

CURCUMIN AS A CURE; COMPARISON OF THE EFFICACY OF SYSTEMIC AND TOPICAL ADMINISTRATION OF CURCUMIN IN ORAL SUBMUCOUS FIBROSIS PATIENTS: A CROSS-SECTIONAL STUDY

¹Dr. Ankit Dhimole, ^{2*}Dr. Anil Kumar Nagarajappa, ³Dr. Sreedevi Reddy, ⁴Dr. Neha Bhasin, ⁴Dr. Neha Dwivedi and ⁵Mr. Rajeev Tiwari

¹PG student, Department of Oral Medicine and Radiology, Hitkarini Dental College and Hospital, Jabalpur (MP), 482005.

²Professor and HOD, Department of Oral Medicine and Radiology, Hitkarini Dental College and Hospital, Jabalpur (MP), 482005.

³Professor, Department of Oral Medicine and Radiology, Hitkarini Dental College and Hospital, Jabalpur (MP), 482005.

⁴MDS, Oral Medicine and Radiology, Hitkarini Dental College and Hospital, Jabalpur (MP), 482005.

⁵R and D, Sanat Products Ltd. New Delhi, India.

Article Received on
15 March 2017,
Revised on 05 April 2017,
Accepted on 26 April 2017
DOI: 10.20959/wjpr20175-8428

*Corresponding Author

**Dr. Anil Kumar
Nagarajappa**

Professor and HOD,
Department of Oral
Medicine and Radiology,
Hitkarini Dental College and
Hospital, Jabalpur (MP),
482005.

ABSTRACT

Background: Previously designated as a premalignant condition oral submucous fibrosis is a chronic insidious disease affecting the oral cavity now comes under the heading of potentially malignant disorders (WHO 2005). Oral submucous fibrosis has shown its higher prevalence in south Asian population due to the heavy consumption of areca nut in this area dominating over the rest of the world. Curcumin is an active component of turmeric which is widely used as a spice for cooking. Curcumin being highly potent anti-inflammatory, antioxidant and anti-cancer agent holds great potential in the world of research medicine. **Methods:** 45 healthy adult subjects were randomly divided into 3 groups of 15 each based on the treatment they received. Group I was administered commercially available curcumin tablets Group II was administered topical application of turmeric, Group III was

administered a multivitamin group of drugs. **Results:** The study

revealed significant decrease in burning sensation after 6 months of therapy in groups receiving systemic and topical application of curcumin. Also, significant improvement in mouth opening with patients receiving therapy with systemic curcumin. **Conclusion:** The present study substantiated that systemic therapy of curcumin is best in improving clinical signs and symptoms of the disease.

KEYWORDS: Oral cancer; Oral mucosa; Submucous Fibrosis; Tobacco; Curcumin.

INTRODUCTION

Oral submucous fibrosis (OSMF) has been described 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 a juxta-epithelial inflammatory reaction followed by a fibro-elastic change of the lamina propria, with epithelial atrophy leading to stiffness of the oral mucosa and causing trismus and inability to eat.”^[1] Almost 600 million betel nut consumers are spread across the globe, with a hot spot throughout the Western Pacific basin and South East Asia. This makes betel the fourth most-consumed drug after nicotine, ethanol, and caffeine.^[2] The use and dependence on areca nut in the form of so called pan-masala / Gutkha is rapidly increasing especially among youth in India.^[3] This could be because of the widespread branding and promotion of such products in Indian market. What the masses don't realize is that this poses a huge threat on modern society which can be afflicted by OSMF or even oral cancer.^[2] Main aspects of OSMF include burning sensation inside the oral cavity after during consumption of hot and spicy food, Increased salivary function, Xerostomia and blanching of oral mucosa indicating fibrosis. Later on, the mucosa turns leathery and loses its elasticity with marked presence of vertical fibrous bands initiating restriction of mouth opening. Eventually, OSMF can cause problems in swallowing, hindrances of speech and hearing and in few patients even defective gustatory sensation.^[3]

