RESEARCH COMMUNICATION

Pentoxifylline Therapy in the Management of Oral Submucous Fibrosis

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Abstract

Objectives: Oral submucous fibrosis is a common premalignant condition in the Indian subcontinent and is caused by chewing areca nut and other irritants in various forms. Its medical treatment is not yet fully standardized. In this study we compared the efficacy of Pentoxifylline as compared to placebo. Materials and methods: 75 patients suffering from oral submucous fibrosis were randomly divided into two groups A and B. Group A patients received placebo, while Group B patients received 400 mg. Pentoxifylline for a period of 7 months. Treatment outcome was evaluated on the basis of improvement in symptom and sign scores. Student's 't' test was applied for comparing the results. Results: The improvement in total (i.e. symptoms + sign) score was 25% in group A and 49.15% in group B. This difference was found to be statistically significant. ($p < 0.05$) Conclusion: Treatment regimen of group B was more effective. No significant side effects were seen. A follow up study is required to assess long term outcome of this therapy.

Keywords: Oral submucous fibrosis - pentoxifylline - therapy

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Introduction

Oral submucous fibrosis (OSMF) is a chronic disease of the oral cavity which is common in patients chewing areca nut in the Indian subcontinent. It is characterized by the progressive build up of constricting bands of collagen in the cheeks and adjacent structures of the mouth which can severely restrict mouth opening and tongue movement as well as cause problems with speech and swallowing (Aziz, 2009; Fedorowicz et al, 2008).

Treatment options include iron and multivitamin supplements including lycopene - an extract of tomato, and a range of medicines (e.g. intralesional injection of steroids, hyaluronidase, human placenta extracts, chemotrypsin, 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. There are few controlled clinical trials in this area. Keeping in view the widespread prevalence of the disease in this region Mehrotra 08) and the lack of effective therapy, a comparative study was planned to assess the usefulness of Pentoxifylline versus placebo in the treatment of OSMF. Rajendran et al had earlier tried Pentoxifylline as treatment of patients with OSMF and reported good results. (Rajendran, 2006)

Materials and Methods

FThe study was conducted in patients attending the Otolaryngology outpatients department of S.R.N. Hospital, MLN Medical College, Allahabad, India with clinically diagnosed OSMF. Institutional ethical committee approval was obtained prior to starting the trial. The study was undertaken with the understanding and written consent of each subject and according to ethical principles, including the World Medical Association declaration of Helsinki. Patients, 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 had a histopathologically confirmed diagnosis of OSMF were included. Patients who refused scalpel biopsy as well as those with medical problems or dental appliances such as orthodontic or other fixed prostheses that could potentially interfere with the examination were not included in the study. 75 patients were enrolled in the study and out of these 62 patients came for regular follow-up and took regular treatment, thus 13 patients were excluded. All patients were examined with a conventional overhead examination light and then divided randomly into the drug or placebo groups.

Neither the patients nor the investigators knew which group they were allocated to i.e. patients who received the drug as compared to those who received placebo. Both the interventions were similar in and packaging and taste. The dosage regimen was also the same.

The demographic information of each patient, including age, gender and history of tobacco use was

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obtained. 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 including pre-treatment biopsy for confirmation of histological diagnosis were done. Biopsy samples, obtained under local anesthesia using the standard scalpel technique, were analyzed by two pathologists who were blinded to the clinical data.

Clinical assessment of maximal jaw opening was carried out monthly and outcomes were expressed by measured change in the inter-incisor distance. We had used the scoring system reported in our previous report in which each symptom/sign and histopathological grade of OSMF was given a particular score, before and after completion of therapy, as per the working proforma (Singh et al, 2010). Improvement was noted on the basis of these scores. Group A (n=30) patients were given placebo (multivitamin) therapy. Group B (n=32) patients were given Tab. Pentoxifylline 400 mg for a period of 7 months. The drug Pentoxifylline was administered as an inductive regime for the initial 30 days at a reduced dosage of 2 tablets daily and then the dose was hiked to 3 tablets daily for 6 more months as per previous studies (Rajendran et al, 2006).

Efforts were made to encourage habit cessation in patients and to monitor the progress in cessation of habit as the trial progressed when the patients came for follow-up. The response to treatment was evaluated monthly on the following basis:

Primary outcomes included: (1) Resumption of normal eating, chewing and speech. (2) Change or improvement in maximal jaw opening, measured by the interincisal distance.

