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COMPARISON OF SYSTEMIC CURCUMIN AND INTRALESIONAL STEROID INJECTIONS IN THE MANAGEMENT OF ORAL SUBMUCOUS FIBROSIS: A CLINICAL STUDY

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Abstract

Objective: To compare the efficacy of curcumin to intralesional steroid injections in the treatment of oral submucous fibrosis (OSMF).

Study design: Forty patients with clinically and histologically proven OSMF were divided into 2 groups. Group I patients were given oral administration of 2 capsules of curcumin 300mg once daily for 3 months. Group II patients were given weekly intralesional injections of a combination of dexamethasone and hyaluronidase for six weeks and antioxidant capsules (Cap. SM Fibro - Alpha lipoic acid 50mg, Beta-carotene 10mg, Elemental copper 1mg, Elemental selenium 75mcg, Lycopene 5mg, Vitamin E 10 IU, Zinc sulphate 27.45mg) once daily for 3 months. Patients were assessed for burning sensation, inter incisal distance, cheek flexibility and tongue protrusion at an interval of every 15 days for 3 months. Physiotherapy for mouth opening was advised twice daily for 6 weeks in both the groups and assessed in each visit.

Results: Both curcumin group and intralesional injection group showed reduction in burning sensation with $p<0.05$ which was statistically significant at 75 days. Statistically significant improvement was noted in inter incisal distance, cheek flexibility and tongue protrusion at 30 days and 75 days of the study period in the both the groups.

Conclusion: Curcumin capsule is effective, safe and alternative treatment modality in OSMF.

Introduction

Oral submucous fibrosis is an insidious chronic, potentially malignant disorder affecting any part of oral cavity and sometimes the pharynx. Although occasionally preceded by and/or associated with vesicle formation, it is always associated with juxtaepithelial inflammatory reaction followed by a fibroelastic change of lamina propria with epithelial atrophy leading to stiffness of the oral mucosa, progressively limiting mouth opening and causing inability to eat.[1] The etiology of the disease was thought to be multifactorial and recent reports suggests that OSMF is caused by areca nut, a masticatory substance used predominantly by Indians and South Asians.[2] Areca nut is made up of alkaloid and flavonoid components that play a major role in the pathogenesis of OSMF by causing an abnormal increase in collagen production.[3]

The management of OSMF includes medical, surgical and physiotherapeutic modalities. Few of the medical modalities include intralesional injections of corticosteroids, placental extracts and hyaluronidase alone or in combination, IFN-α, oral administration of peripheral vasodilators, immune milk, aloe-vera, lycopene and micronutrient supplementation. Among the various medical modalities, intralesional steroid therapy along with hyaluronidase is most commonly used by professionals.[4] The mainstay treatment of this potentially malignant disorder include not only the improvement of signs and symptoms of OSMF such as burning sensation, reduced mouth opening but also to reduce the further progression of this condition. Various treatment modalities have been tried, but none have found to be curative and reduced the morbidity significantly. Hence, the search for an effective treatment modality still continues.[5]

Curcumin (diferuloylmethane) is a polyphenol compound isolated from ground rhizomes of the plant (*Curcuma longa*) L. (Zingiberaceae) found in South Asia. Curcumin is naturally occurring yellow pigment of turmeric having wide spectrum of biological action. Curcumin has been used extensively in ayurvedic medicine for centuries, as it is nontoxic and has a variety of therapeutic properties including antioxidant, analgesic, anti-inflammatory, antiseptic activity, chemopreventive, chemotherapeutic activity, anti-tumour, antimicrobial properties and antiplatelet acticvity.[6] All such properties of curcumin suggest the possibilities of its usage in the management of OSMF.

Hence, the present study was aimed to compare the efficacy of curcumin with intralesional steroid injections along with hyaluronidase in the treatment of OSMF.

