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An In Vivo Study to Compare the Efficacy of Pentoxifylline in OSMF

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ABSTRACT

Oral sub mucous fibrosis is the potential malignant disorder affecting the oral cavity and most prevalent in young generation. The etiology of this condition is consumption of betel nut causing finally the fibrosis of mucosa. The subjects have the symptoms like burning sensation, trismus, and difficulty in swallowing, alter speech, shrunken uvula. So the disorder to be prevented and controlled by stoppage of habit, conservative, medicines, mouth opening exercises and surgery .In the medicines antioxidant, corticosteroids (topical), turmeric, immused milk,vasodilators are used and found to be effective. The study was undertaken on 60 subjects suffering from Grade I and Grade II OSMF with fifteen days interval and prescribed on pentoxifylline and placebo for three months. There was significant improvement in burning sensation and mouth opening of OSMF subjects.

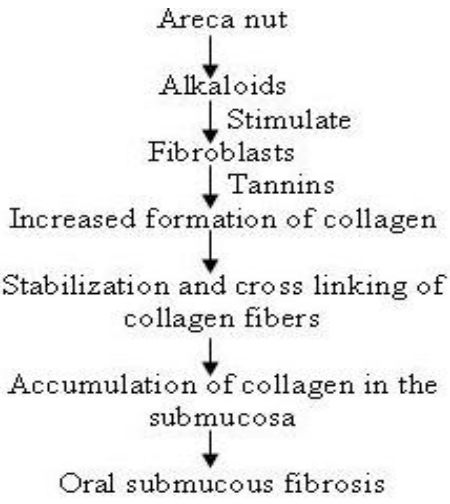
Keywords: Self-determination; Motivation; Medicine; High school students

INTRODUCTION

Oral submucous fibrosis (OSMF) is now called as a potentially malignant disorder of the oral cavity, oropharynx and hardly ever the larynx.[1] It was foremost described in the contemporary literature by Schwartz in 1952 who coined the term atrophica idiopathica mucosa oris to illustrate an oral fibrosing disease.[2] Joshi later coined the termed oral submucous fibrosis (OSMF) for the condition in 1953.[3] This condition has been referred under a integer of names like diffuse oral submucous fibrosis,[4] idiopathica scleroderma of the mouth,[5] idiopathic palatal fibrosis.[6]

The most common cause of this disease is chewing areca nut.Excessive use of areca nut may cause fibrosis due to increased synthesis of collagen and induce the production of free radicals and reactive oxygen species, which are responsible for high rate of oxidation / peroxidation of polyunsaturated fatty acids which affect essential constituents of cell membrane and might be involved in tumorogenesis.[7,8]

Chewing betel nuts is an important and popular cultural activity in many Asian countries. It is often chewed at ceremonies and gatherings and their preparation techniques vary from region to region. Betel quid is chewed for many reasons including for its stimulants effect, to satisfy hunger, to sweeten the breath and as a social and cultural practice.[9,10]



Chilies are thought to irritate the oral mucosa and cause chronic inflammation which leads to fibrosis formation.[11]

A possible autoimmune basis to the disease with demonstration of various auto-antibodies and an association with specific HLA antigens A10, DR3, DR7, and probably B7 along with haplophytic pairs A10/DR3, B8/DR3, and A10/88 has been found.[12] These pairs together with the presence of autoantibodies and chronic inflammation of the oral mucosa have been suggested as an autoimmune basis of oral submucous fibrosis.

It manifests as a burning sensation in the mouth, intolerance to eating hot and spicy foods, blanching and stiffness of the oral mucosa,trismus, vesiculation, excessive salivation, ulceration, pigmentation change, recurrent stomatitis, defective gustatory sensation, dryness of the mouth , gradual stiffening and reduced mobility of the soft palate and tongue leading to difficulty in swallowing and hyper nasality of voice, hoarseness of voice (with laryngeal involvement) and occasionally, mild hearing loss due to blockage of Eustachian tube.[13]

The non surgical management of such disease includes discontinuation of the habit, avoidance of spicy foods, nutritional support, medicinal measures like corticosteroids, peripheral vasodilators, placental extracts, recombinant human interferon gamma (γ-IFN), enzymes . Alternative Medicine including antioxidants, immunised milk, turmeric,aloe vera are used.[14] Surgical measures includes simple excision of the fibrous bands, excision of bands with myotomy with or without coronoidectomy, coverage of the raw area with skin grafts, fresh amnion, collagen membrane, buccal pad of fat, local flaps or vascularised free flaps, followed by active post-operative jaw physiotherapy with anti-oxidants and proper nutrition and regular follow-ups to ensure maintenance of oral opening and early detection of malignant changes if any. Use of lasers for band excision also has been documented.Coverage of the area with fibrin glue or absorbable Atelocollagen also is being tried [15]