Secondary outcomes included (1) Discomfort or pain as a result of the intervention: patient-assessment using a validated pain scale. (2) Hospital admission: length of stay. (3) Quality of life and patient satisfaction as assessed by a validated questionnaire.

Subjective improvement in symptoms: 1) Burning sensation in mouth; 2) Repeated vesiculation/ ulceration in oral mucosa; 3) Resumption of normal eating, chewing and speech.

Objective improvement in signs: 1) Trismus; 2) Ankyloglossia; 3) Vesicles/ Ulcers; 4) Fibrosis.

Clinical follow-up of all the patients was carried out for 18 months 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.

Results

Some 37% of the patients suffering from OSMF were in the third decade (followed by second decade (22%) and fourth decade (20%) of life. The youngest patient seen was 16 years and the oldest was 70 years old. The mean age of presentation was 35.1 years. Male to female ratio was 4.29: 1. Most of the males were in the age group of 21 - 30 years, whereas majority of females were between 41-50 years. 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).

Table 1. Characteristics of the Patients

Characteristic		No (%)
Median age (minimal-maximal)		54 (23-73)
Sex	Male	35 (63.6%)
	Female	20 (36.4%)
Symptoms	Rectal hemorrhage	31 (56.4%)
	Pain	2 (3.6%)
	Constipation	3 (5.5%)
	RH + pain	15 (27.3%)
	RH + constipation	4 (7.3%)
Tumor localization according to anal verge	1-5 cm	15 (27.3%)
	5-10 cm	19 (34.5%)
	10-15 cm	7 (12.7%)
	>15 cm	1 (1.8%)
	Unknown	13 (23.8%)
ECOG performance status	0	20 (36.4%)
	1	28 (50.9%)
	2	7 (12.7%)
Surgical procedure	LAR	37 (67.3%)
	APR	16 (29.1%)
Histological differentiation	Well	18 (32.7%)
	Intermediate	24 (43.6%)
	Poor	2 (3.6%)
	Unknown	11 (20.0%)
Tumor status	T1	1 (1.8%)
	T2	7 (12.7%)
	T3	44 (80.0%)
	T4	3 (5.5%)
Nodal status	N1	34 (61.8%)
	N2	21 (38.2%)
TNM stage	III A	10 (18.2%)
	III B	24 (43.6%)
	III C	21 (38.2%)

LAR, low anterior resection; APR, abdominoperineal resection

Fibrosis was present in all patients. The soft palate was involved in 100% of patients followed by buccal mucosa in 90% (unilateral-10%, bilateral-80%), retromolar trigone in 90% (unilateral-28%, bilateral/L-62%), anterior faucial pillar in 80% (unilateral-16%, bilateral-62%), floor of mouth in 24 %, and tongue in 20% of patients.

The participants did not complain of any discomfort or pain due to therapy, nor were any of them admitted to the hospital. The participants' compliance was 62/75 (82%) for drug treatment.

The total symptoms score improved by 38.2% in group A and 85.8% in group B. Burning sensation in the mouth upon consumption of spicy or hot foods improved by 39.4% in group A, and 86.6% in group B. Repeated vesicles and ulcer formation in the mouth improved by 35.5% in group A, and 84.1 % in group B. The total sign score improved by 19.9 % in group A and 38.5% in group B. Mean improvement in score per patient was 1.4 and 2.1 in groups A and group B respectively. Trismus improved by 15.4% in group A and 35.7% in group B. Mean improvement in trismus in terms of millimeters was calculated in each group separately and was found to be

Table 2. Adverse Events Due to Treatment (according to CTCAE v3.0)

Side effects	Grade	
	I / II	III / IV
Leukopenia	14 (25.5%)	5 (9.1%)
Anemia	8 (14.5%)	2 (3.6%)
Thrombocytopenia	0	0
Infection	2 (3.6%)	0
Febrile neutropenia	0	2 (3.6%)
Neuropathy	45 (81.0%)	5 (9.1%)
Renal toxicity	1 (1.8%)	2 (3.6%)
Hepatotoxicity	6 (15.8%)	3 (5.5%)
Diarrhea	14 (25.5%)	12 (21.8%)

6 mm and 10 mm in-group A and group B respectively. Ankyloglossia improved by 22.6% in group A and 39.3% in group B and presence of fibrotic bands improved by 19.5% in group A, 32.9% in group B.

