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Management Of Oral Submucous Fibrosis – An Update

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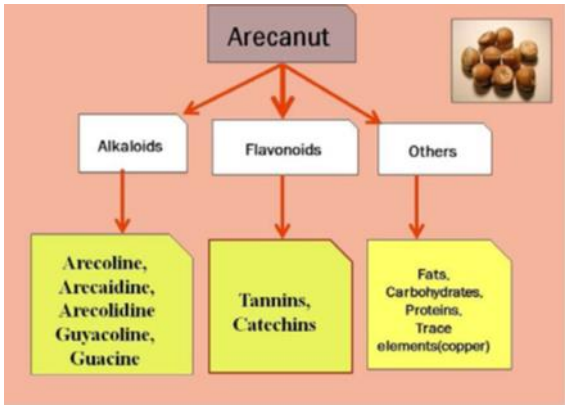
ABSTRACT:

Oral submucous fibrosis (OSF) is an insidious, chronic, progressive, debilitating disease. It is mostly prevalent in the South-east Asian countries. Areca nut chewing usually causes the condition. The hallmark of the disease being sub mucosal fibrosis that affects most parts of the oral cavity, pharynx and upper third of the oesophagus and its clinical presentation depends on the stage of the disease at detection. As the disease has a spectrum of presentation, the management differs with the various stages of the disease. This article reviews the various medical management techniques of oral submucous fibrosis.

KEYWORDS: *Arecanut; Etiopathogenesis; Management; Oral submucous fibrosis*

INTRODUCTION:

Oral submucous fibrosis was first described by Schwartz in 1952 among five Indian females living in Kenya and he coined the term Atrophia Idiopathica Mucosae Oris.OSF is defined by Pindborg J.J. and Sirsat S.M. (1966) as 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 related to juxtaepithelial inflammatory reaction followed by a fibro-elastic change of the lamina propria with epithelial atrophy resulting in stiffness of mucosa and causing trismus and inability to eat".



ETIOPATHOGENESIS:

1. Areca nut: Areca nut constitutes

Areca nut in the pathogenesis of OSF, the alkaloids cause the stimulation of fibroblast and gene expression hence leading to increased collagen production. The flavanoids increase the cross-linking of collagen and copper causes the up-regulation of lysyl oxidase and hence stimulating fibrogenesis.[1]

2. Genetic susceptibility

Collagen -related genes COL1A2, COL3A1, COL6A1, COL6A3 and COL7A1 have been identified as targets of transforming growth factor-b (TGF- b) and induced fibroblasts at an early stage of the disease. These genes play an important role in the homeostasis of collagen in the body.[1]

3. Autoimmunity

Patients with OSMF have increased frequency of HLA-A10, HLA-B7 and HLA-DR3. Increase in CD4 cells and cells with HLA-DR in these diseased tissues shows activation of most lymphocytes and increased number of Langerhans cells. The immuno - competent cells and high of CD4:CD8 ratio in OSMF tissues show the activation of cellular response which results in deranged immuno - regulation and an altered local tissue morphology. These changes may be due to changes in tissue antigenicity leading an autoimmune response.[1]

4. Nutritional deficiencies

Deficiency of iron (anaemia), Vitamin B complex, minerals, and malnutrition are promoting factors that disturbs the repair process of the inflamed oral mucosa, thus leads to deranged healing and resultant scarring and fibrosis.[1]

CLASSIFICATION:

1. CLASSIFICATION BASED ON CLINICAL FEATURES OF OSMF ARE AS FOLLOWS:

JV Desa (1957) divided OSMF into three stages as follows:[2]

STAGE I	Stomatitis and vesiculation
STAGE II	Fibrosis
STAGE III	As its sequelae

Pindborg JJ (1989) divided OSMF into three stages as follows:[2]

STAGE I	Stomatitis includes erythematous mucosa, vesicles, mucosal ulcers, melanotic mucosal pigmentation and mucosal petechiae.
STAGE II	Fibrosis occurs in healing vesicles and ulcers which is the hallmark of this stage. Early lesions: blanching of the oral mucosa Older lesions: vertical and circular palpable fibrous bands in the buccal mucosa and around the mouth opening or lips. Special findings: reduction of mouth opening, stiff and small tongue, blanched leathery floor of the mouth, fibrotic and de-pigmented gingiva, rubbery soft palate with decreased mobility, sunken cheeks.
STAGE III	Sequelae: LEUKOPLAKIA is found in more than 25% of individuals in OSMF Speech and hearing deficit may occur because of involvement of tongue and the eustachian tube.

