



PENTOXIFYLLINE – A BOON IN MEDICAL MANAGEMENT OF ORAL SUBMUCOUS FIBROSIS ??

Dental Science

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ABSTRACT

AIM- OSMF is very prevalent and most premalignant condition in South East Asian population especially in India now days. There is numerous management modalities documented but still it is challenging to come up with definitive treatment of OSMF. In the wake of searching the effective medical management of OSMF here we have compare the two drugs Pentoxifylline and Antioxidant over 50 affected individuals.

KEYWORDS

OSMF, Pentoxifylline, Antioxidant.

INTRODUCTION-

Oral submucous fibrosis (OSMF) is a clinically benign but potentially malignant disorder^{1,2} which brings in the need for the oral physician to primarily diagnose and treat the condition at the earliest.

OSMF has been known to be a disease of the tropics^{3,4}. In India itself approximately 5- 10 million peoples are suffering from OSMF⁵. This was first well documented by Schwartz in 1952 and termed it Atrophia idiopathica (tropica) mucosae oris. Later on, this condition known by other various terms like Oral Submucous Fibrosis (OSMF)¹, Diffuse Oral Submucous Fibrosis, Idiopathic Scleroderma of the mouth, Idiopathic Palatal Fibrosis, Sclerosing Stomatitis and Juxta-Epithelial Fibrosis⁶.

Pindborg (1966) defined OSMF as, "An insidious, chronic disease affecting any part of the oral cavity and sometimes the pharynx. Although occasionally preceded by and/or associated with vesicle formation, it is always associated with juxta-epithelial inflammatory reaction followed by fibroelastic change of the lamina propria, with epithelial atrophy leading to stiffness of the oral mucosa causing trismus and inability to eat"⁷

According to National Sample Survey Organization (1998-99) 193.2 million populations in India are consuming tobacco in either form including smoke or smokeless⁷. Highest prevalence of this disease is found in India, especially in the southern states like 0.36% in Ernakulam, Kerala, and 0.04% in Srikakulam district of Andhra Pradesh (both in the south), and 0.16% in Bhavnagar, Gujarat and Uttar Pradesh and Bihar (in the north) and also overseas cases have been reported in China (Province of Taiwan and Hainan Island), Malaysia, South Africa (Natal), Papua-New Guinea, Sri Lanka , Myanmar (Burma), the United Kingdom , and Canada.⁸ Malignant transformation rate is quite high approximating to 4.5%⁹.

Prevalence by sex varies widely in the different published studies till now. Previously the ratio of affected females was much higher than males but now the scenario has changed from females to males i.e. males are much more affected than females¹⁰. The younger generation is addicted to these products especially gutkha and panmasala¹¹. The general female preponderance may be related to the deficiency of iron and vitamin B complex among many Indian women.

History of Oral submucous fibrosis (OSMF) is very interesting. Sirsat and Khanolkar^{12,13} reported majority of OSMF cases belonged to the age group of 20-40 years. Sinor et al¹³ reported 79 per cent of the OSMF cases were under the age of 35 years and maximum numbers of cases were in 25-44 years of age group.

There are various predisposing factors for oral submucous fibrosis like areca nut/betel nut, tobacco, lime, malnutrition, immunological disorders, collagen disorders, capsaicin (a prime component in chillies) etc. Association of areca nut catechu in the occurrence of Oral Submucous fibrosis has been proved by many studies^{1,5,8,14}.

There is very well established etiopathogenesis of role of areca nut causing OSMF by generation of free radicals and immunosuppression in the body⁸. There are wide spread options instituted for treatment of OSMF ranging from Iron and multivitamin supplements including Lycopene, Intralesional injections of Steroids, Hyaluronidase, Human placental extracts to surgical interventions^{2,5,8,16,17,18,19}. However none of them have been identified as established modalities. Treatment with a definite cure remains a challenge. One of the current treatment modalities being explored against Antioxidants for treatment of OSMF is Pentoxifylline²⁰.

