Chapter 8
Oral Submucous Fibrosis

Divya Mehrotra

Introduction

Oral submucous fibrosis (OSMF) is a chronic, insidious, progressive oral mucosal disease affecting the oral cavity, pharynx, and upper digestive tract, causing stiffness of the oral mucosa, restricted mouth opening, and impaired ability to eat, speak, or care for oral hygiene [1].

The WHO initially defined OSMF as an oral precancerous condition associated with a significantly increased risk of cancer [2]. Later at an Oral Cancer and Precancer Workshop by the WHO in the UK, precancer was referred to as "potentially malignant disorders" as it was noted that all disorders described as precancer eventually do not transform into cancer [3].

Terminology

In Sushruta Samhita, OSMF was described as vidari, a swelling within the throat. It presented as burning, prickling pain, haemorrhage, putrid, and necrosed muscle. Schwartz [4] described it in five Indian women in Kenya and termed it "atrophia idiopathies (tropica) mucosae oris". Joshi in 1953 termed it oral submucous fibrosis (OSMF) [2]. Other names suggested for this condition include "diffuse oral submucous fibrosis", "idiopathic scleroderma of the mouth", "idiopathic palatal fibrosis", and "sclerosing stomatitis". Although Pindborg and Sirsat [5] suggested it to be known as "juxta-epithelial fibrosis", oral submucous fibrosis was the most popular term designated to this disease.

D. Mehrotra (✉)
Department of Oral & Maxillofacial Surgery, Faculty of Dental Sciences, King George's Medical University, Lucknow, India

© Peter A. Brennan, Tom Aldridge, Raghav C. Dwivedi, Rehan Kazi 2019

Peter A. Brennan et al. (eds.), *Premalignant Conditions of the Oral Cavity*,
Head and Neck Cancer Clinics, https://doi.org/10.1007/978-981-13-2931-9_8

Historical prevalence: Pindborg, a Danish pathologist and WHO consultant, travelled to Southeast Asia to study tropical diseases, wherein, with his Indian colleagues, he planned field studies and examined over 200,000 Indian villagers over 30 years. They together published the epidemiology and clinicopathological aspects of OSMF in over 30 scientific papers [6].

Geographical Distribution and Prevalence

Studies have shown that the number of cases of OSMF has increased rapidly in India, from an estimated 250,000 cases in 1980 to two million in 1993 and five million in 2002. This happened with the vast usage of newly commercially available areca nut preparation: the pan masala [7]. It was extensively used by the younger generation because of its easy access, low price, and marketing strategies [8]. The increasing use of pan masala, with or without tobacco, seems associated with an earlier age of onset of OSMF.

It has been estimated that up to 20% of the world's population consumes betel nut, so probably the incidence of OSMF is higher than what has been reported [7]. Currently, OSMF is considered a public health issue in India, the UK, and South Africa. With an ever-increasing Indian immigrants to the USA, OSMF would soon be seen in the USA too in the near future [9].

OSMF is predominantly encountered among the populations of Southeast Asia or among people migrating from these countries. The prevalence rates of oral submucous fibrosis in Southeast Asia range from 0.04% to 24.4%, 1.0–3.03% in China [10], 0.15–14.4% in Vietnam [11], 0.086–17.6% in Taiwan [12], and 0.2–1.3% in India [13].

Within India also, the prevalence of OSMF varies and has been reported as 1.3% in North India and 0.55% in South India (12). Studies have reported its prevalence in different cities of India: 0.36% in Ernakulam, Kerala, 0.31% in Trivandrum, 0.04% in Andhra Pradesh, and 0.16% in Gujarat. In cities including Lucknow, Bombay, Bangalore, and Trivandrum, a hospital-based survey recorded prevalence of OSMF as 0.51%, 0.50%, 0.18%, and 1.22%, respectively. The prevalence of OSMF has increased not only in India but also in countries like Taiwan, from 8.3 (per 100,000) in 1996 to 16.2 (per 100,000) in 2013, with men having a significantly higher prevalence than women [14].

Premalignant Potential

Paymaster [15] first described its premalignant potential [2] which has now been observed as 7–30% [16]. The 10-year oral cancer transformation rate for OSMF is much higher than that of leukoplakia, 0%, and OSMF, 11%, and when both are seen together, it is greater than 15%. Combination of leukoplakia and OSMF has a much higher malignant transformation rate [17].

Aetiology

The aetiology of OSMF is thought to be multifactorial, although areca nut is the major risk factor. Areca nut chewing, local irritants (chillies), nutritional deficiency, and autoimmune disease are all held responsible for OSMF. Areca nut is consumed alone or as an ingredient of betel quid. The other ingredients of quid like betel leaf, slaked lime, or tobacco have not been established as causative factor for OSMF.

Association with Areca Nut

The association of areca nut consumption with OSMF is based on studies undertaken in India, Pakistan, Sri Lanka, and Taiwan, which estimate a relative risk (RR) of 1.8–172.

Pakistan

RR was estimated by comparing 157 OSMF patients and 157 controls in Karachi, Pakistan, and was observed as 154 (95% CI 34–693) in areca nut users.

Sri Lanka

A study of 74 OSMF and 74 controls in a hospital-based study confirmed a strong association of OSMF with areca nut used in betel quid (odds ratio: 171.83; 95% confidence interval (CI): 36.35–812.25).

Taiwan

Three forms of betel quid with areca nut were used in Taiwan: betel quid, lao-hwa quid, and stem quid. All reported studies have indicated a significant association between OSMF and areca nut.

China

In a study in China [18], 43% of OSMF patients chewed areca nut alone.

India

Areca nut chewing habit in OSMF patients in India ranges from 34% to 100%; but these habits differ in men and women (men prefer to chew gutkha, mawa, and kharra, while women chew solely areca nut). In Maharashtra, 4.2% of females who chewed areca nut only suffered from OSMF. Men are seen to develop OSMF comparatively at a younger age.

The odds ratio of OSMF at 95% confidence interval ranges from 4.77 to 6.88 with usage of tobacco-less pan masala and 4.55–9.71 with tobacco pan masala. When areca nut was used as mawa (tobacco and lime added), RR was observed as 29.9 [19]. In a study conducted in Lucknow, the OR assessed using multivariate analysis was 14.09 for tobacco-less pan masala and 5.39 for tobacco pan masala [20].

Areca Nut

Arecoline, an areca nut alkaloid, is the main culprit that decreases collagen breakdown and subsequently leads to increased fibrosis causing OSMF. Other active components of areca nut include alkaloids, polyphenols, and trace elements (sodium, magnesium, chlorine calcium, vanadium, manganese, copper, and bromine). Polyphenols of areca nut cause collagen fibres to cross-link, making them less susceptible to collagenase degradation.

Aetiopathogenesis

The pathogenesis of OSMF is believed to be multifactorial: (1) Long-term exposure of areca nut causes fibroblasts to produce a high amount of collagen; (2) decreased secretion of collagenase, due to stabilization of collagen by catechin and tannins; (3) production of stable collagen by fibroblasts; (4) increased collagen cross-linking by upregulation of lysyl oxidase; (5) deficiency in collagen phagocytosis, and (6) deficiencies in micronutrients and vitamins.

- **Changes in extracellular matrix (ECM)**: Areca alkaloids induce contraction of the buccal mucosal fibroblast. Arecoline stimulates connective tissue growth factor production through reactive oxygen species (ROS). It increases the production of tissue inhibitor of metalloproteinase-1 (TIMP). At concentrations of 0.4–0.8 mM, arecoline induces cytotoxicity and apoptosis. Prolonged exposure to arecoline suppresses endothelial cell proliferation, leading to impairment of vascular function, decreased vascularity, and eventually atrophy of the epithelium. Hypoxic environment predisposes the tissue to carcinogenesis.

