A clinicobiochemical evaluation of curcumin as gel and as buccal mucoadhesive patches in the management of oral submucous fibrosis

Aditi Chandrashekar, MDS,[a] Rajeshwari G. Annigeri, MDS,[b] Usha VA, MDS,[c] and J. Thimmasetty, MPharm, PhD[d]

Objective. The objective of this study was to evaluate and compare the efficacy of topical curcumin gel and buccal mucoadhesive patches in the management of oral submucous fibrosis (OSMF).

Study Design. Forty patients clinically diagnosed with OSMF were randomly divided into 2 groups. Group A received curcumin gel and group B received curcumin mucoadhesive patches, to be used twice daily for 8 weeks. Evaluation was done every 2 weeks. Serum lactate dehydrogenase (LDH) levels were measured before and after treatment and also in 20 healthy controls.

Results. A 100% reduction in burning sensation was observed in all 40 patients at the end of 4 weeks. Mouth opening improved by 5.45 ± 1.64 mm in group A and 5.9 ± 2.00 mm in group B. Pretreatment LDH was 359.72 ± 77.02 IU/L in patients with OSMF, which was significantly higher than that in healthy volunteers (173.2 ± 46.20 IU/L). In group A, LDH values reduced from 341.85 ± 71 IU/L to 264.95 ± 65.09 IU/L and in group B, values reduced from 377.6 ± 79.76 IU/L to 286.15 ± 72.95 IU/L after treatment.

Conclusion. Curcumin gel and mucoadhesive patches were effective in improving mouth opening and reducing burning sensation in patients with OSMF. They can therefore be considered as safe, noninvasive modalities for treatment of OSMF. (Oral Surg Oral Med Oral Pathol Oral Radiol 2021;131:428–434)

Oral submucous fibrosis (OSMF) is a chronic, debilitating potentially malignant oral disease. The Indian subcontinent has the highest prevalence of OSMF, up to 6.42%.[1] The most important etiologic factor for OSMF is the consumption of areca nut and its products.[2]

OSMF is a chronic inflammatory and immune-mediated disease, associated with increased oxidative stress. This has been attributed to its high rate of malignant transformation.[3] Lactate dehydrogenase (LDH) is an enzyme indicator of oxidative stress. Increased levels have been demonstrated in oral cancers[4] and potentially malignant diseases like leukoplakia,[4] lichen planus,[5] and OSMF.[6]

Numerous therapies have been tried for OSMF, such as steroids in combination with enzymes (hyaluronidase) and placental extracts,[7] antioxidants,[8] peripheral vasodilators,[9] physiotherapy,[10] and surgical excision.[11] Although effective, they have proven to be symptomatic and temporary. Natural herbs have garnered renewed interest over the past several decades. Turmeric, one of the oldest known dietary spices, has potent anti-inflammatory, antioxidant, antifibrotic, immunomodulatory, and anticarcinogenic properties. The active component of turmeric is curcumin (diferuloylmethane), responsible for the yellow color and most of the biological properties.[12]

Oral route in the most commonly used mode of drug delivery. However, it has significant drawbacks, such as hepatic first pass metabolism, reduced bioavailability, varying serum concentrations, and difficulty in maintaining the drug at the desired site. Transmucosal delivery through various body surfaces, such as the oral mucosa, overcome these disadvantages. Various oral transmucosal forms using the phenomenon of mucoadhesion have been developed, such as tablets, patches, sprays, gels, etc.[13] Mucoadhesive patches are convenient, easy to use, low cost, and painless.[14]

The aim of this study was therefore to evaluate and compare the efficacy of topical curcumin gel and curcumin buccal mucoadhesive patches in the management of OSMF and to evaluate serum LDH levels before and after treatment. To the best of our knowledge, this study was the first of its kind to evaluate curcumin gel and mucoadhesive patches in OSMF.

