Original Article

DOI: 10.7860/JCDR/2013/7085.3849

Dentistry Section

Spirulina and Pentoxyfilline – A Novel Approach for Treatment of Oral Submucous Fibrosis

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ABSTRACT

Background: Oral submucous fibrosis is a habit associated insidious precancerous condition of the oral cavity commonly found in Asian countries. Many treatment modalities have been attempted in treating the condition apart from steroids which have been the main stay. Hence the present study was designed to assess the efficacy of spirulina and pentoxyfilline and also to compare them in oral submucous fibrosis.

Material and Methods: Fourty Patients with clinico-histological diagnosis of oral sub mucous fibrosis were selected and divided into two groups with 20 in each group by simple randomization method. Group I received Pentoxyfilline and Group II Spirulina for period of 3 months. The efficacy was assessed by parameters like mouth opening, burning sensation and tongue protrusion using vernier caliper, visual analog scale and a metric scale respectively along with the side effects.

Results: Student's t-test was applied to obtain the results. Both Pentoxyfilline and Spirulina groups showed statistically significant results (p=0.000) in all the three parameters namely mouth opening, burning sensation and tongue protrusion. On comparing both the drugs statistically insignificant results were obtained for mouth opening (p=0.35) and tongue protrusion (p=0.25) but statistically significant difference was seen in subjective parameter i.e burning sensation (p=0.04). Side effects like bloating of stomach, nausea and gastritis were noted in the pentoxyfilline group in contrast to Spirulina group.

Conclusion: Newer drugs Pentoxyfilline and Spirulina showed promising results in treatment of Oral sub mucous fibrosis. Spirulina was used for the first time for treatment of Oral submucous fibrosis (OSMF) and it proved to be superior than pentoxyfilline as no side effects were observed. Also it was superior in reducing burning sensation and hence can be advised in OSMF patients suffering from severe subjective symptoms.

Keywords: Pentoxyfilline, Spirulina, Oral submucous fibrosis (OSMF), Potentially malignant disorder

INTRODUCTION

Oral sub mucous fibrosis (OSMF) is a potentially malignant disorder affecting the oral cavity and was first described by Schwartz in 1952 [1,2]. Of all the collagen disorders affecting the oral mucosa, OSMF is of great interest because of the various signs and symptoms associated [3]. Etiology and pathogenesis of this entity is not well known, although several hypotheses have been put forward such as areca nut chewing, green chilli, nutritional deficiency, genetic susceptibility, autoimmunity and collagen disorders [4-8].

The fact of having a multifactorial etiopathogenesis has made it a complex disease with no single standard mode of treatment [6-8]. Moreover the nature of the disease to progress even after treatment exists. Conventional treatment includes steroids, enzymes like hyaluronidase, trypsin, chymotrypsin and placental extracts advocated intralesionally along with oral drugs like carotenoids, Alpha lipoic acid (ALA), lycopene, vitamins, microelements and tea pigments have been advocated [7,9]. Surgical modalities of Oral sub mucous fibrosis remains controversial [10].

Physiotherapeutic treatment includes interpositioning of tongue spatulas between teeth and adding a new spatula every 5 to10 days [11,12]. Newer modalities like gamma Interferon [13], Pentoxyfilline, and tea pigments also have been found to be beneficial [14].

Pentoxyfilline, a methylxanthine derivative known to have vasodialating, anti inflammatory and immune modulation properties is found to be effective in few pilot studies of OSMF [15]. Spirulina, a blue green algae is rich in carotenoids and other micronutrients which have chemo preventive potential was used to test the clinical activity in reversing the oral precancerous lesions like leukoplakia [16].

Hence the present study was conducted to evaluate the efficacy of these two newer modalities pentoxyfilline and spirulina and also to compare their efficacy in Oral sub mucous fibrosis.

MATERIAL AND METHODS

The study was conducted in the Department of Oral Medicine and Radiology and the study group consisted of 40 patients of OSMF. Initial sample size composed of 50 patients with 25 in each group were included by simple random sampling method, however 10 patients were excluded at the end of the study due to inconsistent reporting and drop outs due to personal reasons. Finally 40 patients with 20 patients in pentoxyfilline and 20 patients in spirulina group were present at the completion of the study. All the procedures were in accordance with the ethical standards of declaration of Helsinki. Pentoxyfilline group received oral pentoxyfilline 400mg twice daily for period of 4 months and spirulina group received oral spirulina capsules 0.5gm twice daily for a period of 4 months along with mouth opening excersises for 20 min daily. Inclusion criteria was clinically and histopathologically diagnosed cases of OSMF and exclusion criteria were subjects with hypertension, diabetes mellitus, anaemic stomatitis, radiation fibrosis, scleroderma, immunosuppressive diseases, peptic ulcer bleeding disorders, cardiac disorders. Patients who have received treatment of oral sub mucous fibrosis before and those who were hypersensitivity to the study drugs were all excluded.