Materials and Methods:

The study was conducted in forty patients at an age of 20-40 years who were clinically and histopathologically diagnosed with OSMF visiting outpatient Department of Oral Medicine and Radiology, The Oxford Dental College, Bangalore between November 2016 and September 2018. Institutional ethical clearance was obtained for the study. Patients who were ready to stop the habit and who had signed the informed consent were included in the study. Patients presenting with co existing malignancy/white lesions, with known allergy to drugs, those who had received prior treatment for OSMF, not willing for biopsy and patients with any systemic disease were excluded.

Detailed history with special emphasis on type, frequency in a day and duration of habit (areca nut, gutkha or combination of both), whether they swallowed the product or spitted it out were noted. Clinical examination was done through the assessment of subjective symptoms like burning sensation, objective signs like inter incisal distance (IID), tongue protrusion and cheek flexibility.

1. Intensity of burning sensation was recorded using a Visual Analogue Scale, (VAS) of 0-10, where 0 indicated no burning sensation and 10 indicated the worst possible burning sensation.
2. The interincisal distance was measured using a metal scale and divider from the mesioincisal angle of upper central incisor to the mesioincisal angle of lower central incisor and recorded in millimeters.
3. Cheek flexibility was measured according to the method by Mathur and Jha as quoted by Bailoor and Nagesh. CF= V_2-V_1, 2 points measured between; V_2 was marked at $1/3^{rd}$ the distance from angle of mouth on a line joining the tragus of the ear and the angle of the mouth and V_1= the subject was asked to blow his cheeks fully and the distance was measured between 2 points marked on the cheek.
4. Tongue protrusion was assessed from normal mesioincisal angle of upper central incisor to the tip of tongue when maximally extended with mouth wide open.

The routine hematological (complete blood picture) and blood sugar investigations were conducted. Punch biopsy was taken from the buccal mucosa, depending on the severity, under local anesthesia and was subjected to histopathological evaluation. Forty patients were randomly allocated into two groups (Group I and Group II). The Group I was given oral administration of 2 capsules of curcumin 300mg once daily for 3 months. The Group II was given weekly intralesional injections of a combination of dexamethasone 4mg/ml and hyaluronidase 1500 IU for a period of six weeks and antioxidant capsule (Cap. SM Fibro- Alpha lipoic acid 50mg, Beta-carotene 10mg, Elemental copper 1mg, Elemental selenium 75mcg, Lycopene 5mg, Vitamin E 10 IU, Zinc sulphate 27.45mg) once daily for 3 months. The selection sites of injection were based on clinical judgment. Injections were given at multiple sites with an insulin syringe, given on both the sides. The patients were recalled every 15 days for 3 months to evaluate burning sensation, interincisal distance, tongue protrusion and cheek flexibility. Physiotherapy consisting of lip, cheek and tongue exercises twice a day for 6 weeks was advised in both the groups. Same baseline parameters were measured and recorded at an interval of 15 days for 3 months.

Statistical Analysis

Statistical Package for Social Sciences [SPSS] for Windows Version 22.0 was used to perform statistical analyses. Mann Whitney U test was used to compare the mean VAS scores between 02 groups at different time intervals. Independent Student t test was used to compare the mean inter incisal Distance (in mm), tongue protrusion (in mm) and cheek flexibility (in mm) between 02 groups at different time intervals. Friedman's Test was used to compare the mean VAS scores between different time intervals in each study group. Repeated measures of ANOVA was used to compare the inter incisal distance (in mm), tongue protrusion (in mm) and cheek flexibility (in mm) between different time intervals in each study group.

Results:

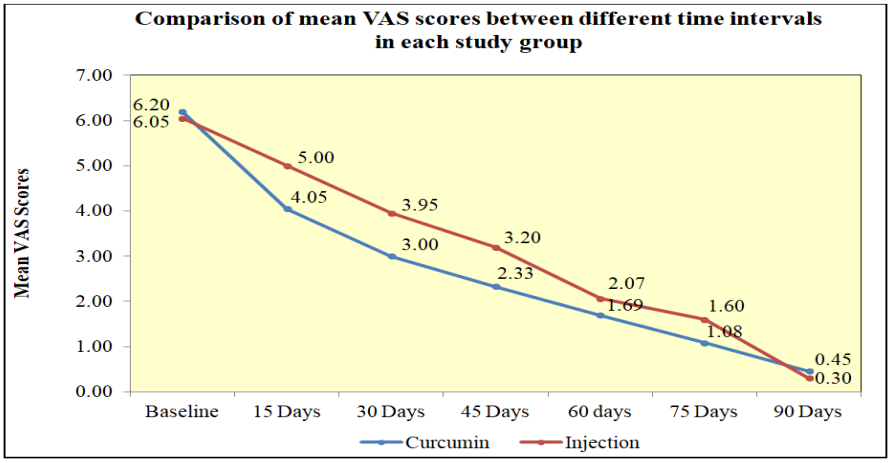
The study comprised of 16 (80%) male and 4 female (20%) patients within age range of 22 to 40 in Group I and 20 to 40 in Group II. Mean age of subjects in Group I was 32.0±4.69 years whereas in Group II, mean age noted was 31.95±5.53 years. Gutkha chewing along with arecanut chewing was the most prevalent habit noted (50%) in both the groups. 20% of subjects had habit of chewing arecanut, 10% of the subjects reported to have only guthka, arecanut chewing habit with smoking and gutkha with smoking in Group I. In Group II, 30% of subjects had habit of only arecanut chewing, 15% of subjects had habit of ghutkha with smoking followed by 5% of subjects had habit of arecanut and smoking.

Of the 40 study subjects, 19 were lost for the follow up. The dropout rate in Group I and Group II was 22.5% and 25% respectively. The comparison of baseline parameters between the groups is not statistically significant.

Patients in Group I, at baseline had mean VAS score of 6.20±1.32 for burning sensation. A statistically significant ($p<0.05$) decrease were noted at 15 days, 30 days and 75 days with a mean VAS score of 4.05±1.28, 3.00±1.30, 1.08±0.29 respectively. Even Group II had a statistically significant reduction ($p<0.05$) in mean VAS score for burning sensation from 6.05±1.36 to 1.60±0.79 (Table 1). From baseline to 90 days the reduction was 6.8±1.17 to 0.45±0.52 in Group I. Group II also showed significant reduction from 6.10±1.52 to 0.30±0.48 (Graph 1).

Table I: Comparison of mean VAS scores between 2 groups at different time intervals using Mann Whitney U Test

Time	GROUP	Mean	P-value
Baseline	Group I (Curcumin)	6.20±1.32	0.71
	Group II (Injection)	6.05±1.36	
15 Days	Group I	4.05±1.28	0.03*
	Group II	5.00±1.30	
30 Days	Group I	3.00±1.30	0.04*
	Group II	3.95±1.36	
45 Days	Group I	2.33±1.09	0.14
	Group II	3.20±1.74	
60 days	Group I	1.69±1.20	0.66
	Group II	2.07±1.64	
75 Days	Group I	1.08±0.29	0.03*
	Group II	1.60±0.70	
90 Days	Group I	0.45±0.52	0.48
	Group II	0.30±0.48	