Statement of Clinical Relevance

Transmucosal delivery of curcumin gel/mucoadhesive patches is efficient in improving burning sensation and mouth opening in oral submucous fibrosis. Hence, they can be considered safe, easy-to-use, and noninvasive modalities in the management of oral submucous fibrosis.

[a]Post graduate, Department of Oral Medicine and Radiology, College of Dental Sciences, Davangere, Karnataka, India.
[b]Professor and Head, Department of Oral Medicine and Radiology, College of Dental Sciences, Davangere, Karnataka, India.
[c]Reader, Department of Oral Medicine and Radiology, College of Dental Sciences, Davangere, Karnataka, India.
[d]Professor, Bapuji Pharmacy College, Davangere, Karnataka, India.
Received for publication Aug 10, 2020; returned for revision Nov 24, 2020; accepted for publication Dec 23, 2020.

2212-4403/$-see front matter
https://doi.org/10.1016/j.oooo.2020.12.020

MATERIALS AND METHODS

The study was conducted on patients with OSMF reporting to the Department of Oral Medicine and Radiology over a period of 10 months. The study was in accordance with the Declaration of Helsinki and approved by the institutional review board (CODS/IRB/2551/2017-2018).

Fortypatients clinically diagnosed with OSMF were included in the study, based on the following criteria: patients who have (1) already quit the gutkha/arecanut chewing habit or have effectively quit after counseling, (2) not received treatment for OSMF in the past, and (3) a mouth opening of more than 20 mm. Patients with (1) the presence of other oral mucosal lesions with OSMF, (2) pericoronal infections and temporomandibular joint dysfunctions, and (3) other adverse habits such as alcohol use, smoking, vaping, or e-cigarette use with or without gutkha chewing were excluded from the study. None of the patients consumed gutkha/areca nut after enrolling in the study.

The study design was explained to the patients and they provided informed consent. Computer-generated randomization was used to divide patients into 2 groups of 20.

Preparation of curcumin gel and patch

Pure curcumin powder was obtained from Rajesh Chemicals Company (Mumbai, India; ISO certification 9001:2000). Curcumin gel and patches were prepared in the pharmacy college.

A 2% curcumin gel was prepared by homogenization with gel base of sodium carboxymethylcellulose, distilled water, and methyl paraben as preservative. Mucoadhesive patches with a dissolvable matrix were prepared by the solvent casting technique[15] using curcumin powder, hydroxypropyl methyl cellulose, glycerin, and water. The patches were cut into sizes of 2 × 3 cm, wrapped in wax paper, and placed under sterile conditions until use. Each patch contained 2% curcumin.

Study parameters

The primary outcome measures evaluated were reduction in burning sensation and improvement in mouth opening. Cheek flexibility and tongue protrusion were also measured. Burning sensation was recorded on a 10-cm visual analog scale and mouth opening and tongue protrusion were measured using Vernier calipers (in millimeters).

Baseline parameters were recorded and patients were divided into 3 stages based on mouth opening: stage I, >40 mm; stage II, 31 to 40 mm; and stage III, 21 to 30 mm.

Group A. Curcumin gel. Approximately 5 mg (quantified by a scoop) of the gel was to be applied on bilateral buccal mucosa twice daily, after food intake.

Fig. 1. Application of curcumin mucoadhesive patch.

Group B. Curcumin mucoadhesive patch. One patch was to be placed on right and left buccal mucosa each, twice daily after food intake. Vigorous mouth movements that may displace the patches were to be avoided. Method of application was demonstrated on the first visit (Figure 1).

Duration of use of patches/gel was 8 weeks and follow-up was done every 2 weeks. Patients were instructed to swallow saliva pooling in the mouth and to avoid eating, drinking, and rinsing the mouth for half an hour following application. Patients in both groups were also instructed to perform mouth opening exercises 3 times daily for the duration of the study. Patient compliance with the use of the gels/patches was based on self-report and treatment response.

