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A Meta Analysis–*Tridoshaj Sarvasara Mukhapaka Vis-À-Vis* Oral Submucous Fibrosis

Aparna Sharma[1], Ashok Kumar[2], Shamsa Fiaz[3]

1. Associate Professor, Dept of Shalakya Tantra, National Institute of Ayurveda Deemed to Be University, Jaipur.
2. Associate Professor, Dept of Shalya Tantra, National Institute of Ayurveda Deemed to Be University, Jaipur .
3. Head, Dept of Shalakya Tantra, National Institute of Ayurveda Deemed to Be University, Jaipur.

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Corresponding author-
Aparna Sharma, Associate Professor, Dept of Shalakya Tantra, National Institute of Ayurveda Deemed to Be University, Jaipur 302002.
Email: appu07@gmail.com

ABSTRACT:

Oral Submucous Fibrosis (OSMF) is a chronic disease characterized by the deposition of the abnormal collagen. It is a pre-malignant condition in approximately 2% of the cases. Ayurveda mentions a few matching conditions as *Tridoshaj Sarvasara Mukhapaka* & suggests various treatment modalities; local therapies as *Gandusha* & systemic ones as consumption of *Rasayana*, *Tridoshaghna* herbs & herbals, along with *Nidana Parivarjana* / Abstinence from addictions. This article reviews various aspects as literary & clinical studies pertaining to OSMF / *Tridoshaj Sarvasara Mukhapaka* as per the modern medicine, including prevention, Surgery, diet, lifestyle, physiotherapy, Ayurveda with other Complementary Alternative Medicines are reviewed here.

Keywords: Surgery, *Tridoshaj Mukhapaka*, Prevention, Oral submucous fibrosis, Herbs

INTRODUCTION

Ayurveda mentions innumerable health conditions; named or otherwise covering multiple diseases under one or more common etiology, symptoms, complications and / or treatments. *Sarvasara Mukhapaka* is such an extensive term that can reflect a variety of related / unrelated medical conditions; OSMF a probable one.[1,2] *Vata*, *Pitta*, *Kapha*, singly or mixed, cause *Mukhapaka*, as per *Sushruta Samhita*. Oral submucous fibrosis (OSMF) is a crippling disease with specialized features of focal inflammation in the deep connective tissues and degenerative changes in the muscles of the oral cavity.[3] Epidemiological studies revealed that betel nut chewing was the prime causative actor in the disease[4]. The variations in the cases of OSMF depend on the ethnicity, addictions, region and deficiency of the essential minerals like iron, vitamin B complex and culture[5].

Prime mechanism is the classic *Injury- Healing* process, with fibrous tissues replacing the normal tissues eventually, leading to palpable fibrous bands & reduced inter-incisal distance. Collagen homoeostasis is lost, leading to excessive fibrosis. *Ayurveda Samprapti* can best be related to *Vata-Kaphaja Granthi Visarpa* representing most of the symptoms comparable with the western pathology of the condition. The symptoms of OSMF include pain, burning sensation, intolerance to spicy food, taste disorders, dry mouth, reduced opening of mouth, dysphagia, altered tone and decreased mobility of the tongue[6]. Reduced puffing of cheeks was observed in many

patients. Blanching can be seen in the labial mucosa of tongue, palate, anterior pillars, gingivae and buccal mucosa[7]. The buccal mucosa can be leathery in consistency and multiple vertical bands could be felt on palpation.

Supari chewing is a more important addiction than smoking, as Arecoline, the main active ingredient in betel nut promotes formation of the cross links between collagen peptide chains and that makes collagen resistant to degradation by collagenases.[8, 9] The addictive habits such as the consumption of tobacco and smoking tobacco along with the intake of alcohol can increase the risk of OSMF[10, 11]. The habit of *Supari* / betel nut chewing along with the intake of alcohol can increase the risk of the disease[12, 13]. Statistical report of World Health Organization (WHO) stated that there are more than five million patients of OSMF[14, 15]. The conversion rate to Oral Cancer within 3 to 16 years in India is greater than 7.6%[16, 17]. Though people of any age group can be affected, common age group affected is 20 -40 years[18]. The etiological factors of OSMF include deficiency of vitamin B and iron, auto-immunity, infection of human papilloma virus (HPV) and genetic mutations. [20,21,22,23,24]

