

Efficacy of Garlic in Conjunction with Pentoxifylline in the Management of Oral Submucous Fibrosis - A Cross-Sectional Pilot Study

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Abstract

Introduction and Objectives: Oral submucous fibrosis (OSMF) is a chronic, progressive, and irreversible disease of the oral mucosa. Though numerous modalities have been tried but all are palliative and have no curative value. Pentoxifylline possessing vasorelaxive and antifibrotic properties believed to potentiate the anti-inflammatory, anti-oxidant and immune modulating properties of garlic. So, the present a cross-sectional pilot study was undertaken to evaluate the efficacy of Garlic in conjunction with pentoxifylline in the management of OSMF.

Methods: The study consisted of 10 OSMF patients. Pentoxifylline (400 mg) was administered thrice daily along with garlic pearls, 2 pearls; thrice daily. Drugs were administered systemically after food for a duration of 2 months. Patients were evaluated every 15 days for the assessment of clinical parameters, i.e. Burning sensation, reduction in mouth opening, tongue protrusion and cheek flexibility. Pre and post treatment study parameters were measured and compared. The improvement was assessed at the end of the study.

Results: All the patients were males with the mean age of 26.04 years. Patients exhibited a mean reduction of 95.68% in burning sensation and an increment of 5.37 mm in mouth opening. The cheek flexibility and tongue protrusion also showed significant improvements in the study groups. All the patients showed significant ($p > 0.001$) improvement in SOD levels following treatment.

Conclusion: Overall assessment of the all clinico-biochemical parameters showed a significant improvement. Thus, choice of such therapy is beneficial, affordable, easily available and most importantly a non-invasive treatment modality for OSMF.

Keywords: *Oral Submucous Fibrosis; Pentoxifylline; Garlic*

Introduction

Oral submucous fibrosis (OSMF) is a chronic debilitating and a well-recognized potentially malignant condition of the oral and oropharyngeal mucosa with initial inflammation followed by pro-

gressive fibrosis of the underlying connective tissues. The morbidity and mortality rates are associated with significant masticatory dysfunction and oral discomfort as well as an increased risk of developing squamous cell carcinoma. This condition was first described in ancient Indian medical manuscripts by Sushruta in

around 600 B.C. describing it as "Vidari", the symptoms of which resemble symptomatology of OSMF. It was first described in the modern literature by Schwartz in 1952. Joshi first described the condition in India and suggested the name oral submucous fibrosis. The prevalence of OSMF in India varies between 0.03% and 3.2% according to various epidemiological studies. The strongest evidence regarding the etiology of OSMF associates it with the habit of areca nut chewing and is prevalent in the population of South Asian, South-East Asian and among South Asian immigrants in Western countries as the etiology of the disease is not singlet, many treatment modalities have been tried and validated in the literature. Steroids, antioxidants, enzymes like collagenase, chymotrypsin, and hyaluronidase, placental extracts, Interferon- γ , lycopene, peripheral vasodilators levamisole, immune milk, physiotherapy and surgical modalities have been cited in the literature, yet they have been palliative and proven to be of minimal benefit. Although intralesional steroids have shown improvement, but are associated with significant discomfort, pain and infection at the injection site and reduction in mouth opening over a period of follow-up as rebound fibrosis is often precipitated as mechanical and chemical injuries in the oral mucosa heal by fibrosis.

Pentoxifylline is a tri-substituted methyl xanthine derivative, with several biological actions. It has been tried in various clinical trials and proved beneficial in the management of OSMF. Various hypotheses have been put forward regarding the mechanism of action of pentoxifylline and its cellular and molecular effects, based on human and animal studies. This includes hemorheological, anti-fibrinolytic, immune modulation, anti-tumour necrosis factor (TNF) effects along with its effects on endothelial cells and adhesion molecules. Since OSMF is antecedent by various inflammatory and immunological factors which progressively lead to fibrosis of sub mucosa, so the property of pentoxifylline that may be far-reaching in the management of OSMF, is perhaps its effect on the fibroblast and its role in fibrinolysis, immunomodulation and inhibition of TNF- α .

There are hundreds of herbs used throughout the world that are beneficial in various disorders. By using herbs in their complete form, the body's healing process utilizes a balance of ingredients provided by nature. One such therapeutic modality is garlic, possessing immunomodulatory, antioxidant, chemo preventive, anti-inflammatory and vasorelaxive properties. All these properties of garlic make it a promising approach in the treatment of OSMF.

