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# Non-invasive management of Oral submucous fibrosis: a review

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### Abstract

**Aim:** To review the literature of non-invasive treatment of OSMF.

**Material and methods:** A literature search was conducted in January 2010. The following key words were used in “PUBMED” and “Google search”.

- OSMF and treatment
- Oral submucous fibrosis and treatment

**Results:** The search words “OSMF and treatment” retrieved 14 papers while the search words “Oral sub mucous fibrosis and treatment” retrieved 124 articles from 1965 to 2009. Among the retrieved articles, only 17 articles were related to non-invasive treatment procedures.

**Conclusions:** Very few studies could be traced that had adequate sample size and follow-up.

**Key words:** Oral submucous fibrosis; Review; Non-invasive treatment.

### Introduction

It has been more than half a century since **Schwartz** described oral submucous fibrosis in the tobacco-chewing women of Indian origin in East Africa (1).

Since then this condition evoked an intense enthusiasm among many researchers in India and throughout the world. Various authors had investigated the condition thoroughly and proposed several factors that play a role in the etiopathogenesis of this condition. Current evidence suggests that arecoline in the areca nut is the key factor in initiating the disease process (2).

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## Non-invasive management of OSMF

Almost after 4 years of OSMF description its precancerous condition was described by Paymaster (1956) and further substantiated by Pindborg in 1972 (3). Malignant transformation rate of OSMF is 7.6 % over a period of 10 years has been reported (4). Recent epidemiological data indicates that, the numbers of OSMF cases are rising every year. The reasons for the rapid increase of the disease are reported to be due to an upsurge in the popularity of commercially prepared areca nut preparations (pan masala) in India and an increased uptake of this habit by young people due to easy access, effective price changes and marketing strategies (5). Because of its premalignant nature it is mandatory to start treatment at early stage.

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. The noninvasive treatment regimens include dietary supplementation with iron, Vitamin A or Vitamin B and antiinflammatory agents like steroids as well as injection of degradative enzymes to facilitate fibrous tissue removal.

The purpose of this paper is to review various non-invasive treatment modalities for OSMF that have been published during the years 1965 to 2009.

### Material and Methods

The intention of this paper was to review the literature regarding various non-invasive management procedures for OSMF. A literature search was conducted in January 2010. The following key words were used in "PUBMED" and "Google search".

- OSMF and treatment
- Oral submucous fibrosis and treatment

Only those articles that discussed the non-invasive therapies for OSMF and review

articles were included. All the articles were included irrespective of their study design and level of evidence. Articles that were in English were only considered. Studies on surgical intervention of OSMF and those which were not related to the study purpose were excluded.

### Results

The search words "OSMF and treatment" retrieved 14 papers while the search words "Oral sub mucous fibrosis and treatment" retrieved 124 articles from 1965 to 2009. Among the retrieved articles, only 17 articles were related to non-invasive treatment procedures and three articles reviewed the management of OSMF. Two articles were in French and Chinese, 20 papers discussed the surgical interventions and the remaining dealt with etiology, pathogenesis or prevalence of the OSMF.

### Discussion

Most of the treatment modalities for OSMF in practice are circumstantial and most of the studies that tested various treatment regimens lacked good design and follow up. Treatment of OSMF has largely been symptomatic. Though there are many therapeutic procedures available for OSMF, prevention is likely to be more effective than treatment.

#### Micro nutrients and minerals

Micronutrients such as vitamins and minerals play an important role in the normal human metabolism. Few studies conducted in the previous decade observed that Vitamin A given at a concentration of 50,000 IU would cause symptomatic improvement (6-8). It is well evident that vitamin A plays an important role in maintaining normal growth and repair of epithelial tissues.

Other than Vitamin A, Vitamin E has been extensively studied for its role in the treatment of OSMF. Reddi suggested that

## Non-invasive management of OSMF

Vitamin E given concomitantly with the Hyalase and betamethasone was better than as compared with Hyalase and betamethasone alone (9). The efficacy of vitamin E was attributed to its antioxidant property.

On the other hand, Singh observed that vitamin C given in combination with placentrax and liver extract gave better results than institution of vitamin C alone. It was believed that Vitamin C reduces the oedema between the collagen bundles and helps in regeneration of new collagen bundles with good approximation (10).

