Received: 20th January 2016 Accepted: 03rd April 2016 Conflict of Interest: None

Source of Support: Nil

Original Research

Doi: 10.2047/jioh-08-06-09

A Comparative Study of the Clinical Efficacy of Lycopene and Curcumin in the Treatment of Oral Submucous Fibrosis using Ultrasonography

Rajiv Kumar Chowdary Kopuri[1], Chitra Chakravarthy[2], Sanjay Sunder[3], Ravi S Patil[4], W Shivaraj[4], Gururaj Arakeri[4]

Contributors:

[1]Senior OMFS Resident, NIMHANS, Bangalore, Brundavan Dental Care, Guntur, Andhra Pradesh, India; [2]Head, Department of Oral and Maxillofacial Surgery, Navodaya Dental College and Hospital, Raichur, Karnataka, India; [3]Professor, Department of Oral and Maxillofacial Surgery, Navodaya Dental College and Hospital, Raichur, Karnataka, India; [4]Reader, Department of Oral and Maxillofacial Surgery, Navodaya Dental College and Hospital, Raichur, Karnataka, India.

Correspondence:

Dr. Kopuri RK. Brundavan Dental Care, 1st Lane Brundavan Gardens, Guntur - 522 007, Andhra Pradesh, India. Phone: +91-9985613333/8494913333. Email: rajiv.kopuri@gmail.com

How to cite the article:

Kopuri RK, Chakravarthy C, Sunder S, Patil RS, Shivraj W, Arakeri G. A comparative study of the clinical efficacy of lycopene and curcumin in the treatment of oral submucous fibrosis using ultrasonography. J Int Oral Health 2016;8(6):687-691.

Abstract:

Background: Oral submucous fibrosis (OSMF) is a chronic condition of the oral mucosa that has been largely reported among Indians and to lesser extent in other Asian people and other countries. There has been no satisfactory treatment for OSMF. The aim of this study is to measure the submucosal layer thickness using ultrasonography during the treatment of OSMF with lycopene and curcumin over a period of 3-month.

Materials and Methods: Based on inclusion and exclusion criteria, 30 study subjects were included in the study. The patients have signed an informed consent before the start of the study. Patients under Group A (n = 15) were given lycopene 8 mg/day in 2 divided doses prescribed for 3 months. Patients under Group B were given curcumin 800 mg/day in 2 divided doses prescribed for 3 months. A clinical examination was carried out at every recall visit and the findings compared with those at the beginning of the treatment. The results were analyzed with unpaired t-test, Chi-square test, and ANOVA test.

Results: At 3-month follow-up, all the patients in both groups showed significant improvement in mouth opening and severity of burning sensation and blanching. When measured using ultrasound, a decrease in the thickness of fibrous bands was noticed in all patients in Group A and Group B.

Conclusion: Lycopene is better when compared to curcumin in the treatment of OSMF, but studies with larger sample and long-term follow-up are needed for better understanding of curcumin in the treatment of OSMF.

Key Words: Curcumin, lycopene, oral submucous fibrosis, ultrasonography

Introduction

Oral submucous fibrosis (OSMF) is a chronic disease of insidious onset featuring the deposition of fibrous tissue in the submucous layer of the palate, fauces, cheek, lips, pharynx, and esophagus. The underlying muscles of mastication may be affected resulting in trismus and disability.[1] The etiology of OSMF appears to be obscure. A multifactorial origin has been suggested. Nutritional deficiency (deficiency of vitamins and iron), use of chilies, immunological processes, and betel nut chewing have been implicated, with a high incidence of the disease associated with consumption of betel quid (containing areca nut, tobacco, slaked lime, and other spices). A genetic predisposition has also been suggested in the development of OSMF, which explains why not all betel quid users develop the disease. The condition has been shown to be precancerous and carries a high relative risk for malignant transformation.[2] There is no widely accepted treatment till date. Most common treatment is with antioxidants. The mode of action of antioxidants involves stimulation of the immune system or direct action on the tumor cells. They are antimutagenic and antimitogenic and operate by the common mechanism of breaking the free radical chain reactions.[3] One such type of antioxidant is lycopene. It is a phytochemical, synthesized by plants (tomatoes) and microorganisms but not by animals. It is a potent anticarcinogenic and has demonstrated profound benefits in precancerous lesions such as leukoplakia.[4-6] Curcumin a polyphenol derived from the herbal remedy and dietary spice turmeric possesses wide-ranging anti-inflammatory and anticancer properties. It is not toxic to humans at doses up to 8000 mg/day. Topical application of curcumin has also been shown to inhibit chemical carcinogenesis of the skin.[7-9]

There are no studies till date to compare the efficacy of lycopene and curcumin in the treatment of OSMF. Hence, the present study was carried out to evaluate and compare the clinical efficacy of lycopene and curcumin in the treatment of OSMF using ultrasonography (USG).

