Management Strategies for Oral Submucous Fibrosis- An Update

Running title: ***Management Strategies for OSMF***

ABSTRACT:

There are plentiful management trials in Oral Submucous Fibrosis (OSMF), such as drugs, herbs, and Chinese medicines, but none proved to be entirely successful. So in this review, there are different management strategies tried in the management of OSMF, mechanism of action, and the dosage regimen.

KEYWORDS:

Oral Submucous Fibrosis (OSMF), potentially malignant disorder, management

INTRODUCTION:

Oral submucous fibrosis (OSMF) is a chronic disease associated with significant functional morbidity and an increased risk for malignancy. OSMF predominantly affects the Asian population and Asian migrants living in other parts of the World (Kerr et al., 2011).

But in most of the research the management of OSMF was based on Clinical, Histopathological and fuctional staging proposed by several authors (Gupta H et al.,2018).

The management of OSMF has been discussed previously by several authors (Jiang et al.,2009, Fedorowicz et al.,2008 & Kerr AR et al.,2011). This Review updates the different management protocols available and tried for OSMF.

VARIOUS MANAGEMENT OF OSMF IS CATEGORIZED AS FOLLOWS:

1. **Habit counseling**
2. **Basic regimen**
3. **Medical management**

4. **Physiotherapy**
5. **Surgical management**
6. **Laser Management**

1. **Habit counseling:**

The first and foremost treatment plan in OSMF is strict discontinuance of habit with motivation and intense councelling session for educating and creating awareness about the disease and its malignant potential (Deshpande A et al.,2013).

2. **Basic regimen:**

The second line of approach for the management of OSMF is the nutritional supplementation like Vitamins and Iron. It has been observed in a study that majority of the OSMF patients has Vitamin B12 and Iron deficiency due to inability to eat (Agarwal V, Maiti S et al.,2020).

3. **Medical management:**

The management of OSMF has significant challenges for treatment options. Even Though several options are available still an established treatment regimen is lacking. So such treatment options available are discussed in table 1. The medical management strategies are categorized with following heading as steroids,nutritional supplements,biogenic stimulators,enzymes, penetration enhancers,vasodilators, immunomodulators, alternative medicine and others.future therapies suggested are molecular targeted therapies, Imatinib, Pirfenidone, nintedanib, Clostridium histolyticum collagenases, Simtuzumab, Hyperbaric Oxygen therapy,and personalized Medicine (More, C. B., Jatti Patil, D., & Rao, N. R., 2020).

TABLE 1 Different drugs tried as management protocols are discussed in the table.

Sl no	Drugs	Mechanism of action	Duration	Dosage	Route of administration
		STEROIDS			
1.	Hydrocortisone (Gupta et al., 1980)	Anti-inflammatory action by inhibiting the generation of inflammatory factors and increasing the apoptosis of inflammatory cells.[2]	once a week for 12 weeks	1.25 cc of injection hydrocortisone on each side	Intralesional
2.	Dexamethasone (Gupta et al., 1988)		10 weeks	4 mg	Intralesional
3.	Triamcinolone acetonide (Khanna et al., 1985)		Divided doses at 10 day intervals for a period of 2 - 3months	150-200 mg	Intralesional
4.	Triamcinolone diacetate (Borle et al., 1991)		4 weeks	10 mg/ml	Intralesional
5.	Betamethasone (Borle et al., 1991)		6 hours for 3 weeks	0.5 mg/ml	Topical
6.	Prednisolone (Laskaris et al., 2004)		2-4 weeks	20-30 mg	Systemic
~~7.~~	~~(Triamcinolone acetonide and~~		~~Steroid for 10 weeks and antihistamines for 3 months~~		~~Intralesional steroids~~

	~~antihistaminics~~ ~~(Kavarana et al., 1987)~~				
7.	Steroids and Physiotherapy (Gupta DS, Gupta MK, Golhar BL.,1980).	Microwave diathermy at 2450 MC/s and injection of hydrocortisone, vitamin A and B complex.	20 minutes with 15 sittings	20-25 Watts	Selective heating of Juxtaepithelial connective tissue Madalli V et al.,2014)
		NUTRITIONAL SUPPLEMENTS			
8.	Vitamins and minerals (Gupta et al., 2004)	The main action is eliminating the deficiency status and normalizing the cellular activity to prevent pathological mechanisms like carcinogenesis. *The hypothesis of vitamin E mechanism* 1. Preventing the formation of oxidation products. 2. Free radical scavenger Prevent nerve-related pathologies 3. Increase the life span of erythrocytes	6 weeks	Beta Carotene 50mg, vitamin A palmitate 2500 IU, vitamin E acetate, 10 IU with vitamin C, zinc, copper and manganese	oral