Being a chronic disease no any particular drug gives 100% cure in this disease. Many drug regime are tried among which steroid is supposed to be the first choice of drug. Steroids were the first group of drugs to be used in the treatment of OSMF patients. Steroids act as immunosuppressive agents for prevention or suppression of the fibro productive inflammation found in OSF lesions, thus ameliorating this fibro-collagenous condition.[16]

Pentoxifylline has been recently shown to have significant improvement in the management of OSMF patients. Pentoxifylline is a tri-substituted methylxanthine derivative, with numerous biologic activities. It is termed as a “rheologic modifier.” It improves microcirculation and decreases aggregation of platelet as well as granulocyte adhesion. It increases leukocyte deformability as well as inhibits neutrophil adhesion and activation. It increases production of prostaglandin E2 and prostaglandin I2 by vascular epithelium and maintain cellular integrity

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and homeostasis after acute injury. In addition, it causes degranulation of neutrophils, promotes natural killer cell activity and inhibits T-cell and B-cell activation. Pentoxifylline has also shown a direct effect on inhibiting burn scar fibroblasts.[17] It is also be used in dentistry for treatment of apthous ulcer, bechet disease, osteoradionecrosis, graft versus host disease and AIDS.[18]

In this study we are comparing the efficacy of pentoxifylline in Grade I and Grade II OSMF cases for 3 months. The burning sensation and mouth opening is observed.

Aim:

To compare the efficacy of Pentoxifylline and Placebo in OSMF patients

Objective of the study:

To evaluate the efficacy of Pentoxifylline and Placebo in Grade I & Grade II OSMF.

RESULTS:

The study was conducted in the Department of Oral Medicine and Radiology which includes 60 subjects who had been clinically diagnosed as Grade I and Grade II Oral Submucous Fibrosis with burning sensation and reduced mouth opening. They were divided into two groups consisting of 30 subjects in each group, all the subjects were given medications group wise as given below and recalled after every 15 days till 3months (90days) for follow up to check improvement in burning sensation and mouth opening.

Group 1: Tab. Pentoxifylline 400 mg three times a day

Group 2 : Cap .Placebo once in fifteen days

All the 60 subjects were males, out of which 21 subjects were of Grade I OSMF (35%) while 39 subjects were of Grade II OSMF (65%), Statistically there was significant difference observed between Grade I and Grade II patients ($p<0.05$) (Table 1)(Graph 1).

Overall improvement at the end of study in the subjects suffering from reduced mouth opening in Grade I OSMF 21 subjects 15 subjects showed improvement (71.42%) while out of 39 subjects in Grade II 20 showed improvement (51.28%) .Although there was difference in mouth opening between Grade I and Grade II but it was not stastically significant (Table 2)(Graph 2).

Overall improvement at the end of study in the subjects suffering from burning sensation on having hot and spicy food found that in Grade I OSMF 17subjects out of 21 showed improvement (80.95%) in burning sensation while in Grade II OSMF 29 subjects out of 39 showed improvement (74.35%) (Table3) (Graph 3). There was difference in burning sensation between these two group was noted but it was not stastically significant.

Group 1 visit wise follow up showed 40% improvement in burning sensation in first visit, followed by 65% in second visit, 90% in third visit and 95% in fourth visit, 100% in fifth and sixth visit while improvement in mouth opening was O% in first visit, followed by 35% in second visit,65% in third visit,80% in fourth visit and 85% in fifth and sixth visit .

Group 2 showed 0% improvement in burning sensation in first, second visit ,5% in third visit and 15 %fourth ,25%fifth and 30% in sixth visit. Improvement in mouth opening was O% in first and second visit,5% in third ,fourth ,fifth visit and 10% sixth visit.

All the subjects were divided into five age groups from 18years to 68 years with maximum number of subjects were between the age group of 18-28 years while after sixty years group only 1 case was recorded. The youngest subject was of 19 years and older subject was of 60 years old.

DISCUSSION:

Oralsubmucous fibrosis is a potentially malignant disorder affecting millions of individuals and is likely to reach an alarming proportion in the near future. The onset of oral sub mucous fibrosis is insidious over a period of two to five years. The patients initially complain of burning sensation in the oral cavity while consuming spicy food.As the disease progresses the oral mucosa becomes blanched, slightly opaque and fibrous bands appear leading to difficulty in opening the mouth, inability to whistle and difficulty in swallowing. Due to habit of chewing areca nut there is constant contact between the areca nut mixture and oral mucosa in persons with these diseases. The alkaloids released from the areca nut get absorbed into the oral mucosa and undergo

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metabolism and facilitates the diffusion of alkaloids and flavinoids into the subepithelial connective tissue resulting in the juxtaepithelial inflammatory cell infiltration.[19]

