



ASSESSING EFFECTS ON VARIOUS CLINICAL PARAMETERS OF ORAL SUBMUCOUS FIBROSIS BY PROVIDING ANTIOXIDANTS AND CONSERVATIVE THERAPY: A COMPARATIVE STUDY

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ABSTRACT

Background: Oral Submucous Fibrosis (OSMF) is a potentially malignant disorder, with 7.6% malignant transformation rate. This is one of the major health threats in Asia; particularly in India this has high prevalence so this also called as Indian's disease. Areca nut is one of the etiologic factors which show sequential cellular changes.

Methodology: Total 30 OSMF patients of age range 16 to 30 years were randomly selected after their consents. Further these patients were divided into 2 groups, with 15 patients in each group. One group was given established Antioxidant tablets, whereas others were given conservative management, and routine follow up was scheduled at interval of 15 days for 6 months.

Results: The clinical parameters assessed in this study are; burning sensation, vesicles and inter incisal mouth opening (IIO). The group which was on antioxidant therapy showed better improvements in all clinical parameters, as compared to the group which was on conservative management ($p < 0.05$). Though both the intervention approaches are safe and economic to the patients, but antioxidants can be better option to avoid future OSMF relate complications and further large sample size studies are needed to validate this.

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INTRODUCTION

Oral Submucous fibrosis (OSMF) is a potentially malignant disease, with its high magnitude towards oro-facial healthcare problems. Even after progress in the field of healthcare technology, graph of oral submucous fibrosis shows a gradual increase. This is a matter of concern mainly in India and Asia; not only because of rise in incidence rates but also due to involvement of younger age group.^{1,2} According to WHO this is "a generalized pathological state of the oral mucosa associated with a significantly increased risk of cancer."³ Similarly, other definition is the mirror replica of this disease which states that "it is an insidious chronic disease affecting any part of oral cavity and sometimes pharynx although occasionally preceded by and/or associated inflammatory reaction followed by fibro elastic changes in lamina propria with epithelial atrophy leading to stiffness of oral mucosa, causing trismus and inability to eat."⁴ This potentially malignant disease becomes devastating when it adds more oro-facial health hazards in the form of oral squamous cell carcinomas. The malignant transformation rate of this disease is 7.6% which is sufficient enough to state it as one of the potentially malignant disease.⁵ Today's widespread coverage of geographic areas due to alterations in the trends of habits among Asian countries, mainly India, there is no wonder to call it as a disease of Indians. In spite of well known facts of literatures on OSMF, there is no clear thought about cancerous changes of this potentially threatening disease. So far

according to theory of carcinogenesis, neoplastic changes are taking place via different changes at cellular levels, such as Initiation, Promotion and Propagation. These stages are based on dysplastic changes taking place due to chemical or biological components coming in contact to tissues. However during these changes there can be a crucial role of intraoral trauma which may act as co-carcinogen to promote disease towards cancer.⁶

Historical Background: The disease has very old history of around 600 BC in India. The so called ancient physician Sushruta described oral lesions similar to present oral submucous fibrosis and termed "Vidari" in his valuable book "Sushruta Samhita". Along with clinical features, he also correlated the disease with faulty food habits.⁴ However, the disease gained popularity in the scientific literature after its terminology as "Atropica idiopathica (tropical) mucosa oris" (Schwartz J 1952)⁷. Since then, oral submucous fibrosis gradually became popular among researchers to add further knowledge. With due course, there was change in terminology of the disease. In 1953, an ENT specialist Joshi called it as "Oral Submucous Fibrosis of palate and pillars", whereas the practicing dental surgeon termed it as "diffuse oral submucous fibrosis".⁸

Epidemiology of Oral Submucous Fibrosis

This potentially malignant chronic disease has sound impact over the Indian population with prevalence rate ranging from