- **Stage-specific alterations in ECM**: Overexpression of collagen type III in the lamina propria and submucosa is seen in the early-stage OSMF. In the intermediate stage, extensive and irregular deposits of elastin are found around muscle fibres. In the advanced stage, collagen type I dominates the ECM.
- **Matrix metalloproteinases (MMPs) and TIMPs**: A balance between MMPs and TIMPs is mandatory to maintain the normal integrity of connective tissue. In OSMF this equilibrium is disturbed, causing increased deposition of ECM.
- **Inflammatory cytokines and growth factors**: Upregulation of cytokines (transforming growth factor, TGF) triggers increased collagen production and decreased matrix degradation. Downregulation of bone morphogenetic protein 7, a known negative modulator of fibrosis, allows more fibrosis.
- **Epithelial mesenchymal transition (EMT)**: Chemical cell injury produces ROS that triggers both MAPK and NF-kB pathways involved in the EMT, leading to secretion of a variety of inflammatory mediators, such as prostaglandin E2, interleukin-6, TNF-a, and TGF-b. HIF-1a enhances EMT and promotes fibrinogenesis by increasing the expression of lysyl oxidase genes.
- **ROS and apoptosis**: At higher arecoline concentrations, oxidative stress may induce epithelial cell death and apoptosis, while sublethal concentrations upregulate the stress responsive genes.
- **Genetic polymorphisms**: Various chromosomal, genetic, and molecular alterations are associated with the pathogenesis of OSMF. A microarray study in OSMF has shown upregulated 716 genes and downregulated 149 genes. Polymorphisms of various genes like cytochrome P450 and genetic polymorphism of lysyl oxidase may also contribute to an increased susceptibility to OSMF.

Other Factors

Indian habit of chewing "pan" has led to the assumption that it causes OSMF, but it has been seen that many afflicted with OSMF have never even used "pan".

Although the data emerged over the past 15 years has expanded our understating of the aetiological role of areca nut, only 1–2% of the population chewing areca nut develop OSMF. This suggests either a genetic predisposition [17] or sensitization of the oral mucosa by iron and/or vitamin B complex deficiencies. Such conditions are much more commonly seen among Indian females, which explains the higher incidence among females. It is for this reason vitamin and iron deficiencies have been given aetiologic importance in OSMF.

It is suspected that continuous prolonged action of mild irritants, such as capsaicin found in green chillies, is also responsible for OSMF. Alcohol consumption and trauma by sharp teeth may enhance the possibility of OSMF. However, it must be remembered that OSMF has also been reported in patients with no habit of tobacco chewing or smoking.

Autoimmunity

Evidence on OSMF supports an autoimmune aetiology. The high frequency of HLA haplotypic pairs in OSMF and scleroderma suggests its immunological derangement. There is increasing evidence that immune response genes are related to HLA complex.

Role of Copper in Pathogenesis of OSMF

- There is a high copper content in areca nut as well as in saliva and serum of areca nut chewers, which suggests its role in OSMF. These copper levels vary in mild OSMF to severe. The enzyme lysyl oxidase, copper-dependent and critical for collagen cross-linking and organization of ECM, appears to be responsible for causing OSMF in areca nut chewers.
- A raised concentration of copper in drinking water stimulates the activity of lysyl oxidase leading to fibrinogenesis [21]. Although copper is rarely found in drinking water, home corrosion of copper piping can contaminate drinking water. This suggests development of OSMF in low socioeconomic strata in the developing countries.

Salivary Pooling

Sites of areca nut chewing and saliva collecting play an important role in the occurrence of OSMF. As the lower lip is a favourable site to place pan masala, and also saliva pools here due to gravity, fibrosis occurs in the lower lip [22].

Symptoms

Prodromal Symptoms

The onset of the condition is insidious and presents as a burning sensation in the mouth on consumption of spicy food. Other early symptoms are blisters, ulcerations, or recurrent stomatitis. Vesicles may be found in the soft palate, anterior faucial pillars, buccal mucosa, or lower lip. Increased salivation, abnormal gustatory sensation, and sometimes even dry mouth can present clinically in the early stages of OSMF.

Later Symptoms

Few years later, there is stiffening of the buccal mucosa, leading to restricted mouth opening, difficulty in swallowing, and inability to whistle or to blow candle. Extension of fibrosis into the oropharynx may cause referred pain in ears or deafness due to occlusion of the Eustachian tubes. Vesicles may sometimes appear even in the later phase. Sometimes a nasal voice may also be observed due to involvement of the nasopharynx.

Clinical Features

- Males are affected more common than females, though both sexes are at risk equally.
- Second or third decade usually but even reported in as early as 8-year-old boy.
- Facial appearance shows sunken cheeks (Fig. 8.1).
- Vesicles develop in the soft palate, anterior faucial pillars, buccal mucosa, or lower lip, with ulcers on rupture. Culture of the vesicular fluid does not reveal any specific organism.
- Oral pain and burning sensation on eating spicy foodstuff.
- Subsequently oral mucosa becomes blanched, opaque, and white, with development of fibrous bands.
- The fibrous bands in buccal mucosa run vertically, while they are circular in the lip, running parallel with the fibres of the orbicularis oris muscle, causing thinning and stiffening of lips. Intense fibres present in the soft palate radiate in an arched manner, from pterygomandibular raphe or anterior faucial pillar across the soft palate to the retromolar area and the base of the tongue.
- Palate and faucial pillars were believed to be the areas initially affected, but it has been observed that the buccal mucosa and lower lip are affected earlier, may be due to the shift of habit from smoking to smokeless tobacco.
- The palate and/or buccal mucosa are the sites with maximum involvement and gingivae and upper lip the least.
- Cheeks may present mottled appearance due to alternating areas of fibrosis and pigmented mucous membrane.
- Vertical fibrous bands may be felt in both cheeks under the mucous membrane, and these can become quite tense when the patient attempts to open mouth.
- Gradual inability to open mouth restricted mouth movements (e.g., eating, whistling, blowing, sucking).
- The soft palate sometimes becomes inelastic and pearly white, with restriction of movements.
- The faucial pillars appear thick, short, and firm, and the palatine tonsils appear pressed between them.

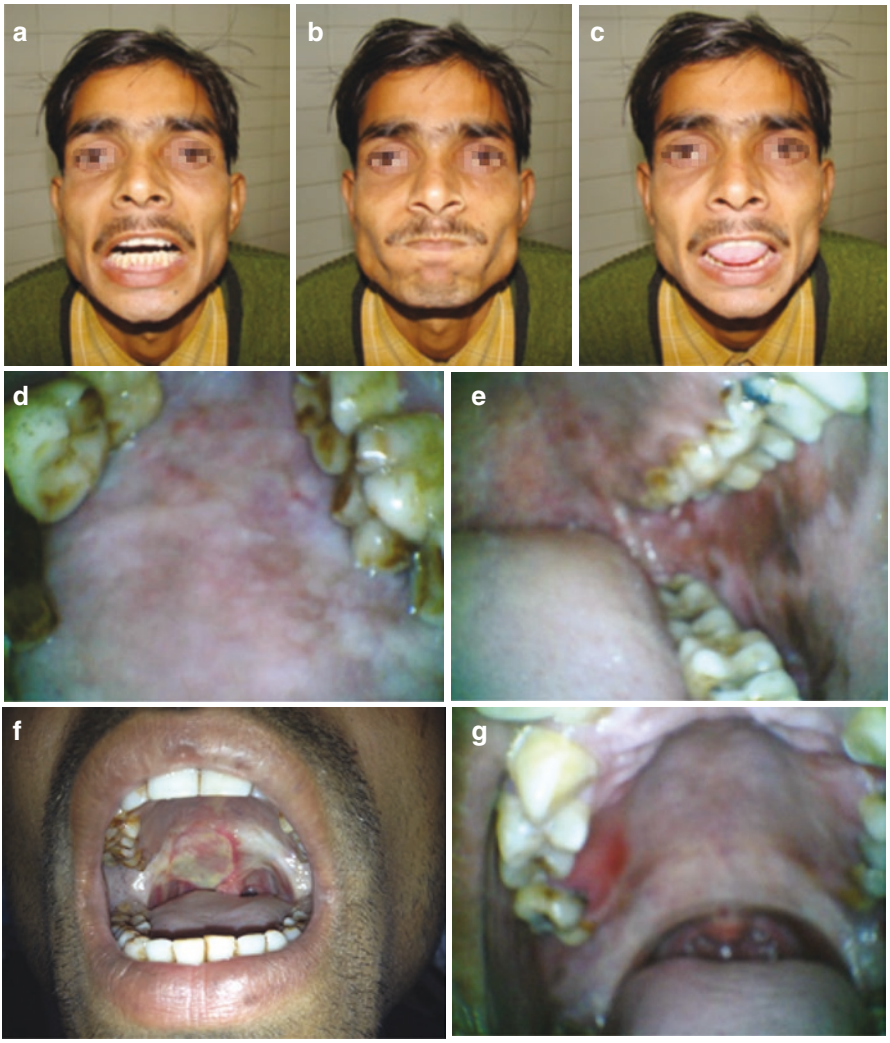


Fig 8.1 Clinical presentation. (**a**) Inability to open mouth. (**b**) Inability to puff cheeks. (**c**) Inability to protrude the tongue. (**d**) Blanched palate. (**e**) Mottled buccal mucosa. (**f**) Blanched soft palate with ulceration. (**g**) Shrunken uvula