Consuming *Gutka* is linked with toxicities in the immune, reproductive and cardiovascular system.[26]

There is no effective treatment available in the modern science. The holistic management of OSMF includes proper counselling of the patient, right patient education and assurance to the patient about the success rate of the treatment.[27,28,29,30]. The management of the disease includes medical management, physiotherapy and surgical treatment. The medical management includes antioxidants, Micronutrients, corticosteroids, Hyaluronidase and placental extracts. The surgical treatment includes excision of the fibrotic tissue and covering that area with fresh human amnion and buccal pad fat grafts. Oral stent may be used to avoid surgical relapse. Usually its too late too little relief available when the disease is deep set in. Prevention through education & awareness at School level is imperative.

Ayurveda can offer resolve through *Nidana-Parivarjana, Agni Vardhan, Panchakarma, Rasayana*, and effective drugs. There are matching symptoms in ancient texts that can be correlated to OSMF as *Krichchhen Vivrinoti Mukham* (restricted mouth opening), *Mukhdaha, Usha* (burning sensation in oral cavity), *TikshnaAsaha* (intolerance to the spicy food), *Mukhasosha* (Xerostomia), and *Arasagyata, Alparasagyata, Virasagyata* (Altered Taste Sensation).[31]

MATERIAL & METHODS

Various articles, books, and scholarly articles were reviewed for an improved understanding of the condition and exploring new insights wrt probable treatment modalities.

Understanding the OSMF

Classification of OMSF

The clinicians have proposed various methods of the classification. The few of them are given below-

Ahuja & Agrawal classified disease clinically based on the extent and type of fibrosis.

Class I: Localized fibrous bands in the cheek.

Class II: Generalized diffuse hardening of sub epithelial tissues.

Class III: Combination of the above two types, where the fibrous bands are associated with a generalized diffuse form of submucous fibrosis.

Bhatt & Dholakia clinically grouped patients into three grades.

Grade I: Comprising mild and early cases with very slight fibrous bands and little closure of the mouth.

Grade II: Cases with moderately pronounced symptoms of disease and fibrous band extending from the cheek to the palate area.

Grade III: Cases with excessive fibrous bands involving the cheek, palate, uvula, tongue and lips and narrowed mouth opening.

Gupta et al clinically classified four stages of submucous fibrosis according to the increasing intensity of trismus.

Very early stage: Complaints of burning sensation in the mouth or ulceration without any difficulty in the opening of mouth

Early stage: Burning sensation, slight difficulty in opening the mouth.

Moderately advanced stage: Marked trismus, that the patient cannot open their mouth more than two finger-widths.

IV. Advanced stage: Patient is undernourished, anemic and shows marked trismus and/or other symptoms, as mentioned above.

Mathur & Jha classified clinical features of OSF into three stages.

Stage 1: Early OSF

a. Mild blanching

b. No restriction in mouth opening.

c. No restriction in tongue protrusion, measuring from mesio-incisal angle of an upper central incisor to the tip of the tongue when maximally extended with mouth at

maximal opening.
d. Burning sensation only on ingesting spicy foods, hot liquids, etc.
Stage 2: Moderate OSMF
a. Moderate to severe blanching
b. Mouth opening reduced by 33%, tongue protrusion reduced by 33%
c. Burning sensation even in absence of stimuli
d. Presence of palpable bands
e. Lymphadenopathy, either uni-or bilateral
f. Demonstrable anaemia on haematological examination
Stage 3: Severe OSF
a. Very severe burning sensation, patient unable to perform day-to-day work.
b. More than 66% reduction in mouth opening, cheek flexibility and tongue protrusion. In many cases, the tongue may appear fixed.
c. Ulcerative lesions may appear in cheek.
d. Thick palpable bands.
e. Bilateral Lymphadenopathy.
Khanna & Andrade categorized OSF into different stages, as follows-
Group I: Very early - normal mouth opening - burning sensation - excessive salivation - acute ulceration and recurrent stomatitis
Group II: Early cases - mouth opening: 26-35 mm (interincisal opening) - soft palate and faucial pillars primarily affected - buccal mucosa appears mottled and marbled, with dense, pale, depigmented and fibrosed areas alternating with pink normal mucosa - red erythematous patches - widespread sheets of fibrosis
Group III: Moderately advanced - mouth opening : 15-25 mm (interincisal opening) - trismus - vertical fibrous bands can be palpated and are firmly attached to underlying tissue - patient unable to puff out the cheeks..