The subject was comfortably seated in dental chair and an elaborated history was noted which included chewing habits, type, form, brand used, frequency and duration of chewing, site of keeping the quid, duration and whether the quid was swallowed or spit out.

A thorough clinical examination was performed and recorded in the proforma. The objective and subjective variables namely, burning sensation, measurement of maximum mouth opening and

maximum tongue movements were recorded as follows:

Burning sensation on taking food was recorded on visual analogous scale(VAS) [17]. Mouth opening was noted by measuring the distance between the maxillary and mandibular central incisors on maximum opening using vernier caliper in millimeters (NAYASA JAPAN) [17]. Tongue protrusion was recorded by measuring the distance between tip of tongue and mandibular central incisors on maximum protrusion using a metal graded scale [15].

All the subjects were clinically graded according to Ranganathan K et al., as [18].

Group 1: Only symptoms, with no demonstrable restriction of mouth opening. **Group 2:** Limited mouth opening, 20mm and above. **Group 3:** Mouth opening less than 20mm. **Group 4:** OSMF advanced with limited mouth opening with precancerous or cancerous changes seen throughout the mucosa.

Punch biopsy was performed for histopathological confirmation after routine blood investigations on initial visit for each subject. On histopathological confirmation the subjects were randomly distributed to either of the groups. The subjects were divided into 2 groups with 20 patients in pentoxyfilline group and 20 patients in spirulina group. Pentoxyfilline group received oral pentoxyfilline 400mg twice daily for period of 3 months as advised by Rajendran et al., [15]. The spirulina group received oral spirulina capsules 0.5gm twice daily for a period of 3 months. This dosage was followed by Mathew et al., in treating oral leukoplakia [16]. Mouth opening exercises for 20min daily was also advised

Recalls were done for 15 days for both groups for a period of 3 months. Patients were advised to report immediately if they experience adverse effects.

Each patient was reviewed up to 5 consecutive visits at specific intervals and the data obtained was assessed for burning sensation, mouth opening and tongue protrusion. Pre and post -treatment comparison was done individually for each group and also among the groups.

RESULTS

The results were obtained by applying descriptive statistics, two tailed paired t-test and unpaired t-test.

The descriptive statistics of the study are illustrated in [Table/Fig-1]. Predominant male predliction (100%) was noted in group 1, whereas Group 2 consisted of one female patient (05%) and 9 male patients (95%). The mean age in Group 1 was 31.95 years and Group 2 was 31.6 years.

Pre and post-treatment evaluation in Group 1 “pentoxyfilline group”.

Mouth opening – mean value in pre treatment was 2.63mm and post-treatment was 2.93mm with the p-value of <0.001. Burning sensation - the mean value before the treatment was 6.05 and after treatment was 1.60 with the p-value was p <0.001. Tongue protrusion – pre treatment mean value was 1.82mm and post-treatment was 2mm with p-value of <0.001 [Table/Fig-2].

Pre and post-treatment evaluation in Group 2 “spirulina group”.

Mouth opening – mean value in pre treatment was 3.38mm and post-treatment was 3.73mm with the p-value of <0.001. Burning sensation - the mean value before the treatment was 6.95 and after treatment was 1.55 with the p-value was p <0.001. Tongue protrusion – pre treatment mean value was 1.93 and post-treatment was 2.09 with p-value of <0.001 [Table/Fig-2].

Comparison of Group 1 and Group 2 (Pentoxyfilline group and Spirulina group).

The mean of pre and post-treatment difference with standard deviation was calculated for all three parameters as shown in [Table/Fig-3]. Statistically significant (p = 0.04) result was observed only in burning sensation.

	Group 1	Group 2
Sample size	20	20
Gender	M=20	M=19 F=1
Age (mean value) years	31.95	31.6

[Table/Fig-1]: Represents sex and age difference between two groups

Group		Mean	SD	p-value
1	Mouth opening pre-treatment	2.63	0.78	0.00*
	Mouth opening post-treatment	2.93	0.77	
	Burning sensation pre-treatment	6.05	1.67	0.00*
	Burning sensation post-treatment	1.60	0.94	
	Tongue protrusion pre-treatment	1.82	0.45	0.00*
	Tongue protrusion post-treatment	2.00	0.42	
2	Mouth opening pre-treatment	3.38	1.29	0.00*
	Mouth opening post-treatment	3.73	1.26	
	Burning sensation pre-treatment	6.95	1.00	0.00*
	Burning sensation post-treatment	1.55	1.32	
	Tongue protrusion pre-treatment	1.93	0.44	0.00*
	Tongue post-treatment	2.09	0.41	

[Table/Fig-2]: Significant difference in mean pre-treatment and post treatment test scores for all the parameters among Group 1 and 2

	Group	Mean	SD	p-value
Mouth opening	1	0.30	0.0725	0.35
	2	0.36	0.27	
Burning sensation	1	4.45	1.191	0.04*
	2	5.40	1.353	
Tongue protrusion	1	0.18	0.089	0.25
	2	0.16	0.1095	

[Table/Fig-3]: Comparison of ‘Mean’ between G roup 1 and 2 for all three parameters. p-value<0.05 - statistically significant

DISCUSSION

OSMF is a complex precancerous condition of oral cavity. It is considered as major oral health problem with high degree of malignant potential [19,20]. Lack of a specific treatment modality pose a greater challenge in treating this condition.