Other than vitamins several minerals also have been used as an adjunctive in treatment of OSMF. Anil *et al.*, administered Zinc (220mg) in combination with vitamin A and observed good results. Zinc plays essential role in DNA synthesis and cell division (6). Apart from zinc, Magnesium also plays essential role in many enzyme reactions and exerts stabilizing effects on excitable membranes.

A study was conducted in Karachi, Pakistan to assess the efficacy of combination of micronutrients (vitamins A, B complex, C, D, and E) and minerals (iron, calcium, copper, zinc, magnesium, and others) in controlling the symptoms and signs of OSMF and the outcome was beneficial clinical response (11).

### Antioxidants

It is known that the process of carcinogenesis occurs by generation of Reactive Oxygen Species, which act by initiating lipid peroxidation (LPO). Prevention against LPO mediated damage is done by antioxidants and it has also been reported that oral premalignant lesions can be successfully treated by antioxidant supplementation which led many clinicians to consider antioxidants in the treatment of OSMF (12).

Carotenoids are natural pigments synthesized by plants and are responsible for the colors of fruits and vegetables. Lycopene is the carotenoid that gives tomato its bright

red color, and it is one of the major carotenoids in Western diets. It accounts for 50% of the carotenoids in human serum. It has been shown to have several potent anti-carcinogenic and antioxidant properties and has demonstrated profound benefits in precancerous lesions. Kumar advocated Lycopene (16mg) and concluded that it produced better response (13).

Furthermore, Gupta *et al.*, (14) carried out a study on 34 cases of OSMF. They have advocated one tablet of antoxid thrice daily for 6 weeks and observed improvements and amelioration of the symptoms.

### Steroids

Steroids have therapeutic effects like anti-inflammatory and are well known to act as immunosuppressive agents for the prevention or suppression of fibro-productive inflammation found in OSMF (15).

Sinha and Jain (16) have tried local injection of hydrocortisone 1.5 cc and found hydrocortisone to be effective. Moreover Kakar *et al.*, (17) found that injection of Dexamethasone (4 mg) and 1500 IU of hyaluronidase locally for 7 weeks gave superior results if it is followed by 3 weeks of hyaluronidase.

### Enzymes

Among the enzymes that have been tested in the treatment of OSMF, collagenase and chymotrypsin have showed good results in the treatment of OSMF.

Collagenase is a lysosomal enzyme, Lin and Lin found that intralesional injection of collagenase resulted in significant improvement (18).

Chymotrypsin, an endopeptidase is used as a proteolytic and anti-inflammatory agent in treatment of OSMF. Gupta and Sharma (1988) gave injected Chymotripsin (5000 IU), hyaluronidase (1500 IU) and dexamethasone (4 mg) twice weekly for 10 weeks submucosally and observed good results (19).

## Non-invasive management of OSMF

### Vasodialator

Occlusive blood vessels encountered in OSMF restrict nutrients and therapeutic substances from reaching the affected tissue, which may be one of the reasons for the unsatisfactory therapeutic effect of drug treatment of OSF. Thus vasodilators were used in the therapy of OSMF (18).

Lai (1995) has carried out treatment for OSMF using buflomedial HCL (3 tablets of 450 mg each per day) and topical trimacetonolone acetonide 0.1% on mucosal ulcers at bed time. He observed positive results (20).

Buflomedial HCL (peripheral vasodialator) has been found to affect the tissues in diffuse fibrosis to a noticeable degree by the relief of local ischemic effect.

Rajendran (2006) used pentoxifylline, a methylxanthine derivative that has vasodialating properties. It was administered as 400 mg thrice daily for a period of more than 12 months and observed improvement in symptoms of OSMF (21).

Fibroblasts cultured in the presence of pentoxifylline produce twice as much collagenase activity and decreased amount of collagen, glycosaminoglycans and fibronectins. IL-1 induced fibroblast proliferation was inhibited by the addition of pentoxifylline.

### Others

Apart from the above mentioned treatment modalities placental extract, milk, turmeric, interferon gamma and microwave diathermy have been considered in the treatment of OSMF.

### Placental extract

The injection placentrax is an aqueous extract of human placenta. The action of placental extract is essentially biogenic stimulation and its use is based on the tissue therapy method. According to this theory when animal and vegetable tissues are severed from the parent body and exposed to unfavourable conditions, but not mortal to their existence, undergo biogenic readjustment leading to development of

substance in the state of their survival. Such tissues or their extracts when implanted or injected into the body after resistance of pathogenic factors stimulate metabolic or regenerative process thereby favouring recovery (22).