- Uvula may be hooked up like a hockey stick, due to fibrosis, appearing budlike and shrunken.
- Impaired tongue movement and sometimes atrophy of the tongue papillae.
- Gingivae and the floor of the mouth may be affected too.
- Oropharynx may appear blanched and indurated.
- Dysphagia to solids (if oesophagus is also involved).
- Xerostomia.
- Altered gustatory sensation.
- Deafness or impaired hearing due to stenosis of the Eustachian tubes.

- Nasal tone.
- Higher incidence of caries and periodontitis due to restriction of access for oral hygiene and dental care.

Laboratory Findings

- ESR raised.
- Anaemia is often present.
- Eosinophilia.
- An increased gamma globulin may be present.

Histological Features [23]

There is epithelial atrophy with juxta-epithelial inflammation. Excessive collagen fibres are seen in lamina propria, submucosa, muscle fibres, and salivary glands.

These histopathologic findings are explained as mucosal changes and submucosal changes:

Mucosal Changes

- Epithelial atrophy with epithelial atypia.
- Loss or sawtoothing of rete ridges and liquefaction degeneration of the basal layer.
- Pigment-containing cells increase in epithelium, and golden-brown pigment granules get scattered in the basal cells and lamina propria.
- Superficial ulceration: The ulceration is replaced by granulation tissue. Signs of secondary infection like necrosis and suppuration can be noted.
- Hyperplastic changes include hyperkeratosis, acanthosis, parakeratosis, basal cell hyperplasia, papillomatosis, and pseudo-epitheliomatous hyperplasia.
- Dysplastic changes include slight variation in size and shape, enlargement of nuclei, prominent nucleoli, and mitotic activity.
- Lamina propria shows fibrosis and hyalinization with a chronic inflammatory infiltrate.

Submucosal Changes

– These are labelled as **mild** if there is early fibrosis, **moderate** if diffuse fibrosis, and **severe** if diffuse fibrosis is with hyalinization and atrophic changes in minor salivary glands and skeletal muscle.
– Increased dilated and congested capillaries.

– Band-like chronic inflammatory infiltrate (lymphocytes, plasma cells, macrophages, neutrophils, and eosinophils) in the upper submucosa.
– Oedema and congestion.
– Subepithelial vesicle formation in some cases.

Radiographic Assessment

An OPG (orthopantomogram) is advised to check for mandibular coronoid process enlargement, as prolonged trismus leads to elongation of the coronoid process.

Classifications

Pindborg [24**]** divided OSMF into three stages:

- **Stage 1**: Stomatitis, erythematous mucosa, vesicles, mucosal ulcers, melanotic mucosal pigmentation, and mucosal petechiae.
- **Stage 2**: Fibrosis occurs in healing vesicles and ulcers.
- **Stage 3**: Leukoplakia in more than 25% of OSMF cases. Speech and hearing deficit due to involvement of the tongue and Eustachian tube.

Mehrotra [25**], clinical grading:**

- **Grade 1**: Stomatitis, burning sensation in buccal mucosa but no detection of fibres
- **Grade 2**: Palpable fibrous bands, involvement of the soft palate, maximum mouth opening 26–35 mm.
- **Grade 3**: Blanched oral mucosa, involvement of the tongue, maximal mouth opening 6–25 mm.
- **Grade 4**: Fibrosis of lips, maximal mouth opening 0–5 mm

Khanna and Andrade [26**]**: Classification based on clinical and histopathological features:

- **Group I**: Very early cases—burning sensation in the mouth, acute ulceration and recurrent stomatitis, and no restriction in mouth opening.
- **Histology**: Fine fibrillar collagen network interspersed with marked oedema, blood vessels dilated and congested, plump young fibroblasts with abundant cytoplasm, and inflammatory cells (polymorphonuclear leukocytes with few eosinophils) aggregated. The epithelium is normal.
- **Group II**: Early cases—buccal mucosa is mottled and marble like, with widespread sheets of palpable fibrous bands, mouth opening of 26–35 mm.
- **Histology**: Juxta-epithelial hyalinization, collagen as thick separate bundles, blood vessels dilated and congested, moderate amount of young fibroblasts,

inflammatory cells (polymorphonuclear leukocytes, few eosinophils, and occasional plasma cells), and flat or short epithelial rete pegs with varied keratinization.

- **Group III**: Moderately advanced cases—trismus, mouth opening 15–25 mm, buccal mucosa pale firm, atrophy of vermilion border, vertical fibrous bands palpable at soft palate, pterygomandibular raphe, and anterior faucial pillars.
- **Histology**: Juxta-epithelial hyalinization, thick collagen bundles, residual edema, constricted blood vessels, mature fibroblasts with scanty cytoplasm and spindle-shaped nuclei, inflammatory exudates (lymphocytes and plasma cells), atrophic epithelium with loss of rete pegs, and muscle fibres with thick and dense collagen fibres.
- **Group IVA**: Advanced cases—severe trismus, mouth opening less than 15 mm, thick faucial pillars, shrunken uvula, restricted tongue movement, and circular band around lip and mouth.
- **Group IVB**: Advanced cases—hyperkeratotic leukoplakia and/or squamous cell carcinoma.
- **Histology**: Collagen hyalinized smooth sheet, extensive fibrosis, obliterated mucosal blood vessels, eliminated melanocytes, absent fibroblasts within the hyalinized zones, total loss of epithelial rete pegs, presence of mild-to-moderate atypia, and extensive degeneration of muscle fibres.

Diagnosis: OSMF is diagnosed on the basis

- Clinical features
- Histological features
- Radiographic features

Management

The management goal is to treat the signs and symptoms, inhibit progression, and reduce risk of malignant transformation, although various treatment methods have been proposed. The current protocol consists of:

- Preventive: discontinuation of habit and counselling
- Medical treatment
- Nutritional supplementation
- Surgical management
- Physiotherapy

Abstinence from the habit of chewing areca nut is the first step towards treatment of OSMF. Instructions should be given to minimize consumption of spicy foods and maintain proper oral hygiene. Explanation about the probable malignant potential and counselling for de-addiction is important. Any sharp teeth or cusps are rounded off to prevent trauma to the cheek. Extraction of all third molars is recommended to avoid undue trauma on the inflamed and atrophied mucosa.

Medical Management

Medical treatment is designed to increase maximal inter-incisal mouth opening and alleviate burning sensation, vesiculation, and fibrosis. Based on the possible aetiopathogenesis, drugs, such as steroids, enzymes, antioxidants, vitamins, and microelements have been advocated to treat OSMF [27].

Steroids

Steroids have been used extensively over the past decades in the treatment of OSMF because of their anti-inflammatory properties. These include short-acting (hydrocortisone), intermediate-acting (triamcinolone), and long-acting (betamethasone and dexamethasone).

Cytokines and growth factors produced by inflammatory cells induce proliferation of fibroblasts, upregulate collagen synthesis, and downregulate collagenase production. Glucocorticoids inhibit the generation of these inflammatory factors and also increase their apoptosis, thereby relieving the symptoms but fail to reverse the abnormal deposition of fibrotic tissues or recover the suppleness of mucosa. Hence, the use of steroids is associated with a high relapse rate and unwanted side effects on prolonged use. Steroids are therefore used as an adjunct therapy [28].