Many treatment modalities in current practice for OSMF are circumstantial and most of the studies which tested various therapies lacked good design and planning. Hence, need of a good research and awareness still pertains to clinicians as well as patients. Curcumin, 1, 7-bis (4-hydroxy-3-methoxyphenol)-1, 6-heptadiene-3, 5-dione, is an active substance extracted from *Curcuma Longa L.* rhizome. It is economical, has good availability with almost nil side effects; used as an ingredient in kitchen and house hold remedy since ages. Curcumin has some important biological properties such as its role in reducing inflammation, its ability to

remove reactive oxygen species and cancer prevention. All these properties add-up as an advantage for treating potentially malignant conditions particularly OSMF. Recently, many studies have reported curcumin's role in reduction of fibrosis caused by various harmful stimuli. Key function of curcumin is it induces cell cycle arrest in myofibroblasts. Myofibroblast persistence is a dominating factor in fibrotic diseases like OSMF.^[4]

MATERIALS AND METHODS

Study design: The present clinical research was planned and designed in the department of Oral Medicine and Radiology, Hitkarini Dental College and Hospital, Jabalpur, Madhya Pradesh. The study was approved by the Institutional ethical committee. All the subjects participated in the study were recruited from subjects attending outpatient department of Oral Medicine and Radiology, Hitkarini Dental College and Hospital. A pre-enrolment screening questionnaire was used to record the history regarding the subject's complaints. A detailed case history was recorded in a specially designed proforma for the study and thorough clinical examination was performed.

Inclusion and Exclusion criteria: Patients without any previous treatment history of OSMF in past 3 months and who are willing to quit gutkha, arecanut and/or tobacco chewing habit and ready to attend regular follow ups were included in the study. OSMF patients with coexisting systemic illness or in association with other Pre-malignant lesions and malignancy were excluded.

Subjects: Patients were diagnosed with oral submucous fibrosis through examination of clinical features like reduced mouth opening, vertical palpable bands on buccal mucosae, burning sensation, reduced cheek flexibility and limited tongue protrusion. 45 healthy adult subjects were randomly divided into 3 groups of 15 each based on the treatment they received.

Methodology: Group I was administered commercially available Turmix tablets containing 300mg curcumin and 5 mg piperine (manufactured by Sanat products, Delhi, India) twice daily through oral administration after food for 3 months. Group II was administered topical application of turmeric, Heal plus gel (Manufactured by Sanat products, Delhi, India) containing 10mg extract of curcuma long which was massaged over the buccal and labial mucosa for 5 minutes by the patient after having food three times a day. Group III was

administered a multivitamin group of drugs: SM fibro manufactured by Warren Dental private Ltd.

Follow up: A follow up at 15 days for a period of 3 months followed by every 1 month for a total of 6 months was carried out for the patients in each group. The following clinical parameters were assessed during follow up:

1. **Burning sensation:** using Baker wong VAS (Visual analog) scale; patient was asked to choose a reading in between 0-10 and accordingly severity of burning sensation was assessed. Reading 0 meant absence of burning sensation while readings ranging between 1-3 revealed; mild symptoms, 4-6; moderate symptoms, 7-10; severe symptoms.
2. **Mouth opening (LAI DR):**^[5] Inter-incisal mouth opening was assessed by asking the patients to open their mouth wide enough and patients were grouped according to the clinical staging criteria: Stage I : >35 mm, Stage II: Between 30 mm and 35 mm, Stage III: Between 20 mm and 30 mm, Stage IV: < 20 mm.
3. **Cheek flexibility (Bailoor DN and Nagesh KS):**^[5] CF = V1-V2, Two points measured between V2 = was marked at one third the distance from the angle of the mouth over the line between the tragus of ear and angle of the mouth. V1 = the subject was then asked to blow his cheeks fully and the distance measured between the two points marked on the cheek.
4. **Tongue protrusion (Bailoor DN and Nagesh KS):**^[5] Mesio incisal angle of upper central incisor to the tip of the tongue when maximally extended with mouth wide open.

Statistical Analysis: Burning sensation on VAS were compared using Person's chi-square test. Data for mouth opening, cheek flexibility and tongue protrusion followed normal distribution hence One-Way ANOVA followed by Tukey Post Hoc test was applied for comparison between different groups. P value <0.05 was considered statistically significant.

