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Review Article

Treatment Modalities in Oral Submucous Fibrosis: A Review

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ABSTRACT:
Oral Submucous Fibrosis (OSMF) is a chronic progressive debilitating high risk precancerous condition resulting in increased juxtaepithelial fibrosis of oral mucosa, the oropharynx, and rarely, the larynx leading to burning and stiffness of oral mucosa and often leads to ongoing reduced mouth opening. A number of treatment modalities for OSMF have been proposed with little reliable evidence for the effectiveness of each/any of these in the management of this condition. These treatment protocols can dilute the signs and symptoms of OSMF, but no single treatment modality can be identified which can provide a complete cure of this disease. The present review highlights the importance of habit control, physical therapy, intraoral appliance, medicinal and surgical interventions in the management of OSMF and identify gaps in our knowledge to encourage further research to help develop targeted therapies.

Key words: Oral submucous fibrosis, corticosteroids, management

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INTRODUCTION

Oral Submucous Fibrosis (OSMF) is a chronic progressive debilitating high risk precancerous condition which was first reported by Schwartz in 1952. Schwartz used the term "atrophica idiopathica (tropica) mucosae oris."[1]It results in increased juxtaepithelial fibrosis of oral mucosa, the oropharynx, and rarely, the larynx which leads to burning and stiffness of the oral mucosa and often leads to ongoing reduced mouth opening. The submucosa and deeper tissues may also get affected in later stages of OSMF. The risk for its transformation into malignancy is found to be varied from 7% to 30%.[2]Vig et al in his study reported only 2 out of 108 cases of OSMF which transformed into cancer.[3]

The etiopathogenesis of OSMF is not completely understood so far, but areca nut has been identified as the major etiological factor of OSMF.[4] Arecoline and Tanin present in areca nut leads to increased collagen synthesis and its decreased breakdown.[5]Other etiologic factors are chillies, tobacco, lime, nutritional deficiency, defective iron metabolism, collagen disorders, bacterial infection, immunologic disorders, genetic susceptibility and altered salivary composition.

OSMF is most prevalent in India and South East Asia affecting 0.2% to 0.5% of the general population of India with gender variation of 0.2-2.3% in males and 1.2-4.5% in females. It has wide age distribution ranging between 20 and 40 years.[6] According to a ten year study conducted by Vig et al nearly all patients of OSMF were South Asian out of which nearly half were females. 12% were under the age of 30.[3]

Symptoms of OSMF vary as the disease progresses. Initial symptoms are mucosal ulcerations and burning sensation. Stiffening and blanching of oral mucosa occurs as the disease continues, with palpable fibrous bands being the most distinctive feature of OSMF.[7,8] OSMF results in marked rigidity and developing inability to open mouth.[9,10] Normal movements of the tongue are also crippled by the expanding fibrosis.

A number of treatment modalities for OSMF have been proposed with little reliable evidence for the effectiveness of each/any of these in the management of this condition. These treatment protocols can dilute the signs and symptoms of OSMF, but no single treatment modality can be identified which can provide a complete cure of this disease. Cessation of areca nut consumption is the most vital step in the management of OSMF. No active agent

has been found yet which can act as replacement of areca nut to help users in ceasing the habit of areca nut chewing. Management of OSMF includes terminating use of areca nut, medical care, physical therapy, surgery and combined therapy. Nutrients, micronutrients, antioxidants, biogenic stimulation, proteolytic enzymes, immune modulation and promotion of blood flow has been tried as medical interventions for the treatment of OSMF.Physical exercise regimen, splints and microwave diathermy have been tried in physical therapy. Surgical interventions include laser excision, coronoidectomy and muscle myotomy, excision and flap procedure, excision and grafts/stents. [11]

Recently, cucurmurin, aloe vera, and tea pigments have been found to have antioxidant properties and have been tried in OSMF. Clostridium histolyticum collagenase, imatinib, pirfenidone, and simtuzumabhave also been tried in the management of OSMF. Targeted therapies could also be designed as possible molecular targets have been revealed. [11]

The present review highlights the importance of habit control, physical therapy, intraoral appliance, medicinal and surgical interventions in the management of OSMF and identify gaps in our knowledge to encourage further research to help develop targeted therapies.

