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PUBLISHED PAPER'S TITLE : ROLE OF PENTOXIFYLLINE IN ORAL SUBMUCOUS FIBROSIS: A CLINICAL TRIAL

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Research Paper

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ROLE OF PENTOXIFYLLINE IN ORAL SUBMUCOUS FIBROSIS: A CLINICAL TRIAL

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Declaration

The Declaration of the author for publication of Research Paper in Asian Journal of Modern and Ayurvedic Medical Science (ISSN 2279-0772) We Dr. Amber Kesarwani* Dr. Rajesh Kumar**, the authors of the research paper entitled Role of Pentoxifylline in Oral Submucous Fibrosis: A clinical trial declare that ,we take the responsibility of the content and material of my paper as we ourself have written it and also have read the manuscript of our paper carefully. Also, we hereby give our consent to publish our paper in ajmams , This research paper is our original work and no part of it or it's similar version is published or has been sent for publication anywhere else.we authorise the Editorial Board of the Journal to modify and edit the manuscript. we also give our consent to the publisher of ajmams to own the copyright of our research paper.

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Abstract:

Aims: Oral submucous fibrosis (OSMF) is a well-recognized potentially malignant condition of unknown aetiology. This clinical trial was done to evaluate the effectiveness of Pentoxifylline in OSMF and study of its side effects. **Materials and Methodology:** This clinical trial was done in Department of E.N.T., I.M.S.-B.H.U. on 75 patients which were divided in two groups. Group I consists of 50 patients who were given oral Pentoxifylline at a dose of 400 mg TDS for 6 months while Group II included 25 patients which served as Control group (age and sex matched) who were given multivitamins. All the patients were asked to quit substance abuse and were taught jaw dilator exercises. Follow up record was maintained at 1st, 3rd and 6th month of beginning of treatment. **Observations and Results:** Significant improvement in patients receiving Tab. Pentoxifylline was observed. Total improvement in symptoms score is 89.7% after 6 months of treatment in Group I while in Group II it was just 43.5% ($p<0.05$). The trismus improved by 5.46 mm in group I and 1.36 mm in group II ($p<0.05$). **Conclusion:** Pentoxifylline is effective in alleviating symptoms and signs of OSMF from the preliminary data. However, long term administration and side effects may decrease its compliance in patients.

Keywords: Oral Submucous Fibrosis, Pentoxifylline, Trismus
Source of Support: None
Conflict of Interest: None

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Introduction:

Oral submucous fibrosis (OSMF) is a chronic and potentially malignant condition of the oral cavity. It is characterized by a juxtaepithelial inflammatory reaction followed by fibroelastic changes in the lamina propria and associated epithelial atrophy. The disease affects most part of the oral cavity as well as the upper third of the esophagus [1]. The pathogenesis of OSMF is not well established, but is believed to be multifactorial. The chewing of betel quid (containing areca nut, tobacco and slaked lime) has been recognized as one of the most important risk factors for OSMF [2-4]. The vascularity of diseased mucosa is always debatable. Due To fibrosis, there is poorly vascularised stroma which is supposed to be factor causative of epithelial atrophy. In an epidemiological study, conducted over 17 years in Indian subcontinent, transformation rate of OSMF into squamous cell carcinoma was found to be 7.6% [5]. Over the years, the incidence of OSMF has increased manifold in various parts of the Indian subcontinent including Varanasi and other parts of Eastern Uttar Pradesh. Many treatment options are tried till date for this potentially malignant disease including iron and multivitamin supplements, lycopene - an extract of tomato, and a range of medicines (e.g. intralesional injection of steroids, hyaluronidase, human placenta extracts, chymotrypsin, Pentoxifylline and collagenase). Laser ablation and surgery, including cutting of the fibrous bands of the jaw muscles and temporomandibular joint, has been used for more extreme cases [6]. But no effective therapy is formulated till date.

Keeping in view the increasing prevalence of the disease in this region and lack of effective therapy, a randomized clinical trial was planned to assess the usefulness of Pentoxifylline in the treatment of OSMF in respect to placebo.

