

A novel clinical protocol for therapeutic intervention in oral submucous fibrosis: An evidence based approach

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Abstract

Oral submucous fibrosis (OSMF) is a chronic, progressive, debilitating, scarring and crippling disorder of the oral cavity. It is a potentially malignant oral disease which predominantly affects people of South and Southeast Asia, especially Indian subcontinent, where chewing of areca nut and its commercial preparation is rampant. However, due to increase in immigration of people from the Indian subcontinent, the health professionals in many developed countries do come across this disease very often. Since decades, many treatment modalities are suggested and studied using medicines, surgery and physiotherapy, with varying degrees of benefit, but none have been able to cure this disease completely, and hence, it has become a challenging condition. The present article emphasizes on various therapeutic interventions used till date to curb the menace of this disease and the principal author with his vast academic research and clinical experience in treating this disease has proposed the stage-wise treatment regimen for OSMF. The current article is an attempt to compile the available treatment, its current status and future perspectives, so as to assist early intervention of the disease with evidence-based approach. This article will ignite the research minds of dental clinician, oral medicine specialist, otolaryngologist and general physician in treating OSMF.

Keywords: Areca nut, evidence-based treatment, oral submucous fibrosis, protocol, therapeutic interventions, tobacco

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INTRODUCTION

Oral cavity is rightly described as mirror of the body as it reflects the health of the individual. Oral mucosa is a unique tissue, lined by keratinized and nonkeratinized stratified squamous epithelium and underlying connective tissue (lamina propria). The oral mucosa is continuously exposed to chemicals, microorganisms, thermal changes and mechanical irritants (tobacco, areca nut, alcohol, etc).

The epithelial and connective tissue components of the oral mucosa demonstrate acute and chronic reactive changes in response to the above stressors.^[1,2] The keratinized epithelium which is present on the dorsum of the tongue, such as hard palate and attached gingiva, shows less reactive changes to the stressors as compared to the nonkeratinized epithelium, which is seen everywhere in the oral cavity including the buccal mucosa, labial mucosa, alveolar mucosa and specialized mucosa.

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Changes indicative of disease are seen as alterations in the oral mucosal lining.^[2-6]

Oral submucous fibrosis (OSMF) is a chronic, insidious, progressive, debilitating, scarring, irreversible, complex and crippling disorder of the oral cavity.^[4-8] This oral potentially malignant disorder (OPMD) a collagen disorder was first described as early as 600 BC by Sushruta, the renowned Indian physician, as Vidari. Schwartz in 1952 after observing similar features in five Indian women of Kenya described this condition as progressive inability to open the mouth due to loss of elasticity and development of vertical fibrous bands in the labial and buccal tissues. He termed it as *atrophia idiopathica mucosae oris*. In 1953, Dr. S.G. Joshi coined the term OSMF for the disease.^[5-8] Subsequently, various researchers classified OSMF both, clinically and histologically – Desa (1957), Pindborg and Sirsat (1966), Agarwal et al. (1971), Pindborg (1989), Katharia et al. (1992), Nagesh and Bailor (1993), Maher et al. (1996), Ranganathan et al. (2001), Rajendran (2003), Kiran Kumar et al. (2007), Tinky Bose and Anita Balan (2007) and Chandramani More (2012).^[5,8]

OSMF is predominantly seen in people of South and Southeast Asia – India, Bangladesh, Sri Lanka, Pakistan, Taiwan, Southern China, etc., where chewing of betel quid, areca nut or its flavored formulations is frequently practiced. The rapid increase in the prevalence of this disease is due to an upsurge in the popularity of commercially available areca nut and tobacco preparations – gutkha, pan masala, flavored areca nut, mawa, etc., in Asian countries [Table 1]. It causes significant morbidity, in terms of loss of mouth function as tissues become rigid and mouth opening becomes difficult, and mortality because of transformation into squamous cell carcinoma.^[4-6,8-12]

The prevalence rate of OSMF in Indian population differs geographically. The male-to-female ratio of OSF was 4.9:1.^[8,10,11] A considerable difference in the prevalence of OSMF in Europe, UK, USA and Middle East countries has been reported on Asian migrants. Sporadic cases among the non-Asians have also been reported in the literature.^[8,12-14]

