

Original Research

Use of pentoxifylline in the treatment of oral submucous fibrosis patients: A comparative study

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ABSTRACT:

Aim: The present study was aimed to evaluate the effectiveness of drug pentoxifylline in the management of OSMF and to correlate the clinical parameters evaluated before and after treatment. **Methods:** This investigation was conducted as a case-control study incorporating a Control Group in comparison to a Study Group where pentoxifylline 400 mg was administered 3 times daily, as coated, sustained release tablets prescribed for 3 months. The stipulated period for the study was 8 months and a total of 50 cases of oral submucous fibrosis (25 test subjects and 25 controls) were included in this study and 100% acquiescence was reported at the end of the test period. **Result:** Mild dizziness and gastric irritation were the only untoward symptoms reported in 2 of the volunteers in the study group during this trial. These were managed by diet protocols. A review of the patients and controls was done at an interval of every 4 weeks for 3 months. The subjective and objective measurements were recorded. **Conclusion:** This study showed the effectiveness of pentoxifylline as an additional therapy in the routine management of oral submucous fibrosis.

Keywords: Oral submucous fibrosis, Pentoxifylline, Treatment

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INTRODUCTION

Schwartz in 1952 described a condition affecting the oral mucosa including the palate and faucial pillar, called "atrophiaidiopathica mucosae oris" among five Indian women from Kenya. Later, the term "oral submucous fibrosis (OSMF)" was coined by S.G Joshi in 1953. The disease is predominantly seen in India among Asian countries, with a reported prevalence ranging up to 0.4% in Indian rural population. Based on a study conducted in 2002, more than 5 million people in India suffer from OSMF, 0.5% of Indian population.¹

Oral submucous fibrosis (OSMF) remains the most common potentially malignant disorder largely seen in the south Asian countries and emigrants from these countries to other regions. It affects 0.2–0.5% of the Indian population. Evidence shows that the fibrogenic potential of areca nut alkaloids and tannin is the main cause of this disorder. The degree of vascularity of the diseased mucosa in OSMF has

always been an enigma. The atrophic epithelium is foreseen to pre-dispose to malignant transformation when brought in contact with oral carcinogens.²

The habit of betel quid chewing is widespread throughout India and Southeast Asia. Moreover, it is widely prevalent in teenagers and young adult.^{3,4} Buccal mucosa, faucial pillar, and soft palate are predominantly affected. Underlying muscles and the muscles of mastication can also be involved. Currently, pentoxifylline, a tri-substituted methylxanthine derivative, is reported to have satisfactory results in the management of OSMF due to their immune modulation, alteration of fibroblast physiology, rheologic modification, and anti-inflammatory property.⁵ Pentoxifylline is a methylxanthine derivative that has vasodilating properties. It is believed to increase the vascularity of the mucosal layer also.

The objectives of this clinical study was to determine the effect of pentoxifylline on the

microvascularity and clinic pathological progression of oral submucous fibrosis.⁶ This investigation was carried as a comparative study incorporating a control group (multi-vitamins) in comparison to the study group (pentoxifylline 400 mg thrice daily) administered in the form of coated sustained release tablets.

METHODS

This study was conducted from June 2018 to January 2019. Before starting the study, ethical clearance was obtained from the institutional ethical committee.

The sample size was calculated by using the following formula: $n = \frac{m^2 t^2 p (1-p)}{e^2}$ in which n = required sample size. t = confidence level at 95% (standard value of 1.96). p = estimated prevalence of OSMF in the project area. m = margin of error at 5% (standard value of 0.05). 120 clinically diagnosed cases of OSMF of either sex in the age range of 20 to 60 years were included in the study.

The inclusion criteria were as follows:

1. Patients with clinically diagnosed OSMF.
2. Patients who have not undergone any treatment for OSMF in past.
3. Patients who were willing to quit gutkha, areca nut and/or tobacco chewing habit.
4. Patients who were ready to attend regular follow-ups.