Serum LDH[16] levels were evaluated in patients with OSMF before and after treatment and also in 20 age- and sex-matched volunteers having no adverse habits, no mucosal lesions, and no systemic illnesses. A flow diagram of the various stages of the study is shown in Figure 2.

Statistical analysis was done using SPSS software, Version 21.0 (SPSS, Chicago, IL). Descriptive analysis was used for assessing means, numbers, and percentages. Paired *t*-test, independent *t*-test, and one-way analysis of variance were applied. A P value $\leq .05$ was considered statistically significant.

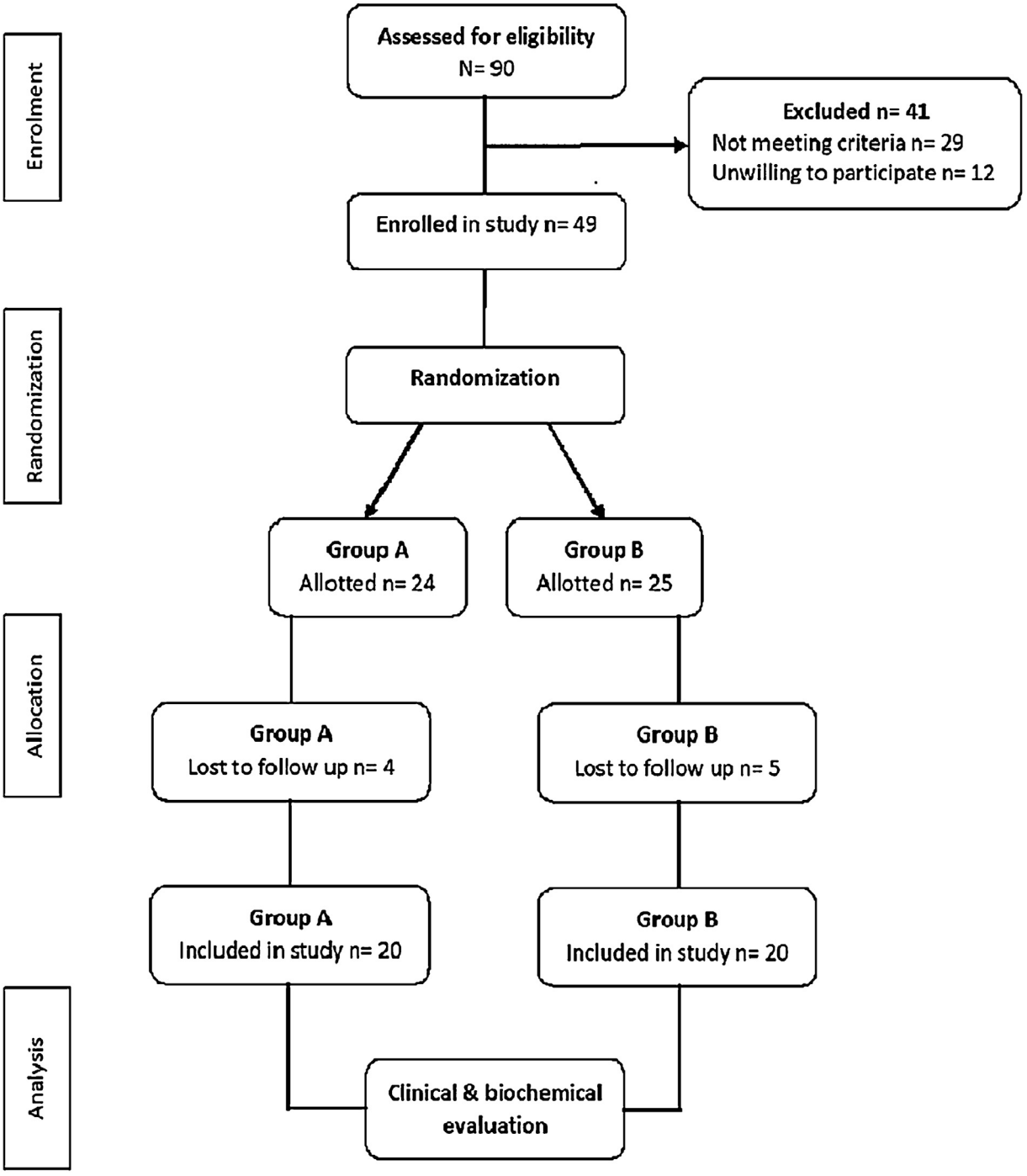

Fig. 2. Flow diagram indicating various stages of the study.

RESULTS

Ninety patients with OSMF were assessed for eligibility and 41 were excluded. The remaining 49 were divided randomly into 2 groups. Nine patients (group A, $n = 4$; group B, $n = 5$) were lost to follow-up. Five of these patients were from lower socioeconomic backgrounds, such as daily wage earners, and found it difficult to make frequent trips to the hospital. Following the initial reduction in burning sensation and absence of symptoms, the other 4 patients dropped out. The final study included 40 patients with OSMF. All patients were males, between the ages of 18 and 55 years (30.17 ± 7.71), and 87.5% were below the age of 40. All patients had a positive history for the use of gutkha.

A highly significant reduction ($P < .01$) in burning sensation was observed at 2 weeks (77% in group A

Table I. Clinical parameters before and after treatment