Reviews on previous works

Prevention is the only cure seems to be the Mantra against OSMF, like in other Non Communicable Diseases. One has to work hard, for years to have this disease. Once set in, it is too refractive to normalize. This is why, correction in lifestyle in general, and quitting Smoking & Betel Nut Chewing are the first approaches against OSMF. No treatment can help if the additions are not gotten rid of.
Among treatments, General Nourishment, Nutraceuticals, Antioxidants, Physiotherapy, Homoeopathy, Ayurveda through Herbs & Panchakarma, and other Complimentary Alternative Medicines are found effective upto some degree in relieving the subjective parameters. Surgery is one of the final resorts when Inter Incisal Distance is grossly compromised, sometimes reaching less than10 mm.

RESULTS & ANALYSIS

Some of the noticeable observations from various studies are discussed as under-

Safety of Ayurvedic Management- A comprehensive electronic search was conducted in Pubmed, Scopus, and other databases from January 2011 to June 2020 according to the PRISMA guidelines, to identify all the clinical studies for the medicinal management of OSMF with definite keywords and defined criteria. Among the 32 included clinical studies 23 were randomized controlled studies and 9 were case-control studies. The treatment outcomes were diverse, and the majority of the studies showed improvement in the subjective signs and symptoms of OSMF. Only a few studies noticed the side effects. No single treatment modality is effective in the management of OSMF. The concurrent use of triple therapy is efficacious. The naturally occurring herbal medicines have an immense potential in the management of OSMF. Therefore, high-quality, longitudinal, multicentric randomized controlled trials with larger samples need to be conducted to further assess the efficacy of various medicinal formulations in conjunction with physiotherapy in the management of OSMF[32].

Ayurveda Black Box Design- In an open-label nonrandomized clinical trial with black box design comprising of holistic Ayurvedic approach, 22 patients of OSMF completed the treatment. In all of them after *Koshthashuddhi* (mild purgation) and *Shodhana Nasya* (errhinetherapy); *Pratisarana* (external application) with *Madhupippalyadi Yoga*, *Kavala* (gargling) with *Ksheerabala Taila* and internally *Rasayana Yoga* were given for 2 months and followed for 1 month. It revealed statistically highly significant relief in almost all signs and symptoms as well in inter incisal distance improvement. Furthermore, sustained relief was found in follow-up[36].One study recently completed by the same Author Trio established significant efficacy of *Berberis aristata* when used in various forms in 60 known cases of OSMF.

Modern Medicine - Three hundred twenty-six patients with oral submucous fibrosis were divided into two groups and treated either with conventional sub-mucosal injections of steroids and hyaluronidase, or with topical vitamin A, steroid applications, and oral iron preparations. The results were compared. The conventional treatment with injections was found to be hazardous, whereas the

conservative treatment was found to be safe. Both treatments were purely palliative[33].

Another study undertook a review of the literature on drug treatment of oral submucous fibrosis. An electronic search was carried out for articles published from January 1960 to November 2011. Studies with high level of evidence were included. The levels of evidence of the articles were classified after the guidelines of the Oxford Centre for Evidence-Based Medicine. The main outcome measures used were improvement in oral ulceration, burning sensation, blanching and trismus. Only 13 publications showed a high level of evidence (3 randomized controlled trials and 10 clinical trials/controlled clinical trials), with a total of 1157 patients. Drugs like steroids, hyaluronidase, human placenta extracts, chymotrypsin and collagenase, pentoxifylline, nylidrin hydrochloride, iron and multivitamin supplements including lycopene, have been used. Only systemic agents were associated with few adverse effects like gastritis, gastric irritation and peripheral flushing with pentoxifylline, and flushing warm skin with nylidrin hydrochloride; all other side-effects were mild and mainly local. Few studies with high levels of evidence were found. The drug treatment that is currently available for oral submucous fibrosis is clearly inadequate. There is a need for high-quality randomized controlled trials with carefully selected and standardized outcome measures[40].

Surgery - One hundred known patients were registered and the lesions were biopsied. The condition was staged into four categories. Very early and early cases were treated by local injection of triamicinolone acetonide, while advanced cases were treated by surgical intervention. A new surgical technique of a palatal island flap based on the greater palatine artery in combination with temporalis myotomy and bilateral coronoidectomy was used in 35 cases. A follow-up ranging from 6 months to 3 and half years showed good results[34].

