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RESEARCH ARTICLE

AN APPROACH TO MANAGEMENT OF ORAL SUBMUCOUS FIBROSIS: CURRENT STATUS AND
REVIEW OF LITERATURE

¹Dr. Ramesh Ram Fry, ²Dr. Samta Goyal, ¹Dr. Pavneet Kaur Pandher and
^{*1}Dr. Jatinder Pal Singh Chawla

¹Department of Oral and Maxillofacial Surgery, M.M. College of Dental Sciences and Research, MMU, Mullana

²Department of Oral and Maxillofacial Surgery, Saraswati Dental College, Lucknow

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ABSTRACT

Oral submucous fibrosis is a chronic inflammatory disease that results in progressive juxtaepithelial fibrosis of the oral soft tissues that can cause increasing difficulty in chewing, swallowing, speaking, and mouth opening. Many treatment regimens for oral submucous fibrosis have been proposed to alleviate the signs and symptoms of the disorder. In severe cases, surgical intervention is the only treatment modality, but relapse is a major problem. Even after 6 decades of its description as a separate entity, no concrete treatment is available due to its multi-modal pathogenesis. Thus, adding to the morbidity associated with it. Current article is an attempt to compile the available treatment aids, their current status and future perspectives, so as to aid early intervention of the disease.

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INTRODUCTION

It is 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 (Pindborg and Sirsat 1966).

MATERIALS AND METHODS

The intention of this paper is to review the literature regarding various management procedures for OSMF. A literature search was conducted in June 2014. The following key words were used in "science direct" and "Google search".

- OSMF and treatment
- Oral submucous fibrosis and treatment

Only those articles that discussed the therapies for OSMF and review articles were included. All the articles were included irrespective of their study design and level of evidence.

**Corresponding author: Dr. Jatinder Pal Singh Chawla,
Department of Oral and Maxillofacial Surgery, M.M. College of
Dental Sciences and Research, MMU, Mullana.*

Articles that were in English were only considered. Studies on etiology, pathogenesis or prevalence of OSMF and those which were not related to the study purpose were excluded.

RESULTS

The search words "OSMF and treatment" retrieved 14 papers while the search words "Oral sub mucous fibrosis and treatment" retrieved 124 articles from 1965 to 2014. Among the retrieved articles, only 21 articles were related to non-invasive treatment procedures and six articles reviewed the management of OSMF. Two articles were in French and Chinese, 20 papers discussed the surgical interventions and the remaining dealt with etiology, pathogenesis or prevalence of the OSMF

Discussion/Management

- A) Restriction of habits/ Behavioral therapy
- B) Medicinal therapy
- C) Surgical therapy

A) Restriction of habits/behavioral therapy

The consumption of pan, betel nut, chilies, spices and commercially available, pan masalas, guthkas with or without tobacco is increasing in India. So people should be encouraged

to stop these habits. Affected patients should be explained about the disease and possible malignant potential of OSMF. Possible irritants should be removed and nutritional supplements should be prescribed as placebo or an alternative to habit consumption material.

B) Medicinal therapy

Physical therapy

- Physical exercise regimen/ physiotherapy
- Splints or other mouth opening devices
- Microwave diathermy

Medical therapy

- *Modulators of inflammation:*
- Steroids
- Interferon gamma
- Placental extracts
- Immunised milk
- *Modulators of vascularity or relief of ischaemia (Vasoconstrictors)*
- Buflomedil hydrochloride
- Pentoxiphylline

Nutritional support and to combat reactive oxygen species (Antioxidants)

- Beta-carotene
- Lycopene
- Vitamins
- Micronutrients
- Fibrinolysis:
- Collagenase
- Hyaluronidase
- Chymotrypsin
- Ayurvedic treatment: Turmeric (*Curcuma longa* L.) Tea pigments Oxitard
- Aloe Vera