Visit	*Burning sensation (VAS)*		*Mouth opening (mm)*		*Tongue protrusion (mm)*		*Cheek flexibility (mm)*	
	A	*B*	*A*	*B*	*A*	*B*	*A*	*B*
Baseline	6.7	5.45	29.55	28.45	43.45	46	5.1	5.5
First	1.5	1.2	31.05	30.2	44.95	46.85	5.75	6.1
Second	0	0	32.4	31.6	46.25	47.7	6.35	6.8
Third	0	0	33.75	33.05	47.5	48.7	7.3	7.41
Fourth	0	0	35	34.45	48.5	49.45	7.75	8.16
Mean improvement			5.45	5.9	5.05	3.45	2.65	2.66

VAS, visual analog scale.

and 78% in group B). A 100% reduction was observed at 4 weeks in all 40 patients (Table I, Figure 3). Mouth opening increased by a maximum of 7 mm (5.45 ± 1.64 mm) in group A and 8 mm (5.9 ± 2.00 mm) in group B ($P < .01$; Table I, Figure 4). Maximum increase in tongue protrusion was 6 mm in both groups ($P > .05$) with a mean of 5.05 ± 2.13 mm in group A and 3.45 ± 2.52 mm in group B (Table I). Cheek flexibility increased by 5 mm in both groups (2.65 ± 0.57 mm in group A and 2.66 ± 0.53 mm in group B). Although the improvement in cheek flexibility was significant in each group ($P < .01$), there was no significant difference between the groups ($P > .05$; Table I).

The mean serum LDH level in the 20 healthy volunteers was 173.2 ± 46.20 IU/L, and the mean LDH level in patients with OSMF was 359.72 ± 77.02 IU/L ($P < .01$). Following treatment with curcumin, LDH levels reduced to 275.55 ± 69.08 IU/L in patients with OSMF ($P < .01$). Pretreatment serum LDH levels in group A were 341.85 ± 71.71 IU/L and reduced to 264.95 ± 65.09 IU/L ($P < .01$) after 8 weeks. In group B values reduced from 377.6 ± 79.76 IU/L to 286.15 ± 72.95 IU/L ($P < .01$; Figure 5).