OSMF affects the upper digestive tract – oral cavity, oropharynx and upper third of esophagus and is characterized by Juxta – epithelial inflammatory reaction, followed by fibroelastic changes due to progressive fibrosis of the submucosal tissues (lamina propria and deeper connective tissues) with epithelial atrophy leading to stiffness and rigidity of the oral mucosa and eventual inability to open the mouth.^[4,8,10,11,13,14]

The etiology of OSMF is obscure, although various hypotheses are proposed, suggesting multifactorial origins, such as chewing of areca nut and its flavored formulations (most common), chronic nutritional deficiencies (especially iron, Vitamin B complex and protein) and genetic predisposition, autoimmunity Excessive use of areca nut and its flavored formulations disrupts the hemostatic equilibrium between synthesis and degeneration.^[4,7-9,11,15,16] The copper ion in areca nut increases the activity of lysyl oxidase leading to unregulated collagen production, thereby causing oral fibrosis. This leads to the production of free radicals and reactive oxygen species, which are responsible for high rate of oxidation – peroxidation of polyunsaturated fatty acids.^[2,4,8,17-19]

OSMF is a disease of middle age group with peak incidence observed in the second to fourth decade of life. The sex distribution of OSMF varies geographically. The most common oral site for OSMF is buccal mucosa and retromolar region, followed by soft palate, faucial pillars, floor of mouth, tongue, labial mucosa and gingiva^[2,4,6,8,11,12] [Figure 1].

Table 1: Commercially available arecanut preparations

Preparations	Description
Flavoured Supari	Ingredients: Mixture of Arecanut Pieces, Artificial Sweetener, Sugar, Menthol & Natural Food Colours. Available in attractive small sachets in multiple flavours. Used as mouth freshener.
Mawa	Ingredients: Mixture of Arecanut pieces or shavings, Watery Slaked Lime, Dried Crushed Tobacco Leaf and Catechu. Freshly made local preparation, prepared in thin transparent plastic cellophane paper, tied like a small 'ball' and the mixture is rubbed on the palm of hand for 2-3 min or till it is soft.
Betel quid (Pan)	Ingredients: Mixture of Arecanut pieces or shavings, Catechu and Watery Slaked Lime and sometimes dried crushed tobacco leaf with flavourings (Cinnamon, cloves, sandalwood, cardamom, coconut, ginger) and sweetening agents (sugar, rose petal jam); is wrapped in fresh green Betel Leaf.
Gutkha	Ingredients: Mixture of Crushed Arecanut Pieces Dried Crushed Tobacco Leaf, Catechu, Slaked Lime, Paraffin Wax, Magnesium Carbonate, Arsenic and Sweet & Aromatic Flavourings. Available in attractive small, medium and large size sachets. The contents may weigh from 50 milligram to 10 grams. It is granular and powdery, and is light brown to white in colour.
Pan masala	Ingredients: Mixture of Arecanut pieces, Slaked lime, Cardamom, Cinnamon, Fennel Seeds, Menthol, and Sweet & Aromatic Flavourings. It may or may not contain tobacco. Available in attractive small tins, zipper pouch and sachets. The contents may weigh from 2 grams to 100 grams.