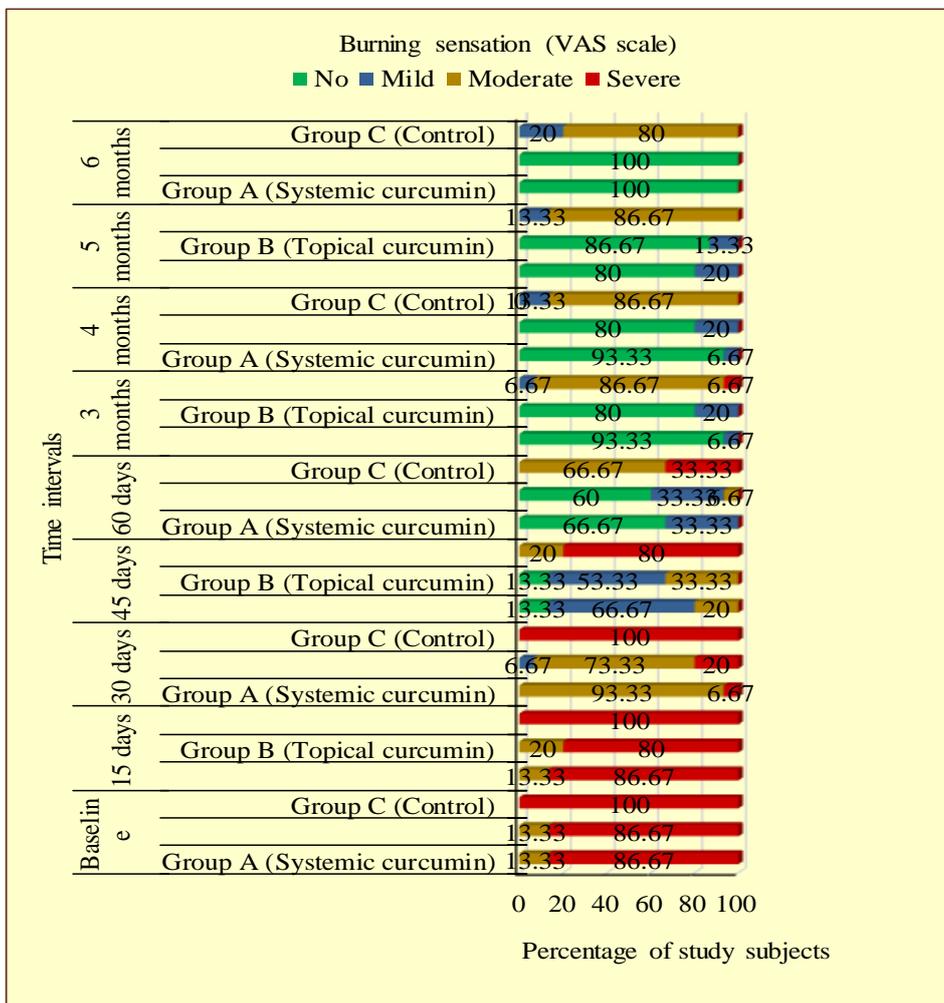
RESULTS

All the 45 subjects participated in the study were recruited from patients attending outpatient department of Hitkarini Dental College and Hospital and the subjects were equally divided into 3 groups of 15 each based on the treatment they received. The age of subjects ranged from 21.00-58.00 years in group A, from 25.00 – 56.00 years in group B and from 25.00 – 50.00 years in group C. There were only male subjects in group A and group C (n = 15, 100.00%). In group B there were 14 (93.33%) males and 01 (6.67%) female. In group A, there were 05 (33.33%) subjects in stage II, 08 (53.33%) subjects in stage III and 02