Pentoxifylline is a trisubstituted methylxanthine derivative and competitive nonselective phosphodiesterase inhibitors with diverse pharmacologic properties such as peripheral vasodilatation, immune modulation and alteration of fibroblast physiology and enhance peripheral tissue oxygenation. It relaxes smooth muscles, causes vasodilation or prevents spasm. It also increases the flexibility of red blood cells which contributes to the improvement of the ability of blood to flow through peripheral vessels known as haemorheologic action. Pentoxifylline promotes platelet deaggregation and thus contributes to decrease in blood viscosity. It also deactivate T cell and Macrophages and decreases the cytokine level, IL-6, TNF- α and TGF- β at the site of chronic inflammation thus acts as an immunomodulator drug. At tissue level it has a property of antithrombin, antiplasmin, and fibrinolytic activity and inhibits the increased collagenase activity²¹.

In the wake of searching the newer treatment modality of Oral Submucous Fibrosis the study is planned as a randomized controlled study and divided into two groups. One with Pentoxifylline test drug group and other with Antioxidant standard drug group. This study compares and evaluates the outcome of the both drug groups in the treatment and management of OSMF.

METHODOLOGY-

The study was carried out in Department Of Oral Medicine And Radiology, I.T.S. Dental College, Hospital and Research Centre, Greater Noida. Sample size of study is 50 and sampling method of study is Randomised Controlled Trial (RCT). Period of study was 6 months (routine periodic clinical follow up every month for 6 months). Drug used - Tab. Pentoxifylline – 400 mg 1 tab TDS \times 6 months and Antioxidant 1 cap BD \times 6 months. A sample of 50 patients of either sex within 15-50 yrs of age; with clinically and histopathologically diagnosed OSMF was considered. The studying patients was randomly divided equally in two groups, Group A was Pentoxifylline group and Group B was Antioxidant. The inclusion criteria was (a) Patients who are conscious, cooperative and willing for the treatment. (B) Patients with sign and symptoms of Oral Submucous Fibrosis with histopathologic confirmation of the disease. And exclusion criteria was (a) Patients without any past or present systemic disorder. (b) Patients with known allergy or contraindication to the study drug. (c) Patients with other mucosal lesions. (d) Patients with limited mouth opening due to any other cause. Following Parameters was evaluated during

and after the treatment- Mouth opening, Burning sensation in the Mouth, Tongue Protrusion, Difficulty in deglutition, Blanching of the buccal mucosa, Shape and size of Uvula and Cheek flexibility.

The comparison of both the drugs Pentoxifylline and Antioxidant was chiefly on the basis of four points namely- mouth opening, tongue protrusion, cheek flexibility and burning sensation- VAS scale. Mouth opening was measured by measuring the inter-incisal edge distance between the maxillary and mandibular central incisors. For tongue protrusion the distance measured between mesial contact area of mandibular central incisor and tip of the tongue on maximum protrusion. The cheek flexibility was measured by placing the two equidistant dots over the imaginary line from corner of the mouth to the tragus on same side. Cheek flexibility was measured by comparing the distance between the two dots at the resting position of cheeks, with the distance between the dots while holding the air in the mouth. For the assessment of pain and burning sensation in the mouth, use of VAS scale (Visual Analogue Scale). The score of 0-1 was considered as absent, score of 2-4 was considered as mild and a score of 5-7 was considered as moderate and score between 8 to 10 was severe in intensity. The all relevant data was collected and analyzed by using Unpaired T-Test for mouth opening, One-way ANOVA, Post-hoc comparison – Bonferroni test.