Table 2: Clinical Oro- facial manifestations

Stage of OSMF	Manifestations	
	Intra oral	Extra oral
Early Stage	Burning sensation Stomatitis Excessive salivation Blister formation Blanching of oral mucosa Sparse brownish black pigmentation Presence of thin palpable fibrous bands	No Significant features
Moderate Stage	Burning sensation Stomatitis Gradual decrease in mouth opening Xerostomia Loss of taste sensation Difficulty in blowing the cheeks Difficulty in whistling Defective gustatory sensation Vesicle formation Petechiae Rigid oral mucosa Blanching of oral mucosa, esp. soft palate, buccal mucosa, labial mucosa, tongue, floor of mouth, faucial pillars etc. Presence of thick palpable fibrous bands Shrunken uvula with altered shape (inverted, hockey stick, bud like, deviated)	Prominent masseter muscle Prominent antegonial notch Mild hearing impairment Nasal twang Sunken Cheeks Thinning of lips Hoarseness of voice Difficulty in deglutition Loss of Naso-labial fold Mild Cachexia
Advanced Stage	Burning sensation Stomatitis Reduced mouth opening (may be nil) Xerostomia Restricted tongue movement Defective gustatory sensation Loss of taste sensation Unable to blow the cheeks Unable to whistle Blanching of oral mucosa esp. soft palate, buccal mucosa, labial mucosa, tongue, floor of mouth, faucial pillars etc. Loss of suppleness of mucosa Mottled or opaque or white marble like appearance of oral mucosa Thick palpable fibrous bands on buccal and labial mucosa De-papillation of tongue Shrunken uvula with altered shape (inverted, hockey stick, bud like , deviated) Involvement of the pharyngeal and oesophageal mucosa.	Sunken Cheeks Prominent malar bones Increase in philtrum area Ellipsoid mouth opening Thinning of lips Severe hearing Impairment due to stenosis of Eustachian tube Nasal intonation of voice Hoarseness of voice Difficulty in deglutition Hypertrophy and stiff masseter muscle Prominent antegonial notch Decreased elasticity of cheek skin Atrophy of facial musculature Multiple folds on cheeks after wide opening of mouth Severe Cachexia Loss of naso-labial fold. In severe OSMF cases where inter-incisal mouth opening is less than 5 mm, radiographically there is alteration in Condylar form and fibrous Ankylosis of TMJ is observed



Figure 1: Oral submucous fibrosis involving various areas of the oral cavity. (a and b) Significant blanching and presence of palpable, thick fibrous bands on the left and right buccal mucosa. Note the brownish-black pigmentation in the posterior vestibular region in b. (c and d) Blanching of the soft palate and faucial pillars. Note the shrunken uvula and its altered shape. (e) Blanching of the floor of mouth and loss of surface texture. (f-i) Blanching and palpable fibrous bands of the upper and lower labial mucosa. Note the stiff labial mucosa and presence of blanching of attached gingiva in f and g

Table 3a: For Stage I OSMF

Stage	Treatment Regimen	Dosage and Duration	Actions and Major Side Effects	Remarks
I	1. Tablet/Capsule - Vitamin A (50,000 IU) or β-carotene (10-20mg) or Vitamin E (400mg) or Lycopene (4mg) and micronutrients (either alone or in combination)	Once a day, for Six months to Twelve months	Action: Antioxidant/Anti carcinogenic activity. Major Side effects: Excessive intake can cause toxicity especially involving Skin and nervous system.	Mandatory
	2. Topical Corticosteroids	Thrice daily for One to Two months	Action: Anti-inflammatory and Immunosuppressive effects through regulation of pro-inflammatory cytokine genes and cells. Side effects: Hypersensitive reactions.	Optional. Only in case of Stomatitis
	3. Tablet Curcumin (300 mg)	Once daily for a period of Six to Eight months	Action: Curcumin is a pleiotropic molecule that targets molecular mediators of inflammation. It has antioxidant, antimicrobial, pro-apoptotic, anti-inflammatory and antifibrotic activity on human myo-fibroblasts. Major Side effects: In high dosage nausea, diarrhoea, and hepatotoxicity	Mandatory