Modalities of Corticosteroids Used in the Treatment [29]

Topical

Triamcinolone acetonide—0.1%
Betamethasone—0.5%

Systemic

Prednisolone—20 mg/day
Dexamethasone—4 mg/day
Triamcinolone—12 mg/day

Intra-lesional

Dexamethasone—4 mg/ml
Triamcinolone—40 mg/ml
Hydrocortisone—25 mg/ml

Short-acting drugs: Hydrocortisone intra-lesional injection 1.5 cm^3 given once a week for a duration of 12 weeks has proven to be beneficial. Systemic corticosteroids are useful in only early and mild cases.

Intermediate-acting drugs: Topical triamcinolone acetonide 0.1% and local injection of triamcinolone acetonide can be used in the early stages of OSMF.

Long-acting drugs: Dexamethasone 4 mg intra-lesional injections are given twice a month for 2–3 months and also if given in combination with hyaluronidase give better long-term results. Betamethasone is given as 4 mg/ml intra-lesional injections biweekly. It is more effective in combination with lycopene or hyaluronidase and vitamin E.

Enzymes

Collagenase is a lysosomal enzyme that can degrade esters, proteins, polysaccharides, and glycosides. Collagenase treatment has been reported to be approximately fivefold more effective than triamcinolone [29]. A 2 mg of collagenase dissolved in 1 ml of distilled water is used for injection and has shown significant improvement in mouth opening and hypersensitivity to spices, sour, cold, and heat. Adverse reactions like pain swelling and trismus may be seen after injections of collagenase which is considered to be an allergic reaction of this agent.

Hyaluronidase has shown a much faster but short-term response in improving the burning sensation and ulceration than dexamethasone. It acts by depolymerizing hyaluronic acid, the ground substance in connective tissue, lowering the viscosity of the intercellular cement, and thus reducing collagen formation. Intra-lesional injections of 1500 IU of hyaluronidase mixed with 2% lignocaine twice daily for 10 weeks have been tried with satisfactory results in improving mouth opening.

Chymotrypsin, an endopeptidase that hydrolyzes ester and peptide bonds, has also been used as a proteolytic and anti-inflammatory agent in the treatment of OSMF. Local injection of chymotrypsin, such as Chymotrypsin (5000 IU), twice weekly as submucosal injections for 10 weeks has proved to be successful in treating OSMF.

Peripheral Vasodilators

Pentoxifylline, a methylxanthine derivative with vasodilating properties and ability to reduce blood viscosity, can suppress leukocyte function, alter fibroblast physiology, and stimulate fibrinolysis. Pentoxifylline 400 mg three times daily, as coated, sustained release tablets, has been used as an adjunct therapy for improvement in mucosal suppleness.

Buflomedil, another vasoactive agent, has shown quicker symptomatic relief but with little improvement in mouth opening.

Nylidrin hydrochloride, a peripheral vasodilator, diffuses fibrosis by relieving the local ischemic effect and helping the nutritional substances to be transported to the affected tissues.

Tea pigments, oxidized polyphenols derived from tea leaves, also decrease blood viscosity and improve microcirculation. Tea-pigment tablets have shown an overall success rate of 58.8% in the treatment of OSMF.

Placental Extracts (Placentrex)

Placentrex, an aqueous extract of human placenta, can be subdivided into four fractions such as aqueous, lipoidal, immune gamma globulins, and tissue coagulants. The aqueous extract of placenta acts as a biogenic stimulator in the cellular metabolism and anti-inflammatory and analgesic, increases blood circulation and tissue vascularity, arrests growth stagnation, and lowers the immune response factor.

Aqueous extract of fresh human placenta contains enzymes, nucleotides, vitamins, amino acids, steroids, fatty acids, and trace elements: cadmium, potassium, calcium, magnesium, copper, iron, phosphorous, and silicone. A 2 cm^3 of placentrax injection intra-lesional at weekly intervals for 10 weeks has been found to be superior to cortisone. A combination of dexamethasone, hyaluronidase, and placental extract gives better results than a single drug.

Antioxidants

Antioxidants reduce the free radical reaction that can cause DNA mutations and changes in lipid peroxidation of cellular membranes and changes in enzymatic activities.

Lycopene, an unsaturated carotenoid that gives red colour to the tomatoes, is a powerful antioxidant, with about twice the potency as of β-carotene, and has shown anti-proliferative properties both in animals and in vitro studies. It has shown to modulate dysplastic changes by inhibition of abnormal fibroblasts, upregulation of lymphocyte resistance to stress, and suppression of inflammatory response. A 16 mg of lycopene daily in 2 divided doses for 2 months or in combination with intralesional injections of betamethasone has shown marked improvement in mouth opening and associated symptoms.

Beta-carotene is the precursor of vitamin A and a powerful antioxidant. Topical application improves the integrity of oral epithelium as well as induces reversal of dysplastic epithelium. Regular intake of beta-carotene combined with routine measures considerably reduces the risk of malignant transformation. Six weeks of beta-carotene and vitamin E tablets taken thrice daily have shown a marked increase in mouth opening and tongue protrusion in OSMF.

Alpha-lipoic acid is a sulphur-containing substance, acts as a coenzyme in the Kreb's cycle, and is claimed to be the near-perfect antioxidant. It has a good potential action of scavenging free radicals and can dissolve in both water and fat. Alpha-lipoic acid 100 mg, 1 capsule per day for 30 days, has shown reduction in burning sensation and improved mouth opening.

Antoxid tablet (containing beta-carotene 50 mg, vitamin A 2500 IU, vitamin E 10 IU, vitamin C, zinc, manganese, and copper) given thrice daily for 6 weeks has been a significant clinical improvement in patients with OSMF.

Recombinant Human Interferon Gamma (γ-IFN)

Interferon-γ (IFN-γ), an anti-fibrosis factor, causes downregulation of fibroblast proliferation and collagen synthesis and upregulation of anti-fibrotic cytokine and collagen synthesis in the basal layer of epithelium and lamina propria. Patients treated with γ-IFN showed improvements in mouth opening of 8 ± 4 mm (42%) [30]. Injections of IFN gamma produce headache, flu-like symptoms, and myalgia. Intra-lesional injection of γ-IFN (0.01–10.0 U/ml) is advocated three times daily for 6 months.

Immunized Milk

Immunized milk is skimmed cow milk, immunized with multiple human intestinal bacteria to gain good anti-inflammatory effect. It contains vitamins A, C, B1, B2, B6, and B12, nicotinic acid, pantothenic acid, folic acid, micronutrients (iron, copper, zinc), and 20–30% higher concentration of IgG type I antibody than in commercial milk. Its anti-inflammatory properties suppress the inflammation and modulate cytokine production. Tai et al. [31] advocated 45 g of immunized cow milk twice daily, for 3 months, and reported 69.2% success by improving the maximum mouth opening by more than 3 mm.

Stem Cell Therapy

Intra-lesional injection of autologous bone marrow stem cells induces local angiogenesis, decreases fibrosis, and improves mouth opening [32, 33].

Herbal Extracts

Turmeric

Turmeric (haldi), a rhizome of *Curcuma longa*, is a yellow-orange spice full of flavour. An orange pulp contained in the rhizome constitutes the source of turmeric medicinal powder. Components of turmeric are named curcuminoids and include curcumin [34]. Curcumin inhibits the products of inflammation such as prostaglandin and leukotrienes by inhibiting cyclooxygenase and lipoxygenase pathways of inflammation. It has a scavenging effect on superoxide free radicals, hydroxyl radicals, and lipid peroxidation; and its fibrinolytic action leads to inhibition of lipid peroxidation, checking cellular proliferation, and inhibition of collagen synthesis.

Hastak [35] studied the effect of turmeric oil (600 mg), its alcohol extracts (3 g), and oleoresin (600 mg) on cytogenetic damage in OSMF after daily intake for 3 months and concluded that turmeric oil with oleoresin acts synergistically in vitro and protects DNA damage.