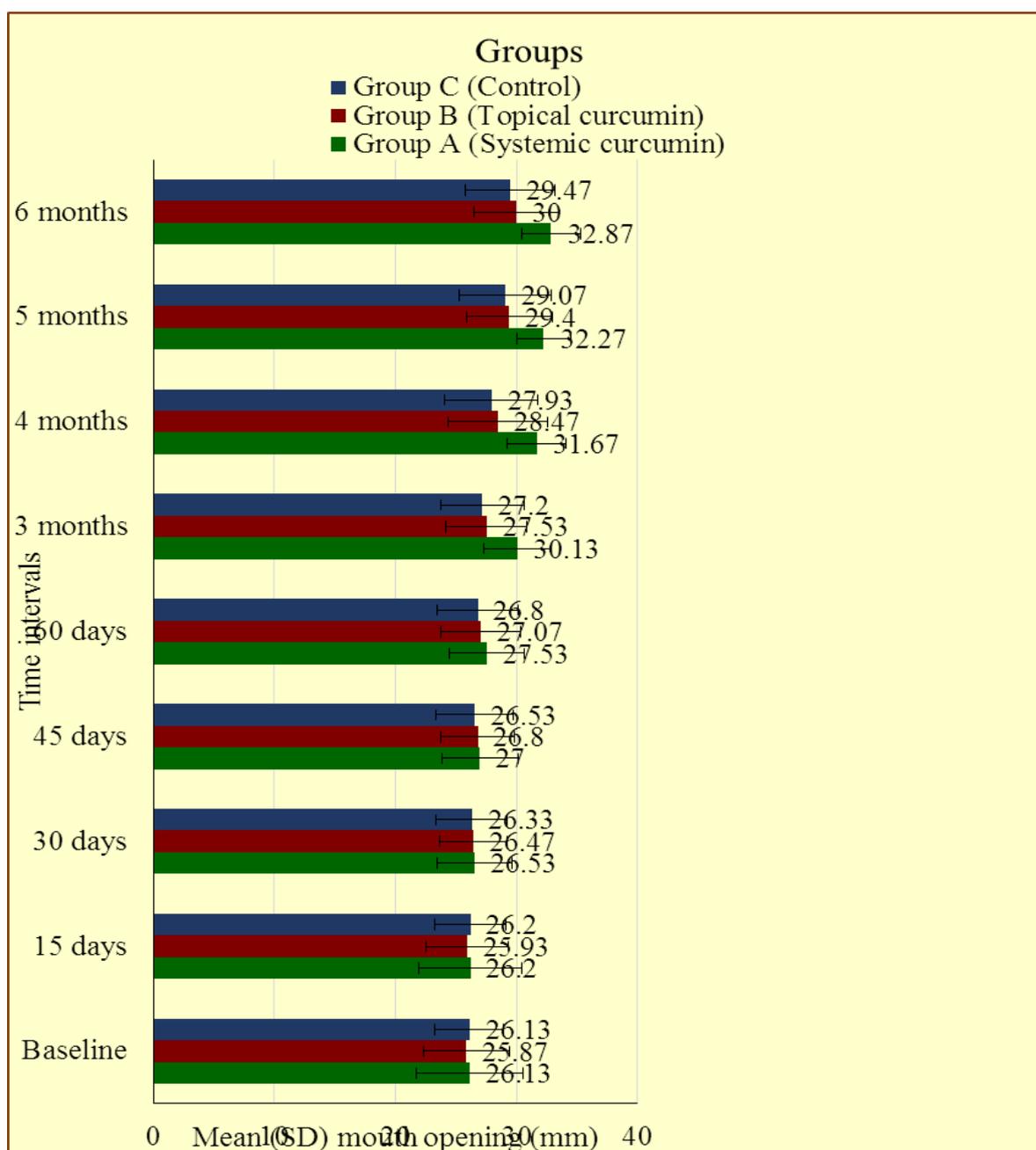
(13.33%) subjects in stage IV. In group B, there were 05 (33.33%) subjects in stage II, 07 (46.67%) subjects in stage III and 03 (20.00%) subjects in stage IV. In group C, there were 10 (66.67%) subjects in stage II and 05 (33.33%) subjects in stage III.

Comparison of burning sensation between group A, B and C at different time intervals:

At baseline in group A and group B, 02 (13.33%) subjects reported moderate and 13 (86.67%) reported severe burning sensation. In group C, all the subjects (15, 100%) reported severe burning sensation. At 3 months in group A, 14 (93.33%) subjects reported no and 01 (6.67%) subject reported mild burning sensation. In group B, 12(80.00%) subjects reported no, 03 (20.00%) subjects reported mild burning sensation. In group C, 1(6.67%) subject reported mild, 13 (86.67%) subjects reported moderate and 01 (6.67%) subject reported severe burning sensation. At 6 months in group A, all the subjects (15, 100.00%) reported no burning sensation. In group B, all the subjects (15, 100.00%) reported no burning sensation. In group C, 3 (20.00%) subjects reported mild, 12 (80.00%) subjects reported moderate burning sensation. (Graph I)