9	Thioctic acid (Bhandarkar, G. P., Shetty, K. V., & Kulkarni, A.,2018).	Antioxidant	30 min before or 2 hours after food	600-1800 mg daily. Iv Dose 300-600 mg	
		BIOGENIC STIMULATORS			
10	Placental extracts (Gupta et al., 1988)	It is an aqueous extract of the human placenta that contains nucleotides, enzymes, vitamins, amino acids, and steroids. The mechanism through "biogenic stimulation, and by increasing the recovery (Kisave et al., 2020).	10 weeks	2 cc	Intralesional
11.	Papain and urea (Gupta et al., 1992)	Proteolytic enzymes breakdown the inappropriate connective tissue fibrosis (Kerr et al., 2011).	2 to 3 times daily for 15 days	100 gms urea and 100 gms papain	Intraoral
		ENZYMES			
12.	Chymotrypsin (Gupta et al., 1988)	Proteolytic enzymes breakdown the inappropriate fibrosis (Kerr et al., 2011).	Biweekly	5000 IU	Intralesional
13.	Hyaluronidase(Gupta et al., 1988)		Biweekly for 10 weeks	1500 IU	Intralesional
14.	Collagenase (Lin et al 2007)		once a week for 6 weeks	1 ml of collagenase (1% solution) mixed with 1 ml of xylocaine	Intralesional
		PENETRATION ENHANCERS			

15.	Borneol (Dai et al., 2009)	Anti-fibrosis activity inhibits fibroblasts mitosis, collagen, and TIMP-1 production and can be used as a penetration enhancer (Dai et al., 2009).	Incubation period of 24,48 and 72 hours.	serial dilution of borneol (18.75, 37.5, 75, 150–300 lg⁄ml)	Penetration enhancing effects tried in mice fibroblast Invitro study
		VASODILATORS			
16.	Nylidrin hydrochloride (Sharma et al., 1987)	Nylidrin relaxes and dilates the blood vessel ensures more excellent blood supply to ischemic tissues with little or no change in the blood pressure and heart rate (Sharma et al., 1987).	3-8 weeks	6 mg	Oral
17.	Pentoxifylline (Rajendran et al., 2006)	It is a methylxanthine derivative with vasodilating properties and was envisaged to increase mucosal vascularity Rajendran et al., 2006).	3 times daily for 7 months	400mg	Oral
18.	Buflomedial hydrochloride (Lai et al., 1995)	The mechanism is through vasodilation, mild anticoagulant properties, immune modulation, and antioxidant properties have been reported (Kerr et al., 2011).	4 weeks	450 mg TID	Oral

19.	xantinol nicotinate (Singh et al., 2006)	Peripheral vasodialator	4 months	Biweekly	Intralesional
		IMMUNOMODULATORS			
20.	Levamisole and vitamin A (Rao et al.,1993)	Immune modulation diminishes pro-fibrotic inflammation and enhances pro-fibrinolytic immune-mediated pathways (Kerr et al., 2011).	4 days OD for one week followed by biweekly for one month	150 mg of levamisole along with aqua sol caps 50000 iµ	Oral
21.	Interferon gamma (Haque et al., 2001)	*IFN γ* is an antifibrotic cytokine.	Twice a week for 8 weeks(15 intralesional injections)	Eutectic Mixture of Local Anesthetics cream for 15 minutes then followed by IFN-© application of 0.25 ml (50 mg) of	Intralesional
		ALTERNATIVE MEDICINE			
22.	Immune milk (Tai et al., 2001)	It contains a highly active anti-inflammatory compound that suppressed the experimentally induced inflammation in animal models.	Twice a day for 3 months	45 gm	Oral

