

Review Article

Past and Present Progress in the Management of Oral Submucous Fibrosis

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Introduction

Many etiological variables contribute to OSMF, including chewing areca nuts, consuming a lot of chilli, having high copper toxicity levels in meals and chewing agents, vitamin insufficiency and malnutrition, anaemia, and hereditary predisposition. The major cause of OSMF is continuing chewing areca nuts. There is currently no particular therapy for OSMF, implying that novel therapeutic strategies and understanding of the underlying processes are urgently needed [1].

By evaluating the most recent research on the genesis, diagnosis, and treatment of OSMF, prevention should be prioritized. To lower the risk of OSMF, local health and medical organizations could spread OSMF knowledge, such as not eating betel nut and paying attention to nutrient intake. It is possible to reduce the incidence, recurrence rate, and malignant transformation rate of OSMF through a better understanding of OSMF pathogenesis and related carcinogenesis, as well as the advancement of scientific research and medical level, particularly in stem cells, exosomes, and other related emerging fields [2].

The main objective of treating OSMF is to cure the signs of symptoms of patients like, burning sensation, pain, ulcers, and difficulty in eating, limited mouth opening and also improving the quality of life of affected individuals. OSMF is a progressing disease and identified as premalignant condition, timely treating this condition helps to prevent disease progression and malignant transformation.

To date, a variety of treatments have been tried to manage oral submucous fibrosis (OSMF) with varying degrees of success,

Abstract

As the prevalence of oral submucous fibrosis and its associated morbidity rises, a complete evaluation is needed to examine the efficacy of current and rapidly developed treatment methods, as well as to propose strategies for future notable research. Several studies regarding different treatment modalities have been carried out previously. Hence, this review was undertaken to consolidate existing oral submucous fibrosis therapeutic strategies, update the literature with recent clinical data, and add insight into the field.

Various electronic databases like Google Scholar, EMBASE, PubMed, SCOPUS, and Web of Science were searched for articles published until March 2022. Keywords, oral submucous fibrosis, management, medicinal interventions, surgical interventions were used to search the data base.

Keywords: Oral Submucous Fibrosis; Management; Medicinal Interventions; Surgical Interventions

including pharmacological management, surgical therapy, and physiotherapy, but none has been successful in curing this condition till date. Medical management is usually symptomatic and frequently addressed by enhancing the mouth opening. Caniif et al. have stated that the medical therapy of OSMF is both experimental and inadmissible [1]. The initial step of a preventive measures ought to be to instruct the patient for the discontinuation of the habit through education, counseling, and encouragement.

The Therapeutic Aspects of Managing OSMF

The patient should be properly counseled and strictly discouraged from chewing betel nut preparations and should be informed about the nature of the disease and its possible malignant potential [2].

Current Treatment Strategies for OSMF Include [2]:

- Nutritional support
- Antioxidants
- Anti-inflammatory and immunomodulatory drugs
- Physiotherapy
- Local drug delivery
- Surgical management
- Combined therapy
- Newer options

Nutritional Support

Supplementary diets administered to OSMF patients are mainly for high protein and calorie requirements. Supplements such as

vitamin A, B, complex, C, and other vitamins and minerals are commonly employed in combination with other therapeutic agents.

Hennekens CH [3] stated that the protective effect of micronutrients is attributed to their antioxidant activities. Antioxidants act by reducing the free radical reaction that can cause DNA mutations and changes in lipid peroxidation of cellular membranes and changes in enzymatic activities.

Anil Kumar [4] divided 82 OSMF patients into five groups and administered zinc alone or in combination with other vitamins A or local cortisone to each group. Oral zinc therapy, either alone or in combination with pharmacological doses of oral vitamin A, proved to be significantly better for the treatment of grade I and II OSMF patients. Oral zinc in combination with local cortisone therapy proved to be significantly better than the currently preferred local cortisone therapy in grade III OSMF patients.

Du X [5] suggested that micronutrients such as vitamin A, B complex, C, E and carotenoids (beta-carotene), selenium and beta-carotene decrease the evidence of epithelial cancer, hence their use can be justified in managing OSMF patients.