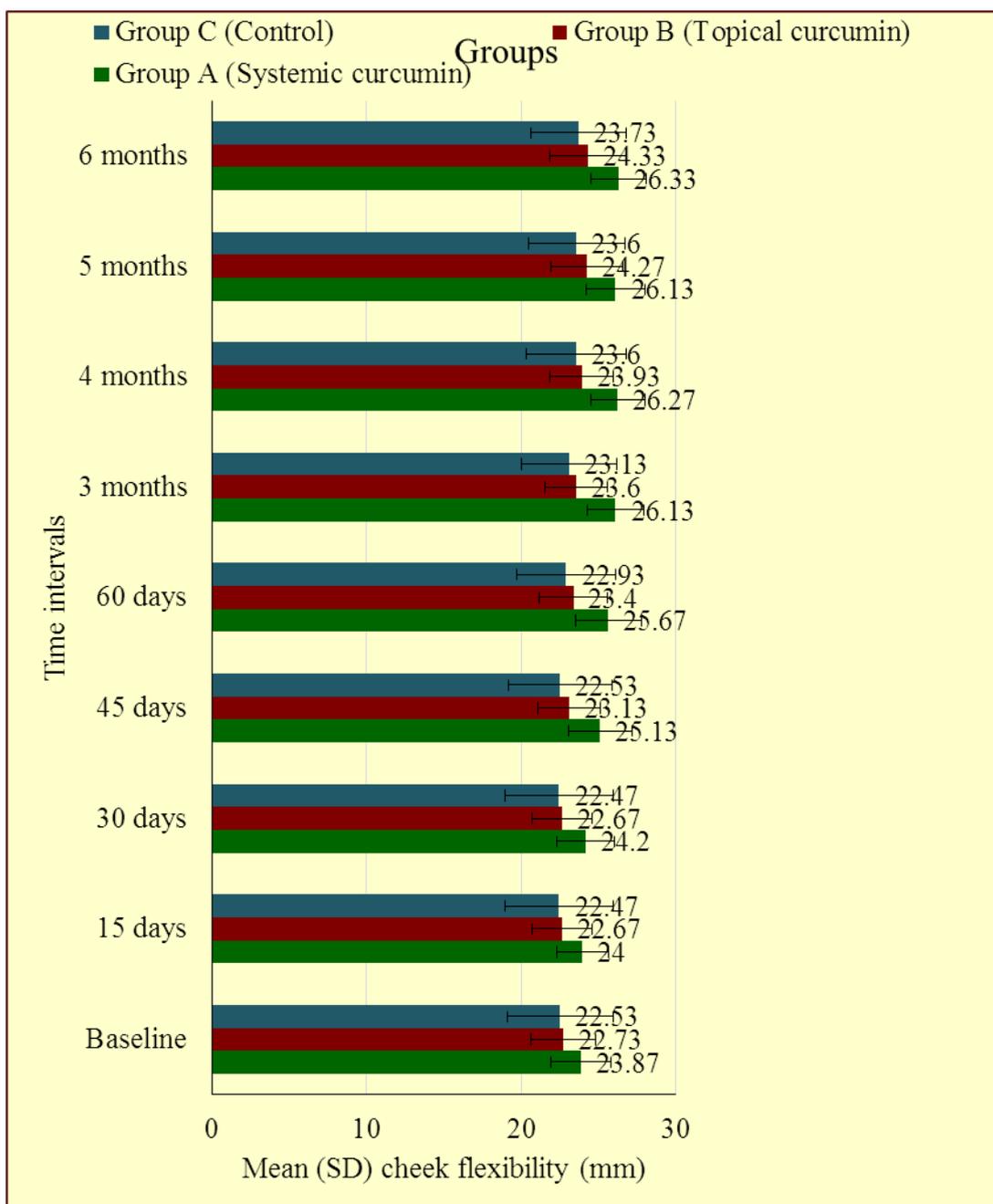


Comparison of mouth opening between group A, B and C at different time intervals: At 15 days, the mean with standard deviation of mouth opening in group A was 26.20 ± 4.28 mm, in group B was 25.93 ± 3.41 mm and in group C was 26.33 ± 2.94 mm. At 3 months, the mean with standard deviation of mouth opening in group A was 30.13 ± 2.80 mm, in group B was 27.53 ± 3.36 mm and in group C was 26.80 ± 3.32 mm. At 6 months, the mean with standard deviation of mouth opening in group A was 32.87 ± 2.42 mm, in group B was 30.00 ± 3.53 mm and in group C was 29.47 ± 3.70 mm. mouth opening in group A was significantly higher than group C. There was no significant difference between group A and group B; and group B and group C. [(A > C); (A = B); (B = C)]. (Graph II).