23.	Turmeric (Hastak et al., 1997)	Anti-inflammatory, antioxidant, anti-cancer properties.	3 months	Turmeric Oil (600 mg TO mixed with 3 g Extracts of Turmeric/day)	Oral
24.	Lycopene (Kumar et al., 2007)	Anticarcinogenic, antioxidant, highest physical quenching	2 months	16 mg	Oral
25.	Tea pigments and vitamins (Li et al., 1998)	The main action is by eliminating the deficiency status and normalizes the cellular activity to prevent pathological mechanisms like carcinogenesis (Kerr et al., 2011).	????	?????	????
26.	Mangifera indica, Withania somnifera, Daucus carota, Glycyrrhiza glabra, Vitis vinifera, Emblica officinalis, Yashada bhasma, oils of Triticum	Herbal antioxidant formulation.	3 months	2 capsules Mangifera indica-94 mg, Withania somnifera-71 mg, Daucus carota-47 mg, Glycyrrhiza glabra-29 mg, Vitis vinifera-12 mg, Emblica officinalis-141 mg, Yashada	Oral

	sativum (Singh et al., 2009)			bhasma-2.5 mg, oils of Triticum sativum 6.5 mg (Oxitard Capsule 2021)	
27.	Aloe vera (Sudarshan et al., 2012)	Antioxidant, anti-inflammatory, and immunomodulation	3 times daily for 3 months	5 mg gel	Topical
		OTHERS			
28.	Gold, Iodine and Arsenotyphoid (Joshi SG.,1953)	With the surgical cutting of bands, Large Internal doses and Injection respectively			
29.	Glucosidorum tripterygii totorum, vitamin A and E, nicotinic acid (Liu et al., 1997)	The main action is by eliminating the deficiency status and normalizes the cellular activity to prevent pathological mechanisms like carcinogenesis (Kerr et al., 2011).			
30.	Danxuan koukang, salvia miltiorrhiza (Tan et al., 2006)	The mechanism is through vasodilation, mild anticoagulant properties, immune modulation, and antioxidant properties have been reported (Kerr et al., 2011).			
31.	Turmeric and black pepper (Pipalia et al., 2016)	Anti-inflammatory, antioxidant, anticarcinogenic, antifibrotic, immunomodulatory	3 months	Turmeric 400 mg Black pepper 100 mg 2 capsules TID	Oral
32.	Nigella sativa (Pipalia et al., 2016)	Anti-inflammatory, antioxidant, anticarcinogenic, antifibrotic, immunomodulatory	3 months	500 mg 2 capsules TID	Oral
33.	Spirulina in combination	antioxidant, anti-inflammatory and	3 months	BID	Oral

	with isometric exercises/threaded tapered screw/mouth stretching device (Kanjani et al., 2019)	immuno-modulation			
34.	Pentoxifylline and garlic pearls (Jain et al., 2016)	Garlic has immunomodulation, vasodilator, antioxidant, anti-inflammatory, and chemopreventive Pentoxifylline has antifibrinolytic, immunomodulation, anti-TNF effect, and hemorheological properties.	3 months	Pentoxifylline 400 mg and garlic pearls 0.25% BID	Oral

4. Physiotherapy

Physiotherapy over the affected area to generate heat and mouth opening has been tried. A study in 2009 conducted on Fifty-four Nepali OSMF patients was managed for four months by randomly assigning them to 3 groups. The first group of patients in the physiotherapy group were asked to do jaw exercises five times a day in which tongue spatulas were placed passively between anterior teeth, spatula number determined by comfortable mouth opening. An extra spatula was added every fifth day, but the spatula was tried on the tenth day in case of pain. The patient was subjected to analgesics 30 minutes before exercise to reduce the pain. The second group was treated with local injection of steroids, and the third group received no active

treatment. The patients subjected to physiotherapy improved mouth opening compared to the other two groups (Cox et al., 2009).

5. **Surgical Treatment**

This form of modality is usually suggested during the severe form of OSMF and when the other forms of modality are unsuccessful. The common method of excision is scalpel which is considered to be the preparatory step for surgical treatment. Different surgical procedures tried are intraoral (tongue, palate, buccal fat pad), extraoral (temporal fascia, nasolabial), distant flaps, grafts, muscle myotomies and oral stents etc. Further a systematic review stated that the choice of procedure depends on the operator. (Kamath V. V., 2015).

6. **Laser**

A systematic review by Gondivkar SM et al. from various databases found that studies with Laser were used for stage II and III OSMF patients. Even though different Laser types and parameters were considered, all studies showed improvement in mouth opening ranging between 6.84mm to 23.7mm. Further two studies showed improvement in tongue protrusion, check flexibility, and reduction in burning sensation (Gondivkar et al., 2020).

The treatment of OSMF is still not satisfactory. Therefore, further clinical trials with newer modalities and combinations are required to manage this potentially malignant disorder and to prevent its malignant transformation.

Ethical Approval:

As per international standard or university standard ethical approval has been collected and preserved by the authors.

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