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

INTRODUCTION-
Oral submucous fibrosis (OSMF) is a clinically benign but potentially malignant disorder 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. In India itself approximately 5-10 million peoples are suffering from OSMF. This was first well documented by Schwartz in 1952 and termed it Atrophia idiopathica (tropica) mucosae oris. Later on, this condition known by various other terms like Oral Submucous Fibrosis (OSMF), Diffuse Oral Submucous Fibrosis, Idiopathic Scleroderma of the mouth, Idiopathic Palatal Fibrosis, Sclerosing Stomatitis and Juxta- Epithelial Fibrosis.

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”.

According to National Sample Survey Organization (1998-99) 193.2 million populations in India are consuming tobacco in either form including smoke or smokeless. 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. Malignant transformation rate is quite high approximating to 4.5%.

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 more much affected than females. The younger generation is addicted to these products especially gutka and panmasala. 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 Kharolka reported majority of OSMF cases belonged to the age group of 20-40 years. Sirner et al. 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.

There is very well established etiopathogenesis of role of areca nut causing OSMF by generation of free radicals and immunosuppression in the body. There are wide spread options instituted for treatment of OSMF ranging from Iron and multivitamin supplements including Lycopene, Intravesical injections of Steroids, Hyaluronidase, Human placental extracts to surgical interventions. 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 Pentoxifylline.

Pentoxifylline is a trisubstituted methylxanthine derivative and competitive nonselective phosphodiesterase inhibitors with diverse pharmacologic properties such as peripheral vasodilation, 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 haemorrhheologic 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 activity.

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 both drug groups in the treatment and management of OSMF.

ABSTRACT
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.

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.

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 ×6 months and Antioxidant 1 cap BD ×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. Check 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. All the 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 (25in 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 4 decade and 42% population to 3 decade followed by 8% in 2 decade and 6% in 5 decade of life. There are only 2 (4%) females among 50 patients with ratio of male: female is 24:1 the study population. In the collected study data, 60% affected individuals consumed tobacco with betal quid followed by 30 % gutkha and 7% population gutkha along with paan and 2% population consumed betal 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 fibroic bands in the retromolar area and anterior fualar pillar along with 40% patients also fibroic 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 (MO0).

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- VAS SCALE-
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 then 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)

<table>
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<tr>
<th>MO0</th>
<th>PENTOXIFYLLINE</th>
<th>Mean</th>
<th>S.D.</th>
<th>T-value</th>
<th>P-value</th>
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<td>32.46</td>
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<td>8.97</td>
<td>0.335</td>
<td>0.335</td>
<td>-2.62</td>
</tr>
</tbody>
</table>

Graph 1- Antioxidant, grade III, (total patient -1), 4%  Antioxidant, grade I, (total patient -3), 12%  Antioxidant, grade II, (total patient -21), 84%

Graph 2- Pentoxifylline, grade III, (total patient -1), 12%  Pentoxifylline, grade I, (total patient -3), 5%  Pentoxifylline, grade II, (total patient -21), 76%

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 cancerization 11. According to Kumar A et al 11(2007), Lycopene exhibits a potent anticarcinogenic property and is also a powerful antioxidant . It modulates the dysplastic changes in...
In the present study group mean increase in cheek flexiblity was significantly higher in Pentoxifylline group as compared to the Antioxidant group [in Pentoxifylline3.52± 2.1 and in Antioxidant 2.56± 1.3]. This increase in cheek flexiblity 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 confirmed that the patient 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. New 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 flexiblity 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 flexiblity 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.

REFERENCES
1. Ashik A et al. Oral submucous fibrosis, a clinically benign but potentially malignant diseases: report of 3 cases and review of the literature. JCDCA,2008;October; vol 74, no 8