Abhinav Kumar [6] divided 58 patients with OSMF into 3 groups, 21 patients of group A received 16 mg of lycopene, 19 patients of group B received 16 mg of lycopene along with biweekly intralesional steroid injections, and 18 patients of group C were given a placebo. The patients were evaluated weekly over a 2-month period. The mouth-opening values for patients showed an average increase of 3.4 mm, 4.6 mm, and 00 mm for patients in group A, Band C, with a pretreatment mouth opening of 31.76 mm \pm 10.14 mm, 25.41 mm \pm 6.83 mm and 30.61 \pm 7.55 mm.

Immunomodulatory Drugs

Glucocorticoids act as immunosuppressive agents and prevent fibrosis by decreasing fibroblastic proliferation and deposition of collagen in OSMF patients.

Desa JV [7] treated 64 cases of OSMF with corticosteroids. All patients experienced relief from burning sensation in the mouth. Return of the normal coloration of the oral mucosa was noted in 20% of the patients. He observed persistence of inability to blow the cheek in spite of treatment in advanced cases and suggested that fibrotic infiltration of the buccinator muscle might play an important role.

Kakar PR [8] tried biweekly injection of 1500 I.U of hyalase dissolved in 1cc of 2% lignocaine. When combined with injection wycort, the therapy was more effective, with relief of symptoms reported in 41.25 to 87.5 percent of OSMF cases.

Rode RM. and Borle SR. [9] reported their clinical trials of treatment in 326 patients with OSMF. They divided 326 patients into two groups and treated them either with conventional submucosal injections of steroids and hyaluronidase, or with topical vitamin A, steroid application, and oral iron preparations. After comparing the results, they found that treatment with injection was hazardous, whereas conservative treatment was found to be safe. Both treatments were purely palliative.

Haque MF [10] studied the effect of intralesional injection of interferon gamma in 29 OSMF patients twice a week for 18 weeks.

They observed a 42% increase in the post-treatment mouth opening. Patients also reported reduced burning dysesthesia and suppleness of the buccal mucosa.

Tat YS [11] studied the effect of immune milk treatment (45 g of immune milk powder twice a day for three months) in 26 OSMF patients. They observed that interincisal mouth opening increased in 69.2% of OSMF patients. 80% of the patients had disappearance or significant improvement of intolerance to spicy foods, and 72% of the patients with xerostomia.

Physiotherapy

Physiotherapeutic measures, such as forceful mouth opening and heat therapy, have been tried. Heat in the form of hot rinses, lukewarm water, or selective deep heating therapies such as short-wave diathermy have yielded positive results

Gupta DS [12] treated 12 cases of OSMF with microwave diathermy and found microwave diathermy to be useful in early and moderate stages of the disease. Microwave diathermy avoids the inadvertent heating of superficial tissues like skin and adipose tissue. Microwave diathermy is superior to short wave diathermy, because it causes selective heating of the juxtaepithelial connective tissue, thereby limiting the area treated.

Local Drug Delivery

Kumar K [13] treated 18 patients with OSMF with collagenase and concluded that there was maximum improvement in the colour of the mucosa, reduced burning sensation, and increased mouth opening from 3 mm to 10 mm but observed variable adverse effects such as pain, swelling, and trismus after each injection of collagenase.

Rajanjaneyulu P and Prabhakara Rao BS [14] treated 10 patients with OSMF by injecting placetrax locally in the fibrotic areas of the oral cavity. The authors observed that the initial improvement of 5 mm with the first injection and later improvement was 2 mm per injection on average. There was a dramatic improvement in the burning sensation in the mouth. Changes in the colour of the oral mucosa indicating improvement in the vascularity of the oral mucosa were also observed.

Kataria SK [15] studied the effect of local injection of placetrax in 22 oral submucous fibrosis patients. The maximum improvement (40.21%) was observed in the burning sensation, followed by 38.55% in mucosal color, 30.59% in fibrous bands, 28.26% in mouth opening, and 18.46% in protrusion of the tongue.