Curcumin mucoadhesive patches stayed in contact with the buccal mucosa for approximately 30 min, after which they began to disintegrate and were completely dissolved by 45 to 50 min. The patches were easy to apply and patients did not report any difficulty or discomfort. None of the patients reported any major adverse effects such as local irritation, itching, salivary or taste alterations, or mucosal thickening or swellings. Mild yellowish discoloration was seen in the buccal mucosa, lips, and tongue of patients in both groups, which was temporary in nature and disappeared after rinsing. Eight patients in the gel group were conscious of this discoloration and brought it our notice. They were advised of its temporary nature and advised to continue treatment.

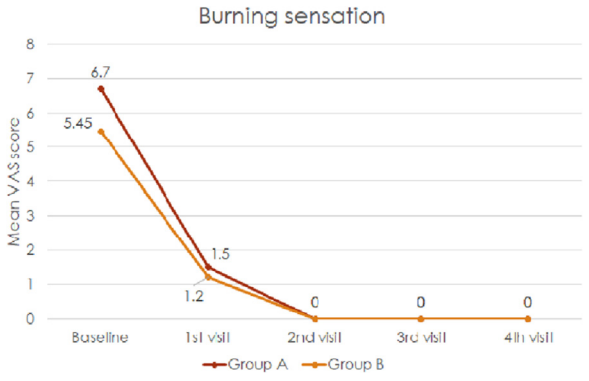

Fig. 3. Reduction in burning sensation.

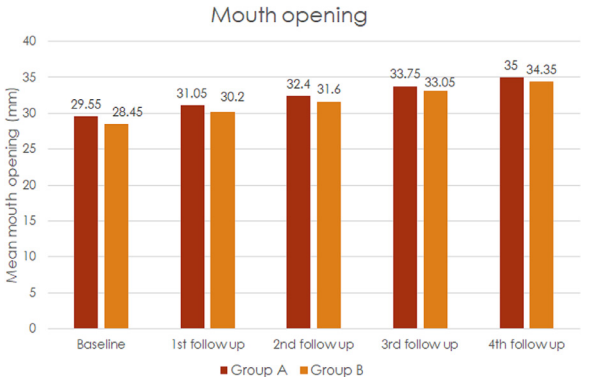

Fig. 4. Improvement in mouth opening.

DISCUSSION

This study highlights the effectiveness of curcumin in the management of potentially malignant diseases such

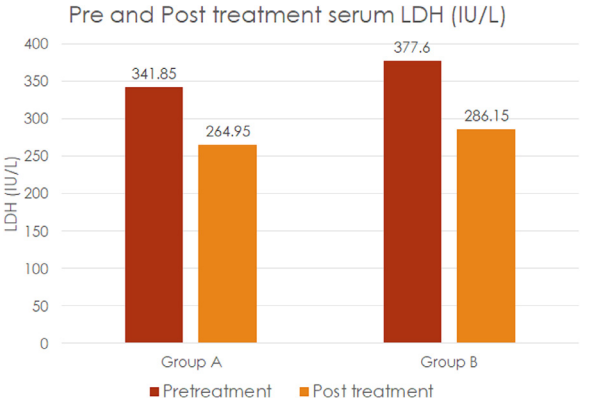

Fig. 5. Pre- and posttreatment serum lactate dehydrogenase levels (IU/L).

as OSMF. OSMF remains an enigma, with several theories explaining its cellular, molecular, genetic, and biochemical mechanisms.[17] The use of smokeless tobacco products like gutkha (tobacco, areca nut, and flavoring agents)[1] is on the rise, especially among the younger population. This was evident in our study: 60% of the patients were below the age of 30, similar to statistics reported by other studies.[18,19]