Aloe vera

Aloe vera is a mannoprotein that contains many wound healing hormones. The polysaccharides in the gel of the leaves have wound healing, anti-inflammatory, anticancer, immuno-modulatory, and gastroprotective properties. It has shown to reduce the burning sensation and gradual recovery of mouth opening. It is relatively safe and can be applied topically in the treatment for OSMF. Topical application of 5 mg of aloe vera thrice daily for 3 months has been reported to reduce burning sensation and improve mouth opening.

Oxitard

Oxitard contains various plant extracts and oils. A dose of 2 oxitard capsules twice daily for a period of 3 months gives significant increase in mouth opening along with decrease in pain [34].

Spirulina

Spirulina, blue-green algae, with a rich natural source of proteins, carotenoids, and other micronutrients [36], has antioxidant properties with high amount of beta-carotene and superoxide dismutase for effective use in OSMF.

Nutritional Support

The rationale of giving nutrients in OSMF patients is to overcome the deficiencies and promote normal cellular processes to protect against carcinogenesis.

1. Supplementing diet with foods rich in vitamins A, B complex, and C and iron.
2. Advice green leafy vegetables, red tomatoes, and fresh fruits.
3. Advice green tea.
4. High-protein diet.
5. Vitamin A is important for maintaining the normal growth and repair of epithelial tissues. It helps in the epithelial differentiation by mucous secretary and keratinization tissues, and in adequate concentration, it delays or even reverses the progress of premalignant cells to cells with invasive malignant potential.
6. Vitamin B complex boosts metabolism, enhances the immune system, and encourages cell growth and division.
7. Vitamin C acts in wound healing, for the integrity of cellular immune responses and anti-inflammatory activities.
8. Minerals like *zinc* are essential for DNA synthesis and cell division and as a constituent of many enzymes. The amount of zinc greatly increases during tissue repair. Moreover, zinc is the antagonist of copper that is released from betel quid to induce lysyl oxidase activity, upregulate collagen synthesis, facilitate collagen

cross-linking, and inhibit collagen degradation. **Magnesium** plays essential roles in stabilizing effects on excitable membranes.

Surgical Management

Surgical treatment is designed to improve the extent of mouth opening and includes excision of fibrous bands, coronoidectomy, and reconstruction of the surgical defect with local or distant flaps. However, recurrence may occur because of secondary contracture of the grafted tissue, resulting in restricted mouth opening.

Surgical measures, such as forceful mouth opening or incising the fibrotic bands under general anaesthesia without any grafting, cause even more fibrosis. Submucosal resection of fibrotic bands and replacement with a graft are the better options, and coronoidectomy, followed by physiotherapy, further improves mouth opening.

Resection of bands: An intraoral incision is made in the buccal mucosa at the level of occlusal plane, 1 cm away from the corner of the mouth to anterior faucial pillars to cut the fibrous bands in the cheek mucosa (Fig. 8.2). After fibrous bands are released, all third molars present are extracted. Maximum mouth opening with the help of Ferguson or mouth gag is recorded.

LASER can also be used for fibrotomy instead of a surgical knife with an advantage of minimal bleeding and no psychological fear of surgery to the patient.

Coronoidectomy: Coronoidectomy with temporal myotomy is recommended to improve mouth opening. The coronoid processes are approached through the same

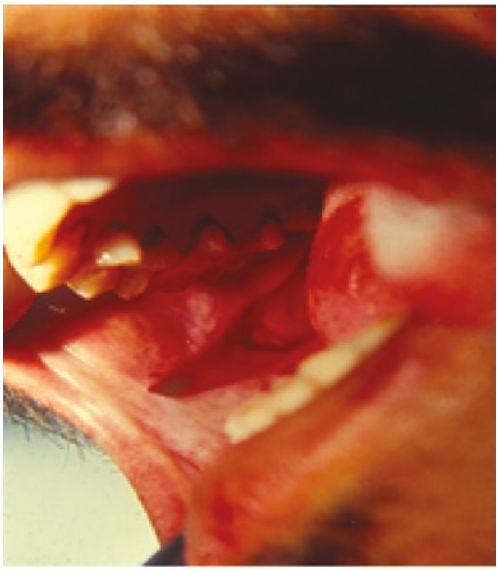


Fig 8.2 Fibrotomy

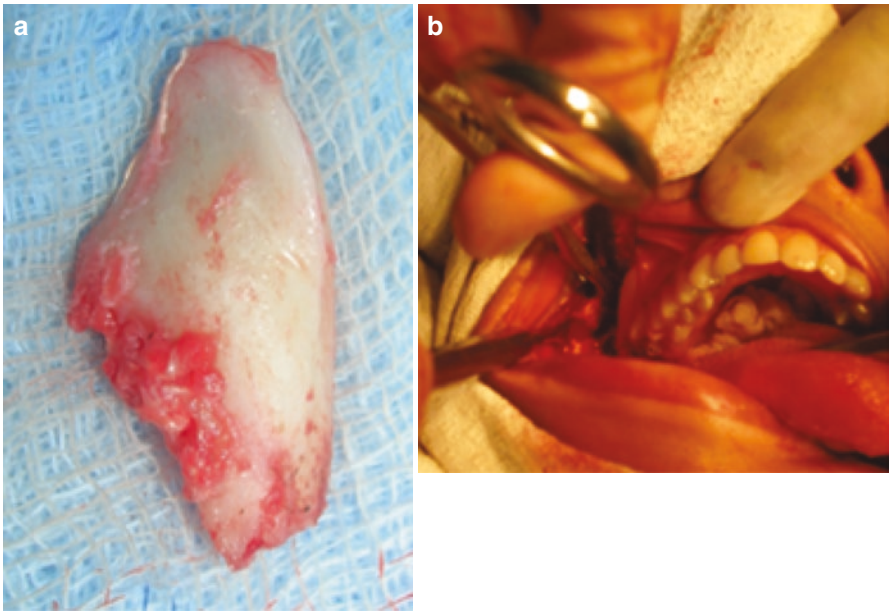


Fig 8.3 (**a**) Coronoidectomy. (**b**) Coronoid process

incision by stripping the temporalis tendon attachment on the anterior border of ramus (Fig. 8.3). Coronoid process is held with forceps, and osteotomy is made extending from the anterior border of ramus to the depth of the sigmoid notch. After completion of osteotomy, coronoid is placed on traction with Kocher's forceps and temporalis muscle, and tendon is detached to facilitate the removal of coronoid. The same procedure is carried bilaterally if needed.

The mean preoperative inter-incisal opening of 14.40 mm in OSMF patients has been reported to increase the mouth opening to 24.60 mm with fibrotomy alone and to 35–44.80 mm after unilateral and bilateral coronoidectomy, respectively [37].

Reconstruction of Surgical Defect

In order to avoid contracture due to scarring after fibrotomy, it is always recommended to reconstruct the surgical defect. Various options of flaps are available for the coverage of defect so produced:

- Buccal fat pad
- Nasolabial flap
- Superficial temporal fascia flap
- Tongue flap
- Split skin graft
- Dermal fat graft

- Collagen graft
- Radial forearm flap

Buccal Fat Pad

Heister [38] was the first to identify buccal fat pad (BFP) and believed it to be glandular in nature and so called it "glandula molaris". In 1801, Bichat described BFP as a fatty tissue. Its use increased after Egyedi described methods of using BFP as a versatile pedicle graft for closure of oronasal and oroantral communications as well as postsurgical maxillary defects [39]. Tideman detailed its anatomy, vascular supply, and surgical technique. It offers the advantage of a rich blood supply to promote healing. The grafted fat pad closes the dead space area, promotes granulation, and limits scar contraction. Also, BFP offers strong anti-infective and reconstructive advantages [40] for medium-sized (5 × 4 cm) defects in the buccal mucosa.