Physiotherapy

Cox and Zoellner (2009) advocated five times daily physiotherapy by interpositioning tongue spatulas between teeth and adding a new spatula every 5–10 days; local injection of hyaluronidase with steroids; or no active treatment. Physiotherapy was to take place without pain, considered a sign of inflammation and potential exacerbation. To reduce discomfort, patients were encouraged to take aspirin (200 mg) or paracetamol (250 mg), 30 minute prior to the exercise. physiotherapy substantially improved oral opening in patients with OSMF. This was consistent with earlier reports where physiotherapy was combined with other treatments in previous studies (Lai *et al.*, 1995; Sharma *et al.*, 1987). Previously, the failure of physiotherapy to address the problem of oral mucosal pain suggests a need to develop and apply a suitable analgesic therapy. Thus, in combination with the physiotherapeutic approach described here may provide a successful strategy for

symptomatic management of OSF, despite continuing uncertainty of the biological basis for the disease.

Splints

Mahajan *et al.* (2010) reported a case of edentulous male patient reported with grade IV OSMF to improve his mouth opening for denture construction. The patient was managed successfully using surgical sectioning of the fibrous bands. Inter occlusal force application for mouth opening during the operation and post operative physiotherapy were facilitated using custom-made occlusal splints. Satisfactory mouth opening was achieved, with good healing and no event of infection or fracture. Here, they propose an easy method to achieve adequate mouth opening in an edentulous patient of OSMF, with atrophic ridges; without the chances of fracture of either jaw. Pravinkumar Patil and Smita Patil (2012) described the fabrication and use of a new mouth-exercising device that helps the patient to squeeze/stretch the cheek mucosa to increase elasticity. The device can be used as a sole treatment modality or can be used in association with pharmacological and surgical treatment modalities for OSMF. Improvement in mouth opening was observed in four OSMF patients treated with a mouth-exercising device for 6 months as a sole treatment modality

Microwave diathermy

Microwaves are quasi optical and are applied by radiation. It therefore produces sharp localized deep heat without undue heating of skin and other subcutaneous tissues such as fat and is thus simple to apply with minimum discomfort. 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.

Steroids

Steroids have therapeutic effects like anti-inflammatory and are well known to act as immunosuppressive agents for the prevention or suppression of fibroproductive inflammation found in OSMF (Lai *et al.*, 1995). Sinha and Jain (1978) have tried local injection of hydrocortisone 1.5 cc and found hydrocortisone to be effective. Kakar *et al.*, (1985) 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.

IFN-gamma

Plays a role because of its immunoregulatory effect. A known antifibrotic cytokine. Through its effect of altering collagen synthesis, appears to be a key factor. Intralesional injections of the cytokine may have a significant therapeutic effect (Haque *et al.*, 2001).

Placental extract

The injection placentrax is an aqueous extract of human placenta. The action of 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 development of substance in the state of their survival. Such tissues or their extracts when implanted or injected into the body after resistance of pathogenic factors stimulate metabolic or regenerative process thereby favouring recovery. Such tissues or their extracts when implanted or injected into the body after resistance of pathogenic factors stimulate metabolic or regenerative process thereby favouring recovery. Katharia *et al.* (1992) 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. 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. They have even found two cortisone resistant cases responded well to placentrax.

Immunized milk

Immune milk contains small amount of vitamin A, vitamin C, vitamin B1, Vitamin B2, Vitamin B 6, Vitamin B 12, Nicotinic acid, panthotenic acid, folic acid, iron, copper and zinc. Immune milk has anti-inflammatory components and modulates cytokine production. 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.

Vasodilators

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 were used in the therapy of OSMF (Jing *et al.*, 2009).

Buflomedil hydrochloride

Lai *et al.* (1995) has carried out treatment for OSMF using buflomedial HCL (3 tablets of 450 mg each per day) and topical trimacetonolone acetone 0.1% on mucosal ulcers at bed time. He observed positive results. Buflomedial HCL (peripheral vasodialator) has been found to affect the tissues in diffuse fibrosis to a noticeable degree by the relief of local ischemic effect

Pentoxifylline

Rajendran *et al.* (2006) used pentoxifylline, a methylxanthine derivative that has vasodialating properties. It was 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.