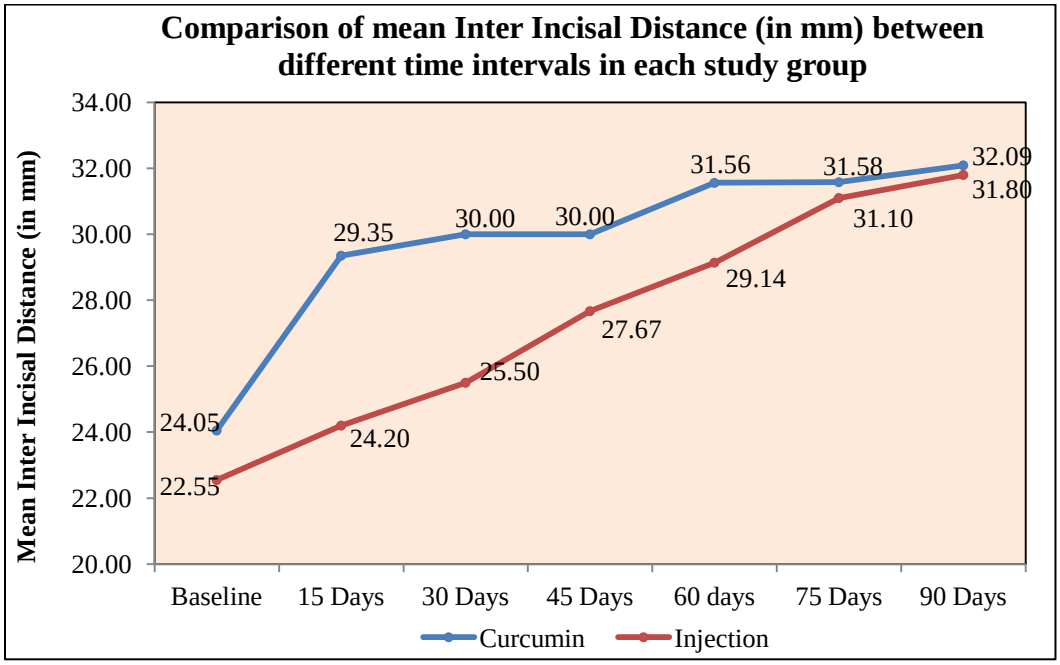


Graph I: Comparison of mean VAS scores between different time intervals in each study group

The increase in mean values for inter incisal distance for both the groups at 15 and 30 days were statistically significant ($p<0.05$). Mean value increase in inter incisal distance was 23.64±1.96mm to 28.09±3.62mm in Group I and 21.30±5.31mm to 24.40±5.40mm in Group II from baseline to 30 days (Table 2). The mean increase in inter incisal distance for Group I and Group II were 32.09±2.07mm and 31.80±3.23mm respectively at the end of 90 days (Graph 2).

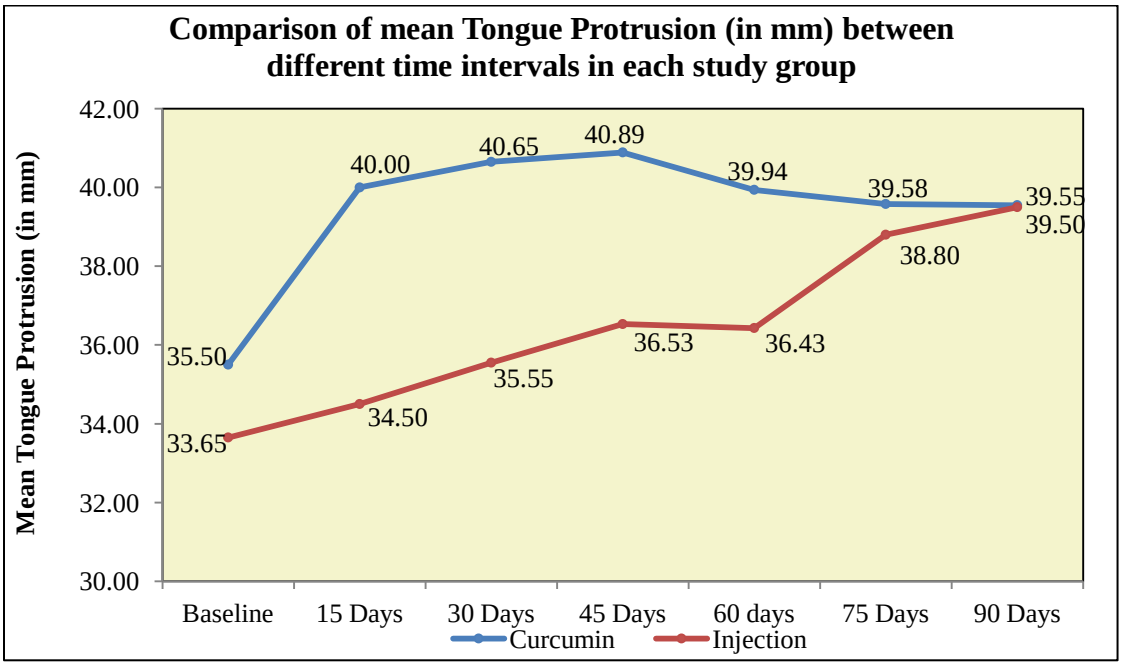
Table II: Comparison of mean Inter Incisal Distance, Tongue Protrusion and Cheek Flexibility (in mm) between 2 groups at different time intervals using Independent Student t Test

