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Review Article

NON INVASIVE MANAGEMENT OF SUBMUCOUS FIBROSIS – A REVIEW

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ABSTRACT

Various treatment modalities were proposed for management of OSMF. Though, several invasive surgical procedures have been experimented to increase mouth opening they are often followed by relapse. Most important aspect of medical treatment is cessation of habit of eating betel quid, arecanut, other local irritants, spicy and hot food, alcohol and smoking. The most common mode of medical treatment had been the use of steroids in its various forms. Used other methods include injection of placental extract, use of trypsin, collagenase, hyaluronidase and elastase and intralesional Interferon-γ (IFN-γ). Oral zinc has been used, as also oral pentoxiphylline and lycopene with varying benefits. The noninvasive treatment regimens include dietary supplementation with iron, Vitamin A or Vitamin B and anti-inflammatory agents like steroids as well as injection of degradative enzymes to facilitate fibrous tissue removal. The purpose of this review is to evaluate all non- invasive methods which are implemented for the treatment of Oral Submucous fibrosis.

Keywords: Oral submucous fibrosis, Non Invasive,Pharmaco-therapeutic.

INTRODUCTION

Oral submucous fibrosis is chronic debilitating disease of the oral cavity characteristics by inflammation and fibrosis of lamina propria and submucous associated with significant morbidity (including pain and reduced mouth opening) and an increased risk of malignancy.[1,2]
OSMF is well known clinical entity since the time of Sushruta and was known as “Vidari” [3]
It was first described by Schwartz in 1952 among five Indian females living in Kenya and he coined the term “atrophica idiopathica mucosae oris” and since then it has remained a subject entity of controversy and interest to clinicians and researchers.[4]
Since then various descriptive terms have been attributed like submucous fibrosis of palate and pillars, diffuse oral submucous fibrosis, idiopathic scleroderma of the mouth, idiopathic palatal fibrosis and sclerosing stomatitis.[1]
Pindborg and Sirsat described oral submucous fibrosis as an insidious chronic disease affecting any part of oral cavity and sometimes the pharynx although occasionally preceded by or associated with vesicle formation, it is always associated with juxta-epithelial inflammatory reaction followed by fibroelastic changes of the lamina propria with the epithelial atrophy leading to stiffness of oral mucosa and causing stiffness and difficulty to eat.[5]

Incidence

It is mainly seen in India, Bangladesh, Sri Lanka, Pakistan, Taiwan and China with reported frequency ranging upto 0.4% in Indian Rural population and prevalence by gender varying from 0.2-2.3% in males and 1.2-4.5% in females.

In recent years there has been marked increases in reported cases in many parts of India like Bihar, Maharashtra, Gujarat and Madhya Pradesh. [6]

Etiology

Over the intervening years the etiology of disease was thought to be multifactorial and several agents have also been implicated as causative factors like consumption of large amounts of chilies, nutritional deficiency, genetic predisposition and autoimmune diseases. However now conclusive evidence exits indicating that OSF is caused by areca nut, the fourth most addictive substance in the world associated with dependency syndrome.[7,8,9]Experiments have shown that ethanolic extracts of areca nut stimulates collagen synthesis in human dermal fibroblasts and also stabilizes the collagen fibrils by catechin and tannin contents of areca nut and render them resistant to degradation by collagenase leading to fibrosis. It has also been found that some amounts of copper is also present in areca nut which up regulates collagen production by increasing lysyl oxidase, involved in collagen synthesis and cross linking.[10,11]

Clinical presentation

The condition is characterized by burning sensation of mucosa,pain and ulceration, blanching of oral mucosa, reduced movement and depapillation of tongue, depigmentation of oral mucosa and progressive reduction of mouth opening, intolerance to spicy foods. Advanced stages of the condition may be characterized by nasal twang due to fibrosis of nasopharynx and hearing impairment due to stenosis of Eustachian tube. [12]

In essence the disease is basically a collagen metabolic disorder with changes in extracellular matrix of lamina propria and in the deeper mucosal tissues of the oral cavity because of both increased collagen synthesis and /or reduced collagen degradation. Epithelial changes mostly occurs secondary to it.