Table 3b: For Stage II OSMF

Stage	Treatment Regimen	Dosage and Duration	Actions and Major Side Effects	Remarks
II	1. Tablet/Capsule - Vitamin A (50000 IU) or β-carotene (10-20 mg) or Vitamin E (400mg) or Lycopene (8mg) and micronutrients (either alone or in combination)	Once a day, for Six months to Twelve months.	Action: Antioxidant/Anti-carcinogenic activity. Major Side effects: Excessive intake can cause toxicity especially involving skin and nervous system.	Mandatory
	2. Topical Corticosteroids.	Thrice daily for One to Two months	Action: Anti-inflammatory and Immunosuppressive through regulation of pro-inflammatory cytokine genes and cells. Side effects: Hypersensitive reactions.	Optional. Only in case of Stomatitis
	3. Tablet Ferrous Ascorbate (100 mg) + Folic acid (1.5mg)	Once daily for a period of Six to Eight months.	Action: To maintain vascularity, normal erythropoiesis, nucleoprotein synthesis and prevent DNA changes. Side Effects: stomach cramps constipation black stools	Mandatory
	4. Tablet Zinc Sulphate (220mg)	Twice a day, for Three to Six months	Action: It improves the immunity and wound healing and plays an essential role in DNA synthesis and cell division and is a constituent of many enzymes. Zinc is an antagonist of copper and may counteract the effects of copper-related up-regulation of lysyl oxidase. Major Side effects: In high dosage allergic reaction, vomiting, dry mouth, eyes or skin.	Mandatory
	5. Tablet Curcumin (300 mg)	Once daily for a period of Six to Eight months.	Action: Curcumin is a pleiotropic molecule that targets molecular mediator of inflammation. It has antioxidant, antimicrobial, pro-apoptotic, anti-inflammatory and antifibrotic activity on human myo-fibroblasts. Major Side effects: In high dosage, nausea, diarrhoea, and hepatotoxicity.	Mandatory
	6. Tablet Pentoxifylline (400 mg) OR	Three times daily for Three to Four months	Action: It improves microcirculation there by increases the mucosal vascularity, alleviates the symptoms in OSMF, Fibrinolytic activity, degranulation of neutrophils, suppresses the leukocyte function, promotes natural killer cell activity, inhibits T-cell & B-cell activation , alters fibroblast physiology, and stimulates fibrinolysis. Major Side effect: leukopenia, neuropathy and diarrhoea.	Recommended only if mouth opening is less than 35 mm
	6. Tablet Isoxsuprine (10 mg)	Three times daily for four to Six weeks	Action: Vasodilator inhibits platelet aggregation and decreases blood viscosity. Side effects: facial flushing, tachycardia, hypotension, allergic reactions.	Recommended only if mouth opening is less than 35mm

Table 3c: For Stage III OSMF

Stage	Treatment Regimen	Dosage and Duration	Actions and Major Side Effects	Remarks
III	1. Tablet/Capsule - Vitamin A (50000 IU) or β-carotene (10-20 mg) or Vitamin E (400mg) or Lycopene (8mg) and micronutrients (either alone or in combination)	Twice a day, for Twelve to Twenty four months	Action: Antioxidant/Anti-carcinogenic activity. Major Side effects: Excessive intake can cause toxicity especially involving Skin and nervous system.	Mandatory
	2. Topical Corticosteroids	Thrice daily for One to Two months	Action: Anti-inflammatory and Immunosuppressive effects through regulation of pro-inflammatory cytokine genes and cells. Side effects: hypersensitive reactions.	Optional. Only in case of Stomatitis