Ramanjaneyalu and Prabhakar Rao (1980) advocated 2 cc placentrax injection at weekly interval for 10 weeks. They have found it to be superior to Cortisone. They have even found two cortisone resistant cases responded well to placentrax (23).

Furthermore Katharia *et al.*, (1992) also carried out a study on 22 OSMF patients and injection of 2ml Placental extract (Inj. Placentrex) was given locally in the predetermined areas, once a week up to a total duration of one month. Effects were monitored in reducing the severity of the disease (22).

### Milk

Immune milk contains small amount of vitamin A, vitamin C, vitamin B<sub>1</sub>, Vitamin B<sub>2</sub>, Vitamin B<sub>6</sub>, Vitamin B<sub>12</sub>, Nicotinic acid, panthotenic acid, folic acid, iron, copper and zinc. Immune milk has anti-inflammatory components and modulates cytokine production.

Tai *et al.*, (2001) advocated 45 gms of immune milk powder twice a day, for 3 months and observed a regression of concomitant leukoplakia and erythroleukoplakia in addition to significant improvement in symptoms of OSMF

### Microwave

Microwaves are quasi optical and are applied by radiation. It therefore produces sharp localized deep heat without undue heating of skin and other subcutaneous tissues such as fat and is thus simple to apply with minimum discomfort. Gupta *et al.*, (1980) advocated diathermy daily for 20 minutes at each site of lesion with 20 -25 watts of energy to produce comfortable warmth. Such 15 sittings were given to each patient and found valuable for the moderately advanced stage of OSMF (25).

## Non-invasive management of OSMF

### Turmeric

Turmeric has been found to inhibit many disease processes through their anti-inflammatory, antioxidant and anticancer properties (26).

In addition, Curcuminoids isolated from turmeric, has been found to have effective antioxidant, DNA-protectant and antimutagen action. A study concluded that usage of turmeric oil daily for 3 months had a beneficial role in treatment of OSMF (27).

It was observed in 58 OSMF patients that turmeric given in any form, i.e., alcoholic extracts of turmeric, turmeric oil and turmeric oleoresin were all effective in decreasing the number of micronucleated cells (which are found to be increased in exfoliated oral mucosal cells and circulating lymphocytes of precancerous oral lesions) both in exfoliated oral mucosal cells and in circulating lymphocytes (28).

In addition, Deepa Das *et al.*, (29) found that turmeric dispensed in the form of curcumin and turmeric oil was effective in the treatment of OSMF which was evident by the positive changes observed in the histopathological examination after treatment along with the significant improvement in clinical signs and symptoms.

### Physiotherapy

Cox and Zoellner (2009) advocated five times daily physiotherapy by inter-positioning tongue spatulas between teeth and adding a new spatula every 5–10 days for 4 months and observed improved oral opening (30).

### Conclusions

In conclusion, we could trace only few articles with sound study design. Most of the studies had small sample size without adequate follow-up. Thus, there is a need for high – quality randomized, controlled trials with adequate sample size and long term follow-up for the management of oral submucous fibrosis.

**Table 1:** Treatment modalities and their details in the treatment of oral submucous fibrosis

TREATMENT	TREATMENT DETAILS
Micronutrients and minerals	Vitamin A, B complex, C, D and E, iron, copper, calcium, zinc, magnesium, selenium and others (6-11)
Milk from immunized cows	45 g milk powder twice a day for 3 months (24)
Lycopene	8 mg twice a day for 2 months (13)
Pentoxifylline	400 mg 3 times a day for 7 months (21)
Interferon gamma	Intralesional injection of interferon gamma (0.01–10.0 U/mL) 3 times a day for 6 months (31)
Steroids	Submucosal injections twice a week in multiple sites for 3 months (16,17)
Placental extracts	2ml Placental extract (Inj. Placentrex) locally in the predetermined areas, once a week up to a total duration of one month (22)
Turmeric	Alcoholic extracts of turmeric (3 g), turmeric oil (600 mg), turmeric oleoresin (600 mg) daily for 3 months (27,28,29)
Chymotripsin, hyaluronidase and dexamethasone	Chymotripsin (5000 IU), hyaluronidase (1500 IU) and dexamethasone (4 mg), twice weekly submucosal injections for 10 weeks (19)
Levamisole + vitamin A	Vitamin A – 50,000 IU (6-8)

## Non-invasive management of OSMF

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