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Oral Sub Mucous Fibrosis: The Treatment Strategies

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ABSTRACT

Oral sub mucous fibrosis is a crippling disease of mouth with high malignant potential that has high prevalence rate in India and South East Asia. The treatment of patients with oral submucous fibrosis depends on the degree of clinical involvement. If the disease is detected at a very early stage, cessation of the habit is sufficient. Medical treatment is symptomatic and predominantly aimed at improving mouth movements. The present article discusses various management modalities available for oral sub mucous fibrosis.

INTRODUCTION

Oral submucous fibrosis (OSMF) is a chronic, insidious, disabling disease involving oral mucosa the oropharynx, and rarely the larynx. It is a pre-malignant condition and has been on a constant rise either due to an increase in the habitual chewing of pan masala or a decrease in the awareness among the public of the danger of chewing pan masala or both. It has been reported mainly in the Indian population, having been established in the Indian literature since the time of Sushruta [1].

Although many factors have been elicited and worked upon, no concrete etiology/ pathophysiology has been elicited and thus no effective treatment is available for this progressively disabling condition.

Thus the present article discusses various treatment modalities in management of OSMF.

DISCUSSION

Management

Oral sub mucous fibrosis is one of the most poorly understood and unsatisfactorily treated disease. All available treatments give the patient only symptomatic relief, which is short lived. This is mainly because the etiology of the disease is not fully understood and the disease is progressive in nature. The younger the age, the more rapid the progression of the disease, and the more likely the recurrence of symptoms [2].

Patient Education and counseling is one of the foremost important step in the management of OSMF which includes:

a. Instruct patients regarding the importance of discontinuing the habit of chewing betel quid.

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b. Instruct patients to avoid spicy foodstuffs.

c. Instruct patients to eat a complete and healthy diet to avoid malnutrition.

d. Instruct patients regarding maintaining proper oral hygiene and scheduling regular oral examinations.

e. Intervention studies and public health campaigns against oral habits linked to OSF may be the best way of controlling the disease at the community level.

f. Educate the community regarding the local adverse effects of chewable agents, which although not inhaled, are still harmful [3].

Treatments proposed for OSMF have been palliative rather than curative. They are aimed at improving the patient's ability to open the mouth, which becomes restricted when more scar tissue is formed as the disease progresses, but none have proved curative or have reduced the morbidity significantly [4].

Treatment stratergies includes the following:

I) The conservative approach of topical application of vitamin A, steroids (betamethasone), and oral iron applications (ferrous fumarate ointment)

II) Local submucosal injection:

- Local injection of Corticosteroids
- Hyaluronidase
- Placental extract (PE)
- IFN-☐:
- Chymotrypsin

III) Surgical treatment:

- Simple excision of the fibrous bands
- Split-thickness skin grafting
- Nasolabial flaps and lingual pedicle flaps
- Submucosal placement of placental grafts
- IV) Multivitamin Therapy
- V) Physiotherapy
- VI) Others

The conservative approach of topical application of vitamin A, steroids (betamethasone), and oral iron applications (ferrous fumarate ointment) for mild cases [2].

Vitamin A has a stabilizing effect on the mucous membranes. The functional and structural stability of epithelium throughout the body depends upon vitamin A. The deficiency of vitamin A causes a loss of mucous-secreting cells and epithelial atrophy, resulting in mucosal irritation. Vitamin A was used with the intention of inducing proliferation of the atrophic epithelium found in OSMF and reducing the irritation caused by lack of natural secretions [2].

Iron preparations are found helpful in reducing the mucous membrane irritation during this study. However, their exact mechanism of action remains unexplained [2].

Steroids help in reducing the inflammation and with topical steroids, the needle trauma could be avoided [2].

Local Submucosal Injection

Local injection of Corticosteroids:

In patients with moderate OSMF, weekly submucosal intralesional injections or topical application of steroids may help prevent further damage [3].

Widely accepted treatment for submucous fibrosis is the local infiltration of the suspension of hydrocortisone and its purified derivatives. It is suggested that cortisones have a fibrinolytic effect.

The starting dose is 1 ml. suspension along with 1 ml (2%) lignocaine hydrochloride solution to be injected under the lesion once in a week or twice as per the severity of the condition. Patients get relief from the trismus but on stopping the injections

there is a recurrence of the condition [5].