Severity of signs and symptoms are highly variable. In mild early disease patients usually have strong inflammatory component and less likely to have fibrosis but burning sensation is a predominant complain. In contrast, severe advanced disease shows irreversible fibrosis and loss in function predominates. Thus understanding the etiology and deducing the causative agents the main aim of treatment were to reverse or ameliorate the signs and symptoms, stop the disease progression and in addition to minimize risk of malignant transformation.[1]

Various therapeutic and surgical treatment modalities have been advocated but till date there is no unison in establishing definitive treatment guideline for the same.

Thus for ease of understanding the available non-surgical treatment modalities have been divided into:

1. Preventive measures – Restriction of habit/ Behavior therapy
2. Nutritional support
3. Physiotherapy – kneading
   Muscle stretching exercise
   Heat- short wave/ microwave diathermy

4. Medical management- allopathic
   Alternative medicines (Herbal extracts and Ayurvedic)
5. Ultrasound [13]

But each treatment has its own limitations. According to Canniif et al the medical management is both empirical and unsatisfactory though it showed significant improvement clinically. [14]
Surgical intervention by scalpel or laser is usually reserved for the more advanced cases. Physical therapy along with combined interventions works well for most of the cases.
Owing to patient acceptance and shift of paradigm towards non-surgical and non-invasive management, this review focuses on :

Non Invasive Topical Pharmaco-therapeutic Management of oral submucous fibrosis which will be discussed under:

- Habit cessation and counseling
- Physiotherapy
- Nutrients – a)chewable vitamin A tablets,
  b) Green Tea extract
  c) Immunized Milk
- Immune-modulations
- Enzymes
- Antioxidants
- Alternative therapy-
  a) Aloe vera
  b) Turmeric
  c) Tulsi
- Ayurvedic management
- Muco-adhesive patch concept (COX inhibitor)
- Ultrasound

1. HABIT CESSATION AND COUNSELLING

Regardless of definitive planned treatment modality, restriction of excessive consumption of chilies, pan,betel nut, spices and commercially available gutkha and pan masala along with individualized counseling of affected patient explaining the possible malignant potential of OSMF have shown significant improvement in the condition of OSMF patients. Avon et al reported improvement in mucosal lesion as well as clinical symptoms subsequent to the cessation of areca nut chewing habit[15]

2. PHYSIOTHERAPY

Rationale for this is to modification of tissue remodeling through promotion of physical movements and localized heat. This produces noteworthy results within physiological limits. This can be accomplished either by planned physical exercise regimen or with customized devices and splints. Various other methods used range from forceful mouth opening with assistance of sticks, hot water gargling and ballooning of mouth as those are intended to put pressure on fibrous bands. Mouth gag and acrylic surgical screw has also been tried producing satisfactory results.[16,17]

Interpositioning tongue spatulas stuck between teeth and addition of new spatulas every 5-10 days for 4 months have been proven for enhanced oral opening as advocated by Cox and Zoellner.[18]

Oral stents have also been advocated for use for 6 months and should be removed only during meal time and at bed time.[19]

3. NUTRITION

Rationale for prescribing additional nutrients and supportive therapy is to correct deficiency states and promote cellular processes present in health and help to protect against adverse effects including carcinogenesis. Micronutrients and minerals such as vitamin A, B,C,D,E and iron, copper,calcium, zinc, magnesium and selenium can play a major role in regeneration

a) VITAMIN A -

Helps in epithelial differentiation , mucous secretion and keratinization of tissues. It can substantially delay, slows and even reverse the progress of precancerous cells to more invasive malignant potential cells.Borle in 1991 evaluated the efficacy of chewable vitamin A tablets which showed remarkable improvement in clinical sign and symptoms. It was attributed to its added benefit of locally increased contribution along with systemic absorption.[20]

b) GREEN TEA:

This works on the rationale of reducing the effects of free radicals. Polyphenols in green tea have considerable free radical scavenging activity thereby providing protection to DNA from free oxygen species. It is alsobeen proven to hinder proliferation of tumor cells.