SK Katharia et al (1992) have given different scores assigned to the patients on the basis of mouth opening between upper and lower central incisors as follows:[2]

Score 0	Mouth opening is 41mm or more
Score 1	Mouth opening is 37 to 40mm
Score 2	Mouth opening is 33 to 36mm
Score 3	Mouth opening is 29 to 32mm
Score 4	Mouth opening is 25 to 28mm
Score 5	Mouth opening is 21 to 24mm
Score 6	Mouth opening is 17 to 20mm
Score 7	Mouth opening is 13 to 16mm
Score 8	Mouth opening is 09 to 12mm
Score9	Mouth opening is 05 to 08mm
Score 10	Mouth opening is 0 to 04mm

Lai DR (1995) divided OSMF based on the inter-incisal distance as follows:[2]

Group A	>35mm
Group B	Between 30 and 35mm
Group C	Between 20 and 25mm
Group D	<20mm

R Mahler et al (1996) In his study, he divided intraoral regions into eight sub-regions viz palate, posterior 1/3rd of buccal mucosa, mid 1/3rd of buccal mucosa, upper labial mucosa, tongue and floor of the mouth.[2]
This was further divided into three categories as follows:

1. Involvement of 1/3rd or less of the oral cavity (if 3 or less of the above sites are involved).
2. Involvement of one to 2/3rd of the oral cavity (if 4 to 6 intra-oral sites are involved).
3. Involvement of more than 2/3rd of the oral cavity (if more than 6 intra-oral sites are involved)

Ranganathan K et al (2001) divided OSMF based on mouth opening as follows:[2]

Group I	Only symptoms, with no demonstrable restriction of mouth opening.
Group II	Limited mouth opening less than 20mm and above.
Group III	Mouth opening less than 20mm.
Group IV	OSMF advanced with limited mouth opening. Precancerous or cancerous changes seen through the mucosa.

Rajendran R (2003) reported the clinical features of OSMF as follows:[2]

1. **EARLY OSF:** Burning sensation in the mouth. Blisters especially on the palate, ulceration or recurrent generalized inflammation of oral mucosa excessive salivation, defective gustatory sensation and dryness of mouth.

2. **ADVANCED OSF:** Blanched and slightly opaque mucosa, fibrous bands in buccal mucosa running in vertical direction. Palate and faucial pillars are the areas first involved. Gradual impairment of tongue movement and difficulty in mouth opening

3. Nagesh and Bailoor (1993):[2]

Stage I early OSMF:	Mild blanching, no restriction in mouth opening

	Male :35 to 45mm Female :30 to 42mm
Stage II moderate OSMF:	Moderate to severe blanching, mouth opening reduced by 33%, cheek flexibility also in absence of stimuli, palpable bands felt. Lymphadenopathy either unilateral or bilateral and demonstrable anaemia on haematological examination.
Stage III severe OSMF:	Burning sensation is severe unable to do day –to – day work, more than 66% reduction in the mouth opening, cheek flexibility and tongue protrusion.

Tinky Bose and Anita Balan (2007) had given clinical classification, categorized, categorized the patients into three groups based on their clinical presentations:[2]

Group A – mild cases:
Only occasional symptoms, pallor, vesicle formation, presence of one or two solitary palpable bands, loss of elasticity of mucosa, variable tongue involvement with protrusion beyond vermillion border. Mouth opening >3cm.

Group B -- moderate cases:
Symptoms of soreness of mucosa or increased sensitivity to chillies, diffuse involvement of the mucosa, blanched appearance, buccal mucosa tough and inelastic fibrous bands palpable, considerable restriction of mouth opening (1.5 to 3cm) and variable tongue movement.

Group C – severe cases:
Symptoms are more severe, broad fibrous bands palpable, blanched opaque mucosa, very little or no mouth opening (less than 1.5 cm), de-papillated tongue and protrusion of tongue considerably restricted.