Time	GROUP	Mean	P-value	Mean	P-value	Mean	P-value
Baseline	Group I (Curcumin)	24.05±2.21	0.24	35.50±3.56	0.30	10.80±2.04	0.10
	Group II (Injection)	22.55±5.22		33.65±7.02		9.65±2.30	
15 Days	Group I	29.35±4.53	0.002*	40.00±6.27	0.01*	10.85±1.93	0.002*
	Group II	24.20±5.32		34.50±7.13		8.90±1.77	
30 Days	Group I	30.00±4.50	0.008*	40.65±6.13	0.02*	11.50±1.47	0.009*
	Group II	25.50±5.60		35.55±6.99		10.10±1.74	
45 Days	Group I	30.00±4.46	0.17	40.89±6.03	0.04*	11.83±1.58	0.04*
	Group II	27.67±5.16		36.53±7.06		10.67±1.54	
60 days	Group I	31.56±3.20	0.11	39.94±4.97	0.15	11.81±1.64	0.71
	Group II	29.14±4.74		36.43±7.88		11.57±1.83	
75 Days	Group I	31.58±2.07	0.69	39.58±4.08	0.74	12.00±1.54	0.68
	Group II	31.10±3.51		38.80±6.66		11.70±1.83	
90 Days	Group I	32.09±2.07	0.81	39.55±4.20	0.99	12.18±1.54	0.80
	Group II	31.80±3.23		39.50±6.57		12.00±1.70	

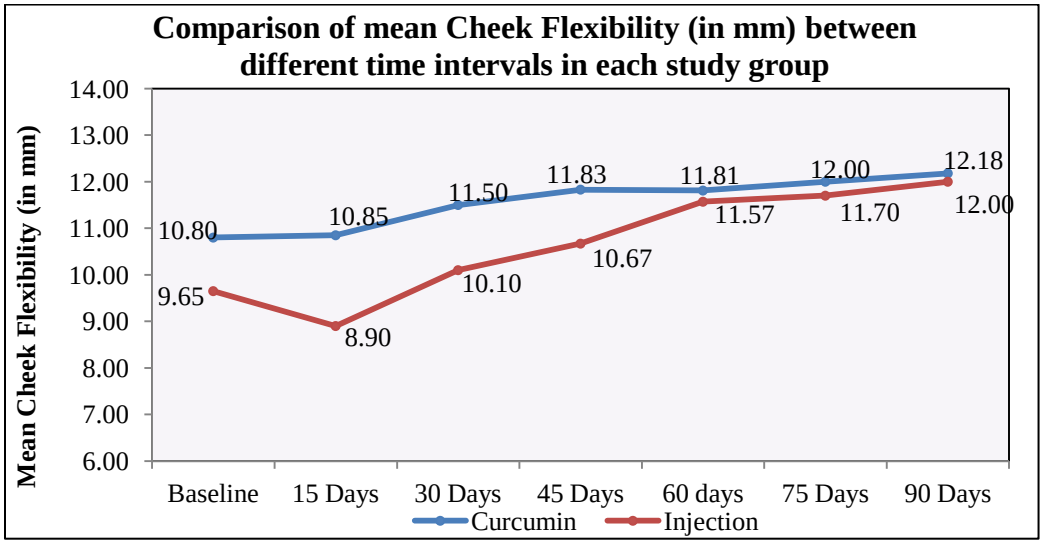


Graph II: Comparison of mean Inter Incisal Distance (in mm) between different time intervals in each study group

Statistically significant ($p<0.05$) results were also seen for both Group I and Group II for tongue protrusion and cheek flexibility at 15 days, 30 days and 45 days. Group II showed a gradual increase in mean values for tongue protrusion (Table 2). For tongue protrusion the mean improvement for Group I from baseline to 90 days was 34.91±2.88mm to 39.55±4.20mm. In Group II, the mean improvement from baseline to 90 days was 33.6±7.47mm to 39.5±6.57 (Graph 3). Group I subjects showed improvement of cheek flexibility of 10.45±2.07mm to 12.18± 1.54mm from baseline to 90 days. In Group II, the improvement of cheek flexibility from baseline to 90 days was 9.10± 2.85mm to 12.0±1.70mm (Graph 4). Overall Group II showed better improvement of cheek flexibility than Group I.