Aim

The aim of this study is to measure the submucosal layer thickness using USG during the treatment of OSMF with lycopene and curcumin over a period of 3-month.

Study setting

The present prospective study was conducted in the Department of Oral and Maxillofacial Surgery, Navodaya Dental College and Hospital, Raichur, Karnataka, India.

Study subjects

The study group comprised 30 patients above age 15 who are already diagnosed with OSMF. Diagnosis criteria included history and presence of characteristic features such as burning sensation, intolerance to spicy food blanching, loss of elasticity of oral mucosa presence of fibrous bands, and restricted mouth opening. All cases were confirmed with USG as described by Rangaiah *et al.*[10]

Inclusion criteria

- Patients who are physically healthy and are well oriented in time place
- A positive history of chewing areca nut or one of its commercial preparations
- Clinical features of OSMF with burning sensation on eating spicy foods, difficulty in swallowing and chewing, blanching of oral mucosa, palpable fibrous bands, restricted mouth opening (20-30 mm).

Exclusion criteria

- Patients with chronic illness, hypertension, pregnancy, and any kind of allergy
- Patients with severely restricted mouth opening (<20 mm), immobility of the tongue, shrunken uvula, and ulcerations.

Materials and Methods

Sterile mouth mirrors, straight probes, scale, tweezers, tongue depressor, sterile gauze pieces, a pair of sterile gloves, and mouth mask. An ultrasound toshiba istyle (NEMIO XG) with a straight probe with frequency ranging between 7.5 and 10 Mhz.

Drugs used

Antoxidants: Capsules

1. Trade name: Lycored
   Contents: Lycopene (2000 mcg), zinc (7.5 mg), and selenium (35 mcg).
   Manufacturing company: Jagsonpal pharmaceuticals Ltd.
2. Trade name: Haridra
   Contents: Curcuma longa 400 mg.
   Manufacturing company: Himalaya herbal healthcare.

Methodology

The subjects were explained about the purpose of the study. History of the personal habits was recorded particularly burning sensation and mouth opening. Intraoral and extraoral clinical examination was carried out under artificial light. Following the establishment of the diagnosis, the patient was informed about the condition and its precancerous potential. The patient was then advised to discontinue the use of areca nut in all preparations. Each patient was then randomly categorized into one of the two groups.

Patients under Group A ($n = 15$) were given Lycored 8 mg/day in 2 divided doses was prescribed for 3 months. Patients under Group B were given Haridra 800 mg/day in 2 divided doses was prescribed for 3 months. Patients were evaluated every month during the treatment period of 3-month. A clinical examination was carried out at every recall visit and the findings compared with those at the beginning of the treatment.

Statistical analysis

Descriptive statistics such as mean, SD, and percentage were used to present the data. Comparison between two groups for continuous data was done using unpaired *t*-test and Chi-square test or Fisher's exact test for small sample for categorical data. A repeated measure of ANOVA test followed by Dunnett multiple comparisons test was used for comparison of follow-up with pre-operative. A $P < 0.05$ was considered as significant. Data analysis was done using SPSS v16.0.

Results

The average mouth opening between the groups before treatment was comparable. Post-treatment mouth opening improved significantly in Group A. The average improvement in

Table 1: Comparison of mouth opening between Group A and Group B.

Mouth opening	Group A	Group B	Mean difference	95% CI of difference	*t* value	*P* value
Pre-operative	24.26±1.53	26.07±2.66	1.80	0.18-3.42	2.27	*P*=0.03
1 months	24.93±1.33	26.53±2.64	1.60	0.03-3.16	2.09	*P*=0.05
2 months	26.93±1.33	27.4±2.72	0.47	−1.14-2.07	0.59	*P*=0.55
3 months	30.07±1.16	29±2.27	1.07	0.28-2.41	1.62	*P*=0.12

CI: Confidence interval

Table 2: Comparison of burning sensation between Group A and Group B.