Kiran Kumar et al (2007) categorized three clinical stages of OSMF on the basis of mouth opening as follows:

Stage I: mouth opening >45mm

Very early stage	Finely fibrillar collagen dispersed with marked edema. Plump young fibroblast containing abundant cytoplasm. Blood vessels are dilated and congested. Inflammatory cells, mainly polymorphonuclear leukocytes with occasional eosinophils are found.
Early stage	Juxta- epithelial area shows early hyalinisation. Collagen still in separate thick bundles. Moderate number of plump young fibroblasts is present. Dilated and congested blood vessels. Inflammatory cells are primarily lymphocytes, eosinophils and occasional plasma cells.
Moderately advanced stage	Collagen is moderately hyalinised. Thickened collagen bundles are separated by slight residual edema. Fibroblastic response is a smaller amount marked. Blood vessels are either normal or compressed. Inflammatory exudate consists of lymphocytes and plasma cells.
Advanced stage	Collagen is totally hyalinised. Smooth sheets with no separate bundles of collagen is seen. Edema is absent. Hyalinised area is barren of fibroblasts. Blood vessels are completely obliterated or narrowed. Inflammatory cells are lymphocytes and plasma cells.

Stage II: restricted mouth opening 20 to 44 mm
Stage III: mouth opening <20 mm [2]

2. **CLASSIFICATION SUPPORTED HISTOPATHOLOGICAL FEATURES OF OSMF**:

Pindborg JJ and Sirsat SM (1966) were the primary to divide OSMF depending only on histopathological features alone are as follows:[2]

3. **CLASSIFICATION SUPPORTED CLINICAL AND HISTOPATHOLOGICAL FEATURES**:

Khanna JN and Andrade NN (1995) developed a group classification system for the surgical management of OSMF: [2]

Stages	Histopathological features	Clinical features
Very early cases	Finely fibrillar collagen dispersed with marked edema. Plump young fibroblast containing abundant cytoplasm. Blood vessels are dilated and congested. Inflammatory cells, mainly polymorphonuclear leukocytes with occasional eosinophils are found	Common symptom is burning sensation within the mouth, acute ulceration and recurrent stomatitis and not related to mouth opening limitation.
Early cases	Juxta- epithelial area shows early hyalinisation. Collagen still in separate thick bundles. Moderate number of plump young fibroblasts is present. Dilated and congested blood vessels. Inflammatory cells are primarily lymphocytes, eosinophils and occasional plasma cells.	Buccal mucosa appears mottled and marble like, widespread sheets of fibrosis palpable, inter-incisal distance of 26 to 35 mm.
Moderately advanced cases	Collagen is moderately hyalinised. Thickened collagen bundles are separated by slight residual edema. Fibroblastic response is a smaller amount marked. Blood vessels are either normal or compressed. Inflammatory exudate consists of lymphocytes and plasma cells.	Trismus, inter-incisal distance of 15 to 25mm, buccal mucosa appears pale firmly attached to underlying tissues, atrophy of vermilion border, vertical fibrous bands palpable at the soft palate, pterygomandibular raphe and anterior faucial pillars.
Advanced cases	Smooth sheets with no separate bundles of collagen is seen. Inflammatory cells are lymphocytes.	Presence of hyperkeratotic leukoplakia.

MANAGEMENT OF OSMF:

1. Patient education, reduction or even elimination of the habit of areca nut chewing is an important preventive measure, at least in the early stages of OSF, it could probably slow the progress of the disease.[1]

2. MODULATORS OF INFLAMMATION:

STEROIDS:

Steroids have their therapeutic effects due to anti- inflammatory and immune-suppressive action for prevention or suppression of the fibro productive inflammation seen in OSF, thus ameliorating the fibro-collagenous condition. It can be applied topically or intra-lesional injections depending upon the clinical stage of the disease.[1]

In the early stages when patient presents with the burning sensation	Topical corticosteroids Triamcinolone acetonide - 0.1% Betamethasone – 0.5% are applied locally for 3 months.
In the clinical stages with palpable fibrous bands	Intra-lesional injection Dexamethasone – 4mg/ml Triamcinolone -10 mg/ml given biweekly for 3 months, at multiple sites parallel to the mucosal surface