	3. Tablet Ferrous Ascorbate (100mg) + Folic acid (1.5mg)	Twice a day for Three to Four months	Action: To maintain vascularity, normal erythropoiesis, nucleoprotein synthesis and prevent DNA changes. Side Effects: Stomach cramps constipation, black stools	Mandatory
	4. Tablet Zinc Sulphate (220mg)	Twice a day, for Three to Six months	Action: It improves the immunity and wound healing and plays an essential role in DNA synthesis and cell division and is a constituent of many enzymes. Additionally, zinc is an antagonist of copper and may counteract the effects of copper-related up-regulation of lysyl oxidase. Side effects: In high dosage Allergic reaction, vomiting, dry mouth, eyes, or skin	Mandatory
	5. Tablet Curcumin (300 mg)	Twice daily for a period of Six to Eight months.	Action: Curcumin is a pleiotropic molecule that targets molecular mediators of inflammation. It has antioxidant, antimicrobial, pro-apoptotic, anti-inflammatory and antifibrotic activity on human myo-fibroblasts. Major Side effects: In high dosage Nausea, Diarrhoea, hepatotoxicity.	Mandatory
	6. Tablet Pentoxifylline (400 mg) OR	Thrice daily for Four to Six months	Action: It improves microcirculation there by increases the mucosal vascularity, alleviates the symptoms in OSMF, Fibrinolytic activity, degranulation of neutrophils, suppresses the leukocyte function, promotes natural killer cell activity, inhibits T-cell & B-cell activation, alters fibroblast physiology, and stimulates fibrinolysis. Major Side effect: leukopenia, neuropathy and diarrhoea.	Recommended only if mouth opening is less than 25mm
	6. Tablet Isoxsuprine (10 mg)	Four times per day for Six to Eight weeks	Action: Vasodilator inhibits platelet aggregation and decreases blood viscosity. Side effects: Facial flushing, tachycardia, hypotension, Allergic reactions.	Recommended only if mouth opening is less than 25mm
	Intra-lesional/Submucosal Injection therapy. Any one of the following regimen diluted in 1.0ml of 2% Lignocaine Hydrochloride			
	7. Mixture of Dexamethasone (4 mg) + Placental Extract (2 ml) + Chymotrypsin (5000 IU) OR	Two Injections per week for total Six to Eight weeks	Action: Dexamethasone suppress inflammatory reactions, thereby preventing fibrosis by decreasing fibroblastic proliferation and deposition of collagen. Placental Extract- contains growth factors and anti-inflammatory, anti platelet activity. The action of placenta is biogenic stimulation and it increases the vascularity of tissues. Chymotrypsin- an enzyme that reduce inflammation and tissue destruction Side effects: allergic reaction, Pain, itching, or redness on injection	Mandatory.
	7. Mixture of Dexamethasone (4 mg) + Hyaluronidase (1500 IU)+ Chymotrypsin (5000 IU)	Two Injections per week for total Six to Eight weeks	Action: Hyaluronidase breaks down Hyaluronic acid, lowers the viscosity of the intercellular substances and also decreases collagen formation. Side effects: allergic reaction, Pain, itching, or redness on injection	Mandatory
8. Tablet Levamisole (50mg)	Thrice daily for three consecutive days for Six to Eight weeks	Action: Immunomodulator. It modifies both cellular and humoral immunity. Major Side effect: On long term therapy, Leukopenia and Agranulocytosis may occur.	Recommended only if mouth opening is less than 30mm	