Treatment with submucosal injections of various drugs leads to aggravated fibrosis, pronounced trismus, dysphagia, and increased morbidity after a certain time due to the mechanical insult to the tissue from the needle sticks that are repeated at multiple sites, chemical irritation from the drugs being injected, and to the progressive nature of the disease. The initial symptomatic relief could be due to the anti-inflammatory action of the steroids, which helps in clearing the juxta-epithelial inflammatory reaction [2].

Hyaluronidase: Stimulates hydrolysis of hyaluronic acid, one of the chief ingredients of tissue cement, which offers resistance to diffusion of liquids through tissues. Used to aid in absorption and dispersion of injected drugs.

Contraindication: Documented hypersensitivity

Interactions: Salicylates, cortisone, corticotropine, estrogens, and antihistamines may decrease effects

Precautions: Avoid injecting into inflamed or cancerous areas; perform intradermal skin test for sensitivity before initiating infusion; discontinue if sensitivity or extravasation occur.

In OSMF it degrades the hyaluronic acid matrix, lowers tissue viscosity and break up the collagen to relieve the trismus. However, rebound fibrosis is often precipitated. The mechanical and chemical injuries in the oral mucosa invariably healed by fibrosis [2].

The use of topical hyaluronidase has been shown to have quicker improvement in symptoms compared with steroids alone. The combination of steroids and topical hyaluronidase shows better long-term results than either agent used alone [3].

Placental extract (PE)

Intralesional injection of aqueous extract of healthy human placenta. The rationale for using placental extract (PE) in patients with OSMF derives from its proposed anti-inflammatory effect, hence, preventing or inhibiting mucosal damage. Cessation of areca nut chewing and submucosal administration of aqueous extract of healthy human PE (Placentrex) showed marked improvement of the condition (Anil) [2,3].

In search of an effective drug without any contraindications and at the same time cheap and safe, local injections of Placentrex were tried in the treatment of Oral submucous fibrosis.

Tissue therapy

Filatov introduced tissue therapy, a new method of treatment of disease in 1933 and later in 1953. This owes its inception to corneal transplantation. His theory was that animal and vegetable tissues when severed from the parent body and exposed to a condition unfavorable, but not mortal to their existence undergo biological readjustment leading to the development of substances in state of their survival to ensure their vitality biogenic stimulators. Such tissues or their extracts when implanted or injected into the body after resistances to pathogenic factor stimulates metabolic or regenerative process thereby favoring recovery [6].

Injection Placentrex is an aqueous extract of human placenta.

Mode of Action

The mode of action is essentially “Biogenic stimulation”. It is also suggested that it stimulates the pituitary, adrenal cortex and regulates the metabolism of tissues. It was proved experimentally to increase the blood circulation by ossicillogram and plethysmogram i.e. it increases the vascularity of tissues. It was observed clinically also by the color changes in the mucosa.

As it contains **(Table 1)** vitamins, ferments and several other substances, it is not possible to postulate the individual action of each constituent. It is imperative to state that each one plays a role in the tissue metabolism and regeneration. It did not produce any untoward effects [6].

Table 1. Contents of Placentrax.

Nucleotides:	Ribonucleic acid, Deoxyribonucleic acid, Adenosine triphoshate (ATP).
Enzymes:	Alkaline and acid phosphates, Glutamic oxaloacetic acid transaminase, Glutamic acid and pyruvic acid transaminase.
Vitamins:	Vitamins E, B1, B2, Panthothenic acid, B6, Nicotinic acid, Biotin, P- Aminobenotic acid, Folic acid, B12, Choline Inositol.
Amino acids:	Alanin, Asparagine, Asparginic acid, Cystein, Glutamic acid, Glycine, Histidine, Leucine, Lysine, Phenylalanine, Proline, Serine, Threonine, Tryptophan, Tyrosine, Valine.
Steroids:	17- Ketosteroids, Cholestrin, Cholesterol, Cholesterin ester.
Fatty acids:	Linoleic acid and linolenic acid (Vit- F) Oleic acid, Palmitic acid
Trace elements:	Cadium, Potassium, Calcium, Magnesium, Copper, Iron, Phosphorous, Silicon.

Interferons

Naturally produced proteins with antiviral, antitumor and immunomodulatory actions. Alpha, beta and gamma interferons may be given topically, systemically and intralesionally.

Interferon gamma (IFN-ϒ)

Believed to act via ability to counteract cell surface expression of proinflammatory or proadhesion molecules on immune cells, among other effects. More studies needed to fully understand mechanisms of action.