RESULTS-

All the 50 patients (25 in each group) were evaluated and histopathologically confirmed for OSMF. The comparison of both the drugs in Pentoxifylline and Antioxidant was chiefly on the basis of four points namely- mouth opening, tongue protrusion, cheek flexibility and burning sensation- VAS scale. The prevalence of OSMF was 1.04 %. 36% study population belonged to low and 58% to medium and 6% belongs to high economic status. In the present study 44% population belonged to 4th decade and 42% population to 3rd decade followed by 8% in 2nd decade and 6% in 5th decade of life. There are only 2 (4%) females among 50 patients with ratio of male: female is 24:1 in the study population. In the collected study data, 60% affected individuals consumed tobacco with betel quid followed by 30 % gutkha and 7% population gutkha along with paan and 2 % population consumed betel quid or supari. 1% had mixed habit including cigarette smoking along with consumption of smokeless tobacco as deleterious habit. On evaluation of sign and symptoms all the affected population had complaint of burning sensation and intolerance to hot and spicy food in the mouth, stiffness in buccal mucosa.

All the affected patients had palpable fibrotic bands in the retromolar area and anterior faucial pillar along with 40% patients also fibrotic bands in buccal mucosa and 6% patients in perioral area. Only 2% population had fibrosis over the tongue.

Only 10% patients had unilateral and 90% had bilateral OSMF in the study groups.

Only 42% study group had history of vesicle or ulceration in the mouth.

In our study group 10% of patients had hearing loss and difficulty in deglutition and 16% patients had changes in voices.

Average Hb% estimation of the population is 12.26 gm /dl irrespective of gender in study group.

Distribution of OSMF patients in Pentoxifylline group and Antioxidant group according to classification of OSMF proposed by Kiran Kumar et al in 2007 (Graph 1 and 2).

MOUTH OPENING –The p- value is not significant (p >0.05) in any visit of the patient for both groups i.e. both the drugs are nearly equally efficient in increasing mouth opening. However in Pentoxifylline group, mouth opening is higher in comparison to the Antioxidant group which also increases with time in successive visits. Significant increase in mouth opening was noticed from the second visit (MO2) from when the patient was enrolled (MO 0).

TONGUE PROTRUSION-

The p- value is not significant in any visit of the patient for both groups i.e. both the drugs did not highly effective in tongue protrusion. Significant tongue protrusion is started from the 5th visit of both groups.

BURNING SENSATION- VASSCALE-

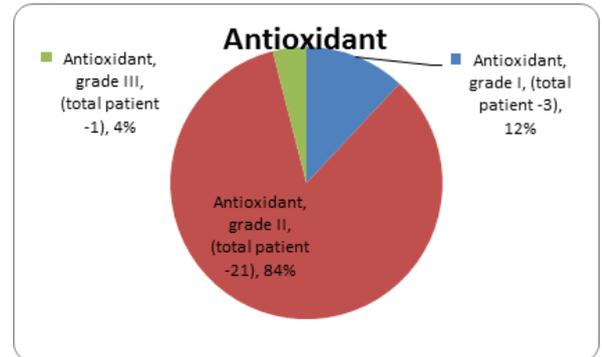
Again the p- value is not significant in any visit of the patient for both groups i.e. both the drugs are nearly equal efficient in burning sensation. Significant relief from burning sensation is started from the 3rd visit in Pentoxifylline group and from 4th visit in Antioxidant group. The p- value is significant in Pentoxifylline group as compared to the Antioxidant group i.e. drug Pentoxifylline is highly effective than Antioxidants in increasing the cheek flexibility. However only in 5th and 6th visits showed a significant change in cheek flexibility.

There is higher significant rate of increasing the cheek flexibility in successive visits in Pentoxifylline group as compared to the Antioxidant group with time.

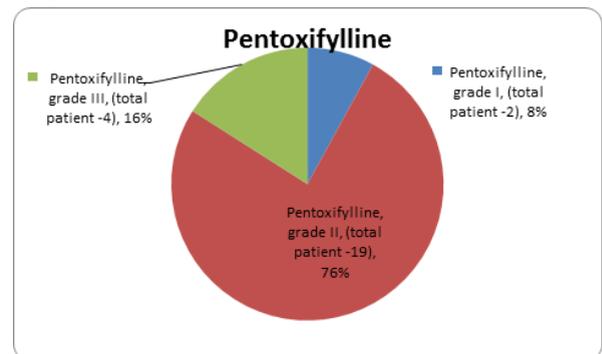
Unpaired T-Test for mouth opening- (Table-1)

