Research Article

EVALUATION OF EFFICACY OF CURCUMIN IN THE MANAGEMENT OF ORAL SUBMUCOUS FIBROSIS – A RANDOMISED CLINICAL TRIAL

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ABSTRACT

INTRODUCTION: The Current Conventional treatment methods of Oral Submucous Fibrosis often prove to be inadequate. Hence, alternative therapy should be explored.

AIM AND OBJECTIVE: To evaluate the efficacy of curcumin in the management of oral submucous fibrosis based on clinical parameters and on serum and salivary markers of oxidative stress.

STUDY DESIGN: A randomized, interventional study.

MATERIALS & METHODS: Twenty patients with clinically and histologically proven oral submucous fibrosis were selected for the study and were randomly divided into two groups. The first group was treated by oral administration of Curcumin capsule (400 mg) twice daily for 3 months and the second group was given both oral administration of Curcumin capsule (400 mg) twice daily and topical application of curcumin oral gel thrice daily for 3 months. Improvement of burning sensation and interincisal distance were evaluated. Serum and salivary samples were collected to measure the levels of MDA and FRAP before and after intervention.

RESULTS: Burning sensation significantly improved in both the groups. The mean increase in interincisal distance was 2.60mm and 2.40mm respectively in group I & II which were statistically significant. In both groups serum and saliva, Ferric Reducing Antioxidant property (FRAP) were found increased, while MDA levels were decreased after the intake of curcumin.

CONCLUSION: There was significant improvement clinically and biochemically after the intervention in group I and II but there was no significant difference between the groups which indicate that the topical curcumin has not showed any added advantage in group II patients.

KEY WORDS : Anti oxidant, Curcumin, Oral submucous fibrosis, Pre cancerous lesion.

INTRODUCTION

Oral submucous fibrosis is a chronic, most common premalignant condition affecting the oral mucosa which was first described by **Schwartz**^[1] 1952. **Pindborg** (**1966**)^[2] defined OSMF as, "an insidious, chronic disease affecting any part of the oral cavity and sometimes the pharynx. Although occasionally preceded by and/or associated with vesicle formation, it is always associated with juxta-epithelial inflammatory reaction followed by fibroelastic change of the lamina propria, with epithelial atrophy leading to stiffness of the oral mucosa and causing trismus and inability to eat".

The prevalence rates of OSF in India range from 0.2 to 0.5%. Interestingly, the prevalence and the incidence rates are high in South India where the incidence of oral cancer is also high. This condition carries a high relative risk for malignant conversion (7.6%) even after the cessation of the habit^[3].

The etiology of OSF is multifactorial: Areca nut (Areca catechu) chewing, the use of chillies (*Capsicum annum* and *Capsicum frutescens*), nutritional deficiencies, autoimmunity, and genetic susceptibility have been thought to play an aetiological role in OSF.

Over the past, various medical and surgical treatment modalities have been attempted for the management of OSMF, but with no promising and consistant results.

All over the world the medicinal plants are being used to treat various diseases as folk medicine. Curcuma longa is one among them having a wide range of pharmacological application..

Turmeric (the common name for *Curcuma longa*) is an Indian spice derived from the rhizomes of a plant and has a long history of usage in Ayurvedic medicine to treat inflammatory conditions. *C. longa* is a perennial member of the Zingiberaceae family and is cultivated in India and other parts of Southeast Asia^[4].

In age-old Indian medicine, it is extensively used for the treatment of sprains and swelling caused by injury, to dispel worms, strengthen the body, and dissolve gallstones, and for menstrual irregularities and arthritis^[4]. The traditional medicine in china uses c. *longa* L. in diseases associated with abdominal pains.

The major constituent, curcumin (Diferuloylmethane) is the most important fraction of *C. longa* L. Natural curcumin, isolated from curcuma longa, contains curcumin I (Diferuloylmethane), as well as curcumin II (6%) and curcumin III $(0.3\%)^{[5]}$.

Turmeric has shown anti inflammatory, anti oxidant, and fibrinolytic actions in OSF patients, and they may reverse precancerous changes in oral sub mucous fibrosis. Its oncoprevention can be speculated to be due to its protection against DNA damage. It has been shown to favorably alter the serum glutathione and super oxide dismutase activity and reduce lipid per oxidation in patients of OSF^[6].

Over the last years there has been increasing interest in turmeric and its medicinal properties. It is being envisaged that incorporation of turmeric in the form of capsules and topical application would greatly enhance treatment of OSF.