Aim of the Study

The aim of the current study is to evaluate the efficacy of Pentoxifylline with Garlic in the management of OSMF.

Materials and Methods

Study setting: The present clinical study was conducted in the Department of Oral Medicine and Radiology.

The study was carried out for a duration of 2 months from June to August 2017.

The study protocol was approved by the Institution Review Board of the same.

Study subjects: A total of 10 clinically diagnosed OSMF patients of either sex were included who were willing to quit gutka/areca-nut chewing habit and who have not undergone any treatment for OSMF in the past 2 months, whereas any patients with coexisting systemic illness and who have taken treatment in any form were excluded.

Written informed consent was obtained from each patient at the outset of the study and all the patients were explained about the need and design of the study.

Before commencing the treatment, patients were counselled regarding habit cessation of areca nut, gutka, pan masala chewing.

Inclusion criteria

A total of 10 clinically diagnosed OSMF patients of age and gender matched were included and OSMF patients who had not undergone any treatment for past 2 months.

Exclusion criteria

Patients with coexisting systemic illness and who have taken treatment in any form were excluded.

Study parameters

A detailed proforma was used to record the patients data. Clinical parameters, i.e. burning sensation, mouth opening, tongue protrusion and cheek flexibility served as a guideline to measure the improvement in signs and symptoms. The Visual Analogue Scale (VAS) of 1-10 was used to measure the intensity of burning sensation.

Mouth opening was measured in mm, using Vernier calliper from the mesioincisal angle of upper central incisor to lower cen-

tral incisor, In edentulous patients, the inter ridge (alveolar) distance along the midline was measured. Three measurements were taken consecutively and the average value calculated and recorded. In This study we followed Khanna J.N. and Andrade N.N. (1995) clinically the patients were categorized into five groups"

- Stage I: > 40 mm
- Stage II: 31 - 40 mm
- Stage III: 21 - 30 mm
- Stage IV: 11 - 20 mm
- Stage V: < 10 mm

Tongue protrusion

The patient was asked to protrude the tongue as much as possible at maximum mouth opening. The distance between the mesioincisal angle of lower left central incisors and the tip of the tongue was measured. If the incisors were absent the crest of the

lower alveolar ridge along the mid line was taken as the point of reference. Three measurements were taken consecutively and the average value calculated and recorded.

Cheek flexibility

A line joining the tragus of the ear and the angle of the mouth was drawn. An imaginary perpendicular line from the outer canthus of the ipsilateral eye was extended downwards to intersect the ala tragus line and the point of intersection was marked as a reference point. This was done on the right and left sides. The distance between the two reference points was recorded at normal centric occlusion at C1. The patient asked to blow the cheeks fully with the lips closed and the distance between the two reference points was recorded as C2. The difference between the two values C1-C2 was used as a measure of cheek flexibility. Three measurements were taken consecutively and the average value calculated and recorded.

SL. NO	Patient name	Age	Sex	Type	Frequency	Duration	Diagnosis
1	Chandaraiah	36	M	Pan with khaini and lime	2 times	1 year	OSMF stage II
2	Sigtula	42	M	Tobacco with betelnut and lime	3 times	1 year	OSMF stage II
3	Vijaykumar	25	M	Pan with betelnut and lime	2 times	10 months	OSMF stage II
4	Gauramma	50	F	Pan with tobacco betelnut, lime	3 times	9 months	OSMF stage II
5	Riyas	30	M	Pan with khaini and lime	4 times	1 year	OSMF stage II
6	Harish	26	M	Pan with betelnut and lime	3 times	10 months	OSMF Stage I
7	Amarnath yadhav	23	M	Pan with khaini and lime	2 times	9 months	OSMF stage II
8	Javeed	28	M	Tobacco with betelnut and lime	3 times	10 months	OSMF Stage II
9	Narayanappa	45	M	Pan with tobacco betelnut lime	3 times	1 year	OSMF stage II
10	Saleem	25	M	Pan with khaini and lime	4 times	1 year	OSMF stage II

Table 1: Patient age, habit type frequency and duration and clinical staging of OSMF.