Materials and Methodology: This randomised clinical trial was conducted in Department of Otolaryngology, Sir Sunder Lal Hospital, IMS, BHU on patients attending Otolaryngology outpatient department from Jan. 2013 to March 2014. Institutional ethical committee approval was obtained prior to starting the trial. The study was undertaken with the understanding and written consent of each subject. Patients with 18 years of age and older, were enrolled in the study and written consent was obtained. Patients who had difficulty in chewing, had restricted mouth opening with the presence of fibrous bands and clinically diagnosed OSMF were included. Patients with medical problems (Uncontrolled diabetes, Severe Hypertension, Cardiac disease, Gastric or duodenal ulcer etc.) or dental appliances such as orthodontic or other fixed prostheses that could potentially interfere with the examination were not included in the study. 92 patients were enrolled in the study and out of these 75 patients came for regular follow up and took regular treatment, thus 17 patients were excluded. All patients were examined with a conventional overhead examination light and then divided randomly into two groups: Group I (n=50) receiving Pentoxifylline 400mg TDS and Group II (n=25) receiving placebo in form of multivitamins.
Detailed clinical examination was performed on each patient to assess the site/size of the oral mucosal lesions and this was recorded on a standard form. All routine investigations were done. Pre-treatment biopsy was done in patients to rule out malignancy in case of suspicion. Information regarding the patients' name, age, sex, occupation, background, dietary habits, dental hygiene, personal habits and present complaints was gathered. Emphasis was given to addictions like areca nut, tobacco and alcohol. Clinical assessment of maximal jaw opening was carried out monthly and outcomes were expressed by measured change in the inter-incisor distance. Staging of the patients were

done according to More CB et al. We had formulated a newer scoring system in which each symptom/sign and of OSMF were given a particular score, before and after completion of therapy. Scoring of symptoms like intolerance to spices, burning sensation in mouth, oral pain, heaviness in throat and repeated vesicles or ulcer formation was done according to verbal complaint rating scale of 0-10 points, where 0 means no symptom and 10 means severe most symptom as perceived by the patient subjectively and signs were scored from 0 to 8 points according to a new criteria. Trismus was scored as 0 means no trismus where inter-incisor distance was 5 cm or more in males and 4.75 cm or more in females, scored as 1 or grade I where inter-incisor distance was more than 3.5 cm but less than normal, scored as 3 or grade II where inter-incisor distance was between 2.5-3.5 cm and scored as 5 or Grade III where inter-incisor distance was between 1.5-2.5 cm and scored as 8 where inter-incisor gap was less than 1.5 cm. Ankyloglossia was scored as 0 when protrusion of tongue was normal (24 .8 mm- 25 mm in both sexes) measured between lower central incisor and tip of the tongue on maximal protrusion, scored as 4 when protrusion of tongue was partial and scored 8 when there was inability to protrude out the tongue. Improvement was noted on the basis of these scores. Group I (n=50) patients were given Tab. Pentoxifylline 400 mg for a period of 6 months while Group II (n=25) patients were given placebo (multivitamin) therapy. Patients were encouraged for habit cessation and jaw dilator exercises were also taught to patients. Clinical follow-up of all the patients was carried out for 6 months and follow up record was maintained at 1st, 3rd and 6th month of starting the treatment and the findings were compared pre and post-treatment. Side effects of treatment, if any, were also investigated. Statistical methods employed in this study included Arithmetic mean, Standard deviation and the Paired't' test.

Observation and Results: Most of the patients suffering from Oral Submucous Fibrosis were in third decade (38.2%) followed by fourth decade (34.6%)**.** Youngest patient seen was 18 year old and the oldest patient was 65 year old. Male to Female ratio of the patients suffering from Oral Submucous Fibrosis were 4.32:1 ($p<0.05$). Most of the males were in age group of 21-30 yrs whereas majority of females were between 41-50 yrs. 65 Patients (86.6%) presented with the complaint of Intolerance to spices, 55 (73.3%) patients with burning sensation, 26 (34.6%) patients with oral pain, 17 (22.67%) patients with heaviness in throat, 29 (38.67%) patients with repeated vesicles/ulceration and 61 (81.33%) presented with reduced mouth opening. 53 (70.66%) patients presented within 12 months of onset of symptoms.Most of the patients presented with Grade II trismus 27 (36%), 22 (29.3%) patients with Grade I trismus, 20 (26.7%) patients with Grade III trismus and 6 (8%) with Grade IV trismus.

The total symptoms score improved by 89.7% in group I and 47.9% in group II. Intolerance to spicy food improved by 89.58% in Group I and 40.77% in Group II, burning sensation in mouth improved by 93.04% in Group I, 47% in Group II, oral pain improved by 95% in Group I, 44% in Group II, heaviness in oral cavity/throat improved by 66.67% in Group I, 50 % in Group II while repeated vesicles and ulcer formation in mouth improved by 86.4% in Group I and 63% in Group II ($p<0.05$) ; except for heaviness in oral cavity/throat. ($p>0.05$)

Side effects noted among Group I patients receiving Tab. Pentoxifylline are dyspepsia and bloating in 13 patients (26%) while 2 patients complained of headache (4%). Among Group II, patients receiving Placebo, no side effects were observed.