Antioxidants

It is known that the process of carcinogenesis occurs by generation of Reactive Oxygen Species, which act by initiating

lipid peroxidation (LPO) (Garewal. 1990). 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 Kumar *et al.* (2007) advocated Lycopene (16mg) and concluded that it produced better response. Gupta *et al.* (2004) carried out a study on 34 cases of OSMF. They have advocated one tablet of antoxid thrice daily for 6 weeks and observed improvements and amelioration of the symptoms. Karemore and Motwani (2012) - original-research. Out of 92, 46 patients were given lycopene and remaining 46 were on placebo drug. Lycopene group patients received 8 mg per day in two divided doses of 4 mg each, while placebo group patients received placebo tablet twice a day. Patients were examined for changes in mouth opening and other clinical symptoms of OSMF during three months and were followed up for next two months.

RESULTS

Lycopene was found to be significantly efficacious in the amelioration of signs and symptoms of OSMF. It was effective in reducing the objective signs of OSMF as demonstrated by the improved maximal mouth opening, percentage of which was 69.56%(P<0.05).

Conclusion

Present study concludes that lycopene, a newer antioxidant, appears to be a very promising drug in the management of OSMF

Micro nutrients and minerals

1) Vitamin A

Few studies (Borle and Borle 1991; Balaji Rao 1993) conducted in the previous decade observed that Vitamin A given at a concentration of 50,000 IU would cause symptomatic improvement. It is well evident that vitamin A plays an important role in maintaining normal growth and repair of epithelial tissues.

2) Vitamin E

Vitamin E has been extensively studied for its role in the treatment of OSMF. Reddi (1993) suggested that Vitamin E given concomitantly with the Hyalase and betamethasone was better than as compared with Hyalase and betamethasone alone. The efficacy of vitamin E was attributed to its antioxidant property.

3) Vitamin C

Singh (1996) observed that vitamin C given in combination with placentrax and liver extract gave better results than institution of vitamin C alone. It was believed that Vitamin C reduces the oedema between the collagen bundles and helps in regeneration of new collagen bundles with good approximation.

4) Minerals

Anil *et al.* (1991) administered Zinc (220mg) in combination with vitamin A and observed good results. Zinc plays essential role in DNA synthesis and cell division. Apart from zinc, Magnesium also plays essential role in many enzyme reactions and exerts stabilizing effects on excitable membranes.

A study was conducted in Karachi, Pakistan to assess the efficacy of combination of micronutrients (vitamins A, B complex, C, D, and E) and minerals (iron, calcium, copper, zinc, magnesium, and others) in controlling the symptoms and signs of OSMF and the outcome was beneficial clinical response (Maher *et al.*, 1997)

Fibrinolysis

1) Collagenase

Collagenase is a lysosomal enzyme, Lai and Lin (48) found that intralesional injection of collagenase resulted in significant improvement.

2) Hyaluronidase

The use of topical hyaluronidase has been shown to improve symptoms more quickly than steroids alone. Hyaluronidase can also be added to intralesional steroid preparations. The combination of steroids and topical hyaluronidase shows better long-term results than either agent used alone. Hyaluronidase degrades the hyaluronic acid matrix, actively promoting lysis of the fibrinous coagulum as well as activating specific plasmatic mechanisms. Therefore, relief of trismus may be expected through softening and diminishing of fibrous tissue Kakar *et al.*, 1985).

3) Chymotrypsin

Chymotrypsin, an endopeptidase is used as a proteolytic and anti-inflammatory agent in treatment of OSMF. Gupta and Sharma (1988) gave injected Chymotrypsin (5000 IU), hyaluronidase (1500 IU) and dexamethasone (4 mg) twice weekly for 10 weeks submucosally and observed good results.

Ayurvedic treatment: Turmeric (*Curcuma longa L.*) Tea pigments Oxitard

Turmeric has been found to inhibit many disease processes through their anti-inflammatory, antioxidant and anticancer properties. Curcuminoids isolated from turmeric, has been found to have effective antioxidant, DNA-protectant and antimutagen action. A study concluded that usage of turmeric oil daily for 3 months had a beneficial role (Kuttan *et al.*, 1985). Hastak *et al.* (1997) observed in 58 OSMF patients that turmeric 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.