Burning sensation	Group A			Group B			*P* value		
	Mild	Moderate	Severe	Mild	Moderate	Severe	Mild	Moderate	Severe
Pre-operative	0	11	4	0	13	2	1.0	0.65	0.65
1 months	0	15	0	0	13	2	1.0	0.48	0.48
2 months	6	9	0	2	15	0	0.21	0.21	1.0
3 months	8	7	0	13	15	0	0.11	0.22	1.0

mouth opening at the end of study in Group A was 6 mm, which was considered highly significant statistically ($P < 0.0001$) and evaluation on a monthly basis showed the changes to attain this high significance from the second month onward (Table 1 and 6). Group B patients showed an average improvement of 3 mm although some individual cases showed maximum improvements of 5 mm and 6 mm which was again considered highly significant statistically ($P < 0.001$) (Table 7). With inter-group comparison, Group A showed a better improvement in mouth opening but did not differ enough to be statistically significant ($P > 0.05$). Out of 15 patients under Group A, 11 presented with moderate pain and 4 with severe pain, whereas in Group B 13 presented with moderate pain and 2 with severe pain. With inter-group comparison, patients under Group B showed a better reduction in severity of burning sensation but did not differ enough to be statistically significant ($P > 0.05$) (Table 2). In the present study, blanching of oral mucosa was present in all the 100% (30) patients. Similar characteristic features such as diffuse blanching of the mucosa, occurrence of hyperpigmented areas were reported in various studies.[11] With inter-group comparison, patients under Group A showed a better improvement in reduction of fibrous bands but did not differ enough to be statistically significant ($P > 0.05$), whereas patients under Group B showed a better reduction of blanching of buccal mucosa but did not differ enough to be statistically significant ($P > 0.05$). (Tables 3 and 4)

Discussion

OSMF is a chronic condition of the oral mucosa that has been largely reported among Indians and to lesser extent in other Asian people and other countries. The prevalence in India ranges from 0.2% to 1.2%, with varying sex ratios.[12] Till date, the disease is one of the most poorly understood and unsatisfactorily treated. This is mainly due to the fact that the etiopathogenesis of the disease is not fully understood. Review of various studies leads to a conclusion that areca nut chewing is an important predisposing factor. Similar to oral cancer and most of its precursor lesions, OSMF is multifactorial.[13,14] Various methods tried to bring about relief from burning sensation, and to decrease fibrous bands, and improve mouth opening include intralesional injections of corticosteroids, placental extracts or hyaluronidase either alone or in combination,[15] intralesional injections of interferon-gamma,[16] micronutrient supplementation,[17] physiotherapy,[18] and surgical excision of fibrous bands followed by placement of split thickness skin graft, nasolabial flaps, fresh human placental grafts, pedicled buccal fat pad, oral stent made of acrylic, palatal island flap, or reconstruction using superficial temporal fascia flap and split thickness skin graft,[19-24] and surgical excision of the bands using Opus-5 diode laser. All patients in our study gave a positive history of areca nut chewing in the raw form as a quid or in a commercial preparation such as gutkha or pan masala, which was proved as a major causative agent for OSMF in the literature.[23] Epidemiologic studies have established the protective role of diets rich in fruits and vegetables with high intake of carotenoids in oral precancerous and cancerous conditions and reduced risk of same.[25] Very few studies although with micronutrients as a conservative mode of treatment in OSMF.[26] Extensive research within the past half century has indicated that curcumin (diferuloylmethane), a yellow pigment in curry powder, exhibits antioxidant, anti-inflammatory, and proapoptotic activities. The induction of reactive oxygen species (ROS) by curcumin may occur through its interaction with thioredoxin reductase, thus altering its activity to nicotinamide adenine dinucleotide phosphate oxidase, which could then lead to the production of ROS.[27] There have also been reports suggesting that curcumin quenches ROS production and thus acts as an antioxidant, while others have reported that curcumin quenches ROS production at low concentrations and induces ROS production at high concentrations. Lycopene a powerful antioxidant obtained from tomatoes has been shown to inhibit various types of cancers and have potent benefits in oral premalignant lesion.[28] Considering existing data, a newer antioxidant like curcumin with more potent properties was compared to lycopene using USG in the present study. All patients in the present study gave a history of areca nut chewing. This was also found to be true by Canniff, Harvey, and Harris in their article on the pathogenesis and management of OSMF back in 1986. The present study showed improvement in both the groups at the end of the study and we are able to establish the normal values of ultrasonographically measured submucosal thickness for the small subite of the Indian population. The study shows a clear association of decrease in submucosal thickness in OSMF patients during the treatment period with good significance when compared to drug response. (Table 5) There were improvements in both the groups, but significant improvements were observed in Group A. The carotenoid lycopene found in tomatoes offers a non-invasive treatment modality for OSMF due to its antiproliferative, anti-inflammatory, and antioxidant activity. A larger study with larger sample size and longer follow-up period is encouraged to get more accuracy in the efficacy of the antioxidants.