Combined Therapy

Gupta D and Sharma SC [16] studied the effects of various treatment regimens in 200 OSMF patients for a period of five years. The patients were divided into 9 groups, each group containing 25 patients; the ninth group contained 14 patients with severe clinical symptoms who did not respond to conservative treatment. They found a combination of local injections consisting of dexamethasone, hyaluronidase, and chymotrypsin to be beneficial. In severe cases, a combination of fibrotic band excision with a fresh human placental graft and local injections was used.

Lai DR [17] treated 150 patients with varying degrees of OSMF. The patients were divided into two groups of 75, one for medical and

Table 1: Summary of conventional and advanced treatment approaches for OSMF.

Treatment modality		Mechanism of action	Specific agent
Behavioral Therapy		Removal of etiological factor	Reduction or even elimination of the habit of areca nut chewing
Physiotherapy		Modify tissue remodeling	Forceful mouth opening with mouth gag and acrylic surgical screw; heat therapy
Medical intervention	Antioxidants	Separating the free oxygen radicals from susceptible molecules and also inactivating the free radicals, repair the damage caused by free radicals	Lycopene, β -carotene, α -tocopherol, Minerals (Zinc, copper, selenium)
	Nutritional Support	Removal of deficiency state	Diet rich in proteins, calorie, vitamins, minerals and antioxidants like lycopene
	Biogenic stimulation	Anti-inflammatory, anti-platelet activity	Placental extract
	Immunomodulatory Dugs	Prevent or suppress inflammatory reactions, decrease Prafraction a fibroblast and collagen deposition	Dexamethasone (Decadron), Triamcinolone acetonide (Aristocort, Kenajeet), Betamethasone valerate (Diprosone) Levamisole
	Antifibrotic cytokine	Altering collagen synthesis	IFN-gamma
	Blood flow promotion	Fibrinolytic activity	Pentoxifylline therapy
	Proteolytic Agents	Hydrolysis of hyaluronic acid	Hyaluronidase: topical and/ m with intralesional steroid preparations
Surgical approach		Removal of fibrosis	Simple excision, Split-thickness skin grafting, palatal island flap, Nasolabial and lingual pedicle flaps, Pedicled buccal fat pad Latest modalities
Recent approach	Laser	Precise action, with improved healing	Diode laser surgery and CO ₂ laser
	Stem Cell Therapy	Induces angiogenesis	Intralesional injection of autologous bone marrow stem cells
Combined Therapy		Combination of advantages of different treatment modalities	Local and Systemic steroids with peripheral vasodilators, vitamins, iodine, placental extract and physiotherapy

the other for surgical treatment. Medical treatment involved:

a), Conservative oral administration of vitamin B complex, buflomedial hydrochloride (peripheral vasodilator, it affects tissues in diffuse fibrosis by relief of the local ischemic effect) and topical triamcinolone 0.1%. Or b) Conventional submucosal injection of a combination of dexamethasone and hyaluronidase, or c) Combination of (a) and (b).

The surgical group was treated by excision of fibrotic tissue and covering the defect with split thickness skin, fresh human amnion, or buccal fat pad (bfp) grafts. Surgical therapy resulted in significant improvement of trismus in severe cases.

The cases were followed up by monthly examinations for at least two years, or when possible, even longer. Combination of (a) and (b) medical treatment was satisfactory in cases of mild impairment (interincisal distance > 20 mm), but in the long term it led to symptomatic relief only. Surgical therapy, on the other hand, when accepted by patients, led to significant improvement of trismus in cases of severe limitation (interincisal distance >20 mm).

Surgical Treatment

Caniff J.P. [18] presented an analysis of 44 patients with OSMF. They felt that although intralesional steroids might improve the mouth opening in mild cases of OSMF, surgery with split thickness skin grafting combined with bilateral temporalis myotomy and coronoidectomy was the only effective treatment for severe OSMF cases.