Burning sensation (0 - 10)		Mouth opening (44.25 mm)		Tongue protrusion (23.89 mm)		Cheek flexibility (9.17 mm)	
Pre	Post	Pre	Post	Pre	Post	Pre	Post
6	4	35.5 mm	36 mm	25 mm	25.5 mm	10 mm	10.03 mm
5	3	37.5 mm	38 mm	26.8 mm	27 mm	10.4 mm	10.6 mm
7	4	36.5 mm	37.5 mm	27 mm	27.03 mm	10.08 mm	11.00 mm
5	2	34.8 mm	35.2 mm	30 mm	30.03 mm	10.06 mm	10.08 mm
6	3	36 mm	36.9 mm	28.9 mm	29.02 mm	10.07 mm	10.09 mm
3	2	40 mm	40.09 mm	35 mm	35.3 mm	10.05 mm	10.07 mm
5	3	34 mm	35 mm	27.05 mm	27.09 mm	10.02 mm	10.05 mm
6	3	37.5 mm	38 mm	26.09 mm	27.02 mm	10.05 mm	10.08 mm
5	2	34.7 mm	35.2 mm	29 mm	29.02 mm	10.08 mm	10.09 mm
6	2	35 mm	35.8 mm	27 mm	27.04 mm	10.04 mm	10.06 mm

Table 2: Burning sensation, mouth opening, tongue protrusion and cheek flexibility pre and post operative changes.

Demographic Characteristics of Study Patients			
Variables	Categories	n	%
Gender	Males	9	90%
	Females	1	10%
Age Group	≤ 30 yrs	6	60%
	≥ 30 yrs	4	40%
Age	Mean and SD	33.0	22.9
	Range	23 - 50	

Table 3: Demographic age, gender distribution.

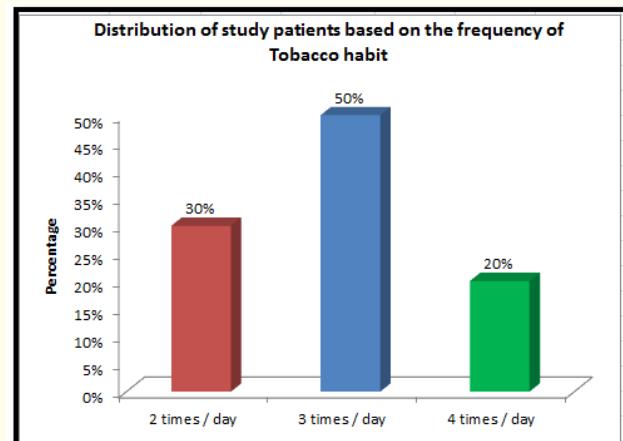
Comparison of mean values of different study parameters between three pre and post treatment period using student paired t Test								
Variables	Time	N	Mean	SD	S.E.M	Mean Diff	t	P -Value
Burning sensation	Pre Rx	10	5.40	1.08	0.34	2.60	9.750	<0.001*
	Post Rx	10	2.80	0.79	0.25			
Mouth opening	Pre Rx	10	36.15	1.79	0.57	-0.70	-9.209	<0.001*
	Post Rx	10	36.85	1.83	0.58			
Tongue protrusion	Pre Rx	10	28.11	2.87	0.91	-0.27	-2.235	0.04*
	Post Rx	10	28.38	2.69	0.85			
Cheek flexibility	Pre Rx	10	10.05	0.03	0.01	-0.11	-1.247	0.24
	Post Rx	10	10.16	0.30	0.09			

Table 4: Comparison of mean values of different study parameters between pre and post treatment period using student paired t test.

traoral examination. Cheek flexibility and tongue protrusion has reduced markedly. All the patients were divided into various clinical stages based on mouth opening.

Results

The study consisted a total of 10 clinically diagnosed OSMF patients. All patients were males with a mean age of 24.46 ± 4.97 years (Range 18 - 38 years). All the patients had the habit of chewing gutka or areca nut in one or the other form. In the present study, patients reported primarily with the chief complaint of burning sensation encountered with hot and spicy food and reduced mouth opening whereas it was an adventitious finding in few patients. Blanching of the buccal mucosa was ubiquitous in all the patients accompanied by palpable fibrous bands over buccal mucosa on in-

**Graph 1:** Distribution of study patients based on the frequency of tobacco habit.

Graph 2: Distribution of study patients based on the frequency of tobacco habit.

Figure 2: Burning sensation 6 to 2 vas score.

Graph 3: Comparison of mean values of different study parameters between the pre and post treatment period.