Deepa Das *et al.* (2010) 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.

Aloe vera

Ramachandran and Rajeshwari (2012) twenty study subjects with OSMF were included in the study. Patients were divided into two groups. There were 10 patients in each group; group A subjects received 5 mg of aloe vera gel to be applied topically three times daily for 3 months and group B subjects received antioxidant capsules twice daily for 3 months. RESULTS: Aloe vera responded better in all the parameters assessed and responded in all the clinicohistopathological stages. Aloe vera showed a statistically significant reduction in burning sensation ($P = 0.008$), improvement in mouth opening ($P = 0.02$), and cheek flexibility ($P = 0.01$) on comparing with the antioxidant group.

C) Surgical treatment

- Fibrotomy
- Fibrotomy with grafts
- Laser treatment
- 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.

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.

- Extraoral 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

Split thickness skin graft

Yeh (1996) carried out a surgical procedure of incising the mucosa down to the muscles from the angle of mouth to the anterior tonsillar pillar, taking care to prevent damage to the stoma of the parotid duct, followed by split skin grafting into the defect, with acceptable results. Canniff *et al.* (1986) described the procedure of split thickness skin grafting after bilateral temporalis myotomy or coronoidectomy along with daily opening exercise and nocturnal props for a further 4 weeks. But the results with skin grafting have a high reoccurrence rate due to graft shrinkage (Khanna and Andrade 1995). The other limitation of the split thickness skin graft is the morbidity associated with the donor site along with maintenance of mouth opening post operatively for 7 to 10 days which is the most unpleasant and uncomfortable experience for the patient (Nataraj *et al.*, 2011).

Temporalis pedicled flap

Mokal *et al.* (2005) advocated the use of vascularised temporal myofascial pedicled flap to bring in good blood supply to the area of affected muscle and mucosa to improve its function. A total of five patients were treated with this technique and all of them showed good mouth opening in long term follow up. The advantages of this flap are 1) There is no donor site morbidity, 2) The incision line is well hidden in the hair bearing area, 3) Technique releases strong muscles of mouth closure such as masseter from its origin and temporalis from its insertion and 4) This procedure has its foundation on anatomical landmarks and physiological facts and is an effective method of treating oral sub mucous fibrosis (Mokal *et al.*, 2005).

Nasolabial flap

Typically classified as an axial pattern flap based on angular artery based superiorly or inferiorly. Kavarana and Bhatena (1987) filled the defect after sectioning of fibrous bands with 2 inferiorly based Nasolabial flaps, with division of the pedicle after 3 weeks, and observed average mouth opening of 2.5 cm, with acceptable external scars and concluded advantages 1)inferiorly based Nasolabial flap is a reliable, economical option, 2)its close proximity to defect, 3)easy closure of donor site, 4)a well camouflaged scar, 5)The technique is easy to master and defects as large as 6 to 7 cm can be closed and 6)The postoperative extra-oral scars are hidden in the Nasolabial fold. The minor complications are loss of the nasomaxillary crease and the creation of an edematous and bulky flap. To counteract complications, A periosteal suture can however be used to recreate the crease and by trimming all of the fat from the flap, the bulkiness can be reduced (Anisha *et al.*, 2011).

Tongue flaps

Borle and Borle (1991) reported disappointing results with skin grafting to cover the raw area and used tongue flap to cover the defect. Tongue flaps were found to be bulky and required additional surgery for detachment. Bilateral tongue flaps caused severe dysphagia and disarticulation along with the risk of postoperative aspiration. Restricted mobility of tongue was observed in the immediate postoperative phase, causing

discomfort to the patient and difficulty in speech, which made it a less ideal choice.