The malignant transformation rate of OSMF over a 12-year period is 7.6% to 12%.[20] Arecoline, the chief alkaloid in areca nut, is a potent carcinogen. It causes lipid peroxidation, DNA damage, mutation, and tumor induction.[21] Turmeric, an Indian spice, has potent antioxidant, anti-inflammatory, anticarcinogenic, immunomodulating, and chemopreventive properties. It can inhibit the initiation and progression of potentially malignant diseases and has successfully been tried in cancers.[22] Curcumin, chemically diferuloylmethane, is the active ingredient of turmeric. At a molecular level, curcumin acts by modulating multiple targets, inhibiting several proinflammatory factors (nuclear factor-kappa beta, interleukin-8, MIP-1, MCP-1, interleukin-1α, and tumor necrosis factor-α induced by inflammatory stimuli), constrains cell proliferation and induces apoptosis.[12] The beneficial actions of curcumin are limited by its poor oral absorption, rapid metabolism, and elimination from the body. The highest plasma concentration in humans is 0.051 μg/mL from 12 g curcumin.[23]

Transmucosal delivery through body surfaces allows rapid onset of action and adequate retention of drugs at the desired site. Transmucosal mucoadhesive devices such as tablets, patches, etc., are based on the principle of mucoadhesion, in which binding of polymers with the mucous layer of the epithelium occurs.[13]

In this study, burning sensation reduced significantly at 2 weeks ($P < .01$; 77% in group A and 78% in group B). At 4 weeks, all patients were relieved of burning sensation in the oral cavity. In addition to habit cessation, anti-inflammatory and antioxidant properties of curcumin delivered locally as gel/mucoadhesive patches contributed to the early and effective response. These results are similar to a study where a maximum 83.3% reduction in burning sensation was obtained after 1 month of treatment with Turmix tablets (curcumin 300 mg, piperine 5 mg).[24] In another study, Turmix tablets along with topical application of turmeric and honey paste showed a 42.4% reduction in visual analog scale scores after 15 days.[25]

Improvement in mouth opening by 5.45 $\pm$ 1.64 mm was observed in group A and by 5.9 $\pm$ 2.00 mm in group B ($P < .01$). These results are similar to a study that reported an improvement of 5.93 $\pm$ 2.37 mm obtained with curcumin lozenges at 3 months.[26] In a study in which 300 mg curcumin tablets were given orally for 6 months, an improvement of 4.1 $\pm$ 4.2 mm was obtained.[27] Pentoxifylline tablets (Trental 400 mg) along with garlic pearls (Ranbaxy) containing garlic oil 0.25% w/w were given to patients with OSMF for 3 months and a mouth opening increase of 5.37 mm was observed, similar to our study.[28] In another study, systemic curcumin (300 mg) compared to intralesional injections of dexamethasone (4 mg/mL) and hyaluronidase (1500 IU) showed an improvement of 1.25 mm and 3.13 mm, respectively, after 3 months.[29] Although a similar improvement in mouth opening was obtained in these studies using different treatment approaches, curcumin gel and mucoadhesive patches showed significant improvement at 2 months.

These findings indicate that topical curcumin appears to be more effective than systemic routes. It also shows a comparable response to other herbal agents as well as intralesional steroid injections, when considered over similar time periods. These results can be attributed to the longer retention of curcumin against the mucosa and reduced salivary washout, which ensured a steady rate of delivery, leading to higher local bioavailability. It also avoided the potential side effects of intralesional therapy such as multiple punctures, discomfort, invasiveness, and possibility of posttreatment fibrosis.

Groups A and B showed an improvement in tongue protrusion of 5.05 $\pm$ 2.13 mm and 3.45 $\pm$ 2.52 mm, respectively. These results are comparable to a previous study using turmeric with black pepper and *Nigella sativa* capsules in patients with OSMF. After 3 months, tongue protrusion improved by 3.1 mm in the turmeric group and 3.2 mm with *Nigella sativa*.[30]

Cheek flexibility improved by 2.65 $\pm$ 0.57 mm in group A and 2.66 $\pm$ 0.53 mm in group B, which was highly significant within each group ($P < .01$). There was no significant difference between curcumin gel and mucoadhesive patches ($P > .05$).