Hence the present study was undertaken to evaluate the efficacy of curcumin in the management of oral submucous fibrosis based on clinical parameters and on serum and salivary markers of oxidative stress.

MATERIALS AND METHOD

Study design

A randomized, interventional study was conducted in twenty patients with clinically and histologically proven oral submucous fibrosis in the time period of 3 months(August – November 2016).

Subjects

The present study was planned and conducted during the period of August – November 2016 in the Department of Oral Medicine and Radiology, Rajah Muthiah Dental College and Hospital, Annamalai University, Annamalai Nagar.

Study consisted of twenty subjects with clinical features of OSF and later confirmed histopathologically. The subjects included in the study were randomly divided into two groups, of 10 patients each.

Patients selected for the study were explained in detail about the condition affecting their oral cavity and about the treatment procedures. After approval from institutional ethical committee a formal informed written consent was obtained from all of them. Only those patients who complied with the treatment and were regular for the follow- up were included in the study. **Inclusion & exclusion criteria**

Patients who were diagnosed with stage 1, stage 2, stage 3 and stage 4 OSMF by clinical parameters with a positive history of chewing areca nut or one of its commercial preparations were included in the study. Patients with chronic illness, bleeding disorders, cholelithiasis, pregnancy, any kind of allergy and who have received treatment for OSMF in the past 2 months were excluded from this study.

PROCEDURE

A complete history and thorough clinical examination with emphasis on adverse habits was done. A thorough examination on findings like site of involvement, distribution of the vertical bands was done and recorded. Inter incisal distance of the mouth opening was recorded using a vernier caliper. Burning sensation was recorded using VAS scale. Patients were given counselling to discontinue the habit and oral prophylaxis was done to all patients to remove extrinsic stains.

After establishing the clinical and histopathological diagnosis, serum and salivary samples were collected to measure the levels of MDA and FRAP before curcumin administration. 20 clinically diagnosed Oral submucous fibrosis patients were randomly divided into two groups, 10 patients in each group. Patients in Group A were given only systemic curcumin therapy, curcumin 400mg capsule twice daily for a period of 3 months. Patients in Group B were given curcumin 400mg capsule twice daily and also with topical application of curcumin oral gel thrice daily for a period of 3 months. No side effects such as nausea, stomach upsets, diarrhoea were reported in any patient.

Follow up

All patients were recalled for a period of 90days, with consecutive visits at 15^{th} day, 30^{th} day, 45^{th} day, 60^{th} day, 75^{th} day and 90^{th} day. In all the visits changes in burning sensation, and mouth opening were evaluated and recorded. On 90^{th} day serum and salivary samples were collected to measure the changes in the levels of MDA and FRAP after curcumin administration.

Statistical method used for the present study:

The baseline profile between the groups was compared using Students t test, Chi- square test and Fisher's exact test. The clinical improvement on a particular regimen (within the same group) before and after treatment was analyzed using paired t test. Comparison between the two groups was done using Student t test.

Statistical software:

The statistical software namely SYSTAT 12 was used for analysis of the data and Microsoft word and Excel have been used to generate graphs, tables.

RESULTS

Table 1: Mean and SD of outcome variables for patients administered curcumin systemically

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	PRE		POST		Paired T test	P value	P value
	Mean	SD	Mean	SD			
Mouth opening (in mm)	29.650	8.293	32.250	9.193	-6.00	< 0.001	
Burning sensation (VAS)	6.10	2.132	1.50	1.080	8.493	< 0.001	
FRAP in serum (µmol/l)	.2843	0.033	.3211	.0391	-12.860	< 0.001	
FRAP in saliva (µmol/l)	.2135	0.088	.2745	.0789	-3.329	.009	
MDA in serum (µmol/l)	3.060	.6213	1.687	.592	6.719	< 0.001	
MDA in saliva (µmol/l)	1.375	.645	1.125	.574	1.809	.104	

 Table 2: Mean and SD of outcome variables for patients administered curcumin both

 systemically and topically

	PRE		POST		Paired T test	P value
	Mean	SD	Mean	SD		
Mouth opening (in	21.800	10.81	24.20	11.66	-6.000	< 0.001
mm)						
Burning sensation	5.00	1.88	2.00	2.00	7.606	< 0.001
(VAS)						
FRAP in serum	.299	.103	.347	.103	-3.841	.004
(µmol/l)						
FRAP in saliva	.126	.064	.290	.243	1.910	.089
(µmol/l)						
MDA in serum	3.12	.589	1.93	.854	6.047	< 0.001
(µmol/l)						
MDA in saliva	2.24	1.069	1.37	.768	4.578	.001
(µmol/l)						