TREATMENT STRATEGIES

HABIT ALLEVIATION

Areca nut usage has to be completely stopped in an OSMF patient before following any treatment protocol. Areca nut is very addictive and its cessation is arduous by the fact that no other agent is available to replace it in the course of quitting this habit. Authors have developed an instrument to measure betel quid dependence: Betel Quid Dependence Scale.[12] Chen et al. composed a self-reporting questionnaire screening test having 11 questions. Areca nut abuser was considered the one having scored equal to 4 or more. [13]

CORTICOSTEROIDS

Corticosteroids are believed to decrease inflammation and reduce collagen production thereby alleviating symptoms of OSMF. In a study conducted by James et al. 28 patients with OSMF were treated by administering intralesional injection of dexamethasone 1.5 ml, hyaluronidase 1500 IU with 0.5 ml lignocaine HCL intralesionally biweekly for two weeks. Improvement in mouth opening in the range of 4-8 mm was observed. There was reduction in burning sensation, painful ulceration and blanching of oral mucosa with subsequent follow ups.[14] Hyaluronidase breaks hyaluronic acid and lowers the viscosity of intercellular cement substance.[15] Dexamethasone acts as immune suppressive and anti-inflammatory agent by its antagonistic activity on soluble factors released by the sensitized lymphocytes succeeding the activation by non-specific antigens.[16]

Tilakaratne M et al. studied the effect of intralesional corticosteroids as a treatment for restricted mouth opening in OSMF. A total of 230 histologically confirmed patients of OSMF were included in his study, of which 116 patients with a 30 mm or less interincisal mouth opening were subjected to intralesional injections of 40 mg methyl prednisolone at monthly intervals for 6 consecutive months. In paired comparison, statistically significant difference (t= -8.78; P< .001) was observed in mouth opening over a period of 12 months in the patients who had corticosteroid injections.[17]

In a comparative study conducted by Borle RM et al. 326 OSMF patients were divided into 2 groups. One group was treated with conventional submucosal injections of steroids and hyaluronidase and the other group was treated with topical vitamin A, steroid applications and topical iron preparations. The conservative treatment was found to be safer as compared to the conventional one.[18]Ameer et al. evaluated effect of intralesional triamcinolone by giving biweekly submucosal injections of 40 mg triamcinolone for 12 weeks and followed up for 1 year. It showed improvement in symptoms and increased mouth opening.[19]

NUTRITIONAL SUPPLEMENTS

Many patients diagnosed with OSMF are reported to have nutritional deficiencies, mostly deficiency of iron and B vitamins.[20] Vitamin A, B complex, C, and E have been tried alone and in combination with other therapies.[18] Oral zinc alone is also beneficial in treating OSMF according to Kumar and Sharma.[21] Magnesium, selenium, manganese and iron have also been tried in treating OSMF.[11] In a study conducted by Mather et al. vitamins and minerals were given to OSMF patients for 1 to 3 years and there was improvement in symptoms.[22] Oral lycopene therapy showed improvement in the signs and symptoms of OSMF.[23] Shetty P et al. studied the efficacy of spirulina in 40 OSMF patients. Spirulina brought about clinical improvements in OSMF patients. [24]