Mouth Opening	Groups	Mean	S.D.	T-test	P-value	Mean Difference
MO 0	PENTOXIFYLLINE	27.56	9.95	-0.954	0.345	-2.48
	ANTIOXIDANT	30.04	8.36			
MO 1	PENTOXIFYLLINE	28.04	9.76	-1.012	0.316	-2.60
	ANTIOXIDANT	30.64	8.34			
MO2	PENTOXIFYLLINE	29.28	10.06	-0.757	0.453	-2.00
	ANTIOXIDANT	31.28	8.56			
MO3	PENTOXIFYLLINE	30.28	10.49	-0.768	0.446	-2.08
	ANTIOXIDANT	32.36	8.56			
MO4	PENTOXIFYLLINE	32.08	10.86	-0.640	0.525	-1.80
	ANTIOXIDANT	33.88	8.94			
MO5	PENTOXIFYLLINE	32.46	9.86	-0.974	0.335	-2.62
	ANTIOXIDANT	35.08	8.97			
MO6	PENTOXIFYLLINE	34.08	9.66	-1.016	0.315	-2.68
	ANTIOXIDANT	36.76	8.79			

Graph 1-



Graph 2-



DISCUSSION-

Till date the literature reveals that the medical and non-invasive management of premalignant condition should include Antioxidants along with the cessation of habit. Antioxidants inactivate free radicals, attenuate free radicals-initiated oxidative reaction, particularly lipid peroxidation and DNA oxidative damage, thereby preventing tissue damage as well as potential cancerization¹⁷. According to Kumar A et al¹⁸(2007), Lycopene exhibits a potent anticarcinogenic property and is also a powerful antioxidant . It modulates the dysplastic changes in

potentially malignant disorders. Lycopene exhibits one of the highest physical quenching rate constant with singlet oxygen. Antioxidants showed improvement in mouth opening; reduction in burning sensation in OSMF affected individuals²¹.

Pentoxifylline has been reported to be beneficial in the management of OSMF [Rajendran et al 2006]²⁰. Pentoxifylline is a methylxanthine derivative with properties similar to theobromine, caffeine and theophylline. It is termed as "Rheologic modifier"²²

It improves microcirculation and decreases platelet aggregation as well as granulocyte adhesion. It also shows antithrombin, anti-plasmin activities and fibrinolytic activity. Rawlins et al in 2006²⁴ reported that Pentoxifylline has a direct effect on inhibiting burn scar fibroblasts. Haddad et al²³ reported a significant improving effect of the Pentoxifylline-vitamin E combination in 34 affected individuals with radiation-induced fibrosis 3 months. According to study conducted by Samlaska et al in 1994²², long term intake of Pentoxifylline causes thrombocytopenia but in the present study only 1 out of 50 patients had reduced platelet count on the 4th visit up to 80,000 lakh. When patients past history was explored patient revealed that he suffered from mild attack of dengue 2 month back. So this decrease in platelet count might be attributed to the effect of dengue rather than the side effect of Pentoxifylline. In the study conducted by Patil S et al²⁵ in 2014; they found 8 patients in Pentoxifylline group had experienced nausea, bloating of stomach, dyspepsia and anxiety.

In our study the age range of patient was from 17 yrs to 50 yrs with a median age of 30 yrs. There were 44% population belonged to 4th decade and 42% population belonged to 3rd decade followed by 8% in 2nd decade and 6% in 5th decade of life. The reason for higher prevalence in younger individuals could be due to the peer pressure, easily available products in a single time use sachets, its use as mouth fresheners and fashion icon symbol.

