is present in 17% of the cases with a small bud or hockey stick appearance[16].

HISTOPATHOLOGICAL FEATURES:

Mostly the cases illustrate atrophy of the epithelium along with loss of rete ridges. There is fibrosis of collagen fibres seen in the lamina propria along with chronic inflammatory cell infiltrate. Later stages demonstrate hyalinization along with atrophic changes in skeletal muscle.

TREATMENT MODALITIES:

This is a progressively disabling condition with high malignant potential. Until now, there is no efficient treatment available. It is thus, a challenge for an oral surgeon.

Different treatment modalities include:

i) Conservative
ii) Medical
iii) Surgical

(I) Conservative:

It can be subcategorized into habit restriction, nutritive therapy and oral physiotherapy.

a. Habit restriction:

A study has demonstrated decrease in the risk of OSMF as a consequence of educating against chewing habits. A drop from 21.3/100,000 to 8.3 among men in intervention cohort and from 45.7 to 29.0 among women in control cohurt was assessed. This showed decreased risk with decline in habit.Patients should be explained about consequences of the disease and associated possibility of malignancy. Full motivation should be given to patients diagnosed at later stages.

b. Nutritive therapy:

Efficient vitamins and minerals include vitamin A, B, C, D, and E, iron copper, calcium, zinc, magnesium, selenium. Consumption of red tomatoes, fresh fruits, green leafy vegetables rise the level of antioxidants that would protect against increased risk of cancer. Tomatoes contain lycopene that has anti-carcinogenic and antioxidant properties. Lycopene reduces hepatic fibrogenesis and is thought to exert likewise inhibition on abnormal fibroblasts in OSMF[17]. Green tea which is rich in polyphenols with its scavenging property will protect the cells from DNA damage which is caused by reactive oxygen species. Skimmed milk which is formed from cows are loaded with human intestinal bacterial flora. It has got anti-inflammatory effect. IgG antibody present in this immunized milk will restrain the inflammatory reaction and modulate cytokine assemblage in OSMF patients[18].

c. Physiotherapy:

Physiotherapy within its physiological limits has given remarkable results. Various forms include splints, devices and exercise regimen. Cox and Zoellner favoured physiotherapy by insertion of

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tongue spatulas between the teeth and adding a new spatula every 5-10 days for 4 months. This proved effective[19].

d. Microwave diathermy:
Lukewarm water, selective deep heating techniques like shortwave and microwave diathermy are efficiently used. They cause fibrinolysis of bands. Microwave diathermy would specifically heat only juxta-epithelial connective tissue and limits the area of treatment. Thus, makes it easier to apply with minimum discomfort. Gupta et al. suggested diathermy for 20 minutes with 20-25 watts of energy at every site of the lesion. 15 sittings of such treatment were found too very helpful and effective.

(II) Medical:
Includes various options such as:
a. Hyaluronidase, dexamethasone and placental extract: **Kakar et al**. conducted a study in 1985 wherein 96 patients with OSMF received 4 regimens of treatment that included local dexamethasone, local hyaluronidase. Local combination of dexamethasone, hyaluronidase, and local placental extract. The group that received hyaluronidase alone showed faster improvement but combination with dexamethasone gave better results[21].
b. Triamcinolone acetonide: A series of 100 patients was presented by **Khanna J.N** in 1995 where in very early cases were treated with triamcinolone acetonide(40mg). This gave a good result with increased mouth opening[22].
c. Collagenase: **Lin H-J etal** conducted a study regarding effectiveness of 1ml collagenase which was mixed with 1ml xylocaine. This proved to be better since there was drastic reduction in hypersensitivity to hot and spicy food along with increased with oral opening[23].
d. Interferon gamma: Intralesional IFN-g proved to be effective in mouth opening. Interincisal distance before treatment of 21±7 mm, to 30±7 mm immediately after treatment and 30±8 mm 6-months later, giving a net gain of 8±4 mm (42%) (Range 4–15 mm)[24].
e. Anti TGF beta drugs: TGF-beta which is an important cytokine plays a vital role in initiation of OSMF which was studied by **Rajlalitha P.** Hence, its effect was nullified by administration of anti-TGF beta drugs[25].
f. Levamisole and beta carotene: **Jirge et al**. conducted a study with levamisole 50mg thrice a day for three alternate weeks and reported improvement by 7.1% that further inclined to 10.7% in upcoming months. Beta-carotene which is a precursor of vitamin A was given for 6 weeks, 2 capsules daily which demonstrated 6.7% increase in mouth opening.[26].
g. Stem cell therapy: Decrease in blanching, improved elasticity of mucosa, reduced burning sensation while eating hot and spicy food along with increased mouth opening was demonstrated by **Sankarnarayanan et al**. in his study of stem cell treatment in OSMF[27].
h. Colchicine: **Krishnamoorthy B** conducted a study of 50 patients who received oral form of colchicine, 0.5mg two times a day, daily reported early decrease in burning sensation along with improvement in movement of the tongue.[28].
i. Pentoxyfilline and spirulina: A study conducted by **Bhavana s.** with 40 patients which was divided into 2 groups where in 1st received pentoxyfilline and 2nd received spirulina. The results portrayed that the group receiving spirulina gave better results[29].
j. Nylidrine hydrochloride: **Sharma et al.** studied with 56 cases wherein he used nylidrine hydrochloride in tablet form with dose of 6mg for 3-8 weeks combined with conventional management gave a success rate of 62.07%.[30]

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k. According to a recent study conducted by **Datarkar et al.**[20] Prednisolone mouth wash (topical corticosteroids) have proved to be reliable in treating all symptoms of OSMF and gives a significant relief from trismus.