An incision is made over oral mucosa adjacent to the maxillary vestibule in the region of the second and third molars, preventing damage to the parotid duct (Fig. 8.4). Blunt dissection through the buccinator muscle leads to the body or its buccal extension, which is gently teased into the defect, taking care not to rupture its delicate capsule. Adequate volume of BFP ensures tension-free closure using Vicryl sutures at the periphery of the graft.

Nasolabial Flap

The nasolabial flap is a pedicled, elliptical transposition flap in the nasolabial fold region supplied by the angular artery. It serves to reconstruct small- to medium-size defects in the oral cavity with minimal aesthetic consequences. The rich blood supply allows it to even cover large defects with cosmetic results [41].

It is designed in sufficient length and width to fill the entire defect without tension. Incision is limited to the subdermal tissues to leave the base of flap intact.

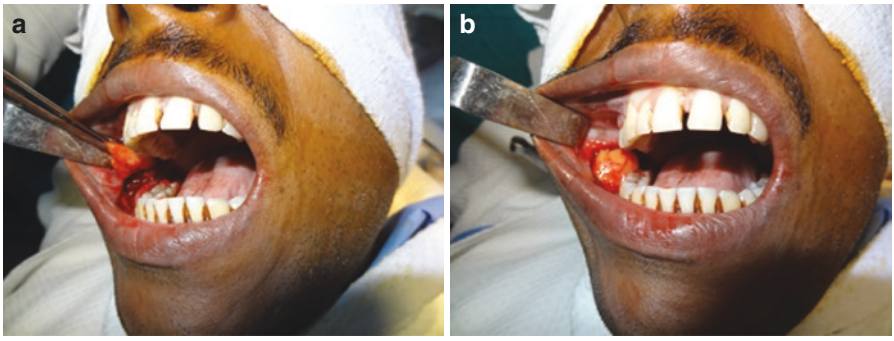


Fig 8.4 (**a**) Buccal fat pad graft pedicled. (**b**) Positioned to cover the surgical defect

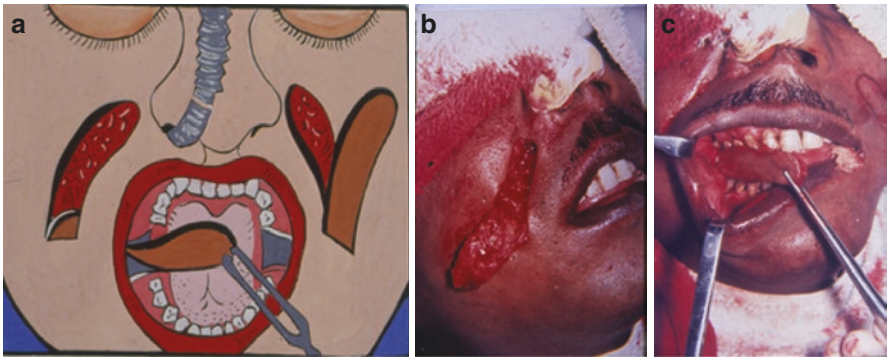


Fig 8.5 (**a**) Nasolabial flap design. (**b**) Incision made. (**c**) Nasolabial flap rotated

Extended nasolabial flaps reach up to the inferior border of the mandible and are raised bilaterally, taking care not to disturb the facial muscles [42]. A tunnel made near the base of the flap facilitates its entry in the oral cavity (Fig. 8.5). De-epithelialization and rotation of the flap in the oral cavity allow closure of the defect and are sutured with 3-0 black silk. The skin is undermined to facilitate its subcuticular closure using 4-0 Prolene. Pressure dressing using antibiotic-soaked sterile gauze or betadine-soaked gauze is placed over the graft intraorally to keep it in contact with mucosal defect. Sutures are removed after 10 days of surgery [43].

Superficial Temporal Fascia Flap

A preauricular incision in the hair-bearing area is extended into the temporal region. Further dissection allows the development of the superficial temporal fascia flap (Fig. 8.6). The superficial temporal fascia flap is passed below the zygomatic arch to be brought intraorally and sutured. This procedure can be performed bilaterally to bring in good blood supply to the fibroses area and improve the clinical result [44].

Tongue Flap

The pedicled tongue flap is used for covering oral defects as a two-stage procedure. Either the anterior two third or posterior third of the tongue can be used for the tongue flap. After around 21 days, the tongue pedicle is divided from its base. All third molars are extracted to prevent trauma to the tongue flap.

The tongue is infiltrated with local anaesthesia solution containing adrenaline (epinephrine). On the dorsolateral aspect of the tongue, an incision is made parallel to the midline of the tongue up to 1 cm behind the tip of the tongue (Fig. 8.7). On the lateral margin of the tongue, it is taken down inferiorly up to the last molar. Deep elliptical tongue flap is raised and rotated outward laterally to cover the raw area in the cheek and sutured. The wound in the tongue is primarily closed. Similar procedure is undertaken on the contralateral side.

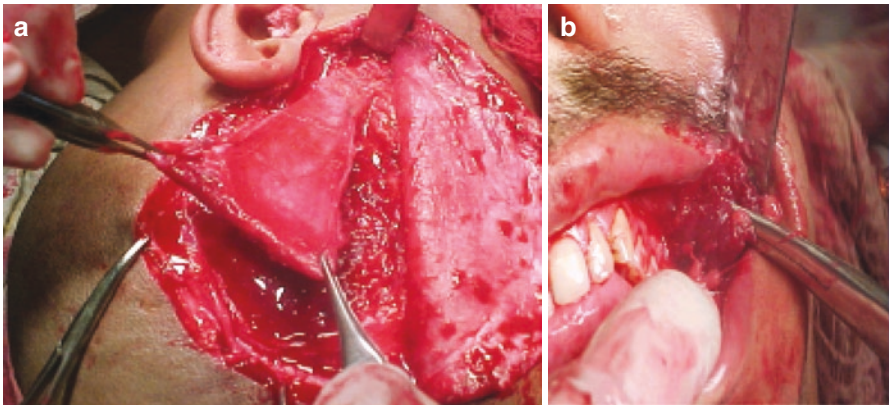


Fig 8.6 (**a**) Superficial temporal flap raised (**b**) Position intraoral

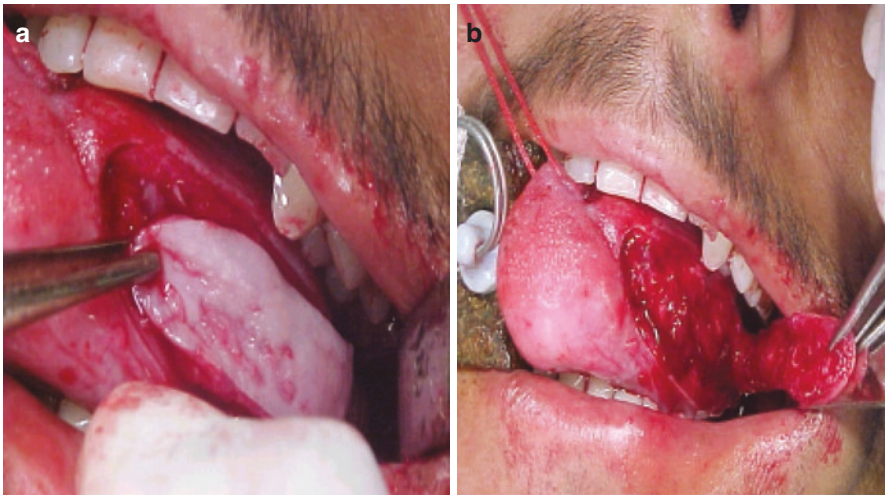


Fig 8.7 (**a**) Tongue flap incision. (**b**) Tongue flap raised

This flap has a high success rate due to its viability and resistance to OSMF. The postoperative mobility of the tongue and articulation become normal in about 4–6 weeks, and dullness of taste sensation is negligible [45]. The reduction in the bulk of the tongue is regained with tongue movements and exercises.