A study done using biweekly submucosal injections of 40 mg triamcinolone for 12 weeks showed significant improvement in mouth opening and improvement in symptoms of burning sensation.[1]

INTERFERON GAMMA:

Interferon gamma have immuno-regulatory effect and has anti-fibrotic cytokine effect and hence its major role in altering collagen synthesis. In vivo studies of Intra-lesional injection of 0.01- 10.0U/ml 3 times a day for 6 months showed improvement of symptoms. Increase in collagen synthesis in vitro in response to arecoline was inhibited in the presence of IFN- γ (0.01–10.0 U/ml) in a dose-related way. The post treatment immunohistochemistry showed a decreased amount of inflammatory cell infiltrate and an altered level of cytokine compared with the pre-treatment lesional tissue.[1]

PLACENTAL EXTRACTS: Placental extracts acts essentially as a "biogenic stimulation." Placentrex contains nucleotides, enzymes, vitamins, amino acids, and steroids, it's an aqueous extract of human placenta which stimulates the pituitary and the adrenal cortex and regulates the metabolism of tissues. Its use is predicted on the tissue therapy method. Intralesional injection of Placental extract 2.0cc given locally in the predetermined areas, once a week for one month showed improvement in the mouth opening of about *28.26%.* [1]

IMMUNE MILK:

Immune milk has anti-inflammatory effect and contains vitamins such as Vitamin A, C, B1, B2, B6, B12, nicotinic acid, pantothenic acid, folic acid, iron, copper and zinc. The milk from cows immunized with human intestinal bacteria (immune milk) contains an anti-inflammatory component which will suppress the inflammatory reaction and modulate cytokine production. 45 g milk powder twice a day for 3 months showed significant improvement in the symptoms.[1]

3. MODULATORS OF VASCULARITY OR RELEIF OF ISCHAEMIA:

PENTOXYPHYLLINE: (A new adjunct in the treatment of oral submucous fibrosis)
Pentoxifylline is a tri-substituted methylxanthine derivative.
It increases red cell deformability, leukocyte chemotaxis, anti-thrombin and anti- plasmin activities and has fibrinolytic activity. Pentoxifylline also decreases red cell and platelet aggregation, it also decreases granulocyte adhesion, fibrinogen levels and blood viscosity. Dosage of 400 mg 3 times a day for 7 months showed significant improvement in the symptom.

They have their role in OSF as pathologically occluded blood vessels due to collagen deposition and hyper coagulated status of blood restrict the nutrients and other therapeutic substances from reaching the affected tissue.[1]

4. FIBRINOLYSIS:

HYALURONIDASE:

Hyaluronidase is a fibrinolytic enzyme. It helps in the breakdown of hyaluronic acid, which lowers viscosity of the intercellular cement substance, it also decreases collagen formation.
1. Dosage of 1500 IU biweekly for 10 weeks. A study used different regimens of
2. Intralesional injections in patients,4mg dexamethsone biweekly1500 IU of hyaluronidase with 1cc of lignocaine biweekly.

3. 4mg of dexamethsone and 1500 IU of hyaluronidase. 2cc placentrex biweekly and located out that combination of dexamethsone and hyaluronidase for seven weeks gave maximum improvement. [1]

CHYMOTRYPSIN:

Chymotrypsin, an endopeptidase, hydrolyses ester and peptide bonds; therefore have a role in OSF cases proteolytic and anti-inflammatory agent. A study using Chymotrypsin 5000IU, biweekly submucosal injections for 10 weeks showed significant results.[1]

5. NUTRITIONAL SUPPORT:

LYCOPENE:
Lycopene is an antioxidant obtained from tomatoes. Lycopene have two major kinds of biological effects:
1.Antioxidative effect: Acting as potent antioxidants, it inactivates free radicals and attenuates free radicals-initiated oxidative reactions, particularly lipid peroxidation and DNA oxidative damage, thereby preventing tissue damage as well as potential cancerization.
2.Non-oxidative mechanisms: The nonoxidative effects are regulation of gap-junction communication (GJC), gene function regulation, hormone and immune modulation, and antiproliferation and pro differentiation activities. A study used 16 mg of lycopene per day in patients with OSMF and found significant improvement in mouth opening.[1]