Contraindications: Documented hypersensitivity; Escherichia coli derivatives or components

Interactions: Live vaccines; rotavirus vaccine

Precautions: Caution in preexisting cardiac disease, seizure disorder, or compromised CNS function; myelosuppression

Action

IFN-ϒ plays a role in the treatment of patients with OSMF because of its immunoregulatory effect. IFN-ϒ is a known antifibrotic cytokine. Patients treated with an intralesional injection of IFN-ϒ experienced improvement of symptoms. IFN-ϒ, through its effect of altering collagen synthesis, appears to be a key factor to the treatment of patients with OSMF, and intralesional injections of the cytokine may have a significant therapeutic effect on OSMF [3].

The primary cause leading to trismus in OSMF may be fibrosis and fibrous band formation in the oral mucosa. Fibrogenic cytokines secreted by activated macrophages or T lymphocytes are very important in the development of fibrotic disorders. Activated macrophages can produce at least six fibrogenic cytokines, such as: IL-1, TNF-α, IL-6, FGF, PDGF, and TGF-β.

Activated T lymphocytes secrete fibrogenic cytokines that act directly on mesenchymal cells, and produce other cytokines that in turn activate macrophages to secrete fibrogenic cytokines that modulate the function of mesenchymal cells indirectly [7].

Cytokines and growth factors produced by inflammatory cells within the lesion may promote fibrosis by inducing proliferation of fibroblasts, up regulating collagen synthesis and down regulating collagenase production [8].

Both IL-1 and TNF- α stimulate fibroblast proliferation in vitro [9]. IL-1β and TNF- α have been demonstrated to upregulate mRNA expression of collagen types I and III [10]. Intradermal injecions of TNF- α stimulate the accumulation of fibroblasts and collagen. TNF- α has also shown to inhibit adherence and phagocytosis of collagen. Similarly, both IL- 6 and IL-8 have also been implicated in the development of fibrosis.

IFN-ϒ is an antifibrotic cytokine that can inhibit collagen synthesis. Improvement of keloids and hypertrophic scare by intralesional IFN-ϒ treatment has been reported. Local injections of IFN-ϒ reduce contracture formation and facilitate mouth opening in OSF patients [7].

Immune Milk

A study was done to test whether immune milk may have some beneficial effects on controlling the symptoms and signs in OSMF patients. The milk from cows immunized with human intestinal bacteria (immune milk) contains an antiinflammatory component that may suppress the inflammatory reaction and modulate cytokine production [7].

The chemical composition of the milk from immunized cows produced under normal dairy processing conditions is identical to that of commercial milk. However, the IgG type I antibody concentration in immune milk is on the average 20-40% higher than normal cow milk. The IgG antibody activities against human gut bacterial pathogens in immune milk are also significantly higher than normal cow milk [11].

In addition, the immune milk contains a highly active anti-inflammatory compound that can suppress the experimentally induced inflammation in animal models and can give a beneficial effect in patients with rheumatoid arthritis [12].

Surgical Treatment

Surgical excision of the fibrotic bands can be attempted but it is observed that such surgical intervention aggravate the condition. However surgical intervention is the only treatment available in the extremely advanced cases of oral submucous fibrosis [9]. It is indicated in patients with severe trismus and/or biopsy results revealing dysplastic or neoplastic changes.

Surgical modalities include the following:

1) Simple excision of the fibrous bands: Surgical excision, especially with a disease like OSMF, causes contractures during healing [2].

2) Split-thickness skin grafting following bilateral temporalis myotomy or coronoidectomy: Changes in the tendon of temporalis muscle secondary to OSMF results in the trismus. Thus, Canniff et al have recommended temporal myotomy or coronoidectomy and skin grafting which seem to be a better palliative treatment in cases where there is severe trismus. A high rate failure with skin grafts is observed [2].

3) Nasolabial flaps and lingual pedicle flaps: Bilateral full thickness nasolabial flaps for severe trismus cases. Surgery to create flaps is performed only in patients with OSMF in whom the tongue is not involved (Kavarana and Hosein) [2,3].

If lingual pedicle flap grafting is done after excision of a limited amount of diseased tissue in the retromolar area, it will certainly relieve trismus for a short period. The tongue, which serves as the donor site, is also involved in OSMF. It is therefore, hazardous to graft a part surrounded by the disease with a graft equally prone to develop the disease. The donor site is also compromised and the gain from surgery is short lived [2].