Of the 40 patients in this study, 1 patient was in stage I, 16 patients were in stage II, and 23 patients were in stage III. The greater number of patients in the late stages of OSMF could be due to the chronic and insidious nature of OSMF, responsible for late detection and also a general lack of concern among patients. All patients showed significant improvements in clinical parameters irrespective of clinical staging.

LDH is a universal enzyme present in the cytoplasm of almost all cells in the body. It catalyzes the final step of anaerobic glycolysis and is released whenever there is damage to cells. It is therefore a useful marker for tissue destruction.[4] Significantly elevated levels of serum LDH were observed in patients with OSMF compared to healthy individuals, which is in accordance with previous studies that observed elevation in serum and salivary LDH.[4-6] There was also a

significant reduction in serum LDH in both groups at 8 weeks posttreatment ($P < .01$), which can be explained by the antioxidant action of curcumin. Other possible reasons could be cessation of areca nut/gutkha habit and improved nutrition intake because of the reduction in burning sensation. There may also have been some amount of systemic absorption of curcumin through the mucosa and swallowing of saliva, albeit in small quantities. This could have potentiated the beneficial effects of curcumin.

Limitations of this study included the inability to estimate the amount of curcumin that penetrated the mucosa via the mucoadhesive patches. The study was also conducted on a relatively small population of patients with OSMF. In addition, following initial improvement in symptoms, a few patients did not return for further treatment. The unequal distribution of patients in different stages of OSMF made stagewise analysis of treatment response difficult. Hence, further studies involving a larger number of patients that would allow stagewise analysis and long-term follow-up is recommended. Permeability studies to highlight the amount of curcumin penetration through the oral mucosa can be carried out to develop new formulations of this multifaceted herb.

CONCLUSION

The results of this study highlight the efficacy of topical curcumin gel and mucoadhesive patches in relieving symptoms of OSMF. Buccal mucoadhesive patches remain an uncharted area in managing oral mucosal diseases. The curcumin mucoadhesive patches and gels used in this study were easy to apply, were well tolerated, and, most importantly, provided a noninvasive mode of treatment for OSMF.

ACKNOWLEDGMENT

We gratefully acknowledge Dr. Nagaraj B.V., Biostatician, College of Dental Sciences, Davangere for providing the statistical analysis for this study.