The exclusion criteria were as follows:

1. Patients who have undergone any treatment for OSMF in past.
2. Those with any evidence of cardiac, gastrointestinal, kidney or metabolic disorders, pregnancy or lactation that may interfere with the study protocol.
3. Patients with coexisting disease or disorder of the orofacial region other than OSMF which may interfere with the study protocol.
4. Patients with dysplastic features.
5. Patients with the inadequate reference point (i.e. incisal edges of the central incisors) for measuring interincisal distance.

Participants were explained about the disease and the medications. They were also advised to refrain from

this deleterious habit before the commencement of the study.

Written consent was obtained from them before their participation in the study. Relevant information was documented in structured proforma. These OSMF patients were selected by a simple random method and were staged by established clinical parameters proposed by Bailoor D et al., 2005 [3].

The volunteers of grades 1, 2 and 3 were randomly allotted to the groups through a lottery method. Grades 4 and 5 were ruled out as they fell into the exclusion criteria.

The patients were grouped into 2, the study or experimental drug group (EDG, $n = 25$) who were treated with pentoxifylline, (Trental 400 mg tablets) and the control or standard drug group (SDG, $n = 25$) who were administered multi-vitamin capsules (B-complex one capsule before sleep daily). Clinical and hematological workup to rule out systemic ailments like hypertension, diabetes mellitus, cardiac diseases, gastroenterological disorders, and bleeding disorders was done before the commencement of the study.

Initially, a reduced dosage of pentoxifylline (i.e. 200 mg thrice daily) was administered to all the patients in the EDG for the first 30 days. After 4 weeks serological tests were done to record any changes. The dose was then hiked to 400 mg thrice daily for 2 more months. Thus the dropout figure recorded was zero. Clinical follow-up and review of all the patients included in the EDG and SDG was carried out at 30 days intervals for the whole trial period of 3 months. During each visit, recordings to evaluate the objective and subjective improvement from the disease of both the groups were assessed and scored and entered in a specially designed proforma charted for the purpose. The same investigator evaluated all the patients during each visit thus preventing bias.

FOLLOW UP PERIOD

All the patients included in this clinical trial were followed up to 6 months after cessation of active medication.

RESULTS

Table 1: Etiologic factors in OSMF patient

Etiologic factor	OSMF I		OSMF II		OSMF III	
	Male	Female	Male	Female	Male	Female
Tobacco with lime (Zarda)	4	0	0	0	4	0
Paan with tobacco	4	2	2	2	0	0
Paan without tobacco	0	0	0	0	0	0
Plain areca nut Processed	0	0	0	0	0	0
Plain areca nut Unprocessed	4	4	2	2	4	2
Pan masala with tobacco	4	4	2	0	2	2
Pan masala without tobacco	0	0	0	0	0	0
No Habits	0	0	0	0	0	0

Table 2: Clinical examination of OSMF patients

Anatomical Site(s) Involved	Blanching No. of Cases	Fibrous Bands No. of Cases
Buccal Mucosa	48	45
Tongue	10	2
Labial Mucosa	5	10
Floor of mouth	8	5
Soft Palate	20	15
Pterygo-mandibular raphe	10	22

Areca nut intake was the most common chewing habit among the patients with 8 in Grade I, 4 in grade II and 6 chewers in grade III OSMF. Other smokeless forms of deleterious habits were zarda, paan with or without tobacco or pan masala with or without tobacco (Table 1). More than one anatomical site of the oral mucosa was either affected by blanching with or without fibrotic bands. Most of the patients had simultaneous involvement of multiple sites (Table 2).