The improvement in total (i.e. symptom + sign) score was 25% in-group A and 49.2% in group B. The difference between the group A and group B proved to be statistically significant ($p< 0.05$) in total (i.e. symptom + sign) score. 16/32 patients in the treatment group came for long term (18months) follow-up and revealed stable progress with none of them going back to chewing habits.

No local or systemic side effect was found in treatment group A. However, side effects were observed in group B. Most frequent were dyspepsia and nausea, which were observed in 24% of the patients. Bloating and flatus were the complaints of 18% patients and headache, vomiting, anxiety and tremors were observed in 2% of patients. These symptoms were relatively mild in nature, lasted for 1-2 weeks and settled on their own without cessation of drug or requiring medication.

Discussion

Treatment for OSMF remains a challenge. It is said that once the disease has developed, there is neither regression nor any effective treatment. Consequently, improved oral opening and relief of symptoms form the main objectives of treatment. In general, the management modalities can be categorized into conservative and surgical (Aziz, 2009; Jiang et al., 2009). A recent study from the author's group recommended the use of combination of triamcinolone acetonide (10 mg/ml)/ hyaluronidase (1500 IU) at 15 days interval for 22 weeks. This was more convenient to the patients because it required only weekly injections, less daily dosing, better patients compliance, and improvement in the sign score (trismus, ankyloglossia, vesicle formation and fibrosis) (Singh et al., 2010). On the other hand, an earlier Cochrane review on this subject concluded that the paucity of data and poor methodological quality of studies indicated a lack of reliable evidence for the effectiveness of any specific interventions for the management of this disease (Fedorowicz et al., 2008)

Pathologically, occlusive blood vessels because of the deposition of collagen fibres (Rajendran et al., 2006) and hypercoagulability of blood (Phatak, 1984) restrict nutrients and therapeutic substances from reaching the affected tissue, which may be one of the reasons for the unsatisfactory therapeutic effect of drug treatment of OSMF.

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 (Samlaska et al., 1994). 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 (Pineda et al., 2007). Rawlins et al reported that Pentoxifylline has a direct effect on inhibiting burn scar fibroblasts (Rawlins et al., 2006). Haddad et al 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 (Haddad et al., 2005). It has been postulated that Pentoxifylline may be a valuable drug for reducing burn scar contractures. Extrapolating this finding, the drug has been also been used to alleviate the symptoms in patients with OSMF, 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 and are therefore minimized by dose reduction.

Rajendren et al (2006)used Pentoxifylline as an adjunct in OSMF treatment and after 7 months trial and 6-12 months follow-up, the patients showed improvement in signs and symptoms as compared to controls. They reported significant improvement in patients in the experimental group as compared to patients in the control group ($P<0.01$). There was improvement in objective criteria of mouth opening, tongue protrusion, and relief from perioral fibrotic bands and subjective symptoms of intolerance to spices, burning sensation of mouth, tinnitus, difficulty in swallowing and difficulty in speech with Pentoxifylline as compared to placebo. All patients also received local heat therapy and underwent forceful mouth stretching exercises (Rajendren et al, 2006). Fedorowicz et al reviewed the trial and found the following lacunae; since the patients also received local heat therapy and underwent forceful mouth stretching exercises, it could not be deciphered if the improvement was due to the drug or to associated heat therapy and stretching exercises. In addition the authors did not mention any assessment of improvement in the range of

jaw movement. Changes in severity of burning sensation were reported, but these parameters were poorly defined not based on any recognized and validated pain scale and the reports did not provide any reliable information on how the assessments were made or how the scores were calculated. They assesses "relief from difficulty of speech" and whilst it included data for both intervention groups the report contained no information on how these speech evaluations were carried out. Secondary outcomes, like) Postoperative discomfort or pain. Hospital stay and quality of life were not measured. Randomization of patients, allocation concealment and blinding of patients/ investigators as well as intention to treat were unclear. (Fedorowicz et al., 2008)

Our study corroborated these findings and strict criteria were applied for blinding the observers as well as the subjects. It is postulated that the improvement in the signs and symptoms even in the placebo group could possibly be due to the cessation of habits as part of counseling of the patients during follow-up visits as well as additional multivitamins.

Preliminary results show a statistically significant improvement in the group of patients receiving Pentoxyfylline. However, before its use can be recommended, a multi-institutional double-blind prospective study for assessment of effects of Pentoxyfylline treatment is recommended.

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