Table 3: Mean	difference	between	pre and	post	intervention	outcome	variables	between
the groups								

	GROUP I		GROUP II		STUDENT T	P VALUE	
	Mean	SD	Mean Changes	SD	TEST VALUE		
Mouth opening (in mm)	-2.60	1.37	-2.40	1.26	339	.738	
Burning sensation (VAS)	4.60	1.712	3.00	1.24	2.38	.028	
FRAP in serum (µmol/l)	0368	.009	0481	.039	.885	.388	
FRAP in saliva (µmol/l)	0613	.058	163	.270	1.168	.258	
MDA in serum (µmol/l)	1.373	.646	1.187	.620	.654	.521	
MDA in saliva (µmol/l)	.250	.437	.874	.604	-2.64	.016	

The mean age of study participants in Group I was 43.20 years with 60% of patients being male whereas in Group II the mean age was 48.60 years with 50% of male patients. 60% of patients in Group I had areca nut chewing habit for a duration of less than or equal to 12 years whereas in Group II it was 70%.

Before intervention the clinical parameters like site of involvement, mouth opening, burning sensation, FRAP in serum and MDA in serum were similar in both the groups but FRAP in saliva and MDA in saliva were not similar.

In Group I the mean changes between pre and post intervention mouth opening, burning sensation, FRAP in serum, FRAP in saliva, MDA in serum and MDA in saliva were -2.60, 4.60, .0368, -.0613, 1.373, .250 respectively. In Group II the mean changes between pre and post intervention mouth opening, burning sensation, FRAP in serum, FRAP in saliva, MDA in serum and MDA in saliva were -2.40, 3.00, -.0481, -.163, 1.187, .874 respectively. Since before intervention there is a significant variation existing between group I and II with respect to FRAP in saliva and MDA in saliva, the comparison of post intervention FRAP and MDA level in saliva was done using ANCOVA test after controlling the pre test influence.

CASE 1: TREATED WITH TURMERIC CAPSULE

PRE





POST

CASE 2: TREATED WITH TURMERIC CAPSULE AND TURMERIC ORAL GEL

PRE





POST

All the study participants tolerated the treatment regimen well, none of the participants reported any side effects. All observed parameters improved with both the interventions. Clinically and biochemically there was no significant difference in both the groups after intervention. But improvement with respect to burning sensation was found to be slightly better in Group I (turmeric capsule) than in Group II (both turmeric capsule and turmeric oral gel).

DISCUSSION

In our study out of 20 cases 60% were male and 40% were female. This male predominance was in accordance with various studies. A male predominance was shown by **Sinor et al**^[7], in India. This male preponderance was due to high usage of gutkha and other related products because of easy availability all over, where as females abstain due to their health and esthetic awareness, leading to a high male to female ratio.

The mean age of patients in group I and group II was 43.20 and 48.60 respectively. This finding is similar to that of **Pindborg et al**^[2], who reported the OSF cases in age group of 40-49 years. But our finding was in contrary with other studies. **Sirsat** and **Khanolkar**^[8] reported that majority of OSF cases belonged to the age group of 20-40 years. Also **Shah** and **Sharma**^[9] from delhi in their study reported the majority of cases from 21-40 years of age.

In our study group all the patients were found to have indulged in the habit of chewing areca nut or commercial areca nut products. Recent epidemiological studies in India point to the habit of chewing areca nut as the major etiological factor of OSF. The findings in the present study, therefore, support the role of areca nut chewing as the single most important factor in the etiology of OSF.

Arecoline present in areca nut induces fibroblastic proliferation and increased collagen formation. Copper content of areca nut up regulates enzyme lysyl oxidase which is responsible for collagen synthesis.

United States Food and Drug Administration has approved curcumin as being GRAS (generally recognized as safe). Turmeric is non toxic and is extremely safe even at higher doses^[10]. This is in agreement with our study since none of the participants in our study reported any side effects.

The mean changes between pre and post intervention mouth opening in Group I and Group II was -2.60 and -2.40 respectively. In both the groups the mouth opening significantly improved after intervention but there was no significant difference between the groups. The clinical and statistically significant increase in mouth opening brought about by curcumin can be attributed to its anti-inflammatory and fibrinolytic properties. **Bhide**^[11] and **Hastak**^[12] in two different studies also achieved an increase in mouth opening when turmeric was used in treatment of OSF patients.