Discussion: OSMF is a challenging disease to treat, as it does not regress by any of the treatment modality. The treatment thus aims to reduce the symptoms and improvement in mouth opening. Many treatment modalities are tried for this enigmatic disease like steroid injection, hyaluronidase injection, collagenase injection, lycopene etc. but none of them was able to cure this disease. However, steroids injections are used extensively among practitioners. Many of the patients are reluctant for this Injectable option and wish to have only oral medications. The unsatisfactory response with the oral medication may be because, pathologically, occlusive blood vessels because of the deposition of collagen fibres [7] and hypercoagulability of blood[8] restrict nutrients and therapeutic substances from reaching the affected tissue and also there are chances of systemic side effects.

Table 1: Showing percentage improvement in symptoms

Symptoms	Improvement in percentage	
	Group I	Group II
Intolerance to spices	89.6%	40.77%
Burning sensation	93.04%	47%
Oral pain	95%	44%
Heaviness in oral cavity/throat	66.67%	50%
Repeated vesicle/ulcer in mouth	86.4%	63%
Total	89.7%	47.9%

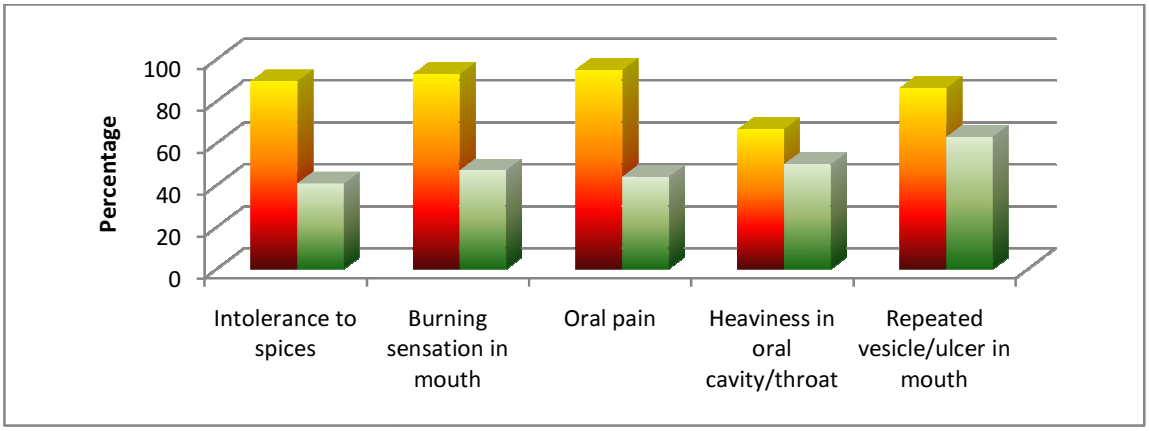

Figure 1: Showing percentage improvement in symptoms

Table 2: Showing Pre treatment and Post treatment score of symptoms

Clinical Parameters	Mean & Standard Deviation			
	Group I		Group II	
	Pre treatment	Post treatment	Pre treatment	Post treatment
Intolerance to spices	8.00 ±4.07	0.83±1.46	8.67±3.46	5.13±2.50
Burning sensation	7.67±4.30	0.53±0.73	8.00±4.07	4.27±2.46
Oral pain	2.00±4.07	0.10±0.55	3.33±4.79	1.87±2.71
Heaviness in oral cavity/throat	1.00±3.05	0.33±1.82	1.67±3.79	0.83±2.30
Repeated vesicle/ulcer in mouth	3.67±4.9	0.50±1.53	5.00±5.08	1.83±2.78
p value	<.05		<.05	