Contd...

Table 3c: Contd....

Stage	Treatment Regimen	Dosage and Duration	Actions and Major Side Effects	Remarks
	9. Intra lesional Interferon gamma (50mg) Injection (0.25ml)	Twice a week for Eight to Ten weeks	Action: It is antifibrotic agent. It down regulates fibroblast proliferation and collagen synthesis and up-regulates antifibrotic cytokine and collagenase synthesis. It reduces the burning sensation, increases suppleness of the mucosa, and mouth opening Major Side effect: mild fever, malaise, headache, hot and cold sensation in hand and feet and peeling of palm & sole skin.	Recommended only if mouth opening is less than 25mm

Table 3d: For stage IVA OSMF

Stage	Treatment Regimen	Dosage and Duration	Actions and Major Side Effects	Remarks
IV A	1. Tablet/Capsule – Vitamin A (50000 IU) or β-carotene (10-20 mg) or Vitamin E (400 mg) or Lycopene (8 mg) and micronutrients (either alone or in combination)	Once a day for Six months to Twelve months	Action: Antioxidant/Anti-carcinogenic activity. Major Side effects: Excessive intake can cause toxicity especially involving Skin and nervous system.	Mandatory
	2. Topical Corticosteroids	Thrice daily for One to Two months	Action: Anti-inflammatory and Immunosuppressive effects through regulation of pro-inflammatory cytokine genes and cells. Side effects: hypersensitive reactions.	Optional. Only in case of Stomatitis
	3. Topical Antifungal - 2% Clotrimazole	Thrice daily for Two to Six months, on the other OPMD'S	Action: kill individual Candida or fungal cells by altering the permeability of the fungal cell wall. It inhibits the biosynthesis of ergosterol and other sterols required for cell membrane production. Side effects: blistering, peeling, stinging, swelling, itching, hives.	Mandatory
	4. Tablet Ferrous Ascorbate (100mg) + Folic acid (1.5mg)	Twice a day for Three months	Action: To maintain vascularity, normal erythropoiesis, nucleoprotein synthesis and prevent DNA changes. Side Effects: Stomach cramps constipation , black stools	Mandatory
	5. Tablet Zinc Sulphate (220mg)	Twice a day, for Three to Six months	Action: It improves the immunity and wound healing and plays an essential role in DNA synthesis and cell division and is a constituent of many enzymes. Additionally, zinc is an antagonist of copper and may counteract the effects of copper-related up-regulation of lysyl oxidase. Side effects: In high dosage Allergic reaction, vomiting, dry mouth, eyes, or skin	Mandatory
	6. Tablet Curcumin (300 mg)	Twice daily for a period of Six to Eight months.	Action: Curcumin is a pleiotropic molecule that targets molecular mediators of inflammation. It has antioxidant, antimicrobial, pro-apoptotic, anti-inflammatory and antifibrotic activity on human myo-fibroblasts. Major Side effects: In high dosage Nausea, Diarrhoea, hepatotoxicity.	Mandatory
	7. Tablet Pentoxifylline (400 mg) OR	Three times daily for Four months to Six months	Action: It improves microcirculation there by increases the mucosal vascularity, alleviates the symptoms in OSMF, Fibrinolytic activity, degranulation of neutrophils, suppresses the leukocyte function, promotes natural killer cell activity, inhibits T-cell & B-cell activation , alters fibroblast physiology, and stimulates fibrinolysis. Major Side effect: leukopenia, neuropathy and diarrhoea.	Recommended only if mouth opening is less than 15mm
	7. Tablet Isoxsuprine (10 mg)	Four times per day for Six weeks	Action: Vasodilator inhibits platelet aggregation and decreases blood viscosity. Side effects: Facial flushing, tachycardia, hypotension, Allergic reactions.	Recommended only if mouth opening is less than 15mm
	Intra lesional/Submucosal Injection therapy. Any one of the following regimen diluted in 1.0ml of 2% Lignocaine Hydrochloride			
	8. Mixture of Dexamethasone (4mg) + Placental Extract (2ml) + Chymotrypsin (5000 IU) OR	Two Injections per week for total Six weeks	Action: Dexamethasone suppress inflammatory reactions, thereby preventing fibrosis by decreasing fibroblastic proliferation and deposition of collagen. Placental Extract- contains growth factors and anti-inflammatory, anti platelet activity. The action of placenta is biogenic stimulation and it increases the vascularity of tissues. Chymotrypsin- an enzyme that reduce inflammation and tissue destruction Side effects: allergic reaction, Pain, itching, or redness on injection.	Recommended only if mouth opening is less than 35mm

Contd...

Table 3d: Contd....

Stage	Treatment Regimen	Dosage and Duration	Actions and Major Side Effects	Remarks
8.	Mixture of Dexamethasone (4mg) + Hyaluronidase (1500 IU) +Chymotrypsin (5000 IU)	Two Injections per week for total Six weeks	Action: Hyaluronidase breaks down Hyaluronic acid, lowers the viscosity of the intercellular substances and also decreases collagen formation. Side effects: allergic reaction, Pain, itching, or redness on injection	Recommended only if mouth opening is less than 35mm
9.	Tablet Levamisole (50mg)	Thrice daily for three consecutive days for Six to Eight weeks	Action: Immunomodulator. It modifies both cellular and humoral immunity. Major Side effect: On long term therapy, Leukopenia and agranulocytosis may occur.	Recommended only if mouth opening is less than 30mm
10.	Intra lesional Interferon gamma (50mg) Injection (0.25ml)	Twice a week for Eight to Ten weeks	Action: It is antifibrotic agent. It down regulates fibroblast proliferation and collagen synthesis and up-regulates antifibrotic cytokine and collagenase synthesis. It reduces the burning sensation, increases suppleness of the mucosa, and mouth opening Major Side effect: mild fever, malaise, headache, hot and cold sensation in hand and feet and peeling of palm & sole skin.	Recommended only if mouth opening is less than 10mm