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0.2 to 1.2%, but comparatively high in south India around 1.2%; where the incidence of oral cancer is also high. According to initial Indian studies carried on 50,915 urban populations, major cities showed prevalence rates of oral submucous fibrosis as follows: Lucknow (0.5%), Mumbai (0.5%), Bangalore (0.2%) and Trivandrum (1.2%). Pindborg J. *et al* (1968).^{9,10} Day by day there is rise in incidence rates of Oral Submucous Fibrosis, particularly due to commercial entry of tobacco traders, who with their selfish motto manufactured different attractive poisonous areca nut based products such as pan masala, gutkha, kharra etc. These commercial irritants are easily available with economical prices, so even school going early age group is also caught into the claws of this habit and affected by disease. This scenario explains, why it called as Indian's disease and contributing as major health threat among two million population, targeting to 5-10% transformations into oral cancers.^{2, 11} The sporadic cases have also documented in other parts of world such as Malaysia, Nepal, Burma, South Africa, Thailand and South Vietnam.^{12, 13} Today there is lot of literature on this disease, but its complex etio-pathogenesis remains an enigma towards interventions. Considering present outbreak of disease and its threat for the society there is need to take necessary steps towards interventions, because early detection and effective treatment is a key to avoid associated malignancies. But there are inadequate effective interventions with this gradually spreading disease. Oral Submucous Fibrosis is high risk potentially malignant disease, which is a major oral health threat in India; attributing 0 - 1.2% prevalence rates. Sporadic cases are also found in Malaysia, Nepal, Burma, South Africa, Thailand and South Vietnam.^{14,15} Total number of cancer patients accounting 2 million in Kerala, South India alone.² There is steady growth of disease and even younger age group seems to be affected with this disease; the reason being easy availability of commercial products such as Pan Masala, Gutkha (Mixture of Areca nut + tobacco + slaked lime etc.) and these products are available even near schools premises, so more and more school children are affected with this.¹ These chemical substances directly act on oral mucosae, leading to gradual increase in collagen fibre bundles and hyalination of these bundles (photographs 1, 2); results in inelasticity as well as blanching causing reduced mouth opening. Dental Unit of Tata Institute of Fundamental Research, Mumbai India, conducted broad survey by Dr Fali S Mehta. This survey was to see the actual situation about oral cancer and precancer in Indian population, by door to door visits. This provided substantial epidemiological facts about Indian population.¹⁶

Aim and Objectives

1. To assess role of established antioxidants in various clinical parameters; such as burning sensation, mouth opening and vesicles caused by oral submucous fibrosis.
2. To correlate different grades of oral submucous fibrosis with antioxidant therapy.
3. To compare clinical results after conservative approach and antioxidant drugs.

MATERIALS AND METHODS

Patients' selection

This is a fraction of my old study, which was based on supplementation of well established antioxidants in the market

and its comparison to conservative management, carried at Dept. of Oral Pathology, GDC Nagpur, India.

Patients were thoroughly informed about study and consent was obtained from all Oral submucous fibrosis (OSMF) patients who were willing to participate in study.

At the onset of providing established antioxidants/multivitamins supplements to the patients, all necessary formalities were done.

Inclusion Criteria

1. Patients willing to participate and cooperate during study were considered.
2. Having sound OSMF related clinical findings such as fibrous bands and blanching on buccal mucosae, vesicles and reduced mouth opening etc.

Exclusion Criteria

1. Inter Incisal Opening (IIO) adequate with normal.
2. Patients undergoing medication for same lesion.
3. Reduced mouth opening for other reasons.
4. Oral Submucous Fibrosis associated with oral cancers and
5. Patients with Diabetes, Hypertension, Pregnancy and other systemic illness.

The study sample comprised of 30 patients between age ranges of 16 to 30 years diagnosed clinically as OSMF were randomly selected. Out of these 30 cases, 23 were males and 7 females. Case history of all patients recorded, including habits (Areca nut, Kharra, Gutkha, Panmasala, Tobacco etc.) and food (spicy contents). During clinical examination; Inter Incisal Opening (IIO), intraoral fibrous bands, vesicles, blanched whitish mucosae and burning sensations were recorded.

With proper aseptic precautions; 5 mm punch biopsy was taken for histopathological confirmation of disease; using H & E stains.

In this study, all 30 OSMF patients were randomly divided into 2 groups of 15 patients each. Amongst these two groups; one group was given antioxidant tablets with OD dose after meals for seven days in a month and other group was given conservative therapy. All patients recalled for 6 months at interval of 15 days. Complete records of patients were maintained regarding notes of various clinical parameters, such as burning sensation, vesicles and mouth opening; followed by distribution of antioxidant tablets for next month. The ingredients of antioxidant (Lycopene) were carrot extract 100 mg (carotenoids and micronutrients), beta carotene -7.5% dispersion 40 mg (natural carotenoids), Vit C 150 mg, Vit E Acetate 25 mg, zinc sulphate 70 mg (equivalent to 45.9 mg of selenium).