Catechin component of tea reduces angiogenesis and tumor cell invasiveness. Enzymes like glutathione S-transferase, the detoxification enzyme have also been shown to be activated which further defended development of malignancy. [21]

Li and Tang found an overall effective rate and concluded that pigments of tea act by decreasing high blood viscosity, improving microcirculation and enhancing the activity of superoxide dismutases.[22]

c) IMMUNIZED MILK

It is type of skimmed milk produced from cows immunized with multiple human intestinal bacteria. It has good anti-inflammatory effect and contains modest amount of vitamin A, C, B1, B2, B6 and B12, nicotinic acid, pantothenic acid, folic acid, iron, copper and zinc.

Though chemically identical yet differs from milk as it contains 20-30% higher concentration of IgG type 1 antibody, it is proven to suppress inflammatory reaction and modulate cytokine production and relief of patient could also be because of micronutrients contained in immune milk powder. [23]

Tai et al advocated 45gm of immune milk powder twice a day, for 3 months and observed regression of concomitant leukoplakia and erythroplakia in addition to significant improvement in clinical symptoms of OSMF.[24]

4. IMMUNE MODULATION

Steroids are well recognized to be immunosuppressive agents causing diminished profibrotic inflammation and also enhancing profibrolytic immune mediated pathways. Steroids also release cellular proteases in the connective tissue which in turn activate collagenase and zymogen that consumes insoluble collagen. [25]

Glucocorticoids are used for treatment of OSMF such as short acting (Hydrocortisone), Intermediate acting (Triamcinolone) and long acting (Betamethasone and Dexamethasone)

Topical forms of intermediate acting are available for use in very early cases namely Triamcinolone acetonide 0.1%(Kenacort) and Betamethasone 0.5% (Betnesol). Steroid ointment applied topically may be helpful in ulcers and painful oral mucosa.[26]
Lai et al evaluated different treatment modalities for OSMF and inferred that 0.1% triamcinolone acetonide was satisfactory in cases of mild impairment with interincisal opening more than 20mm but in the long term cases led to symptomatic relief only. [27]

5. ENZYMES

Proteolytic enzymes works by breaking down connective tissue fibrosis eg.Chymostrypsin, collagenase and hyaluronidase. Most common method of administration is intralesional injections and to some extent topical application.
Hyaluronidase reduces burning sensation and trismus by breaking down hyaluronic acid, lowering the viscosity of intracellular substance and decreasing collagen formation. It modifies the permeability thereby facilitating easy diffusion and absorption.[28]
Kakar et al also revealed improvement of symptoms in patients with use of topical hyaluronidase quickly as compared to steroids.[29]

6. ANTIOXIDANTS

This acts by scavenging or neutralizing effects by free radical reactions thereby preventing damage to DNA to mutation, changes by lipid peroxidation in cell membranes and changes in enzymatic activity. Topical application of beta carotene improves integrity of oral epithelium and also aids in redifferentiation of dysplastic epithelium.[30]

7. ALTERNATIVE THERAPY

ALOE VERA:

Popularly known as “Babosa” , is a plant found native of northeast of Brazil and grown worldwide. Its foliage , extract and resin have excellent antimicrobial , anti-inflammatory and healing properties. Sudarshan et al compared efficacy of A. vera with antioxidants and results clearly discerned that response in all the parameters responded well chiefly in patients with mild stage clinically and early stage histopathologically. It showed that Topical application of 5mg of aloevera thrice daily for 3 months reported decline in burning sensation, improved mouth opening and flexibility.[31]

TURMERIC:

Turmeric is a rhizome of curcuma longa family, a natural yellow pigment widely used in Asian cooking. The components of turmeric are named curcuminoids which include curcumin (diferuloyl methane), demethoxycurcumin and bis-demethoxycurcumin. It exhibits excellent antioxidant , anti-inflammatory and anti-cancer properties.[32]
It inhibits the products of inflammation such as prostaglandins and leukotrienes by inhibiting the pathways of inflammation. By virtue of its scavenging effect on superoxide radicals, hydroxyl radicals and inhibits lipid peroxidation it proves to be DNA protectant. It is also found to have fibrinolytic action by reducing cellular proliferation and inhibiting cellular synthesis thus being chemoprotective as well.[19,33.]
Alcoholic extracts of turmeric (3g), turmeric oil (600mg) and turmeric oleoresin (600mg) daily for 3 months has been proven to be useful in treatment of OSMF. It also provides a base for simple,safe, acceptable and cost effective for earlier stages of OSMF and this hold a promising future in clinical and research directed towards treatment.[34,35]