In the present study data, 60% affected individuals consumed raw tobacco with betel nut followed by 30 % gutkha and 7% consumed gutkha along with paan and rest 2 % population consumed betel quid or supari alone. 1% of study group had mixed habit including cigarette smoking with betel nut or tobacco consumption. This finding was almost similar to the study of Ravi Mehrotra (2011) in which 64% population consumed paan masala or dohra, 20 % consumed paan masala with betel quid, 7% used betel quid with tobacco and 6% were smokers. In accordance the study of Patil S et al in 2014; 58% patients consumed betel nut, 23% tobacco and 42% consumed spicy food. All the affected individuals had fibrosis in retromolar area, anterior faucial pillar along with this 40% population also had fibrosis in buccal mucosa. Only 2% population had fibrosis on the tongue. This result was in accordance with the study of Ravi Mehrotra (2011) in which similar kind of fibrosis was present in all patients. Soft palate was involved in 100% of patients followed by buccal mucosa in 90% , retromolar trigone in 90% , anterior faucial pillar in 80%, floor of mouth in 24% and tongue in 20% of the patients. According to the study of R Rajendran (2006)²⁰ perioral fibrosis was present in 24.3%, 27.7% in anterior buccal mucosa, 79.31% in posterior buccal mucosa, 17.24 % at junction of hard and soft palate. The mean improvement in mouth opening with Pentoxifylline was 35.63± 11.77 and 38.34 ±10.08 in Antioxidant group. This result was not in accordance with the study of Ravi mehrotra (2011) in which in the Pentoxifylline group the mean increase in mouth opening was more as compared to the antioxidant group. A study conducted by Aara A et al in 2012 at Andhra Pradesh, the mean mouth opening in Pentoxifylline group was 5.9 mm and 10.4 mm in Dexamethasone group. In accordance the study of Patil S et al in 2014; they found that the mean increase in mouth opening in Pentoxifylline group was 23.7±2.1 mm and in Placebo group was 22.7±2.07 mm.

In our study mean increase in tongue protrusion is not significant in any visit of the patient for both the groups which was similar to study conducted by R Rajendran (2006). Whereas Patil S et al in 2014; reported the mean increase in tongue protrusion in Pentoxifylline group was 18.5±2.05mm and in Placebo group was 13.4±2.02mm.

In our study mean decrease in burning sensation was not significant on any visit of the patient in both the groups i.e. both the drugs are nearly equally efficient in reducing burning sensation. However in Pentoxifylline group, relief from burning sensation is higher in comparison to the Antioxidant group [in Pentoxifylline 4.8±2.05 and Antioxidant 4.61 ±2.29]. There is higher rate of relief from burning sensation in successive visits in Pentoxifylline group as compared to the Antioxidant group with time.

In the present study group mean increase in cheek flexibility was significantly higher in Pentoxifylline group as compared to the Antioxidant group [in Pentoxifylline 3.52± 2.1 and in Antioxidant 2.56± 1.3]. This increase in cheek flexibility is attributed to increase vascularity due to the property of peripheral vasodilatation .

In our study group only 42% (n= 21) population had a history of vesicle or ulceration in the mouth during the initial stages. In the Pentoxifylline group, none of the patients whereas in Antioxidant group, 20% of the patients still got ulcers in between the course of treatment.

Pentoxifylline significantly improves the other sign and symptoms like hearing loss and difficulty in deglutition in a patient with OSMF.

There is a very remarkable finding in the study which has not been reported elsewhere in the literature. In 1 patient mouth opening was further increased by 4-5 mm under Pentoxifylline group 6 months post discontinuation of the drug. It was reconfirmed with the patient that he had not taken any treatment for OSMF in past 6 months.

CONCLUSION-

Treatment of Oral Submucous Fibrosis has been a challenge ever since its inception. Newer drugs and methodology have been constantly evolving for the management of this complex disease. Present study showed, increase in mouth opening, decrease in burning sensation and improvement in cheek flexibility patients with OSMF. Improvement in the symptoms was better noted with Pentoxifylline as compared with Antioxidants. Although, improvement in all the clinical parameters except cheek flexibility was not statistically significant. Nevertheless, it is concluded that Pentoxifylline is a good alternative treatment for OSMF as compared to Antioxidant.

There is public health campaigns at the community level may be the best way of controlling OSMF by making the people abstains from the habit.

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