OBSERVATIONS AND RESULTS

Total 30 oral submucous fibrosis patients enrolled for study, where females and males were 23.3% and 76.7% respectively; with mean age group of 21.9 years (std. 3.89) (Table I). Out of 30 OSMF patients, clinical grade wise distribution was as follows: Grade- I (10%), Grade- II (10%), Grade- III (56.7%) and Grade- IV (23.3%) (Table II). Clinical grading was based on Bailoor DNC (1993).¹⁷ The distribution of burning sensation, which was grouped as Grade I - Mild (10%), Grade II - Moderate (33.3%) and Grade III - Severe (56.7%). The

important clinical parameters were assessed in this study; mainly burning sensation, vesicles and inter incisal opening (IIO).

Table I Distribution of Gender

	Frequency	Percent
Female	7	23.3
Male	23	76.7
Total	30	100.0

Table II Distribution of OSMF Grade

Grade	Frequency	Percent
I	3	10.0
II	3	10.0
III	17	56.7
IV	7	23.3
Total	30	100.0

However there were variable positive results on clinical outcomes on using antioxidants. Chi-square test was applied for statistical analysis, and considered significant value at $p < 0.05$. There was significant improvement of burning sensation ($p < 0.05$) due to antioxidant drugs as compared to conservative approach. Similarly antioxidants showed positive outcome as compared to conservative approach, in context with other clinical parameters, such as vesicles and mouth opening ($p < 0.05$). Further subdivision was made for better clinical assessment of vesicle eruptions and was graded on the basis of clinical severity; i.e. Grade I (minimal), Grade II (moderate) and Grade III (multiple widespread). This was noticed that, after completion of 6 months follow up, majority patients showed significant improvements in clinical findings (Table III-V).

Table III Effectiveness of drug on burning sensation

Burning Sensation	Antioxidant	Conservative T/T	Total
I	3 100.0%	0 0.0%	3 100.0%
II	7 70.0%	3 30.0%	10 100.0%
III	5 29.4%	12 70.6%	17 100.0%
Total	15 50.0%	15 50.0%	30 100.0%

Table IV Effectiveness of drug on Vesiculation

Grade	Drug		Total
	Antioxidant	Conservative T/T	
I	3 100.0%	0 0.0%	3 100.0%
II	7 70.0%	3 30.0%	10 100.0%
III	5 29.4%	12 70.6%	17 100.0%
Total	15 50.0%	15 50.0%	30 100.0%

Table V Effectiveness of drug on Inter Incisal Opening (IIO) Group Statistics

	T/T	N	Mean	Std. Dev.	T value	P value
Inter incisal opening Initial	Drug	15	26.3333	7.13809	1.097	0.282
	Cons.t/t	15	25.5333	6.83339		
Inter incisal opening Later	Drug	15	30.0667	7.64822	1.575	0.126
	Cons.t/t	15	25.9333	6.69186		
Inter incisal opening Gain	Drug	15	3.7333	1.79151	2.269	0.031
	Cons.t/t	15	2.4000	1.40408		

OSMF Grades: I- No change, II- Mild, III- Moderate, IV- Severe

Scores: 1- No improvement, 2- Fair improvement, 3- Good improvement, 4- Excellent improvement



Figure 1 Photograph showing bands & blanching on cheek mucosa

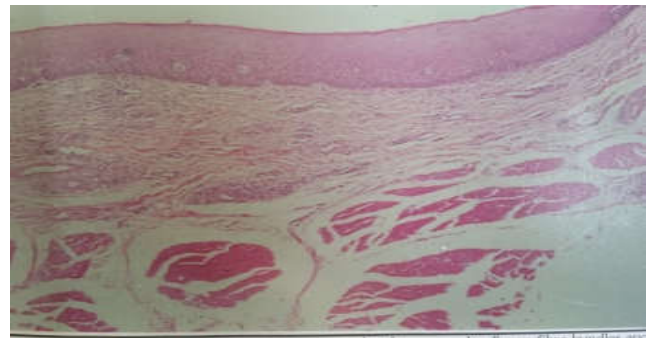


Figure 2 Photomicrograph exhibiting, epithelial changes and connective tissue with aggregation of collagen bundles & inflammatory response (X10)