ENZYMES AND FIBRINOLYTIC AGENTS

Enzymes and fibrinolytic agents help to break down collagen and hence are being used in the treatment of OSMF. Collagenase, hyaluronidase, chymotrypsin and colchicine are under use in the treatment of OSMF. Hyaluronidase is known to break intercellular cement substance and a study showed patients receiving hyaluronidase alone showed quicker improvement in burning sensation and ulcerations, although its combination with dexamethasone gave better long-term results than other regimens.[25]In a comparative study conducted by Krishnamoorthy et al. 50 OSMF patients were randomly divided into 2 groups and were treated separately for 12 weeks. Group 1 patients were administered tablet colchicine orally, 0.5 mg twice daily and 0.5 ml intralesional injection hyaluronidase 1500 IU into each buccal mucosa once a week. Group 2 patients were administered 0.5 ml intralesional injection hyaluronidase 1500 IU and 0.5 ml intralesional injection hydrocortisone acetate 25 mg/ml in each buccal mucosa once a week alternatively. Group 1 patients responded better than group 2.[26] Collagenase can degrade various

esters that are involved in the cross-linking of cement substance. Chymotrypsin is a proteolytic enzyme that helps in the cleavage of peptide bonds and some Indian authors have observed improvement in symptoms after using proteolytic enzymes.[11]

ANTIOXIDANTS

Antioxidants have also been tried in treatment of OSMF as reactive oxygen species, free radicals, and peroxidases have been attributed in its pathogenesis. Some of the antioxidants which have been used are lycopene, tea pigments, β carotene, aloe vera, cucurmurin, and spirulina. In a trial by Jirge et al. systemic administration of β carotene for 15 weeks led to 6.7% improvement in mouth opening.[11]

Lycopene is also an effective antioxidant and it has been tested in several randomized contro; trials. Kumar et al. during his study gave oral lycopene to 21 people in group A, oral lycopene and intralesional corticosteroids to 19 people in group B and an oral placebo to 18 people in group C. There was improvement in mouth opening following the treatment which was 3.4 mm, 4.6 mm and 0 mm for group A, group B and group C respectively.[11]

HUMAN PLACENTAL EXTRACTS

An aqueous extract of healthy human placenta because of its anti-inflammatory effect can be used in OSMF which can prevent further mucosal damage. In a study conducted by Anil et al. cessation of areca nut chewing and submucosal administration of aqueous extract of healthy human placenta (Placentrex) showed marked improvement in the condition.[27]

PERIPHERAL VASODIALATORS

Pentoxifylline, nylidrin hydrochloride, isoxipurine, and buflomedil hydrochloride are some of the vasodialators which are being used in the treatment of OSMF. Vasodialators can increase the vascularity and hence improve nutrient supply to the affected area. Pentoxifylline is also known to stimulate fibrinolysis and the effect of pentoxifylline was studied on the clinical and pathologic course of OSMF in a study in which there were two groups. The control group received multivitamins and local heat therapy while the test group received pentoxifylline 400 mg tid, as coated, sustained release tablets and the authors concluded that pentoxifylline could be used as an adjunct therapy in treatment of OSMF.[28]

Oral isoxipurine as well as dexamethasone with hyaluronidase injections combined to physiotherapy showed improvement in this condition.[28]

CYTOKINES

Alpha, beta and gamma interferons are naturally produced proteins which have antiviral, antitumor and immunomodulatory actions. INF- γ is an antifibrotic cytokine which plays a role in the treatment of OSMF through its effect of altering protein synthesis. Local injections of INF- γ have been reported to facilitate mouth opening in OSMF patients.[29] A cyclooxygenase 2 inhibitor has been tried as a mucoadhesive film applied to the buccal mucosae in a pilot study as a proof of concept to use long-acting topical agents.[11] Apart from the above therapies, immunized cow's milk has shown promising results in OSMF. The milk from cows immunized with human intestinal bacteria contains an anti-inflammatory component which suppresses the inflammatory reaction and modulate cytokine production in OSMF.[28]

TISSUE THERAPY

Tissue therapy was introduced by Filatov in 1933 for the treatment of OSMF. His theory stated that tissues when severed from parent's body are exposed to an unfavourable condition which is not mortal to their existence; undergo biological readjustment leading to development of substances in state of their survival and when such tissues are implanted or injected into the body after resistance to pathogenic factor stimulates regenerative process by "Biogenic stimulation".[30] Injection Placentrex is an aqueous extract of human placenta containing vitamins, trace elements, nucleotides, enzymes, amino acids, steroids, fatty acids and other substances having the ability for biogenic stimulation.