Our study showed significant improvement of burning sensation with mean changes between pre and post intervention 4.60 and 3.00 in Group I and Group II respectively. These findings are similar to those reported by **Das DA et al, 2010**^[10]. Burning sensation was found significantally better in Group I patients than in Group II.

One of the objectives of this study was also to evaluate the oxidative stress level in OSMF patients before and after intervention. Serum and salivary Ferric Reducing Antioxidant property (FRAP) were found increased, while MDA levels decreased in OSF patients after intake of curcumin, as compared to pre-treatment levels. Our results suggest that curcumin significantly increases the local and systemic antioxidant status while it decreases the lipid peroxidation. This

suggests that the anti-cancer effects of curcumin are mediated through pro-oxidant and anti-oxidant pathways.

In our study, the topical usage of curcumin has not shown any significant added advantage in the treatment. This could be evaluated more elaborately.

The patients were extremely pleased with this therapy as they experienced complete relief from clinical symptoms and substantial improvement in mouth opening. This enabled the patients to resume normal functions of mastication and added to their general feeling of well being.

The strengths of our study include randomization of both the groups having similar clinical profile.

The limitations of our study include small sample size, data from a single centre and lack of histopathological confirmation of improvement at the end of the study period.

In addition to its anti-inflammatory and anti-fibrolytic properties, curcumin possesses excellent anti oxidant properties. Thus the choice of curcumin therapy is beneficial, costeffective and a non-invasive treatment modality. Extensive studies involving larger population and longer follow-up may be required to establish the use of curcumin as a definitive treatment modality in treating OSF. It is evident from our study that curcumin holds good promise in the treatment of OSF.

Further studies emphasizing the following hypothesis are warranted:

- ➤ To evaluate the efficacy of different forms of topical curcumin preparation in the management of OSMF with emphasis on enhanced local drug delivery.
- ➤ To Compare the efficacy of curcumin with intra lesional steroid combined with Hyaluronidase injection in the management of oral submucous fibrosis.

CONCLUSION

There was a significant relief from burning sensation, intolerance to spicy foods and improved mouth opening in all the patients. Improvement seen clinically and biochemically in patients those with mild and moderate forms of the disease is an encouraging finding towards the use of curcumin as a therapeutic agent. The regression of the disease process by use of curcumin may indicate its future use as a potential chemo-preventive agent.

REFRENCES

- 1. Schwartz J. Atrophia idiopathica tropica mucosa oris. 11th Int Dent Congress.London 1952.
- 2. Pindborg J, Sirsat S. Oral submucous fibrosis. Oral Surgery, Oral Medicine, And Oral Pathology 1966;22(6):764.
- 3. Rajalalitha P & Valli S. Molecular pathogenesis of oral submucous fibrosis- a collagen metabolic disorder. J Oral Pathol Med 2005; 34: 321-8.
- 4. Ammon HP, Wahl MA. Pharmacology of Curcuma longa. Planta Med 1991;57:1-7.
- 5. Sun, You-min, Wang, 2004 "Theoritical study on the antioxidant activity of Curcumin." Chinese journal of chemistry, 22;827-830.
- 6. Sharma, R.A., McLelland, H.R., Hill, K.A. et al, 2001. "Pharmacodynamic and pharmacokinetic study of oral curcuma extract in patients with colorectal cancer". *Clin. Cancer Res.*, 7 (7), 1894–1900.
- 7. Sinor PN, Gupta PC, Murti PR, et al. A case control study of oral submucous fibrosis with special reference to the etiologic role of areca nut. J Oral Pathol Med 1990;19:94-8.
- 8. Sirsat SM, Khanolkar VR. Submucous Fibrosis of the Palate and Pillars of the Fauces. Indian J Med Sci 1962;16:188-97.

- 9. Shah N, Sharma PP. 1998 "Role of chewing and smoking habits in the etiology of oral submucous fibrosis A case control study". J Oral Pathol Med 27:475-9.
- 10. Das DA, Balan A, SreeLatha KT. Comparative study of the efficacy of curcumin and turmeric oil as chemopreventive agents in oral submucous fibrosis: a clinical and histopatholgical evaluation. JIAOMR. 2010;22:88e92.
- 11. Bhide SV et al 1994. "clinical studies on turmeric treatment of precancerous oral lesions." Proceedings of XVI International cancer congress abstracts, 351.
- 12. Hastak K et al (1997). "Effect of turmeric oil and turmeric oleoresin on cytogenetic damage in patients suffering from OSF". cancer lett 24;116(2) 265-9.