Split Skin Graft

Split skin graft can be easily harvested from the thigh laterally using Humby's knife or approximately 0.014–0.018-in. thick surgical dermatome (Fig. 8.8). Donor site is dressed with antibiotic-impregnated gauze, while the harvested graft is placed on a

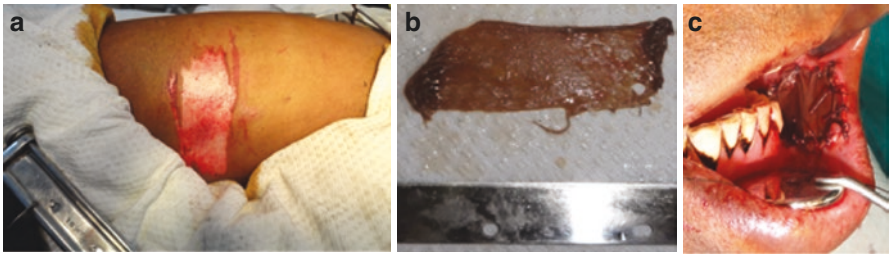


Fig 8.8 (**a**) Split skin harvesting. (**b**) Split skin graft. (**c**) Sutured onto defect

wet wooden slab to be cut into desired size and shape [45]. Puncture holes are made before suturing it to the mucosal margins. A trans-buccal quilt suture is important to minimize the dead space and maintain its close contact with the wound bed. A sterile antibiotic-soaked gauze is placed intraorally to cover the graft for the next few days.

Dermal Fat

An elliptical incision is made supero-medial to iliac crest in the abdomen, and the epidermis is dissected finely and discarded. The underlying dermis and subcutaneous fat are dissected as a dermis-fat graft and sutured intraorally, such that the dermal layer faces the oral cavity (Fig. 8.9).

Collagen Sheath

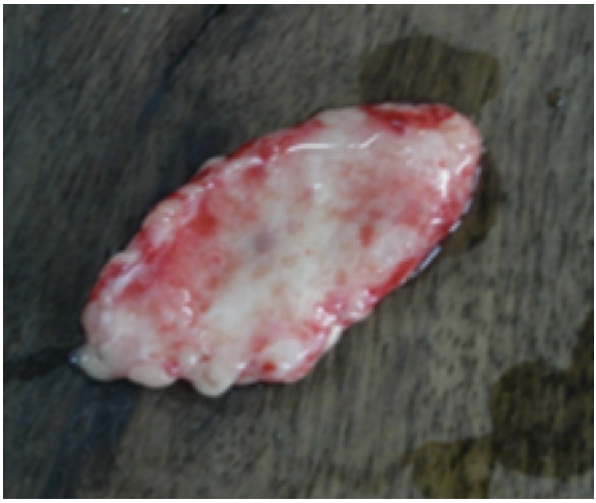
A commercially available collagen sheath may be used as a dressing to cover the surgical defect and sutured to the surrounding mucosa on its edges. A pompom dressing holds the sheath closely adapted to the wound bed. It is shown to allow a faster epithelialization (Fig. 8.10).

Radial Forearm Flap

A bipaddled radial forearm flap can be obtained with at least 4 cm pedicle for microvascular anastomosis to the nearest facial artery and vein. This surgery is simultaneously performed by two teams. The proximal flap is designed to cover the ipsilateral buccal mucosal defect, while the distal flap covers the contralateral buccal defect. The length of the "bridge pedicle" between these two flaps should always be 8–10 cm [46].

Postoperatively, these patients are kept on nasogastric feeding for 10 days [47]. Mouth-opening exercises are started on the fifth postoperative day and continued for 6 months at least.

Fig 8.9 Dermal fat graft



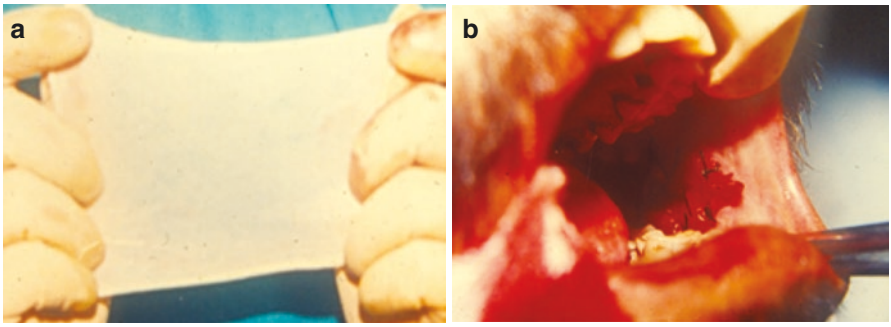


Fig 8.10 (**a**) Collagen sheath. (**b**) Collagen sheath in position

Physiotherapy

Oral physiotherapy supports the surgical treatment of OSMF and helps in improving the range of mouth opening and preventing relapse. Physiotherapy includes forceful mouth opening, heat, or ultrasound massage therapy.

Massage therapy improves the elasticity of fibrous tissues and mobilizes scar tissues. This gentle tissue manipulation improves cheek, tongue, and lip extensibility.

Muscle stretching exercises for the mouth prevent further restriction of mouth movements and relapse. This can be performed by using mouth gag and acrylic surgical stent, ballooning of the mouth, whistling, lip exercising, hot water gargling, and gradually increasing the number of inter-positioned spatula between the teeth. It is recommended to exercise at least for 6 months to get the result.

Heat-shortwave/microwave diathermy: Lukewarm water, hot rinses, or selective deep heating therapies like shortwave or microwave diathermy improve the

suppleness of the oral mucosa, through separation of collagen fibres and softening of the cementing substance. Microwave diathermy is superior to shortwave, as it allows selective heating of the juxta-epithelial connective tissue. Microwave diathermy at 2450 MC/s daily for 20 min at each site, with 20–25 W of energy, 15 sittings, can give good results in moderately advanced but poor in very advanced cases.

Ultrasound: Ultrasound allows increased cell membrane permeability by altering sodium and potassium ion gradients. This increases vasodilatation, accelerates lymph flow, decreases inflammation, and stimulates metabolism. Ultrasound over the cheek for 15 consecutive days, using a 5 cm diameter transducer head for 3–4 min to each side at a frequency of 3 MHz and intensity of 0.5–3 w/sqcm, accelerates healing, increases the extensibility of collagen fibres, and provides pain relief by selectively raising the temperature.

References

1. Li N, Jian X, Hu Y, Xu C, Yao Z, Zhong X. Discovery of novel biomarkers in oral submucous fibrosis by microarray analysis. Cancer Epidemiol Biomarkers Prev. 2008;17(9):2249–59.
2. Arakeri G, Brennan PA. Oral submucous fibrosis: an overview of the aetiology, pathogenesis, classification, and principles of management. Br J Oral Maxillofac Surg. 2013;51(7):587–93.
3. Warnakulasuriya S, Johnson NW, van der Waal I. Nomenclature and classification of potentially malignant disorders of the oral mucosa. J Oral Pathol Med. 2007;36(10):575–80.
4. Schwartz J. Atrophia Idopathica mucosa oris. In: Proceedings of the 11th International Dental Congress; 1952. London, UK.
5. Pindborg JJ, Sirsat SM. Oral submucous fibrosis. Oral Surg Oral Med Oral Pathol. 1966;22(6):764–79.
6. Tilakaratne WM, Ekanayaka RP, Warnakulasuriya S. Oral submucous fibrosis: a historical perspective and a review on aetiology and pathogenesis. Oral Surg Oral Med Oral Pathol Oral Radiol. 2016;122(2):178–91.
7. Ranganathan K, Uma Devi M, Joshua E, Kirankumar K, Saraswathi TR. Oral submucous fibrosis: a case control study in Chennai South India. J Oral Pathol Med. 2004;33:274–7.
8. Gupta MK, Mhaske S, Ragavendra R. Imtiyaz. Oral submucous fibrosis - current concepts in etiopathogenesis. People J Sci Res. 2008;1:39–44.
9. Aziz SR. Oral submucous fibrosis: case report and review of diagnosis and treatment. J Oral Maxillofac Surg. 2008;66:2386–9.
10. Zhang SS, Li WH, Gao YJ, Liu ZW, Liu L, Tang JQ, et al. Betel-quid and oral submucous fibrosis: a cross-sectional study in Hunan province, China. J Oral Pathol Med. 2012;41:748–54.
11. Reichart PA, Nguyen XH. Betel quid chewing, oral cancer and other oral mucosal diseases in Vietnam: a review. J Oral Pathol Med. 2008;37:511–4.
12. Yen AM, Chen SL, Chiu SY, Chen HH. Association between metabolic syndrome and oral pre-malignancy: a community and population-based study (KCIS No. 28). Oral Oncol. 2011;47:625–30.
13. Mehrotra D, Kumar S, Mishra S, Kumar S, Mathur P, Pandey CM, Pandey A, Chaudhry K. Pan masala habits and risk of oral precancer: a cross-sectional survey in 0.45 million people of North India. J Oral Biol Craniofac Res. 2017;7(1):13–8.
14. Yang S-F, et al. Changes in prevalence of precancerous oral submucous fibrosis from 1996 to 2013 in Taiwan: a nationwide population-based retrospective study. J Formosan Med Assoc. 2018;117:147. https://doi.org/10.1016/j.jfma.2017.01.012.