Table 3e: For stage IVB OSMF

Stage	Treatment Regimen	Dosage and Duration	Actions and Major Side Effects	Remarks
IV B	1. Urgent Referral to Regional Cancer centre/Consultant Oncologist for treatment of Oral malignancy	-	-	Mandatory
	2. Tablet/Capsule - Vitamin A (50000 IU) or β-carotene (10-20 mg) or Vitamin E (400mg) or Lycopene (8mg) and Micronutrients (either alone or in combination)	Once a day for Six to Twelve months	Action: Antioxidant/Anti-carcinogenic activity. Major Side effects: Excessive intake can cause toxicity especially involving skin and nervous system.	Mandatory
	3. Tablet Ferrous Ascorbate (100 mg) + Folic acid (1.5mg)	Once a day for Three months	Action: To maintain vascularity, normal erythropoiesis, nucleoprotein synthesis and prevent DNA changes. Side Effects: Stomach cramps, constipation black stools	Mandatory
	4. Tablet Zinc Sulphate (220mg)	Twice daily for Three to Six months	Action: It improves the immunity and wound healing and plays an essential role in DNA synthesis and cell division and is a constituent of many enzymes. Additionally, zinc is an antagonist of copper and may counteract the effects of copper-related up-regulation of lysyl oxidase. Side effects: In high dosage allergic reaction, vomiting, dry mouth, eyes, or skin	Mandatory
	5. Tablet Curcumin (300 mg)	Once daily for a period of Six to Eight months.	Action: Curcumin is a pleiotropic molecule that targets molecular mediators of inflammation. It has antioxidant, antimicrobial, pro-apoptotic, anti-inflammatory and antifibrotic activity on human myo-fibroblasts. Major Side effects: In high dosage nausea, diarrhoea, hepatotoxicity.	Mandatory

The clinical presentation will vary according to the stage of the disease, as mentioned in Table 2.^[2,4,5,7-12,18,20] In contrast to other OPMD's, OSMF is insidious in origin and does not regress, either spontaneously or with cessation of habit. The disease remains either stationary or becomes severe, leaving an individual handicapped, both physically and psychologically.^[2,8,11] Usually, the OSMF lesion shall be biopsied, especially

if there are ulcerative, nodular, erythematous and suspicious areas. The histologically proven severe or moderate epithelial dysplasia shall be treated in the lines of management of carcinoma. Nondysplastic or mildly dysplastic cases must be kept under long-term observation and shall be advised antioxidant therapy after discontinuation of habit.^[8,10,18,21,22]



Figure 2: Various fruits and vegetables having antioxidant properties

Early diagnosis of OSMF is important in both prevention and therapeutic procedures of oral cancers.^[6,8,10,11] The treatment of OSMF in the last few decades is varied and ineffective, but till date, there is no consensus on the most appropriate management of OSMF. Many treatment protocols for OSMF have been proposed by various researchers since its first diagnosis, so as to alleviate the signs and symptoms of the disease and also to stop the disease progression and malignant transformation. In spite of numerous drugs or interventions in practice, the complete remission of OSMF is not achieved and is unsatisfactory. Hence, an attempt of finding a permanent cure is still in progress.

TREATMENTS IN PRACTICE

In recent times, several medicinal (allopathic, homeopathic and Ayurvedic), surgical, physiotherapeutic, etc., have been tried, either alone or in combination, in the treatment of OSMF. In advance cases, surgical intervention is the only treatment modality, but relapse is a major problem. Discontinuation of harmful substance such as areca nut, tobacco and alcohol; increased intake of fresh red fruits and green leafy vegetables [Figure 2] and mineral-rich diet has also been advised.^[8] The authors have also made an attempt to compile the present treatment which is in practice, and several following studies conducted in different parts of the world.

The studies of Borle and Borle,^[13] Khanna and Andrade *et al.*,^[14] Maher *et al.*^[15] and Thakur *et al.*^[16] on multivitamins; Borle and Borle^[13] and Nallapu *et al.*^[17] on Vitamin A; Kumar *et al.*,^[18] Karemore and Motwani,^[19] Selvam and Dayanand,^[23] Patil *et al.*^[21] and Samuel and Renukananda^[22] on lycopene; Hastak *et al.*,^[20] Das *et al.*,^[24] Agrawal *et al.*^[25] and Yadav *et al.*^[26] on curcumin;

Rajendran *et al.*^[27] and Mehrotra *et al.*^[28] on pentoxifylline; Bhadage *et al.*^[29] on isoxsuprine; Gupta and Sharma^[30] on chymotrypsin; Borle and Borle,^[13] Krishnamoorthy and Khan,^[31] James *et al.*^[32] and Shah *et al.*^[33] on hyaluronidase; James *et al.*^[32] on dexamethasone; Katharia *et al.*^[34] and Ali *et al.*^[35] on placental extract; Jirge *et al.*^[36] on levamisole; Haque *et al.*^[37] on interferon gamma; Goel and Ahmed^[38] and Gupta *et al.*^[39] on steroids; Khanna and Andrade *et al.*^[14] Shetty *et al.*^[40] and Mulk *et al.*^[41] on spirulina; Alam *et al.*^[42] and Sudarshan *et al.*^[43] on *Aloe vera*; Cox and Zoellner *et al.*^[44] on physiotherapy exercises; have put forward positive and negative observations in the treatment of OSMF.