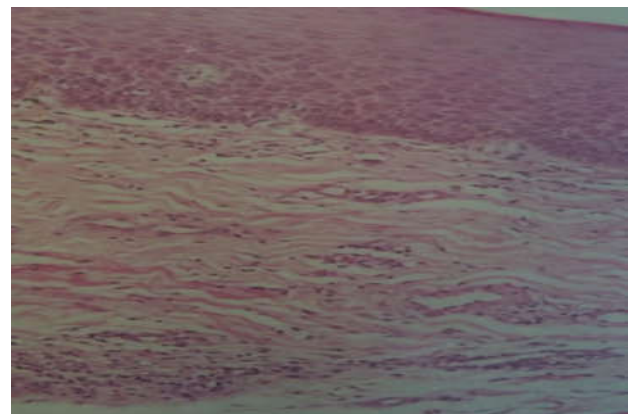


Figure 3 Photomicrograph showing parallel arrangement of collagen fiber bundles (X40)

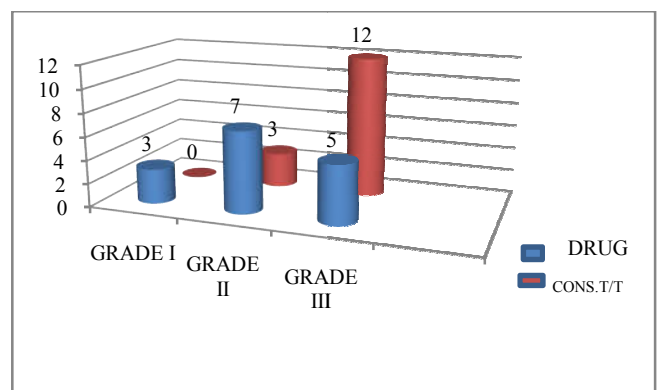


Diagram 3 Effectiveness of drug on burning sensation

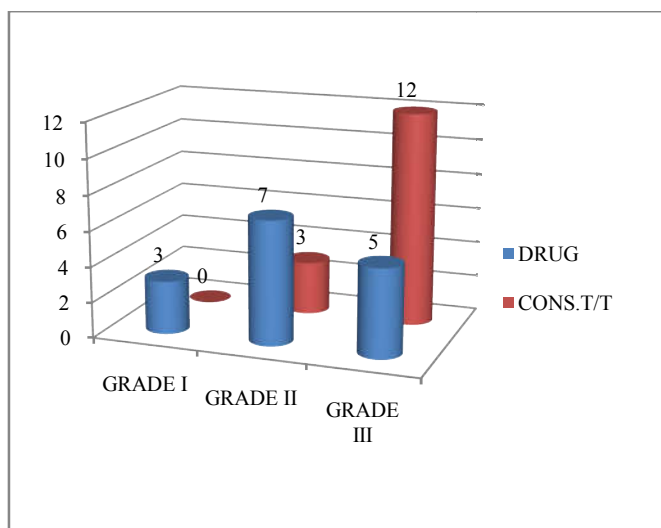


Diagram IV Effectiveness of drug on vesiculation

A) INITIAL

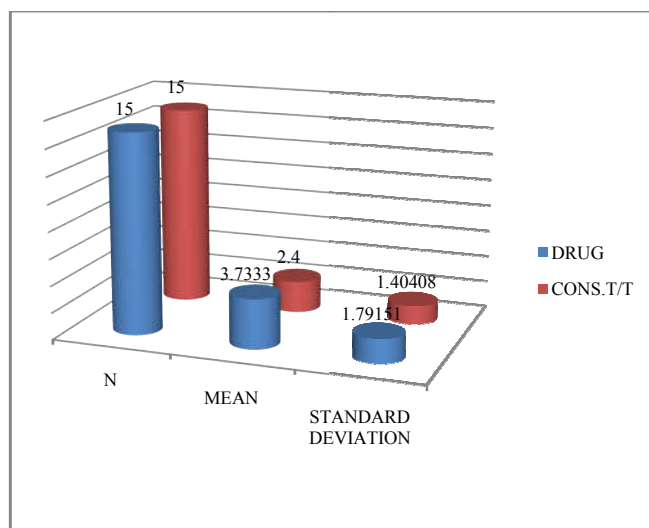


Diagram V-C Effectiveness of drug on inter incisal opening

DISCUSSION

There are many studies about oral submucous fibrosis out of them, some are related to interventions. In this study we have tried to assess individual clinical parameters such as, burning sensation, mouth opening and vesicles. These clinical parameters were assessed and compared after antioxidant and conservative therapy. According to our study, there was overall more improvement in the case those were on antioxidant therapy as compared with conservative approach. Biochemical Aspects of OSMF:

The disease has attributed with lot of etiologic factors but areca nut is one of the significant causes. However, chances of damage to mucosa are aggravated when areca nut is used along with betel leaf, crude lime and spices. Because areca nut contains 15-18% tannic acid and different alkaloids such as arecoline, arecolidine, guavacine and isoguavacine and out of these arecoline is most effective alkaloid. Areca nut has psychotropic and antihelminthic property due to arecoline and they produce parasympathetic properties such as euphoria and fatigue.^{18, 19} Nitrosation of arecoline leads to formation of areca nut specific nitrosamine namely nitrosoguavacoline, 3-propionaldehyde and 3-methylnitrosamino-propionitrile. All these areca nut specific nitrosamines are found to be powerful carcinogens with DNA alkylating properties. (WHO 1998) Metabolism of areca nut specific nitrosamines will lead to formation of cyanoethyl adduct and O'methyl guanine which alters mechanism of DNA. Prolong exposure with this irritant, there is stimulation of micronucleated cells; participating in sister chromatid exchange in peripheral lymphocytes and in some circumstances resulting in malignant transformation. Present study is based on randomized trials of antioxidants which are natural extracts mainly carrots and other components.

Activation of Antioxidants:

- By preventing oxidation of essential cellular constituents such as formation of oxidation products.
- By protecting against various metals, chemicals, irritants and acting as scavenger for free radicals.
- By improving survival of erythrocytes.

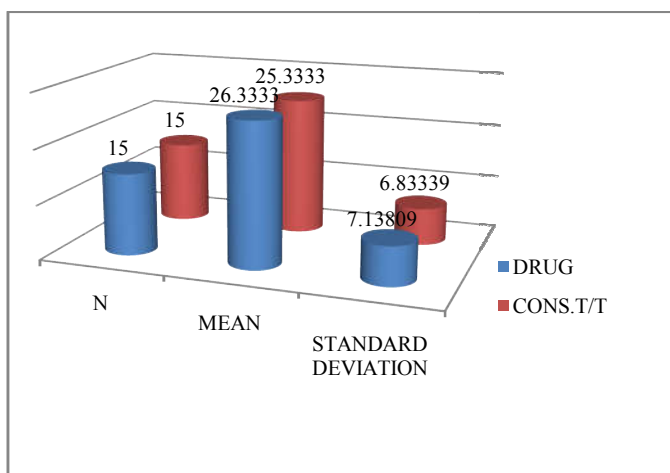


Diagram V-A Effectiveness of drug on inter incisal opening

B) LATER

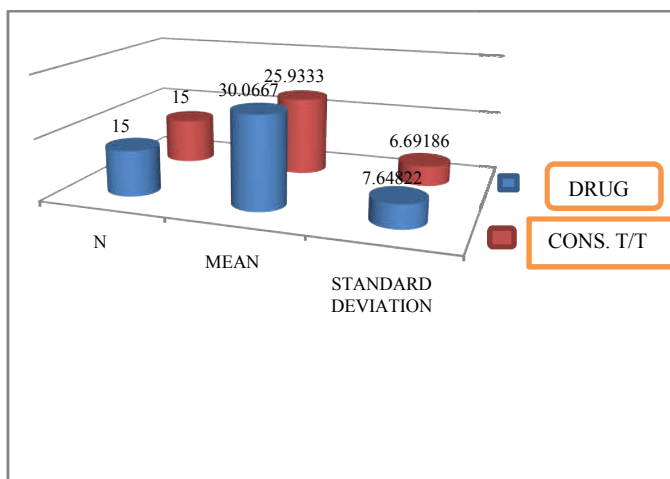


Diagram V-B Effectiveness of drug on inter incisal opening

C) GAIN

According to this study there are remarkable improvements in various clinical parameters of Oral Submucous Fibrosis such as burning sensation, vesicles and mouth opening.

This study is in accordance with Rehana Maher *et al*; where 117 OSMF samples were tested for efficacy of micronutrients, along with different minerals such as iron, calcium, copper, zinc and magnesium. They found recovery in burning sensation and mouth opening.²⁰ One more study conducted by **Haque *et al*** to evaluate rate of IFN-(gamma) which showed improvement in mouth opening with net gain of 8+4 mm and burning sensation; (P<0.031) which favours our study.²¹

CONCLUSION

On the basis of clinical assessment we found positive effects of antioxidant drugs on burning sensation, vesicles and inter-incisal mouth opening. At the same time these drugs are extracted from natural sources, so there was no any side effect to patients. Hence before proceeding for intensive therapies such as, intra-lesional injections and surgery; this is conservative and comfortable treatment for OSMF patients. However by taking large samples; justification can be made with authentic treatment protocol for this potentially malignant disorder.

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