15. Paymaster JC. Cancer of the buccal mucosa; a clinical study of 650 cases in Indian patients. Cancer. 1956;9(3):431–5.
16. Aziz SR. Coming to America: betel nut and oral submucous fibrosis. JADA. 2010;141:423–8.
17. Ho MWS. Patients with both oral leukoplakia and oral submucous fibrosis had a higher rate of malignant transformation compared to patients with oral leukoplakia or oral submucous fibrosis alone. J Evid Based Dent Pract. 2013;13(4):183–4.
18. Shiau YY, Kwan HW. Submucous fibrosis in Taiwan. Oral Surg Oral Med Oral Pathol. 1979;47(5):453–7.
19. Rajendran R. Oral submucous fibrosis: etiology, pathogenesis, and future research. Bull World Health Organ. 1994;72(6):985–96.
20. Mehrotra D, Kumar S, Agarwal GG, Asthana A, Kumar S. Odds ratio of risk factors for oral submucous fibrosis in a case control model. Br J Oral Maxillofac Surg. 2013;51:e169–73.
21. Arakeri G, Hunasgi S, Colbert S, Merkx MAW, Brennan P. Role of drinking water copper in pathogenesis of oral submucous fibrosis: a prospective case control study. Br J Oral Maxillofac Surg. 2014;52(6):507–12.
22. Arakeri G, Colbert S, Patil SG, Hale B, Merkx MAW, Brennan P. Salivary pooling: is it specific to particular regions in oral submucous fibrosis. Br J Oral Maxillofac Surg. 2015;53(3):275–8.
23. Isaac U, Isaac JS, Khoso NA. Histopathologic features of oral submucous fibrosis: a study of 35 biopsy specimens. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2008;10:556–60.
24. Pindborg JJ. Oral submucous fibrosis: a review. Ann Acad Med Singapore. 1989;18(5):603–7. Review.
25. Mehrotra D, Prandhan R, Gupta S. Retrospective comparison of surgical treatment modalities in 100 patients with OSMF. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2009;107:e1–10.
26. Khanna JN, Andrade NN. Oral submucous fibrosis: a new concept in surgical management. Report of 100 cases. Int J Oral Maxillofac Surg. 1995;24(6):433–9.
27. Shevale VV, Kalra RD, Shevale VV, Shringarpure MD. Management of oral sub-mucous fibrosis: a review. Ind J Dent Sci. 2012;4:107–14.
28. Dayanarayana U, Doggalli N, Patil K, et al. Non surgical approaches in treatment of OSF. J Dent Med Sci. 2014;13(11):63–9.
29. Lin HJ, Lin JC. Treatment of oral submucous fibrosis by collagenase: effects on oral opening and eating function. Oral Dis. 2007;13(4):407–13.
30. Haque MF, Meghji S, Nazir R, Harris M. Interferon gamma (IFN-gamma) may reverse oral submucous fibrosis. J Oral Pathol Med. 2001;30(1):12–21.
31. Tai YS, Liu BY, Wang JT, Sun A, Kwan HW, Chiang CP. Oral administration of milk from cows immunized 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.
32. Sankaranarayanan S, Padmanaban J, Ramachandran CR, Manjunath S, Baskar S, Senthil Kumar R, Senthil Nagarajan R, Murugan P, Srinivasan V, Abraham S. Autologous bone marrow stem cells for treatment of oral sub-mucous fibrosis - a case report. Sixth Annual Meeting of International Society for Stem Cell Research (ISSCR), Philadelphia, PA USA. 2008.
33. Nagpal M, Sood S. Role of curcumin in systemic and oral health: an overview. J Nat Sci Biol Med. 2013;4(1):3–7.
34. Patil S, Santosh BS, Maheshwari S, Deoghare A, Chhugani S, Rajesh PR. Efficacy of oxitard capsules in the treatment of oral submucous fibrosis. J Can Res Ther. 2015;11(2):291–4.
35. Hastak K, Lubri N, Jakhi SD. Effect of turmeric oil and turmeric oleoresin on cytogenic damage in patients suffering from oral submucous fibrosis. Cancer Lett. 1997;116:265–9.
36. Mulk BS, Deshpande P, Velpula N, Chappidi V, Chintamaneni RL, Goyal S. Spirulina and pentoxifylline - a novel approach for treatment of oral submucous fibrosis. J Clin Diagn Res. 2013;7(12):3048–50.
37. Gupta H, Tandon P, Kumar D, Sinha VP, Gupta S, Mehra H, Singh J. Role of coronoidectomy in increasing mouth opening. Natl J Maxillofac Surg. 2014;5(1):23–30.
38. Heister L. Compendium anatomicum. In: Weberi GC. Norimbergac, Germany; 1732. p. 146.

39. Jain MK, Ramesh C, Sankar K, Lokesh Babu KT. Pedicled buccal fat pad in the management of oroantral fistula: a clinical study of 15 cases. Int J Oral Maxillofac Surg. 2012;41:1025–9.
40. Rai A, Datarkar A, Rai M. Is buccal fat pad a better option than nasolabial flap for reconstruction of intraoral defects after surgical release of fibrous bands in patients with oral submucous fibrosis? A pilot study: a protocol for the management of oral submucous fibrosis. J Craniomaxillofac Surg. 2014;42(5):e111–6.
41. Borle RM, Nimonkar PV, Rajan R. Extended nasolabial flaps in the management of oral submucous fibrosis. Br J Oral Maxillofac Surg. 2009;47(5):382–5.
42. Agrawal D, Pathak R, Newaskar V, Idrees F, Waskle R. A comparative clinical evaluation of the buccal fat pad and extended nasolabial flap in the reconstruction of the surgical defect in oral submucous fibrosis patients. J Oral Maxillofac Surg. 2018;76:676.e1. https://doi.org/10.1016/j.joms.2017.11.013. ISSN: 0278-2391.
43. Kothari MC, Hallur N, Sikkerimath B, Gudi S, Kothari CR. Coronoidectomy, masticatory myotomy and buccal fat pad graft in management of advanced oral submucous fibrosis. Int J Oral Maxillofac Surg. 2012;41(11):1416–21.
44. Ramadass T, Manokaran G, Pushpala SM, Narayanan N, Kulkarni GN. Oral submucous fibrosis - new dimensions in surgery. Ind J Otolaryngol Head Neck Surg. 2005;57(2):99–102.
45. Mehrotra D, Pradhan R, Mohammad S, Jaiswara C. Random control trial of dermis-fat graft and interposition of temporalis fascia in the management of temporomandibular ankylosis in children. Br J Oral Maxillofac Surg. 2008;46:521–6.
46. Lee JT, Cheng LF, Chen PR, Wang CH, Hsu H, Chien SH, Wei FC. Bipaddled radial forearm flap for the reconstruction of bilateral buccal defects in oral submucous fibrosis. Int J Oral Maxillofac Surg. 2007;36(7):615–9.
47. Warnakulasuriya S, Kerr AR. Oral submucous fibrosis: a review of the current management and possible directions for novel therapies. Oral Surg Oral Med Oral Pathol Oral Radiol. 2016;122(2):232–41.