PROPOSED TREATMENT

Various treatment regimens for OSMF are proposed to alleviate the signs and symptoms of the disease. Even after seven decades of its description as a precancerous condition, no substantial treatment is available because of its multimodal pathogenesis.^[12] The principal author with his vast academic and clinical experience in treating various oral lesions, especially OPMD's, has proposed stage-wise treatment protocol or regimen for OSMF so as to assist early intervention of the disease [Tables 3a-e].

In addition to the above-proposed treatment protocol, each patient of OSMF shall be counseled for discontinuation of habit and must be advised with increase intake of fresh red fruits and green leafy vegetables along with physiotherapy exercises, especially ballooning, blowing of mouth, opening and closing of the mouth, hot water gargling, etc. The frequency of exercise will depend on the severity of the disease.^[8,11,18,23]

DISCUSSION

From the last two decades, use of clinical protocol or guidelines have increased and has become a part of routine practice worldwide. The clinical guidelines are systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances. Most of the hospitals have formulated their own standard operating procedures, which may offer concise instructions on diagnostic or screening test, medical or surgical services, etc. These guidelines act as a tool for making care more consistent and efficient and help in reducing the gap between the clinician's knowledge and the available scientific evidence. Various health specialties and companies are involved in conflict to gain rights over specific procedures or treatments as guidelines or protocols.^[45,46]

The clinical protocol helps in providing quality of care to the patients, but its outcome is not clear; maybe because of difference in understanding, the extent of quality by the stakeholders and hence, the effectiveness of protocol remains incomplete. Protocols have the potential to reduce morbidity and mortality and improve quality of life, at least for some conditions, especially when they promote interventions of proved benefit.^[45-47]

Such protocols empower patients to make choices, their personal needs and preferences in selecting the best option. Certainly, sometimes clinicians may first learn about new protocols from patients. The treatment protocols based on a critical appraisal of scientific evidence explain which interventions are of proved benefit. Sometimes, the most important limitation of the protocols is that the recommendations maybe wrong for individual patients.^[45-48]

There is lack of consistent evidence for the effectiveness of any specific interventions for the management of OSMF, and it is difficult to correlate or even combine their outcomes in a scientifically meaningful manner. The literature remains confused because of lack of clarity in scoring system and agreeable treatment outcome measures. Numerous treatments are tried for OSMF, but only few clinical trials are undertaken. Literature has reported variety of clinical outcomes because of failure to standardize the clinical severity scores for OSMF and clarity in distinguishing treatment designs.

Till date, not a single treatment modality has provided a complete relief for this condition, which has high malignant potential. It is difficult to evaluate the advantages and disadvantages of each treatment, especially in combined treatment protocols, because of the empirical nature of each approach. The proposed evidence-based novel clinical protocol for therapeutic intervention is to improve the quality of life in patients suffering from the debilitating condition, OSMF. The present protocol aims to provide the best possible treatment regimen based on sound evidence. The principal author with his vast academic and clinical experience in treating this disease has proposed the stage-wise treatment regimen for OSMF. An attempt is made to compile the available treatment, its current status and future perspectives, so as to assist early intervention of the disease with evidence-based approach.

CONCLUSION

The evidence for the prevention of any oral disease starts with an understanding of its burden at different stages of life. The time-tested health policies and priority settings

direct to have preventive interventions. A variety of treatments are rendered for OSMF till date. The present article has explored all the treatment options available in the existing literature and has suggested the evidence-based treatment protocols for the intervention of OSMF. There is always a scope for further research in the suggested treatment protocol.

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Conflicts of interest

There are no conflicts of interest.

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