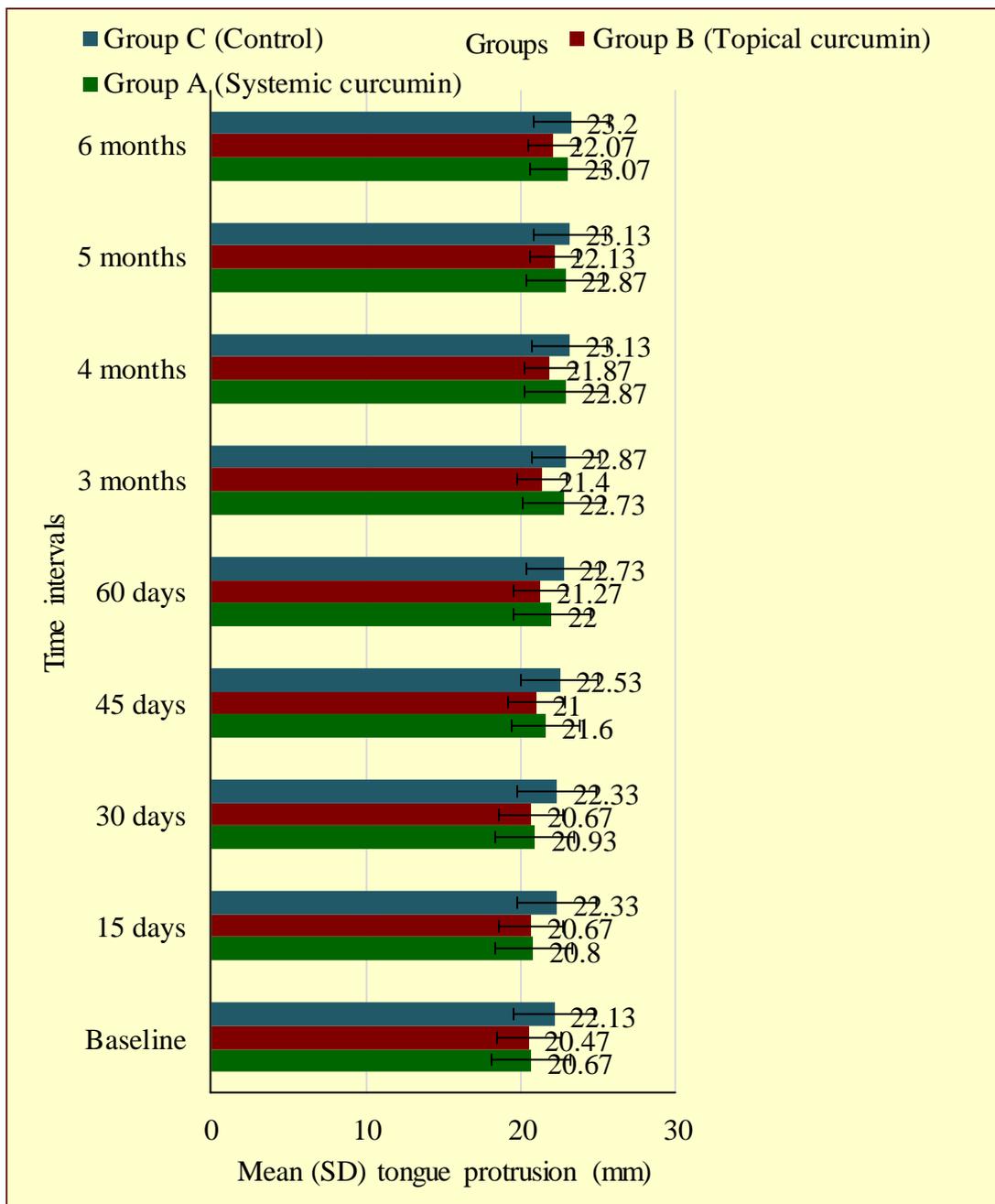
Comparison of cheek flexibility between group A, B and C at different time intervals:

At baseline, the mean with standard deviation of cheek flexibility in group A was 23.87 ± 1.96 mm, in group B was 22.73 ± 2.09 mm and in group C was 22.53 ± 3.44 mm. At 3 months, the mean with standard deviation of cheek flexibility in group A was 26.13 ± 1.81 mm, in group B was 23.60 ± 2.03 mm and in group C was 23.13 ± 3.11 mm. At 6 months, the mean with standard deviation of cheek flexibility in group A was 26.33 ± 1.80 mm, in group B was 24.33 ± 2.47 mm and in group C was 23.73 ± 3.06 mm. Cheek flexibility in group A was significantly higher than group C. No significant difference between groups A and group B; and group B and group C. [(A > C);(A = B);(B = C)]. (Graph III).