Figure 3: Tongue protrusion - 25 to 25.5 mm.

Pre and post treatment pics

Figure 1: Burning sensation 7 to 4 vas score.

Figure 5: Cheek flexibility - 10 to 10.5 mm.

Discussion

Oral submucous fibrosis is a well-recognized potentially malignant condition of the oral cavity associated with betel quid (BQ), areca nut and smokeless tobacco chewing habits. Epidemiological data and intervention studies suggest that areca nut is the main predisposing factor for OSMF. Other etiological factors suggested are chilies, lime, tobacco, nutritional deficiencies such as iron and zinc, immunological disorders, and collagen disorders [1-3].

The pathogenesis of the disease is not well established, but is believed to be multifactorial. Various mechanisms [1,4,5] suggested include:

- Clonal selection of fibroblasts with a high amount of collagen production during long-term exposure to areca nut,
- Stabilization of collagen structure by catechin and tannins from BQ,
- Production of stable collagen (type I) by OSMF fibroblasts,
- Increase in collagen cross-linking by upregulation of lysyl oxidase,
- Deficient collagen phagocytosis, and
- Micronutrient and vitamin deficiencies.

The molecular events in the causation of OSMF takes place through collagen production pathway and collagen degradation pathway. Synthesis of collagen is influenced by variety of mediators including growth factors, hormones, cytokines and lymphokines. Transforming growth factor-beta (TGF- β) plays a major role, it causes deposition of extracellular matrix (ECM) by increasing the synthesis of matrix proteins such as collagen and decreasing its degradation by stimulating various inhibitory mechanisms [1,6,7]. OSMF is regarded as a collagen metabolic disorder with an overall increased collagen production and decreased collagen degradation resulting in increased collagen deposition in the oral tissues, and fibrosis due to alkaloid exposure [3,8,9].

As the etiology of the disease is not singlet, many treatment modalities have been tried and validated in the literature. Steroids, antioxidants, enzymes like collagenase, chymotrypsin and hyaluronidase, placental extracts, Interferon- γ , lycopene, peripheral vasodilators levamisole, immune milk, physiotherapy and surgical modalities have been cited in the literature, yet they have been palliative and proven to be of minimal benefit. Although intralesional steroids have shown improvement, but are associated with significant discomfort, pain and infection at the injection site and reduction in mouth opening over a

period of follow-up as rebound fibrosis is often precipitated as mechanical and chemical injuries in the oral mucosa heal by fibrosis.

Since OSMF is antecedent by various inflammatory and immunological factors which progressively lead to fibrosis of submucosa, so the property of pentoxifylline that may be far-reaching in the management of OSMF, is perhaps its effect on the fibroblast and its role in fibrinolysis, immunomodulation and inhibition of TNF- α [1,4,6,9].

There are hundreds of herbs used throughout the world that are beneficial in various disorders. By using herbs in their complete form, the body's healing process utilizes a balance of ingredients provided by nature. One such therapeutic modality is garlic, possessing immunomodulatory, antioxidant, chemo preventive, anti-inflammatory and vasorelaxive properties. All these properties of garlic make it a promising approach in the treatment of OSMF [9-11].

A study of total 10 oral submucous fibrosis patients was conducted in Department of oral medicine and radiology Bangalore institute of dental sciences and hospital. Patients reported to our department with a chief complaint of burning sensation and reduced mouth opening. Overall intraoral examination was carried out but more specifically in context to

- Mouth opening
- Burning sensation
- Tongue protrusion and movements and blanching
- Presence and absence of bands and cheek flexibility.

These patients were included as a part of study and were treated using pentoxifylline (tablet trendline 400mg thrice per day) and garlic pearls (2 garlic pearls thrice per day) for 2 months of duration.

In our study showed Burning sensation and mouth opening improvement was more significant with p value < 0.001, Tongue protrusion of p value 0.04 and cheek flexibility of p value 0.24nic were less significant.

Less Sample size and daily consumption of garlic which might have interfered with the results were the limitations of the study which can be overcome in future by further studies involving larger sample size and longer periods of follow-ups.

Conclusion

Improvement in the clinical parameters obtained in our patients is a promising finding towards establishing the use of Pentoxifylline in conjunction with Garlic as one of the treatment modalities for the management of OSMF. Thus, choice of such therapy is beneficial, affordable, easily available and most importantly a non-invasive treatment modality to those affected with OSMF.

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