DISCUSSION

Oral submucous fibrosis is a common premalignant condition affecting the oral mucosa with more prevalence among Indian population. Various treatment modalities have been elucidated to alleviate the symptoms associated with OSMF.⁷ Currently, oral pentoxifylline has been proved to be beneficial in treating OSMF because of its anti-inflammatory, fibrinolytic, immune modulatory, and rheologic modifying property. Pentoxifylline improves red blood cell membrane deformability by increasing the amount of membrane adenosine triphosphate. It also alters red blood cell membrane protein phosphorylation patterns, increases protein kinase activity, and decreases Ca²⁺-dependent K⁺ efflux. The results of experimental studies have shown that fibroblasts cultured in the presence of pentoxifylline produced twice as much collagenase activity and decreased amounts of collagen, glycosaminoglycans, and fibronectin. Interleukin-1-induced fibroblast proliferation is also inhibited by pentoxifylline. All these actions of pentoxifylline have made it as an option for the management of oral submucous fibrosis.⁸ The present study was done to evaluate the effectiveness of oral pentoxifylline in the management of OSMF.

Several categories of drugs have been used in the treatment of OSMF, but their effectiveness leaves much to be desired and no treatment regimen has afforded definitive cure.⁹ While oral administration limits the concentration of drugs in lesional tissue and increases the potential for side effects, the intralesional injections are associated with significant mechanical injury and noncompliance on the patient's part because of the accompanying discomfort and pain.¹⁰

In a study conducted by Santosh Patil, Sneha Maheshwari (2014), 58% of the patients had betel nut chewing habit, while 23% of the patients

had tobacco chewing habit. 42% of the patients consumed spicy foods, which were among the main causative factors for OSMF in the study population.¹¹ Ravi Mehrotra, HP Singh, SC Gupta, M Singh, S Jain (2011) in their study found that 64% of the patients were in the habit of using pan masala or dohra (mixture of tobacco and slaked lime – sold locally), 20% patients used pan masala or dohra with betel quid, 7% patients used betel quid with tobacco and 6% were smokers. Those who chewed areca nut in any form were habituated to 1 to 20 chews per day, (median 6.0) for a period of 1 to 25 years (median 6 years).¹²

Berman and Duncan (1989) showed that fibroblasts cultured in the presence of pentoxifylline produce twice as much collagenase activity and decreased the amount of collagen, glycosaminoglycans, and fibronectins.¹³

Rajendran R et al (2006) used pentoxifylline as an adjunct in the treatment of OSMF for 7 months. After a 6–12 month follow-up, he reported significant improvement in subjective symptoms, of intolerance to spices and burning sensation of the mouth, in the experimental group as compared to patients in the control group ($P < 0.01$).¹⁴

In our study, although both the groups showed improvement in burning sensation, pain, tongue protrusion, and cheek flexibility, there was no significant difference between the two groups when compared on basis of mouth opening, EDG showed better response in burning sensation as the improvement was significant from 5th week onwards, which was not in cases of SDG group. Better and faster improvement of pain on opening the mouth was achieved in EDG as against SDG.

The finding of the present study was in agreement with a similar study done by Rajendran R et al (2006) pentoxifylline 400 mg three times daily, which resulted in improvement in mouth opening, tongue protrusion, and relief from perioral fibrotic bands. Improvement in subjective symptoms of intolerance to spices, burning sensation of the mouth, tinnitus, difficulty in swallowing and difficulty in the speech were also recorded at the end of the trial period.¹⁴

The comparison of results of different studies concluded pentoxifylline to be superior in terms of improvement in burning sensation, mouth opening, and tongue protrusion. Thus, the present research states that pentoxifylline is a better and safer

substitute for corticosteroids and intralesional injections.

CONCLUSIONS

Pentoxifylline can be used as promising alternative treatment modality to intralesional steroid for treatment of OSMF. In the present study Pentoxifylline showed significant decrease in burning sensation and pain in oral submucous fibrosis patients as compared to multivitamin capsules although no significant difference was found with respect to mouth opening. Occasional gastrointestinal disturbances during pentoxifylline administration can however have poor patient compliance. Pentoxifylline can be safer and better alternative treatment for oral submucous fibrosis. Larger sample size and longer treatment duration is necessary in this regard to validate results of the current study.

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