Comparison of tongue protrusion between group A, B and C at different time intervals:

At baseline, the mean with standard deviation of tongue protrusion in group A was 20.67 ± 2.55 mm, in group B was 20.47 ± 2.07 mm and in group C was 22.13 ± 2.59 mm. At 3 months, the mean with standard deviation of tongue protrusion in group A was 22.73 ± 2.60 mm, in group B was 21.40 ± 1.60 mm and in group C was 22.87 ± 2.20 mm. At 6 months, the mean with standard deviation of tongue protrusion in group A was 23.07 ± 2.43 mm, in group B was 22.07 ± 1.58 mm and in group C was 23.20 ± 2.43 mm. There was no significant difference between the groups for tongue protrusion ($F = 1.207$, $P = 0.309$, $P > 0.05$). (Graph IV).



The study revealed significant decrease in burning sensation after 6 months of therapy in groups receiving systemic and topical application of curcumin. Also, significant improvement in mouth opening with patients receiving therapy with systemic curcumin. Topical application of curcumin showed significant results while control group showed no significant results. Significant difference in cheek flexibility was observed in patients receiving systemic curcumin therapy only.

DISCUSSION

OSMF has a wide range of treatment options available but none of them has been efficient enough to cure the disease completely. Keeping the above stated fact in mind a search to find a newer treatment modality which is safe and beneficial was planned and executed. Curcumin is an extract of turmeric which is used as a household remedy since ages. It is readily available commercially, more reliable, economical and has little or no side effects when compared to the other treatment modalities available. Therefore the present study was conducted to evaluate the efficacy of systemic and topical application of curcumin in treating OSMF patients and results were obtained. Improvement of burning sensation was noted by many other authors like Monu Yadav *et al.*^[6] in his study on 40 OSMF patients concluded that curcumin is beneficial and effective in reducing burning sensation in OSMF patients as compared to the intra-lesional injections of corticosteroids and hyaluronidase. Rai B *et al.*^[7] in his study on 25 patients also stated that curcumin administration both topical and systemic lead to significant improvement in clinical symptoms (burning sensation) along with reduction in serum and salivary malondialdehyde levels. Positive improvement in burning sensation has also been elicited in studies done by Adit srivastava *et al.*^[8] Kartik PM *et al.*^[9]

Curcumin has shown its role in improving the mouth opening of the patients by increasing the inter-incisal distance In a study conducted by Vinay hazarey *et al.*^[10] on 30 clinically diagnosed OSMF patients assessing mouth opening, the test (curcumin) group elicited 5.93 (± 2.37) mm increase compared to 2.66 (± 1.76) mm of the control group. Kartik PM *et al.*^[9] conducted a study on 30 patients with clinically diagnosed OSMF and concluded that turmeric showed a very good prognosis in the inter incisal mouth opening. However, in a study done by Nitin agarwal *et al.*^[11] on 30 subjects the improvement in mouth opening was not significant. The authors stated that although the improvement in mouth opening was not significant, they still recorded an improvement of 0.69 cm, which could be due to the fact that this was a short-term study.

A statistically significant difference was seen with group A and B ($P < 0.01$); as compared to group C; more with group A when cheek flexibility was measured in our study. As far as our search in the literature goes, no other study has measured the efficacy of turmeric on cheek flexibility on OSMF patients.

A gradual mild increase was evident, in group A and B as compared to group C but was not statistically significant ($P > 0.05$) when tongue protrusion was calculated in the present study. Similar non significant improvement in tongue protrusion was observed in the study conducted by Monu yadav *et al.*^[6] on 40 OSMF patients. The authors stated that conventional method of intralesional steroids was better in improving tongue protrusion. However, Deepa das *et al.*^[12] in her study of forty eight OSMF patients demonstrated better increase in tongue protrusion for patients under turmeric administration. It is of interest to note that, none of the patients in Groups A and B presented a deterioration of their signs and symptoms nor a malignant transformation. Krishnaswamy *et al.*^[13] reported that turmeric inhibits carcinogenesis by polycyclic aromatic hydrocarbons and hence, a prospective chemopreventive agent against oral cancer. Along with the inhibition of arachidonic acid metabolism, they also inhibit superoxide generation, and thus prevent tumor promotion.^[12]