Graph III: Comparison of mean Tongue Protrusion (in mm) between different time intervals in each study group



Graph IV: Comparison of mean Cheek Flexibility (in mm) between different time intervals in each study group

Discussion:

Oral submucous fibrosis is a chronic debilitating condition of the oral cavity characterized by inflammation and progressive fibrosis of the submucosal tissues, well recognized for its malignant potential.[7] Treatment for OSMF remains a challenge. It is said that once the disease has developed, there is neither regression nor any effective treatment.[8]

Curcumin, a yellow pigment in curry powder is derived from Curcuma longa plant, which is commonly known as turmeric.[9] In our study, the subjects in Group I did not report any side effects as curcumin is nontoxic and safe at higher doses when administered at doses of 10 g/day.[10]

One of the pathogenic mechanisms of areca nut has been attributed to the generation of reactive oxygen species, free radicals and peroxidases. Based on this hypothesis several authors have tried various naturally occurring or synthetic anti-oxidants. These include beta carotene, lycopene, and alpha lipoic acid. Administration of nutrient antioxidants to patients with OSMF may have a protective effect along with clinical improvement. In our study, group II subjects have shown improvement in the symptoms. Gupta *et al* treated 6 cases of OSMF with a pharmacological preparation containing beta carotene 50mg, vitamin A palmitate 2500 IU, vitamin E acetate, 10 IU with vitamin C, zinc, copper and manganese. Improvement was seen in the symptoms in all the patients[15].

Muscle stretching exercises for the mouth are helpful in preventing further reduction in mouth opening. Asha and Baruah reported that the mean differences of mouth opening, cheek flexibility and tongue protrusion was found to be maximum in patients receiving both intralesional injections and physiotherapy[16].

Hyaluronidase causes breakage and dissolution of fibrous bands thus providing relief from the condition. It acts by breaking down hyaluronic acid, lowers the viscosity of intracellular substances and decreases collagen formation[17].

Hyaluronidase can also be supplementary to intra-lesional steroid preparations. The mixture of steroids and hyaluronidase showed improved long-term results. Kakar *et al.* found that injection of 1500 IU of hyaluronidase and dexamethasone (4 mg) locally for 7 weeks gave superior results if it was followed by 3 weeks of hyaluronidase injections[18].

In the present study, male predominance was noted in both the groups and most of the study subjects were in the age group of third decade which was similar to the studies conducted by Reddy *et al.*[7], Yadav *et al.*[11]. Male predominance in our study can be due to easy accessibility for males to use areca nut and its product.

The most common complaint of patients with OSMF is burning sensation. In our study, both Group I and Group II showed statistical significant ($p<0.05$) reduction of burning sensation at 75 days with a mean VAS score of 1.08±0.29 from baseline, 6.20±1.32 in Group I and from 6.05±1.36 to 1.60±0.7 in Group II respectively. These findings are similar to those reported by Das DA *et al.*[5] in 2010. Improvement of burning sensation was statistical significant between the turmeric group and multivitamin tablet group. In 2014, Yadav *et al.*[11] reported that complete resolution of burning sensation was noted in turmeric capsule group when compared to injection group. In our study, the reduction of burning sensation is rapid in Group I from baseline to 30 days was 6.20±1.32 to 3.00±1.30. In Group II, at the end of 30 days, the reduction was 3.95±1.36. The reduction obtained in Group II subjects was more gradual.