Anti- Oxidants - Lipid peroxidation product, malonaldehyde (MDA) and antioxidants were estimated in plasma and erythrocytes of 34 cases of oral submucous fibrosis (OSMF) of different grades with equal number of healthy control to evaluate the association of reactive oxygen species (ROS) and OSMF. While plasma MDA was found to be significantly higher in patients (3.3±0.4 nmole/ml, $P<0.001$) as compared to controls (2.4±0.5 nmole/ml), plasma beta carotene and vitamin E levels were found to be decreased significantly in patients (81.7±14.3 µg/100 ml, $P<0.001$; 9.3±0.9 mg/L, $P<0.01$ respectively) with respect to healthy controls (110±20.8 µg/100 ml and 10.1±1.2 mg/L). The decrease in beta-carotene and vitamin E was found to be more significant in OSMF grade II and III than in grade I. After 6 weeks of oral administration of beta-carotene and vitamin E, patients showed increase in plasma level of these two antioxidants along with decrease in MDA level associated with clinical improvement[35].

Homoeopathy - Recent scientific literature reports that people are opting homeopathy over allopathy for relieving medical conditions. Homoeopathy enhances the holistic state of health as whole rather than just treating the disease. Though homoeopathy cannot replace the mechanical art of dentistry but acts as an adjunct to conventional dentistry. The literature supports use of homeopathy in dentistry to treat various dental problems one of them being trismus. Calcareaphosphorica, a homeopathy medicament is used when mouth cannot be opened without pain. Cuprum metallicum is used for trismus of muscles. These can be used to reduce the trismus experienced during OSMF. With advantages of minimal side effects and favorable treatment outcome, homeopathy has emerged as one of the allied therapy in cases of treatment failure or poor response to conventional drugs. The knowledge and understanding of Homeopathy[37].

Physiotherapy- no side effects and could be used as a treatment protocol for patients with OSMF before a more invasive surgical intervention is sought[37].

Tulsi- Haridra- The aim of the present study was to investigate the clinical efficacy of herbal medicines (1 gm of *Tulsi* and 1 gm Turmeric mixed in glycerine base) for the treatment of oral submucous fibrosis (OSMF). Forty-one patients in the age group of 17- 56 years without any systemic complications were included in the study. The patients were treated with medicines, which were to be applied 3-4 times a day. Blood samples were collected before and after treatment to screen for any systemic changes due to these medications. Burning sensation and mouth opening were recorded before and after treatment. Patients were followed up on monthly subsequent visits for three months. Changes in the burning sensation and difference in the mouth opening were analyzed statistically. A statistically significant improvement was seen in both burning sensation and mouth opening. *Tulsi* and turmeric offers a safe and efficacious combination of natural products available for symptomatic treatment of OSMF[38].

***Aloe vera* -** Twenty study subjects with OSMF were included in the study. Patients were divided into two groups. There were 10 patients in each group; group A subjects received 5mg of *Aloe vera* gel to be applied

topically three times daily for 3months and group B subjects received antioxidant capsules twice daily for 3months. The results were analyzed with paired '*t*' test and unpaired '*t*' test. *Aloe vera* responded better in all the parameters assessed and responded in all the clinic histopathological stages particularly in those with mild-stage clinically and early-stage histopathologically. *Aloe vera* showed a statistically significant reduction in burning sensation (*P*=0.001), improvement in mouth opening (*P*=0.02), and cheek flexibility (*P*=0.01) when compared with the antioxidant group. Overall assessment of the parameters depicted that the *Aloe vera* group showed a better treatment response compared to the antioxidants group. It reduces the burning sensation and improves mouth opening thereby enhancing the patients' compliance. It proves to be relatively safe, can be applied topically, easily available, economical, non-invasive, and efficacious in the treatment for OSMF[39].

DISCUSSION & CONCLUSION

The condition is grossly underrated however much more crippling than it seems. Engaging the youth and middle aged, this is a much bigger than a medical condition. The addiction substances being too freely available, grip the victims quickly and de-addiction awareness is far from available. The studies reviewed here are of immense value, however secondary only to *NidanaParivarjana*. School-level awareness programs should be planned and executed in a stringent manner.

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