The increase in mouth opening brought about by treatment with curcumin could be a result of the anti-inflammatory, antioxidant and fibrinolytic properties of curcumin. Turmeric and curcumin are used in Chinese medicine since ages. The fibrinolytic action of curcumin has been attributed because of its three properties namely lipid per oxidation inhibition, monitoring cellular proliferation and inhibition of collagen synthesis.^[12] Turmeric is non toxic and is extremely safe even at higher doses. This is in agreement with our study as nil participants reported any side effects like gastric irritation and anaemia.

CONCLUSION

The present study substantiated that systemic therapy of curcumin is best in improving clinical signs and symptoms of the disease. The study can be further strengthened by evaluating the long term clinical effectiveness of curcumin in the patients of OSMF by involving more number of subjects and improvising combination therapies. Thus, curcumin as a treatment choice in OSMF can be considered as a safe, reliable and economic entity with no reported side effects. Further studies should be conducted to evaluate the efficacy of systemic as well as topical combination therapy in OSMF patients. The encouraging results of the present study indicate that curcumin has a potential to provide cure for premalignant

conditions like OSMF. So in near future curcumin may be included as an additional modality in ever-growing research to manage OSMF.

REFERENCES

1. Kamath VV, Satelur K, Komali Y. Biochemical markers in oral submucous fibrosis: A review and update. *Dent Res J*, 2013; 10(5): 576-584.
2. Wollina U, Verma SB, Ali FM, Patil K. Oral submucous fibrosis: an update. *Clin Cosmet Investig Dermatol*, 2015; 8: 193-204.
3. Agrawal A, Chandel S, Singh N, Singhal A. Use of Tobacco and Oral Sub Mucous Fibrosis in Teenagers. *J Dental Sci Res*, 2012; 3(3): 1-4.
4. Swathi R. Oral Submucous fibrosis and the role of curcumin in its treatment: A review. *Int J Pharm Sci Inv*, 2015; 4(6): 7-10.
5. Priyadharshni B. Classification System for Oral Submucous Grading-A Review. *Int J Sci Res*, 2014; 3(3): 740-4.
6. Yadav M, Aravinda K, Saxena VS, Srinivas K, Ratnakar P, Gupta J, et al. Comparison of curcumin with intralesional steroid injections in Oral Submucous Fibrosis-A randomized , open-label interventional study. *J Oral Bio Craniofac Res*, 2014; 4(3): 169-73.
7. Rai B, Kaur J, Jacobs R, Singh J. Possible action mechanism for curcumin in pre-cancerous lesions based on serum and salivary markers of oxidative stress. *Journal of Ora Sci*, 2010; 52(2): 251-6.
8. Srivastava A, Agarwal R, Chaturvedi TP, Chandra A. Clinical evaluation of the role of tulsii and turmeric in the management of oral submucous fibrosis: A pilot, prospective study. *J Ayurveda Integr Med*, 2015 Jan-Mar; 6(1): 45-49.
9. Karthik PM, Sande A, Ashwinirani SR, Nayak A, Pawar R, Patil P. Comparison of Mouth Opening with different Non-Surgical Treatment Modalities in Oral Submucous Fibrosis. *Am J Drug Del Therap*, 2015; 2(3): 72-77.
10. Hazarey VK, Sakrikar AR, Ganvir SM. Efficacy of curcumin in the treatment for oral submucous fibrosis - A randomized clinical trial. *J Oral Maxillofac Pathol*, 2015; 19(2): 145-152.
11. Agarwal N, Singh D, Sinha A, Srivastava S, Prasad RK, Singh G. Evaluation of efficacy of turmeric in management of oral submucous fibrosis. *J Indian Acad Oral Med Radio*, 2014; 26(3): 6-9.

12. Das DA, Balan A, Kt S. Comparative Study of the Efficacy of Curcumin and Turmeric Oil as Chemopreventive Agents in Oral Submucous Fibrosis: A Clinical and Histopathological Evaluation. J Indian Acad Oral Med Radiol, 2010; 22(2): 88-92.
13. Krishnaswamy K. Turmeric - A Potential Anti-cancer Agent. Nutrition foundation of India [internet].