VITAMINS:
1.Vitamin E acts as an antioxidant and prevents the formation of toxic substances and enhances the concentration of Vitamin A.
2.Vitamin A plays a major role in induction and control of epithelial differentiation in mucous secretary and keratinization tissues and maintains the integrity of epithelium. Vitamin A 50,000 IU orally daily for 12 weeks decrease the progress of premalignant cells, invasive malignant potential is slowed, delayed, arrested or even reversed, it improves the reduction of fibrous bands and mouth opening.[1]

CURCUMIN:

Curmurin has been found to inhibit many disease processes through their anti-inflammatory, antioxidant, and anticancer properties. Curcumin the main yellow pigment in turmeric, curry and mustard suppresses the expression of extracellular matrix genes in activated hepatic cells by inhibiting CTGF gene (connective tissue growth factor) expression. Patients affected by submucous fibrosis got an complete oral dose of turmeric oil (600 mg turmeric oil mixed with 3 g turmeric /day), turmeric oleoresin (600 mg + 3 g turmeric day) and three

grams turmeric /day as an impact for 3 months. It was observed that all three-treatment modalities decreased the number of micro nucleated cells both in exfoliated oral mucosal cells and in circulating lymphocytes.[1]

6. **PHYSIOTHERAPY:**

Physiotherapy modifies tissue remodelling through
promotion of physical movements and heat. Physical exercise regimen like
Muscle stretching exercise
Forceful mouth opening with the help of stick
Tongue movement in the figure of 8
Ballooning of mouth
Hot water gargling
Using mouth gag and acrylic surgical screws for forceful opening of mouth.
Cox S et al. conducted a study in which physiotherapy using mouth opening exercise by tongue spatula was done, their study showed improvement in mouth opening but no improvement in the symptom of pain and burning sensation.[1]

7. **HYPERBARIC OXYGEN THERAPY**— A Novel Treatment Modality in Oral Submucous Fibrosis:

Definition:
The Committee on Hyperbaric Medicine defines HBOT therapy as "A mode of medical treatment during which the patient is entirely enclosed during a pressure chamber and breathes 100% oxygen at a pressure >1 atmosphere absolute (ATA)." ATA is the unit of pressure and 1 ATA is equal to 760 mm of mercury or pressure at sea level.

Extensive fibrosis of the connective tissue causes reduction of vascularity, resulting in subsequent hypoxia in both fibroblasts and surface epithelia. Hypoxia causes atrophy and ulceration of the epithelium by inducing apoptosis. In addition, the over expression of hypoxia-induced factor-1a is seen in OSMF, which indicates changes in cell proliferation, maturation, and metabolic adaptation increasing the likelihood of malignant transformation.[3]

1.HBOT increases oxygen tension

2.Enhances the quantity of dissolved oxygen within the plasma, and

3.Raises oxygen delivery to the hypoxic areas.

4.HBOT improved ischemia via decreasing expression of HIF-1a.

5.The anti-inflammatory effect of HBOT might occur through the relief of hypoxia and the down-regulation of HIF-1a [28].

6.HBOT may have the potential to improve the vascular situation.[3]

Hyperbaric oxygen therapy (HBOT) involves inhalation of 100% oxygen at increased air pressure usually ranging between 2.0 and 2.5 atmospheres for periods between 60 and 120 min. [3]

RECENT ADVANCES IN THE MANAGEMENT OF OSMF:

1. **LASER AS A PROMISING NON-INVASIVE TECHNIQUE TO TREAT OSMF:[4]**

STUDIES USING DIODE LASER FOR TREATING OSMF:

The diode laser has a wavelength ranging from 805 nm to
980 nm that can be well absorbed by melanin and haemoglobin and poorly absorbed by the HA and H2O present in the enamel. It is a portable device that transmits energy in gated or continuous pulse mode delivering rays through a flexible fibreoptic cable and hence can be reached even to poorly accessible areas

such as trismus in OSMF. Its cutting depth is<0.01 mm, and thus preserves tissues beyond this depth. It gives a precise line
of controlled cutting without damaging the muscles and deeper
structures. Therefore, the healing is rapid even without any
graft or biological dressing. The active material used is a
semi-conducting crystal, usually GaAs or similar compounds. It has a good coagulative property, sealing the blood vessels spontaneously, allowing excellent visibility, and precision when dissecting through the tissue planes. The operating time is less
and the entire procedure is carried out intraorally without leaving any extraoral scar. Due to the minimal morbidity associated with this procedure, better patient compliance can be experienced. Also, the procedure can be repeated if required. The limitation of
this laser is its high cost.[4]