Treatment for OSMF remains a challenge. It is said that once the disease has developed there is neither regression nor any effective treatment. There is no definite treatment of OSMF. The main aim of treatment is to relieve the symptoms and improve the mouth opening. The various treatment modalities are mainly medical, surgical, or a combination of both. The treatment depends on the level of clinical involvement. At a very early stage, cessation of the habit is adequate. Medical/surgical treatment is necessary for moderate to severe cases. The non surgical management of such patient includes discontinuation of the habit, avoidance of spicy foods, medicinal measures like local steroids, vitamins, placental extracts, vasodilator pentoxifylline, enzymes hyaluronidase injections singly or in combination and oral anti-oxidant supplements along with jaw opening exercises and ayurvedic therapy.[24] Surgical treatment is the method of choice in patients with marked limitation of mouth opening or in patients not responding to the conservative management.Surgical measures attempting at excision of fibrous bands, coverage of resultant defects with skin grafts, collagen or other dressing materials, buccal pad of fat, local flaps, vascularised flaps, with or without coronoidectomy and post operative active jaw physiotherapy.In the literature there are various treatement modalities of OSMF but none of these is effective.[20] As a result of these the present study was conducted to evaluated the comparision of efficacy of pentoxifylline and placebo in the improvement of mouth opening and burning sensation in grade I and Grade II OSMF subjects.

Pentoxifylline is a tri-substituted methylxanthine derivative and termed as a "Rheologic modifier." The most important action of pentoxifylline is increase in locoregional blood flow. The property of pentoxifylline that may be far-reaching in the management of OSF is perhaps its effect on the fibroblast and the role it assumed in fibrinolysis. Berman and Duncan showed that fibroblasts cultured in the presence of pentoxifylline produce twice as much collagenase activity and decreased amount of collagen, glycosaminoglycans and fibronectins. IL-1 induced fibroblast proliferation was inhibited by the addition of pentoxifylline. Primary immunologic abnormalities have been reported with OSMF and that these immune abnormalities probably mediate local tissue damage and that they appear to be the final common pathway in the pathogenesis of OSMF. Pentoxifylline affects immune modulation by means of increased leukocyte deformability and chemotaxis, decreased endothelial leukocyte adhesion, decreased neutrophil degranulation and release of superoxides, decreased production of monocyte-derived TNF, decreased leukocyte responsiveness to interleukin 1 (IL-1) and TNF, inhibition of T and B lymphocyte activation and decreased natural killer cell activity .It also inhibit the production of TNF-α, which is an important inflammatory mediator with a wide spectrum of activity, predominantly produced by mononuclear cells. Pentoxifylline is also an active inhibitor of already formed TNF. There is also evidence that pentoxifylline may influence other inflammatory cytokines, such as inhibition of IL-1 and IL- 6 . Rajendran et al stated that the anti inflammatory and immunomodulatory actions of pentoxifylline seems to have definite therapeutic advantages in the management of OSMF.[21]

Rajendren et al (2006) conducted a study on subjects who had on regime of 4oomg pentoxifylline twice a day for one month and then 400mg for thrice a day for seven months with one month interval.The results were highly significant for improvement in mouth opening and relief from burning sensation ($p<0.005$).As compared to our study we had included subjects receiving pentoxifylline 400mg thrice a day for three months with fifteen days interval.our study improvement in mouth opening and relief from intoleranace to spicy food showed highly significant results ($p<0.005$). Similarly a study done by Santosh patil et al (2014) showed significant results which supported the findings of our study. [21]

Ravi Mehrotra et al (2011) conducted a study on subjects receiving pentoxifylline 400mg twice a day for one month and then 400mg for thrice a day for six months. The subjects were mostly of third decade of life.We found that there was improvement in burning sesnation by 86.6% and average imrovement in mouth opening was increased by 10 mm.As compared to our study we had included 20 subjects receiving pentoxifylline 400mg thrice a day for three months with fifteen days interval.Similar age group

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subjects were maximum in our study of third decade.In our study improvement in mouth opening and relief from intoleranace to spicy food showed highly significant results at every visit (p<0.005).The average improvement in mouth opening was 2.5 mm.[22]

According to the study done by Amer Kesarwani et al (2015) on subjects who were given 400mg thrice a aday for 6 months and the follow up was done at 1,3,6 month interval.most of the subjects were in third decade.the burning sensation was signifivcantly improved (p<0.005).the average incerase in mouth opening was 5.46 mm .70.66% subjets showed improvement in mouth opening while our study showed 85% improvement in mouth opening. As compared to our study we had included the subjects receiving pentoxifylline 400mg thrice a day for three months with fifteen days interval.Similar age group subjects were maximum in our study of third decade.