Table 3: Comparison of blanching between Group A and Group B.

Blanching	Group A		Group B		*P* value
	Present	Absent	Present	Absent	
Pre-operative	15	0	15	0	1.0
1 months	15	0	15	0	1.0
2 months	6	9	7	8	0.71
3 months	2	13	1	14	1.0

Table 4: Comparison of fibrous bands Group A and Group B.

Fibrous bands	Group A		Group B		*P* value
	Present	Absent	Present	Absent	
Pre-operative	15	0	15	0	1.0
1 months	15	0	15	0	1.0
2 months	5	10	9	6	0.13
3 months	1	14	4	11	0.33

Table 5: Comparison of submucosal layer thickness on USG between Group A and Group B (mean±SD).

USG	Group A	Group B	Mean difference	95% CI of difference	*t* value	*P* value
Pre-operative	1.33±0.25	1.39±0.17	0.053	−0.11-0.21	0.67	*P*=0.5
1 months	1.2±0.28	1.27±0.17	0.07	−0.11-0.24	0.78	*P*=0.44
2 months	0.97±0.18	1.11±0.21	0.13	−0.01-0.28	1.86	*P*=0.07
3 months	0.73±0.17	0.93±0.19	0.21	0.07-0.34	3.05	*P*=0.005

CI: Confidence interval, USG: Ultrasonography, SD: Standard deviation

Table 6: Clinical efficacy of Group A over follow-up for mouth opening.

Mouth opening	Group A
Pre-operative	24.26±1.53
1 months	24.93±1.33
2 months	26.93±1.33
3 months	30.07±1.16
F value	467.7
P value	*P*<0.0001
Mean difference (I-II)	0.67**
Mean difference (I-III)	2.67**
Mean difference (I-IV)	5.80**

Table 7: Clinical efficacy of Group B over follow-up for mouth opening.

Mouth opening	Group B
Pre-operative	26.07±2.66
1 months	26.53±2.64
2 months	27.4±2.72
3 months	29±2.27
F value	93.17
P value	*P*<0.0001
Mean difference (I-II)	0.47*
Mean difference (I-III)	1.33**
Mean difference (I-IV)	2.93**

Discontinuation of the habit alone as an intervention may have a significantly greater effect, in the OSMF patients.

Conclusion

Treatment of OSMF with lycopene and curcumin produced significant improvement in mouth opening and reduction in burning sensation. Lycopene has produced better improvement in mouth opening and reduction in fibrous bands than curcumin. Curcumin has produced better improvement in burning sensation and blanching. Overall, the better response was seen to lycopene, than to curcumin. Further research can be directed at evaluating the combined efficacy of lycopene and curcumin on the improvement of signs and symptoms in OSMF patients.