TULSI:
Adit et al evaluated role of 1gm of tulsi and 1 gm of turmeric in glycerin base in 41 patients in age group of 17-56 years , to be applied 3-4 times per day . Results showed statistically significant improvement in both burning sensation and mouth opening. [36]

8.SPECIFIC ANTI-INFLAMMATORY AGENTS

The specific anti-inflammatory agents (COX-2 inhibitors) target at the molecular level to stabilize the disease in early stages and reducing malignant potential of OSF. Reducing patient discomfort for intralesional injections and with aim of increasing local availability of the drug into the targeted location concept of mucoadhesive patch was introduced. Preliminary study to develop mucoadhesive buccal films of valdecoxib (novel COX-2 inhibitor) was done by Averineni et al producing satisfactory improvement in affected patient. [37]

9. AYURVEDIC MANAGEMENT

An open labeled non –randomized clinical trial with black box design comprising of holistic ayurvedic approach was conducted in which all the patient completed the treatment. For the initial 3 days *ErandabhrishtaHartitaki*powder 5-10 g was administered with luke warm water at bed time for *Koshthashuddhi* (mild purgation) followed by *ShadabinduTailaNasya* (errhine therapy) 4-8 drops in each nostril for 5 days. After that external application of *Pratisarana,*Kavala (gargling) and Rasayan yoga were administered twice a day simultaneously for 60 days. Routine hematological, biochemical –RBS, serum lipid profile, creatinine and routine urine examination were recorded. 9.09% patient showed marked improvement, 72.73% moderate improvement and 18.18% of patient showed mild improvement in clinical signs and symptoms. Therapy was based on rationale of purification from toxins, clearing obstructions of channels, decreasing inflammation along with local therapy to prevent and reverse fibrosis and improving overall immunity which inturn strengthens the oral mucosa and sub mucosa to overcome disease. [38]

10. ULTRASOUND

Ultrasound has been proven to alter cell permeability by altering sodium and potassium ion gradients. This not only increases permeability and improves gas exchange and also promotes healing. It increases vasodilatation, accelerates lymph flow, decreases inflammation and stimulates metabolism.
It is well proven to increase the extensibility of collagen fibers, provide pain relief and selectively raises the temperature in some well circumscribed areas. Clinically Ultrasound ranging from 0.6 to 2.0W/cm^2 pulsed 1:1 or 1:2 (50% or 33.3% duty cycle), frequency of 3 MHz, 5cm diameter transducer head for 3 to 4 minutes to each side over the cheek for 15 consecutive days with permissible one day off each week have been used for the treatment of OSMF.[39]

CONCLUSION:
OSMF is an established precancerous condition with increases prevalence in Indian subcontinent.
From the time it has been first diagnosed, till date there is no predictable treatment elucidated and no complete success has been achieved thus its management is challenging task for clinician.

Varies reason could be the unpredictable etiology, immune response or immune status of individual patient along with varying magnitude of morbidity of patients.
Over years various treatment modalities have been proposed with varying success rates by various authors. However there exists no unison in protocol for treatment of OSMF.
Choice of treatment depends upon the grading of the disease. The stage 1 and stage 2 disease can be managed by medical therapy along with habit cessation and patient counseling, whereas with severing degree i.e the stage 3 and stage 4 disease requires intralesional approach and surgical approach in most advanced stages.
Clinical research and patient acceptance is moving towards more conservative approach with more inclination towards herbal and medicinal approach. Thus, various proposed medicinal approach can be considered as better alternative to surgical approach owing to better patient acceptability, however lack strong evidence or clinical trials. Local medicinal modality offers higher patient comfort and adequacy, satisfactory improvement in clinical signs and symptoms, however lacunae still prevails in evidence based application thus high quality randomized controlled trials offering potential thrust area to be explored.

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