In our study improvement in mouth opening and relief from intoleranace to spicy food showed highly significant results at every visit (p<0.005).The average improvement in mouth opening was 2.5 mm.[23]

CONCLUSION:

The present study was conducted on 60 subjects who has been clinically diagnosed as Grade I and Grade II Oral Submucous Fibrosis .They were divided into two groups consisting of 30 subjects in each group and compared for the efficacy of pentoxifylline and placebo. All the subjects in each group had given Tab.Pentoxifylline and Placebo for three months with follow up of fifteen days interval.The observation of the study was subjected to stasticial analysis and the results were tabulated. We had concluded based on our observation that:

1) The subjects were from the age group of 18-68 years.
2) Most number of cases were in third decade of life.
3) All the subjects were male.
4) There was improvement in both burning sensation and mouth opening in pentoxifyline group as compared placebo group.

Treatment of OSMF has been a challenge ever since its discovery. Newer drugs have been constantly evolving for the management of this complex disease. The results of the present study showed that pentoxifylline,lycopene was found to be effective in the management of OSMF.

In contrast to other management modalities for submucous fibrosis, it offers a non invasive option that yields significant improvements in the symptoms as well as objective signs of the condition, which may be due to its anti-poliferative, anti-inflammatory and antioxidant activity.

This was short term study with small sample size.A long term study with larger sample size with all the variables being taken into consideration would be necessary to get a clear picture about the utility of the drug whether to be used as a first line drug theraphy for the management of OSMF.

Table 1: Total number of subjects:

Parameter	No of subjects	Percentage	Z test	P value
Grade I	21	35%	2.32	P<0.05
Grade II	39	65%		

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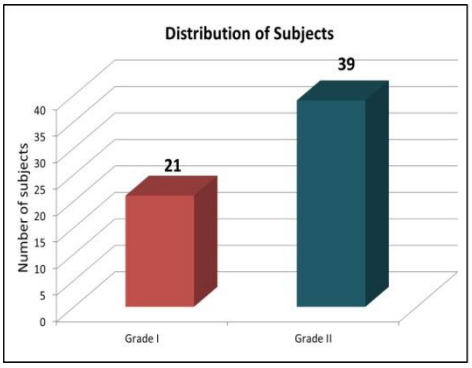
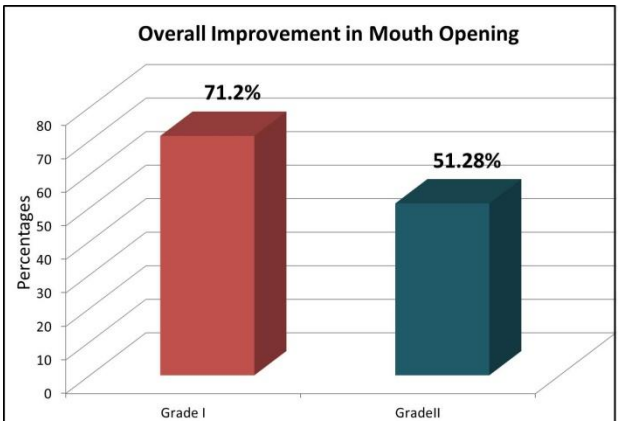


Graph 1: distribution of subjects

Table 2: Overall improvement of mouth opening in Grade I and GradeII cases

Parameter	Total	Improvement cases	Percentage	Z test	Pvalue
Grade I	21	15	71.42	2.279	0.108 (>0.005)
GradeII	39	20	51.28		



Graph 2: Overall improvement of mouth opening in Grade I and GradeII cases

Table 3: Total overall improvement in burning sensation in Grade I and GradeII cases

Parameter	Total	Improvement cases	Percentage	Z test	P value
Grade I	21	17	80.95	o.332	0.406
GradeII	39	29	74.35		

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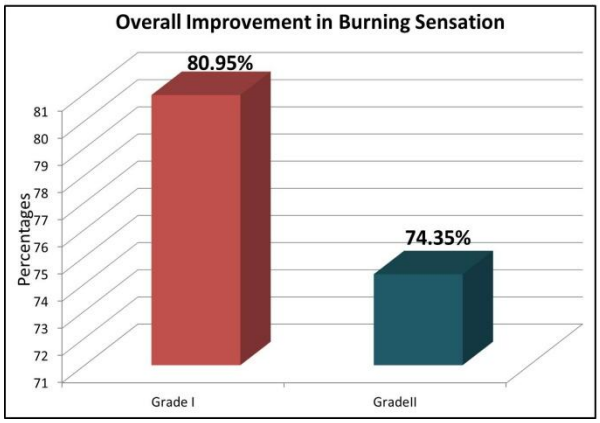

Graph 3: Overall improvement in burning sensation in Grade I and GradeII cases

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