References

1. Cox SC, Walker DM. Oral submucous fibrosis. A review. Aust Dent J 1996;41(5):294-9.
2. Gupta S, Reddy MV, Harinath BC. Role of oxidative stress and antioxidants in aetiopathogenesis and management of oral submucous fibrosis. Indian J Clin Biochem 2004;19(1):138-41.
3. Gowda BB, Yathish TR, Sinhasan SP, Kumar NH, Somayaji P. The response of lycopene to oral submucous fibrosis-A carotenoid antioxidant: A clinicopathological study. J Clin Diagn Res 2011;5(3):36-41.
4. Selvam NP, Dayanand AA. Lycopene in the management of oral submucous fibrosis. Asian J Pharm Clin Res 2013;6(3):58-61.
5. Kumar A, Bagewadi A, Keluskar V, Singh M. Efficacy of lycopene in the management of oral submucous fibrosis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007;103(2):207-13.
6. Kitade Y, Watanabe S, Masaki T, Nishioka M, Nishino H. Inhibition of liver fibrosis in LEC rats by a carotenoid, lycopene, or a herbal medicine, Sho-saiko-to. Hepatol Res 2002;22(3):196-205.
7. Hastak K, Lubri N, Jakhi SD, More C, John A, Ghaisas SD, *et al.* Effect of turmeric oil and turmeric oleoresin on cytogenetic damage in patients suffering from oral submucous fibrosis. Cancer Lett 1997;116(2):265-9.
8. Deepa DA, Balan A, Shreelata KT. Comparative study of efficacy of curcumin and turmeric oil as chemo preventive agents in oral submucous fibrosis. A clinical and histological evaluation. JIAOMR 2010;22(2):88:92.
9. Zhang SS, Gong ZJ, Li WH, Wang X, Ling TY. Antifibrotic effect of curcumin in TGF-ß 1-induced myofibroblasts from human oral mucosa. Asian Pac J Cancer Prev 2012;13(1):289-94.
10. Rangaiah P, Annigeri RG, Lingappa A. Transcutaneous ultrasonographic assessment of oral submucous fibrosis: A preliminary study. Int J Oral med Sci 2010;9(7):137-47.
11. Pindborg JJ, Sirsat SM. Oral submucous fibrosis. Oral Surg Oral Med Oral Pathol 1966;22(6):764-79.
12. Rajalalitha P, Vali S. Molecular pathogenesis of oral submucous fibrosis – A collagen metabolic disorder. J Oral Pathol Med 2005;34(6):321-8.
13. Murti PR, Bhonsle RB, Gupta PC, Daftary DK, Pindborg JJ, Metha FS. Etiology of oral submucous fibrosis with special reference to the role of areca nut chewing. J Oral Pathol Med 1995;24(4):145-52.
14. Canniff JP, Harvey W, Harris M. Oral submucous fibrosis: Its pathogenesis and management. Br Dent J 1986;160(2):429-34.
15. Kakar PK, Puri RK, Venkatachalam VP. Oral submucous fibrosis – Treatment with hyalase. J Laryngol Otol 1985;99(1):57-9.
16. Haque MF, Meghji S, Nazir R, Harris M. Interferon gamma (IFN-gamma) may reverse oral submucous fibrosis. J Oral Pathol Med 2001;30(1):12-21.
17. Maher R, Aga P, Johnson NW, Sankaranarayanan R, Warnakulasuriya S. Evaluation of multiple micronutrient supplementation in the management of oral submucous fibrosis in Karachi, Pakistan. Nutr Cancer 1997;27(1):41-7.

18. Gupta DS, Gupta MK, Golhar BL. Oral submucous fibrosis – A clinical study and management by physiofibrolysis (MWD). J Indian Dent Assoc 1980;52(1):375-8.
19. Kavarana NM, Bhathena HM. Surgery for severe trismus in submucous fibrosis. Br J Plast Surg 1987;40(4):407-9.
20. Gupta D, Sharma SC. Oral submucous fibrosis – A new treatment regimen. J Oral Maxillofac Surg 1988;46(10):830-3.
21. Yeh CJ. Application of the buccal fat pad to the surgical treatment of oral submucous fibrosis. Int J Oral Maxillofac Surg 1996;25(2):130-3.
22. Le PV, Gornitsky M, Domanowski G. Oral stent as treatment adjunct for oral submucous fibrosis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1996;81(2):148-50.
23. Khanna JN, Andrade NN. Oral submucous fibrosis: A new concept in surgical management. Report of 100 cases. Int J Oral Maxillofac Surg 1995;24(6):433-9.
24. Mokal NJ, Raje RS, Ranade SV, Prasad JS, Thatte RL. Release of oral submucous fibrosis and reconstruction using superficial temporal fascia flap and split skin graft – A new technique. Br J Plast Surg 2005;58(8):1055-60.
25. Fang J, Lu J, Holmgren A. Thioredoxin reductase is irreversibly modified by curcumin: A novel molecular mechanism for its anticancer activity. J Biol Chem 2005;280(26):25284-90.
26. Borle RM, Borle SR. Management of oral submucous fibrosis: A conservative approach. J Oral Maxillofac Surg 1991;49(8):788-91.
27. Mishra S, Kapoor N, Mubarak Ali A, Pardhasaradhi BV, Kumari AL, Khar A, *et al.* Differential apoptotic and redox regulatory activities of curcumin and its derivatives. Free Radic Biol Med 2005;38(10):1353-60.
28. Singh M, Krishanappa R, Bagewadi A, Keluskar V. Efficacy of oral lycopene in the treatment of oral leukoplakia. Oral Oncol 2004;40(6):591-6.