STUDIES USING KTP-532 LASER FOR OSMF:

It is a solid, visible laser with a wavelength of 532 nm obtained
by passing an Nd-YAG laser beam through a KTP crystal. This wavelength is selectively absorbed by blood vessels providing this laser excellent haemostatic properties. So, it can be used to excise pigmented, hyperaemic, and vascular lesions. Also, this laser can be delivered through a flexible fibre and hence can be applied to treat relatively unapproachable areas. Another major advantage of KTP-532 laser is its ability to excise the fibrotic bands precisely with minimal collateral tissue damage and a bloodless field even in the presence of trismus allowing spontaneous epithelialization without the need of surface grafting. So, affected areas are easily visible for inspection and hence any malignant change can be detected at the earliest, whereas areas covered by bulky flaps might hide malignancies under them till they are relatively large. The only drawback of this laser is its higher cost than the diode laser. For its unique properties, the KFT 532 laser has been used for fibrotomy in OSMF. Even some of the researchers concluded that this laser had the potential to treat severe cases of paediatric OSMF for the long term management. All patients presented
with improved mouth opening and relief from trismus.[4]

Patients with OSMF underwent fibrotic band release using KTP -532 laser, within the ENT –head and neck surgery department of a tertiary centre. Postoperatively, all patients were instructed to perform mouth stretching exercises using a dental screw (made of acrylic resin) for three to six months. Systemic supplementation with oral alpha lipoic acid was also given, using daily dose for three to six months. The patients were followed up for a period of 12 months.[7]

STUDIES USING CO2 LASER FOR TREATING OSMF:

The CO2 laser is a water or air-cooled laser, containing a gaseous mixture with CO2 molecules. It produces a beam of infrared light having a wavelength of 10600 nm and is well absorbed by water. This wavelength provides ease of cutting and coagulation of soft tissue, thus giving an assess to a clean operating field. Due to water vaporization, the temperature in the target's environment
remains in balance, not rising above 1000. It works in continuous or pulsating mode. Due to all of these properties, this laser has been used in place of a scalpel to excise large tissue pieces, in the peeling of thin surface layers, or merely to vaporize the tissue surface. An articulated mirror arm or a hollow fibre like beam conductor used in this system makes it able to reach all sides of the oral cavity. The best properties of using this laser in surgical procedures are precision, lack of bleeding, minimum scarring and, minimum to none post-operative pain as it induces neural sealing providing local neural anaesthesia and reduces the number of pain mediators. Few limitations are large size, high cost, inability to develop optic fibre for this system, delayed wound healing, and destructive hard tissue interactions. It results in black/brown discoloration of tissues treated which is caused by a carbon residue but becomes normal within the first 10–14 days after the procedure. Although the use of CO2 laser has been widely appreciated in the common practice to treat OSMF, during this research, we could find only two published studies related to its usage in OSMF management. And both studies showed improvement in the symptoms of the disease.[4]

STUDIES USING ErCr:YSGG LASER FOR TREATING OSMF:

ErCr :YSGG laser is used for both hard and soft tissues but has got the limited haemostatic ability as is not absorbed by Hb and has got short pulse duration. It has a wavelength of 2780 µm which has a high affinity for H2O and HA. It follows the ‘‘hydro-photonic process” in which laser energy interacts with water droplets at tissue creating water molecule excitation. This further causes water droplet micro-expansion and propulsion that gives clean and precise hard tissue cut. The presence of air and water spray plays a dual role; first to assist in cutting and secondly, serving as a coolant, preventing any thermal side effects. On soft tissue, this laser works differently, utilizing a small amount of water and air as coolant. ErCr:YSGG laser energy is selectively absorbed in the target tissue via thermal–mechanical tissue ablation and may result in either a cold cut or thermal cut. It limits the amount of collagen damage to as little as 5 µm, leaving the extracellular collagen matrix unaffected. Moreover, this laser demonstrates shallow penetration in the tissues resulting in less thermal risks to deeper tissues. The usage of this laser results in minimal post-operative pain and inflammation due to less release of histamine in the tissues.[4]