Khanna and Andrade [19] divided 100 OSMF patients into four categories. Very early and early cases were treated with local injection of triamcinolone acetonide, while advanced cases were treated by surgical intervention. A surgical technique of a palatal island flap

based on the greater palatine artery in combination with temporalis myotomy and bilateral coronoidectomy was used in 35 cases.

The highlights of this technique are as follows:

- The hard palate, owing to its minimal amount of connective tissue, has a low percentage of fibrosis in oral submucous fibrosis.
- There are no muscles in the flap to undergo fibrosis.
- Because of the use of a mucoperiosteal flap pedicled to the greater palatine artery, the chances of shrinkage, sloughing, and contracture are minimal.
- Increased vascularity to the involved region may help to improve the condition.
- In this study, this surgical procedure was found to be highly effective in grade III and grade IV oral submucous fibrosis patients.

Yeh CY [20] reported the application of the buccal fat pad flap in treating OSMF patients. In his study, 9 patients underwent surgical release of fibrotic bands and the defect created was covered with a pedicle buccal fat pad flap. The postoperative mouth-opening range was 16.38 mm with a follow-up period of 10-38 months

Ramadass T [21] treated 60 OSMF patients using a single-stage rotation tongue pedicle flap on either side of the dorsum of the tongue sutured to the raw area in check. In a 7-year follow-up, they observed that the patient did not develop further fibrosis and the tongue flaps remained intact.

Among the above-mentioned modalities for the treatment of OSMF, none of them can be considered completely effective. Conservative types of treatment are more beneficial in patients with initial changes of OSMF, but in severe forms of oral submucous

fibrosis, the conservative approaches without surgical intervention do not respond favourably.

The results with skin grafting to cover the raw areas have been disappointing. The incidence of shrinkage, contracture, and rejection of the graft was found to be very high because of the poor oral conditions and recurrence of symptoms. Tongue flaps are known to be bulky and require additional surgery for its detachment. Moreover, tongue involvement in oral submucous fibrosis is 38%, precluding its use. Although nasolabial flaps cannot be extended adequately to cover the raw areas and cause facial scars and other undesired effects. Under regular follow-up and continuous physiotherapy, good results could be generated [22].

Hyperbaric oxygen therapy (HBO) is known to promote fibroblast apoptosis, inhibit fibroblast activity, and have anti-inflammatory and antioxidant property, hence it is also tried in the management of OSMF patients. Bone marrow mesenchymal stem cells, dental pulp stem cells, adipose mesenchymal stem cells, etc. known to release cytokines and growth factors to achieve neovascularization; enhance the ability of antioxidants to scavenge free radicals; remove senescent cells in lesions. So they have also used in treating OSMF patients. Ginger butter resin, ginger butter, and turmeric extract have also tried in OSMF patients because of their anti-inflammatory and antioxidant properties. They also inhibit p53, TGF- β , iNOS and also reduce CTGF [23].

Due of their many benefits over existing methods, lasers can be utilized as a substitute for surgical fibrotomy in OSMF. They are less invasive, related with less post-operative fibrosis in the surgical region, and can produce a surgical area that is clearly visible due to less bleeding [24].

The summary of different conventional and advanced treatment approaches for OSMF is mentioned in (Table 1) [25-29].

Conclusion

According to data in the literature, areca nut users who are genetically vulnerable have a high frequency of OSMF. OSMF is a serious public health issue with not only physical but also psychological and social consequences for sufferers and their families. The prevalence of OSMF is likely to be significantly greater than current estimates, which predict that millions of individuals are affected.

Despite the fact that OSMF has a high morbidity rate and a significant probability of malignant transformation, there is no permanent treatment. More study is needed in the areas of malignant transformation prevention, habit cessation, management, and prevention.

In the therapy of OSMF, no single therapeutic approach is efficacious. Numerous conventional and recent natural and chemical agents offer promise in the treatment of OSMF. Physiotherapy and habit reduction are essential components of the therapeutic process. To further investigate the efficacy of various pharmaceutical formulations in combination with physiotherapy in the management of OSMF, high-quality, longitudinal, multi-centre randomised controlled studies with bigger samples are needed.

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