(III) Surgical:
a. Surgical resection of fibrotic bands and split thickness skin graft
b. Palatal island flap
c. Nasolabial flap
d. Artificial dermis
e. Radial forearm flap
f. Buccal fat pad
g. Superficial temporal fascia flap
h. Anterolateral thigh flap
i. Tongue flap
j. Platysmal flap
k. Submental Flap
l. Laser

a.) Surgical resection of fibrotic bands and split thickness skin graft:

Release of fibrous bands is effective in increasing interincisal opening but it also requires aggressive physiotherapy to get sustained results. Surgical release often leaves a huge soft tissue defect which if left to heal by secondary intention, often tends to contract and result in relapse. Therefore, **Yen et al.**[31] in 1982 suggested the use of split thickness graft to show satisfactory result with decrease in trismus and improve in elasticity of buccal mucosa.

b.) Palatal island flap:

In 1995, **Khanna et al.**[22] gave the technique to utilize palatal island flap bilaterally to cover the exposed area. He used it in combination of bilateral coronoidectomy and temporalis myotomy. In his study there was considerable increase in mouth opening (Postoperative mouth opening- 43-45 mm) from preoperative mouth opening (3-25 mm). Rejection or necrosis of flap was not found.

c.) Nasolabial flap:

Kavarna et al.[32] 1987, used bilateral, full thickness nasolabial flap successfully in 3 patients. The flap was used to reconstruct the defect created after release of fibrous bands and a long-term release of trismus was seen in all the patients. In 2008, Borle R.M[33]. evaluated nasolabial flap in 47 patients with OSMF. Preoperative mouth opening was in the range of 3-23 mm which improved to 23-55 mm.

d.) Artificial Dermis:

Omural S. et al.[34], in 1997 used the membrane as it was first described by **Yannas et al**. who developed first collagen-based bilayer membrane. This membranewas placed in the mucosal defects,of 5 patients, created after treating patients from cancer. In all the cases postoperative healing was effective.

e.) Radial forearm flap

Lee et al.[35], treated a total of 10 patients with advanced OSMF with radial forearm flap. The postoperative mouth opening increased to 28.2 mm from preoperative mouth opening which was 2.3 mm after a mean of 21 months follow up. Hence mean increase by the end of the study was 25.9 mm.

f.) Buccal fat pad

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Kothari et al[36], and sharma et al.[37] used BFP in treating OSMF and found it reliable. Mehrotra et al.[38], included total of 100 patients with advanced OSMF and divided randomly into 4 groups with 25 patients in each. After initial release of fibrous bands, in Group I patients he used BFP as reconstructing material, in Group II he used Tongue flap, in Group III he used Nasolabial flap and in Group IV he used Split thickness graft. She concluded that buccal fat pad rotation is superior to other procedures, because it offers ease of surgery, can be performed under local anesthesia as a day care procedure, shows little postoperative morbidity, and has good patient acceptance, and there appear to be no contraindications to its use.

g.) Superficial temporal fascia flap:

Mokal et al.[39] used Superficial temporal fascia flap in his study and achieved interincisal mouth opening of 45 mm on release of mucosa, masseter and temporalis insertion. No graft loss was seen in his study.

h.) Anterolateral thigh flap:

Wei-chen C[40], successfully used bipaddled ALT perforator flap in 2 patients for reconstruction of the surgical defect created after the release of fibrous bands in OSMF patients.

i.) Tongue flap:

Tepan et al.[41] in 1986 successfully used tongue flap in 25 patients with good results and without any complication. **Golhar et al**.[42] used tongue flap in 1987 in 21 patients and had maximum follow up period of 3 years. The postoperative mouth opening achieved was 20-40 mm in comparision to preoperative mouth opening which was 10 mm.

j.) Platysmal flap:

Satyanarayanan et al[43], in 2015 used platysmalmyocutaneous flap for the reconstruction of surgical defect created after release of fibrous bands in 10 patients with OSMF. In his study, no flaps failed and all patients had overall good cosmetic results.

k.) Submental Flap:

Martin et al[47]., in 1993 first described Submental flap for reconstruction in head and neck defects. **Gadre et al[48]**. described an innovative modification submental flap based on concept of bilateral presence of facial and submental vasculature which thus can be used for bilateral cheek defect after release of fibrous bands in grade IV OSMF.

l.) Laser:

Arpit S[44] and Utkarsh L[45], suggested the use of Diode laser in their study. **Zainab C**[46], included 16 patients with moderate OSMF and used Erbium Chromium Yttrium Scandium Gallium Garnet (ErCr:YSGG) laser for fibrotomy under Local anesthesia in combination with topical steroids, lycopene and physiotherapy. Mean increase in mouth opening at the end of 1 year follow up was 17.5 mm. Advantages of using lasers in treating OSMF were the charred tissue obtained after excision of bands provided a protective environment for the incised raw areas until the initial healing took place, resulting in less scar-tissue formation.

CONCLUSION:

This review of literature succumbed wide spectrum of various treatment modalities of OSMF. So far, an exclusive treatment of OSMF is not used. All the recent literature has shown that combination of nasolabial flap along with certain drugs has been proven more effective in management of the disease. Spreading awareness and educating people regarding the disease in early stages is much needed. A more considerable clinical trials with greater number of cases involved, including various other parameters are required to come to a final conclusion.

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