2. **PIRFENIDONE- A MOLECULAR TARGET FOR ORAL SUBMUCOUS FIBROSIS**:

Pirfenidone inhibits the progression of fibrotic lesions and prevent the formation of new lesions following tissue injuries. Pirfenidone has been tested in many in vivo and invitro fibrotic models which showed favourable results. The main mechanism of pirfenidone based on several studies reveals that it can modulate TGF- β expression, which is the central molecule in fibrosis and significantly suppressing the TGF-β1-induced ECM synthesis by attenuating the differentiation of fibroblasts and collagen expression genes, therefore reducing collagen production and [5] proliferation. TGF- β is the best-known inducer of fibrosis and is known to induce the expression of additional fibrogenic mediator. Since the pirfenidone can modulate and suppress TGF- β expression, it can downregulate the fibrosis. Besides anti-fibrotic activity, pirfenidone has also been shown to act as an anti-inflammatory and antioxidant agent. The anti-inflammatory effects of pirfenidone have been established in cell-based assays which reveals that pirfenidone downregulates certain inflammatory cytokines that have proposed roles in the initiation and maintenance of a fibrotic process. These include TNF-alpha, which promotes cell recruitment, fibroblast proliferation, epithelial cell hyperplasia and IL1β, which induces fibroblasts to produce fibrogenic mediators such as PDGF and TGF- β. A thorough understanding of molecular pathogenesis of OSMF and other fibrotic disorders along with the mechanism of pirfenidone can strengthen the idea of using pirfenidone in the clinical setting of OSMF. Despite the diverse and heterogeneous etiology for fibrotic diseases, the underlying pathogenesis of fibrotic conditions are similar and therefore therapeutic approach for fibrosis should involve the agents that targets TGFβ. Like any other fibrosing condition, OSMF also marches down the same pathway of fibrosis after activation of TGF- β by chronic inflammation following the ingestion of betel quid. Besides its antifibrotic property, pirfenidone also has anti-inflammatory and antioxidant which could synergize the effects in the treatment of OSMF. Although there are various in vivo and invitro trials were done for other organs, no clinical trials of pirfenidone in OSMF were tried. Therefore, this suggests that pirfenidone might be a potential novel therapeutic drug for the treatment of oral submucous fibrosis and also encourages clinical trials to scrutinize the efficacy of drug pirfenidone in OSMF [5].

3. POTENTIAL BENEFITS OF NOVEL AGENT TANSHINONE IN THE MANAGEMENT OF OSMF:

Zheng et al. examined the inhibitory effect of TSN on progression of OSMF. The authors found that TSNs inhibitmn arecoline mediated proliferation of primary human oral mucosal fibroblast and reversed the promotive effects of arecoline on epithelial–mesenchymal transition (EMT) process. Oral mucosal tissues in OSMF have extremely low p53 when compared with normal tisues. Arecoline reacts with oral mucosal fibroblasts resulting in reduction of p53[6] and its related downstream molecules p21, Bax and p53 upregulated modulator of apoptosis. Arecoline promotes the hypermethylation of promoter of p53, which was reversed by TSN. In G1-S phase cell cycle, the repair of damaged DNA is facilitated by p53 protein. Along with this, p53 also hampers the cell from entering S phase and may prompt the damaged cells to undergo apoptosis. Arecoline significantly upregulates lysine-specific demethylase (LSD1), but this effect is nullified

by TSN. It should be known that knocking down LSD1 leads to increased p53 levels in presence of arecoline. TSN inhibits LSD1. Arecoline decreases E-cadherin expression but increases N-cadherin and vimentin expression in oral mucosal fibroblasts. TSN reverses these effects of arecoline in dose-dependent manner. TSN is known to decrease tumor growth of oral carcinoma in vivo. It is suggested that TSN decreased the expression of proliferative marker Ki67 in tumor sections of SCC-9 xenografts. They also inhibit invasion and metastasis of cancer cells by altering matrix metalloproteinases. TSN is synergistic with anticancer drugs, such as cisplatin, 5-fluorouracil, doxorubicin, and arsenic trioxide.[6] Anticancer potential of tanshinones is through antiproliferation, pro-apoptosis, anti-angiogenesis, induction of differentiation, and inhibition of adhesion, migration, invasion and metastasis. Although there are very few studies conducted on effects of TSNs in OSMF till date, yet all of them have yielded positive results. Hence, TSNs appear to be promising in the management of OSMF.[6]