The reduction in burning sensation can be attributed to the anti-inflammatory properties of curcumin. The probable mechanisms for the anti-inflammatory action of curcumin are:

- Curcumin down-regulates the activity of cyclooxygenase-2 (COX-2), lipoxygenase, and inducible nitric oxide synthase (iNOS) enzymes;
- Curcumin inhibits the production of the inflammatory cytokines tumor necrosis factor-alpha (TNF-a), interleukin

(IL) -1, -2, -6, -8, and -12, monocyte chemoattractant protein (MCP), and migration inhibitory protein.[12]

- Statistically significant ($p<0.05$) improvement in inter incisal distance was observed for both the groups at 15 days and 30 days. Hazarey, *et al*.[9] in 2015, reported that the test (curcumin) group showed 5.93 (±2.37) mm increase in mouth opening compared to 2.66 (±1.76) mm of the control group. Das DA *et al*.[5] in 2010, reported a mean increase of 0.87 cm of inter incisal with turmeric oil and turmeric capsules and was found to be effective for improvement in inter incisal distance. Group I and Group II showed statistically significant increase in tongue protusion at 15 days, 30 days and 45 days. A gradual increase was noted in Group II at each visit. Yadav *et al*.[11] found no significant improvement of tongue protrusion in turmix group, whereas it was maximal at the end of 1st month with conventional therapy (steroid injection group). In our study, improvement in cheek flexibility was statistically significant at the end of 45 days. From baseline to the end of the study, in Group I improvement in cheek flexibility was 10.80±2.04mm to 12.18±1.54mm whereas in Group II, 9.65±2.30mm to 12.00±1.70mm improvement was noted. At the end of study, the difference in improvement between the groups was not significant.
- The improvement in the parameters like inter incisal distance, tongue protrusion and cheek flexibility caused by curcumin could be due to the following findings:
- *Curcumin inhibits cell proliferation in fibroblasts and myofibroblasts, which is an activated fibroblast that plays an important role in fibrotic diseases including OSMF, scleroderma, pulmonary fibrosis, etc. in a dose-dependent manner.*[13,14]
- Curcumin induces cell cycle arrest in myofibroblasts Cell cycle analysis shows that curcumin treatment results in a dose-dependent increase in the proportion of myofibroblast cells in G0/G1 phase.[14]
- Curcumin induces cell apoptosis in myofibroblasts but the mechanism by which Curcumin mediates is pro-oxidant effects remain unclear.[14]
- Li *et al*. has attributed the fibrinolytic action of curcumin to its three properties namely inhibition of lipid peroxidation, checking cellular proliferation and inhibition of collagen synthesis.[9]
- In the present study, the reduction in burning sensation and improvement in inter incisal distance, tongue protrusion and cheek flexibility between the groups was not statistically significant at the end of the study. The improvement noted in all the parameters was quite high in the present study compared to the other studies in the management of OSMF. Group II showed improvement in all the parameters progressively. The reason could be due to the mode of delivery of the steroid injection in between the palpable bands. In early stages of OSMF, curcumin capsule provides rapid relief of the symptoms, which was observed in this study.

There are few limitations in the study which should be addressed. Loss to follow up in the study participants could be one of the limitations. Less sample size in the study can compromise the study results. The bioavailability of the curcumin is poor as curcumin is lipophilic compound so the maximum effectiveness of the curcumin is not attained in the study group. Lack of histopathological confirmation of the improvement at the end of the study is also a limitation observed in the present study.

Conclusion:

In the present study, the prevalence of OSMF was more in males, which was estimated to be 80%. Gutkha chewing along with arecanut chewing was the most prevalent habit. Both curcumin group and intralesional injection group had marked reduction in burning sensation with $p<0.05$ which was statistically significant at 75 days. Statistically significant improvement was noted with the $p<0.05$ in inter incisal distance, cheek flexibility and tongue protrusion at 30 days and 75 days of the study period. The clinical response to curcumin was comparable to intralesional injections of dexamethasone, hyaluronidase and antioxidant supplements. No serious side effects were reported. Easy of availability, safety of use, cost effectiveness and noninvasiveness attributes of curcumin make it an alternative, effective choice of treatment regime in the management of OSMF.

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