Conventional therapies include intralesional injections of corticosteroids, placental extracts, hyaluronidase, physiotherapy and surgery [21]. These present therapies have inconsistent outcome with several side effects. Corticosteroids are immunosuppressive agents which are believed to decrease inflammation and collagen formation, thereby reducing the symptoms and resulting in increased mouth opening. They have been found to produce side effects like severe adrenal insufficiency, edema, osteonecrosis, osteoporosis, myopathies, peptic ulcers, hypocalemia, euphoria, psychosis, ocular complications and myasthenia [22].

Levamisole modifies both cellular and humoral immunity. The anti-inflammatory effects and its ability to modulate inflammatory cytokines reduces burning sensation but several side effects have been noted nausea, vomiting, diarrhoea, mouth sores, loss of appetite, stomach pain, change in taste and smell, muscle aches, fatigue, dizziness, headache and skin rash [23].

Interferon gamma (IFN-gamma) has anti-fibrotic effect. When given in a dosage of 50 µg (0.25 ml) intralesionally twice a week over 8 weeks, recombinant human INF-γ showed improvement in both mouth opening and burning sensation. Adverse effects included aching muscles, diarrhoea, fever and chills, headache, nausea or vomiting, skin rash, unusual tiredness [24].

Immune milk contains an anti-inflammatory component that may suppress the inflammatory reaction and modulate cytokine

production. Headache, flu-like symptoms and myalgia are few of the known side effects of the drugs [25].

Hence the need for a newer treatment modality is on the rise with various researches being conducted on pentoxyfilline, green tea, aloe vera, lasers and stem cells [26-28].

The present study was designed to assess the efficacy of spirulina and pentoxyfilline in OSMF and compare these two new modalities. The age range of the study subjects was 31 - 32 years. OSMF was predominantly seen in males which are similar to findings by Haider et al, Chaturvedi et al., [29,30]. This can be attributed to the fact that males are more prone to habit of chewing areca nuts, betel nut and guthka. Pentoxyfilline is a methylxanthine derivative which has vasodialating property. It decreases inflammatory mediators, increase production of PGE2 and PGI2 by vascular epithelium and maintain cellular integrity and homeostasis after acute injury. These features are pertinent in treating intermittent claudication caused due to arterial occlusion and hence found to be effective in treating OSMF [15,31]. It was administered for three months which showed statistically highly significant results. However, Rajendran et al., found significant results with mouth opening and burning sensation although results with tongue protrusion were not significant [15].

Spirulina is blue green algae with rich natural source of proteins, carotenoids and other micronutrients [16,28]. It has been primarily assessed in treating leukoplakia with promising results. The chemopreventive capacity to reverse precancerous lesions of spirulina is attributed to the antioxidant property with high amount of beta carotene and superoxide dismutase [16,32,33]. The present study is the first of its kind in which spirulina has been tried in oral submucous fibrosis. Highly significant results were obtained with all three parameters namely burning sensation, mouth opening and tongue protrusion. When efficacy was compared between the two drugs, statistically insignificant results were found for mouth opening and tongue protrusion which means both the drugs were equally efficient. However the difference for burning sensation was statistically significant. Spirulina performed better with patient showing more satisfaction as the subjective symptom was reduced. It also showed no side effects which was similar to the study by Mathew et al., [16,33]. Pentoxyfilline is known to cause side effects with gastrointestinal tract like dyspepsia, nausea, vomiting and central nervous problems like dizziness, head ache, anxiety, confusion and tremors [15,34]. In our study two patients had bloating of stomach, nausea and gastritis.

However inconsistent reporting of patients, small sample size and no long term follow up were limitations of our study. Although multicentric studies should be done for more standardization and better outcome.

CONCLUSION

Treatment of Oral sub mucous has been a challenge ever since its discovery. Newer drugs have been constantly evolving as treatment for this complex disease. Our study was one such attempt where spirulina was used for the first time in Oral sub mucous fibrosis, which showed proximity results with least side effects as compared to pentoxyfilline. However both drugs are found to be effective in the management of Oral sub mucous fibrosis.

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FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Jul 26, 2013**
Date of Peer Review: **Sep 22, 2013**
Date of Acceptance: **Nov 03, 2013**
Date of Publishing: **Dec 15, 2013**