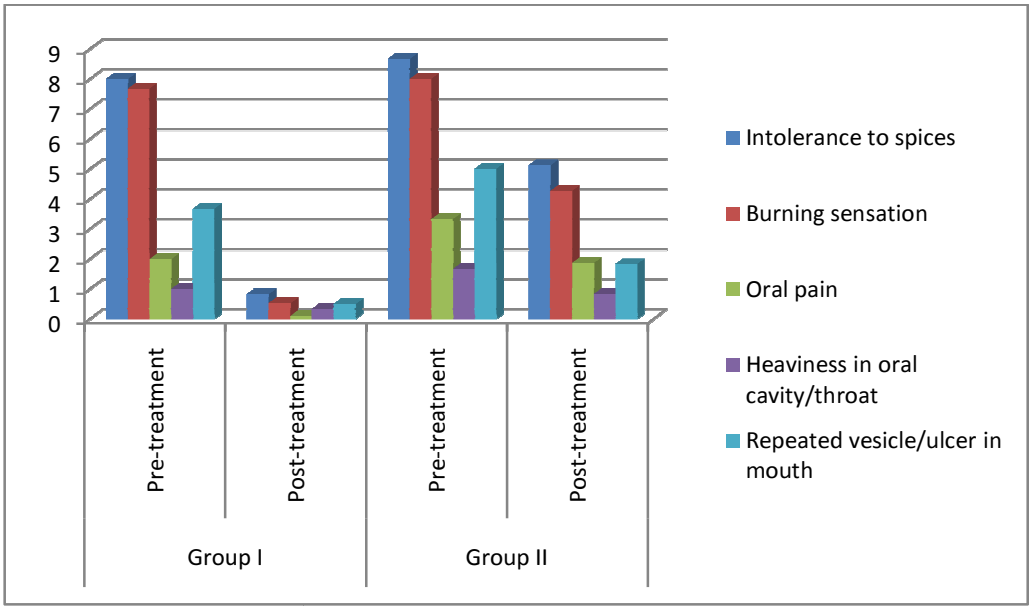

Figure 2: Showing Pre treatment and Post treatment score of symptoms

Trismus improved by 31.6% in Group I and 3.7% in Group II ($p<0.05$). Ankyloglossia

improved by 37.5% in Group I and 0% in Group II. The trismus improved by 5.46 mm in Group I and just 1.36 mm in Group II post treatment. (p<0.01)

Table 3: Improvement in inter incisor gap with the treatment

	Mean & Std. Deviation			
	Group I		Group II	
	Pre treatment	Post treatment	Pre treatment	Post treatment
Trismus (mm)	33.07±9.83	38.53±10.2	28.97±8.57	30.33±9.08
d (mm)	5.46±3.93		1.36±1.27	
p value	<0.001		<0.001	

Pentoxifylline is a tri-substituted methylxanthine derivative, the biologic activities of which are numerous. It is termed as a "Rheologic modifier." It improves microcirculation and decreases platelet aggregation as well as granulocyte adhesion. It increases leukocyte deformability as well as inhibits neutrophil adhesion and activation. The medication also has antithrombin, anti-plasmin activities and fibrinolytic activity. In addition, it causes degranulation of neutrophils, promotes natural killer cell activity and inhibits T-cell and B-cell activation [9]. It is said to maintain cellular integrity and homeostasis after acute injury and has been tried in various medical disorders like stroke, aphthous stomatitis, cerebrovascular insufficiency, peripheral arterial occlusion and pretibial myxedema [10]. Haddad et al.[11] treated 34 radiation-induced superficial fibrotic lesions of the skin with Pentoxifylline and vitamin E for 3 months and reported a significant effect of the Pentoxifylline-vitamin E combination in improving radiation-induced fibrosis[11] . In OSMF, the drug has been used to alleviate the symptoms in addition to its role in improving the vascularity. Most side effects caused by Pentoxifylline involve the gastrointestinal tract and central nervous system. The most frequent gastrointestinal complaints include dyspepsia, nausea and /or vomiting, bloating, flatus, and bleeding. Principal central nervous system side effects include dizziness and headache in a small percentage of patients, whereas tremor, anxiety, and confusion occur in some. Both central nervous system and gastro-intestinal side effects are dose related. [12]

Rajendran et al. reported significant improvement in objective criteria of mouth opening (t=11.285, p= 0.000), tongue protrusion (t= 3.898, p = 0.002), and relief from perioral fibrotic bands (p = 0.0001554) and subjective symptoms of intolerance to spices (p = 0.0063218), burning sensation of mouth (p = 0.0005797), tinnitus (p=0.000042), difficulty in swallowing (p=0.0000714) and difficulty in speech (p=0.0000020) with tab pentoxifylline as compared to placebo at the end of the trial period**.**

Mehrotra R et al. studied the effect of Pentoxifylline against a placebo and found Burning sensation in mouth upon consumption of spicy food or hot foods improved by 39.4% placebo while

86.56% in tab pentoxifylline, repeated vesicles and ulcer formation in mouth improved by 35.5% in placebo and 84.09% in tab pentoxifylline. The trismus improved by 15.38% in placebo and 35.86% in tab pentoxifylline, ankyloglossia improved by 22.58% in placebo and 39.34% in tab pentoxifylline. Improvement in total (sign and symptoms) score was 25 % in group receiving placebo and 49.15% in group receiving tab pentoxifylline ($p < 0.05$)**.**

Our results were comparable to above mentioned studies except no significant side effects were noted in above studies but in our study 26% people complained of dyspepsia and bloating.Grading in our patients were done according to More CB et al. [13]. The improvement in the signs and symptoms even in the placebo group can be due to the cessation of habit of substance abuse as part of counselling of the patients during follow-up visits as well as multivitamin prescribed in Group II.

Conclusion: Pentoxifylline has shown significant improvement in symptoms and signs of OSMF, however, its long term regime and systemic side effects are factors which need consideration and limit its use. A multi-institutional double-blind prospective study for assessment of effects of Pentoxyfylline treatment is recommended before its use.

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