4) Submucosal placement of placental grafts:

These treatments are strictly palliative and they only help in relieving trismus temporarily. Relapse is a common complication that occurs after surgical release of the oral trismus caused by OSMF [4].

Multivitamin Therapy

Vitamins, iron and mineral rich diet should be advised to patients with OSMF. Intake of red tomatoes, fresh fruits and green leafy vegetables should be included in the regular diet. Intake of green tea should be included in the diet chart. Various studies have implicated deficiency of iron both as a cause and effect in etiopathogenesis of OSMF. Thus routine hemoglobin levels followed by iron supplements should be included in treatment plan [13].

Physiotherapy

Muscle stretching exercises for the mouth may be helpful to prevent further limitation of the mouth. This includes forceful mouth opening with the help of sticks, ballooning of mouth, hot water gargling. This is thought to put pressure on fibrous bands. Forceful mouth opening have been tried with mouth gag & acrylic surgical screw.

Role of microwave diathermy

Microwave diathermy has been used in many clinical conditions. Rae & Co-workers found microwave diathermy especially valuable in the treatment of fibrosis and trismus following dental extraction and other musculo-skeletal conditions. It was therefore thought to use microwave therapy in treatment of submucous fibrosis.

Role of Ultrasound

Ultrasound used for therapeutic purpose has a frequency of about 0.8-1 MHz and an intensity of 0.5-3 w/cm^2. Ultrasound selectively raises the temperature in some well circumscribed areas. Though skin of cheek, subcutaneous fat, muscle, connective tissue and buccal mucosa all have different acoustic impedances, the difference is not vast and hence less amount of energy is reflected at the interfaces between any two tissues and maximum energy reaches the lamina propria of the buccal mucosa. Ultrasound thus proves to be an efficient deep heating modality. Most of the heat generated by ultrasound in the buccal tissue is due to volume heating rather than structural heating. Volume heating occurs due to absorption of ultrasound by tissue proteins and its conversion to heat. Structural heating occurs at interfaces between two tissues of different acoustic impedance [14].

Others

a. Vinegar

Dilute organic acid solvent e.g. 0.5 M acetic at an adjusted pH exhibits an increased capacity to induce swelling of most tissues. Dilute acid solvents (pH 2.5) are capable of solubilizing non-cross linked molecules and fibres in which cross links are prevalent owing to the labiality of this type of cross link at acid pH 5. In practical terms, however, this effect of dilute acid solvents is limited to a portion of the collagen in the dermis and some tendons of relatively young organisms, since the more stable form of cross-link is prevalent in the fibres of virtually all other tissues. This observation recorded from animal experimental models.

A form of dilute organic acid (4% acetic acid at pH 6.5) which is commonly used for human consumption as a culinary ingredient (Vinegar) was used. This rather safe and solely noninvasive procedure embodies periodic swabbing of the affected oral mucosa with the active ingredient. using a cotton applicator. It is speculated that atrophied oral mucosa in SF augments the permeability of the mucosa to acetic acid thereby causing swelling and breakage of the collagen cross linkages, which renders it less stable. Given the nature of Submucous Fibrosis collagen, being mature (Type I & III) and normal when it meets dilute acid at a lower pH it was speculated to behave in a pre-determined manner eliciting swelling and partial degeneration. This altered collagen, in principle attracts a macrophage affected scavanging action, thereby inducing progressive collagenolysis [3].

b. Injection of Gold, Vitamin A & Collagenase, and Vasodilator injection can be used in the management of OSMF. Chemotherapeutic agents like topical application of Bleomycin can also be used in severe cases.

c. Turmeric:

Administration of turmeric powder offers protection against benzopyrene induced increase in micronuclei in circulating lymphocytes and it is an excellent scavenger of free radical in vitro. Turmeric oil & turmeric oleoresin both act synergistically in vivo to offer protection against DNA damage [15].

Further outpatient care

Regular physical examinations, biopsy specimen analysis, and cytologic smear testing should be scheduled to detect oral

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dysplasia or carcinoma, especially in patients with severe OSMF. Patients with surface leukoplakias require close follow-up monitoring and repeat biopsies. Patients with dysplasias and carcinomas should receive routine treatment for these entities [3].

CONCLUSION

Treatments proposed for OSMF are aimed at improving the patient's ability to open the mouth, which becomes restricted when more scar tissue is formed as the disease progresses, but none have proved curative or have reduced the morbidity significantly.

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