Palatal flap

Khanna and Andrade (1995) reported the incidence of shrinkage, contraction, and rejection of split skin graft as very high, owing to poor oral condition, with recurrence in 12 cases. Palatal island flap based on the greater palatine artery had been used to cover defect. This technique, accompanied with bilateral temporalis myotomy and coronoidectomy, was a highly effective surgical procedure. However, use of island palatal flap has limitation such as its involvement with fibrosis and second molar tooth extraction required for flap to cover without tension (Alexander, 2000). Bilateral palatal flaps leave a large raw area on palatal bones in palate (Mokal *et al.*, 2005).

Buccal fat pad flap

Yeh (1996) described the application of pedicled buccal fat pad after incision of fibrous bands and suggested that this was a very logical, convenient, and reliable technique for treatment of oral submucous fibrosis, easy, less time-consuming since the donor site is in close proximity to the posterior third of the buccal defect. Improvement in the suppleness and elasticity of the buccal mucosa on clinical examination were noted. The graft begins to show signs of epithelization from 2nd week with mean value of 14.73 days, so does not necessitate coverage with a skin graft (Amin, 2005). Buccal fat pad serves as a good substitute; because it provides excellent function without deteriorating the esthetics and the results obtained were sustained long term.

Collagen membrane

Collagen membrane is used as a biological dressing. Shobha Nataraj *et al.* (2011) used collagen membrane composed of type I and type III bovine collagen (that is similar to human collagen); following excision of fibrotic bands to cover the raw areas during initial phase of healing and observed that collagen membrane had good adaptability to the surgical defect. Collagen when used to cover raw areas provides coverage for sensitive nerve endings thereby diminishing degree of pain. The adherence of collagen membrane is initially due to fibrin collagen interaction & later due to fibro vascular in-growth into the collagen. With time, it slowly undergoes collagenolysis and is eventually sloughed off. However, it resists masticatory forces for sufficient time, to allow granulation tissue to form. None of the cases in their study showed any adverse reaction to the collagen proving its safety as a biological dressing.

Amniotic membrane

Lai *et al.* (1995) there was no acute rejection and its application over partial thickness defects provides for pain relief and re-epithelialization. In patients for whom deep defects were covered by fresh amnion grafts, the inter-incisal distance two years after surgical treatment decreased by 5-10 mm. Therefore, fresh amnion grafts would not appear to be effective in a single layer over deep buccal defects.

Mononuclear Stem Cell Therapy

Sankaranarayanan *et al.* (2013) Conducted 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. Posttreatment improvement in the clinical presentation was assessed and confirmed by histopathological features. The range of follow-up of cases is from 6 months to 5 years.

RESULTS

Reduction in blanching, improved/better suppleness of the mucosa, decrease in the burning sensation while consuming spicy food, increase in the mouth opening was observed. The above mentioned results were found to be sustained in the follow-up period.

Conclusion

From the results obtained, it is evident that the stem cell therapy has played a role in the improvement of the signs and symptoms probably through neoangiogenesis antiinflammatory effects and antifibrinolytic effect. However, as this is only a preliminary attempt to assess the safety of stem cell therapy in OSMF, further randomized control trials with larger sample size are required for using this as a possible alternative therapeutic approach.

We could trace only few articles with sound study design. Most of the studies had small sample size without adequate follow-up. Thus, there is a need for high – quality randomized, controlled trials with adequate sample size and long term follow-up for the management of oral submucous fibrosis. Although reversal of fibrosis is not possible, it is effective in relieving the symptoms. Next, a tailor made therapy should be designed depending on the extent, duration and severity of the disease. Here various permutation and combinations of the available medications can be tried to best suit the individual. Severe or grade III cases may require surgical intervention. No single drug has provided a complete relief from symptoms of OSF. Evaluation of the merits and disadvantages of individual items in treatment is not possible owing to the use of combined treatment protocols, which is unavoidable at present because of the empirical nature of each approach. These studies provided a limited amount of unreliable data which did not permit any firm conclusions to be made. The individual mechanisms operating at various stages of the disease—initial, intermediate and advanced—need further study in order to propose appropriate therapeutic interventions.

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