PHYSICAL EXERCISE

Forceful mouth opening, hot water gargling and ballooning of mouth are some of the physical exercises indicated in OSMF. In a study by Cox et al. 54 Nepali patients were divided into three groups: physiotherapy, injection with a combination of hyaluronidase and steroids, and a control group. After four months, the physiotherapy group showed a significant increase in mouth opening but had no superior effects on subjective measures.[11]

MICROWAVE DIATHERMY

Rae and Co-workers found microwave diathermy especially valuable in the treatment of fibrosis and trismus and hence it was thought to be used in OSMF.[27]

ULTRASOUND

Ultrasound selectively raises temperatures in selected areas by volume heating which occurs due to absorption of ultrasound by tissue proteins and its conversion to heat. Ultrasound used for this purpose has a frequency of about 0.8-1 MHz and an intensity of 0.5-3 w/cm^2. Though layers of skin has different impedances, the difference is not vast and hence little energy is reflected and most of it reaches lamina propria of buccal mucosa.[31] Pal et al. reported an improvement of symptoms in 50% of their cases when treated with ultrasonography.[11]

A NEW INTRAORAL APPLIANCE FOR TRISMUS IN OSMF

A novel intraoral appliance- "Nallan C-H"- has been developed and tried with effective results in three patients of OSMF having trismus. This appliance is non invasive, economical, and had fair compliance with the patients. Patients were encouraged to wear the appliance 12 hours overnight for eight weeks and follow up after 2 months. It

was observed that there was significant increase in mouth opening in all three patients ranging from 2 to 8 mm.[6]

OSTEOPATHIC THEAPY

Goyal et al. conducted a study to explore the effectiveness of osteopathic manipulative treatment (OMT) in patients with OSMF. An OSMF patient was treated with OMT techniques for twice a week for 4 weeks followed by home exercise program. The patient showed a significant increase in mouth opening from approximately 10 mm to 22 mm of mouth opening at the end of the treatment sessions. The osteopathy approach provokes the body's internal mechanisms to heal itself by the use of human hands. The osteopathic treatment centres on the nervous system, the circulatory system, the spine, the viscera, and the thoracic, and pelvic diaphragms.[32] Few studies have reported the utilization of osteopathic manipulative treatment in the management of temporo-mandibular dysfunctions.[33]

SURGICAL THERAPY

Surgery is generally indicated in advanced OSMF patients or patients with malignant changes. Although surgery can aggravate the condition but surgical intervention is the only treatment available in extremely advanced cases of oral submucous fibrosis.[34] Naphade M et al. in his study reported that an OSMF patient with initial interincisal opening of 8 mm after being treated surgically with nasolabial flap technique followed by active mouth opening exercises for 6 months with Hister's jaw exerciser could maintain mouth opening of 32 mm at the end of 18-months follow up.[35]

COMBINED THERAPY

In a study conducted by Shetty et al. 60 patients with grade III OSMF were selected and these patients underwent 3 different modalities of treatment: 1) medical management with injection of hyaluronidase and dexamethasone: 2) surgical management with excision of bands and application of collagen membrane: 3) combined therapy involving surgical excision of bands followed by injection hyaluronidase and dexamethasone along with mouth opening exercises. Patients were evaluated after a period of six months. It was found that patients undergoing combined therapy had best results followed by medical management alone. So it was concluded that surgical management of OSMF should be combined with medical management and aggressive physiotherapy to obtain best results.[36]

CONCLUSION

Treatment strategy in patients of OSMF should be carried out keeping in mind the overall general health of the individual both physically and psychologically. Early risk awareness campaigns focussing on habit cessation and its intervention along with medicinal and surgical therapies have been proposed in improving the condition of the individual. More clinical trials in a larger sample size are needed in finding an integrated treatment measure in OSMF cases.

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