4. A **NEW INTRAORAL APPLIANCE FOR TRISMUS IN OSMF**:

Clinical Procedure and Fabrication of the Appliance

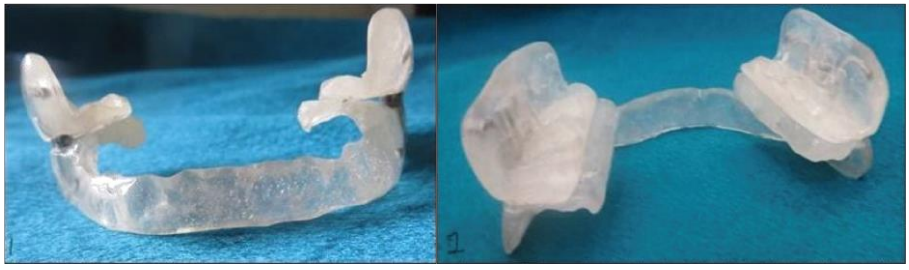
For all patients, maximum mouth opening was recorded using appropriate measuring instrument at baseline before the initiation of the appliance therapy. Necessary precautions were taken during the fabrication of the appliance such as the following:

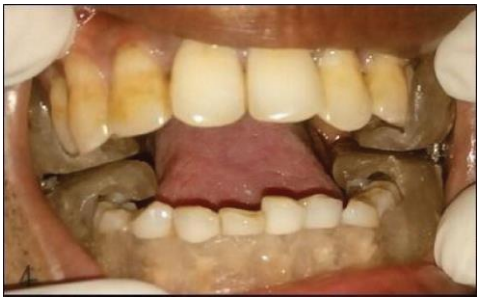
(1) The appliance should not impinge gingival margins

(2) It should be easy to manipulate by the patient

(3) Should be comfortable to use and also rigid enough to resist masticatory forces.[8]

Alginate impression was taken for both upper and lower arches with stock metal trays. Impression was poured using dental stone. The obtained casts were then articulated with an apex articulator. Fabrication of appliance was done by using self-cure acrylic resin and sprinkle on technique covering the sulcus area in the anterior region, which broadens posteriorly to cover the buccal area and occlusal surface of the lower arch. On the upper arch, only the molar area covered the teeth both occlusally and buccally. Mounting of cast in the occlusion was done in a hinge articulator in order that occlusal relation was maintained. The wax was then adapted on the buccal surface of the lower arch to keep the distance of 2mm from the gingiva, so that it did not impinge the soft tissues. Hyrax screws of 12mm gauge were adapted bilaterally on the buccal aspects of the molars on the wax. Precaution was taken to avoid blocking the activation hole of the screws. Once the acrylic had begun to line, the appliance was removed cleaned, trimmed, and polished. A lower labial extension was given for the appliance so as to stop accidental breakage and subsequent aspiration of the appliance.[8]





The appliance was then tried within the patient's mouth
and adjusted consistent with his/her convenience. Care was
taken to avoid excess pressure. The patients were educated regarding proper insertion, removal, and maintenance of the appliance and oral care. Moreover, they were encouraged to wear the appliance 12 hours overnight for 8 weeks and followed up every week to see any improvement. Patients were also encouraged to perform isometric mouth exercises daily according to their comfort. For every visit, the mouth opening was measured and thus the screw was released 1mm on all sides to enhance mouth opening. A follow-up for two months was performed on each patient.[8]

Treatment Evaluation and Follow-Up:

It was observed that there was significant increase in mouth opening altogether three patients starting from 2 to 8mm. None of the patients reported difficulty within the placement of appliance within the mouth during the treatment phase. No significant decrease in mouth opening was observed during post appliance follow-up of two months.[8]

CONCLUSION: "an ounce of prevention is worth a pound of cure" OSMF is a crippled irreversible disease, hence educating the population about the habit and its effect is of utmost importance. Proper habit restriction is required in OSF to ensure the progression of the disease.

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