REFERENCES

1. Hazarey VK, Erlewad DM, Mundhe KA, Ughade SN. Oral submucous fibrosis: study of 1000 cases from central India. *J Oral Pathol Med*. 2007;36:12-17.
2. Rajendran R, Vijayakumar T, Vasudevan DM. An alternative pathogenetic pathway for oral submucous fibrosis (OSMF). *Med Hypotheses*. 1989;30:35-37.
3. Choudhari SK, Chaudhary M, Gadbail AR, Sharma A, Tekade S. Oxidative and antioxidative mechanisms in oral cancer and precancer: a review. *Oral Oncol*. 2014;50:10-18.
4. Patel S, Metgud R. Estimation of salivary lactate dehydrogenase in oral leukoplakia and oral squamous cell carcinoma: a biochemical study. *J Cancer Res Ther*. 2015;11:119-123.
5. Nalin AS, Rajeev R, George GB, Padiath S. Level of serum lactate dehydrogenase enzyme in oral lichen planus—a biochemical study. *IOSR J Dent Med Sci*. 2018;17:20-26.
6. Sivaramakrishnan M, Sivapathasundharam B, Jananni M. Evaluation of lactate dehydrogenase enzyme activity in saliva and serum of oral submucous fibrosis patients. *J Oral Pathol Med*. 2015;44:449-452.
7. Gupta J, Srinivasan SV, Daniel MJ. Efficacy of betamethasone, placental extract and hyaluronidase in the treatment of OSMF: A comparative study. *e-Journal of Dentistry*. 2012;2.
8. Naik V, Prakash S, Thomas LA. Role of free radicals and effectiveness of antioxidants in patients with OSMF and OLP—a systematic review. *Int J Life Sci Pharma Res*. 2018;8:58-69.
9. Rajendran R, Rani V, Shaikh S. Pentoxifylline therapy: a new adjunct in the treatment of oral submucous fibrosis. *Indian J Dent Res*. 2006;17:190-198.
10. Shubha G, Sheshaprasad R, Hebbar P, Pai A, Shubhasini AR, Keerthi G. Efficacy of conservative versus intralesional therapy in OSMF—a comparative study. *J Med Radiol Pathol Surg*. 2018;5:13-17.
11. Angadi PV, Rao S. Management of oral submucous fibrosis: an overview. *Oral Maxillofac Surg*. 2010;14:133-142.
12. Aggarwal BB, Harikumar KB. Potential therapeutic effects of curcumin, the anti-inflammatory agent, against neurodegenerative, cardiovascular, pulmonary, metabolic, autoimmune and neoplastic diseases. *Int J Biochem Cell Biol*. 2009;41:40-59.
13. Patel VF, Liu F, Brown MB. Advances in oral transmucosal drug delivery. *J Control Release*. 2011;153:106-116.
14. Madhav NS, Shakya AK, Shakya P, Singh K. Orotransmucosal drug delivery systems: a review. *J Control Release*. 2009;140:2-11.
15. Thimmasetty J, Pandey G, Babu P. Design and in vivo evaluation of carvedilol buccal mucoadhesive patches. *Pak J Pharm Sci*. 2008;21:241-248.
16. Bais R, Philcox M. Approved recommendation on IFCC methods for the measurement of catalytic concentration of enzymes. Part 8. IFCC method for lactate dehydrogenase (L-lactate: NAD + oxidoreductase, EC 1.1. 1.27). International Federation of Clinical Chemistry (IFCC). *Eur J Clin Chem Clin Biochem*. 1994;32:639-655.
17. Tilakaratne WM, Klinikowski MF, Saku T, Peters TJ, Warnakulasuriya S. Oral submucous fibrosis: review on aetiology and pathogenesis. *Oral Oncol*. 2006;42:561-568.
18. Shah N, Sharma PP. Role of chewing and smoking habits in the etiology of oral submucous fibrosis (OSF): a case-control study. *J Oral Pathol Med*. 1998;27:475-479.
19. Ahmad MS, Ali SA, Ali AS, Chaubey KK. Epidemiological and etiological study of oral submucous fibrosis among gutkha chewers of Patna, Bihar, India. *J Indian Soc Pedod Prev Dent*. 2006;24:84-89.
20. Tilakaratne WM, Iqbal Z, Teh MT, et al. Upregulation of HIF-1 alpha in malignant transformation of oral submucous fibrosis. *J Oral Pathol Med*. 2008;37:372-377.
21. Ekanayaka RP, Tilakaratne WM. Oral submucous fibrosis: review on mechanisms of pathogenesis and malignant transformation. *J Carcinog Mutagen*. 2013;5:002-11.
22. Chattopadhyay I, Biswas K, Bandyopadhyay U, Banerjee RK. Turmeric and curcumin: biological actions and medicinal applications. *Curr Sci*. 2004;87:44-53.
23. Lao CD, Ruffin MT, Normolle D, et al. Dose escalation of a curcuminoid formulation. *BMC Complement Altern Med*. 2006;6:1-4.
24. 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 Radiol*. 2014;26:260-263.
25. Nigam N, Reddy Enja SP, Chandra S, Pandey N. Effect of curcumin in reducing burning sensation in potentially malignant disorders of oral cavity. *J Indian Acad Oral Med Radiol*. 2017;29:7-11.

26. Hazarey VK, Sakrikar AR, Ganvir SM. Efficacy of curcumin in the treatment for oral submucous fibrosis—a randomized clinical trial. *J Oral Maxillofac Pathol: JOMFP*. 2015;19:145-152.
27. Piyush P, Mahajan A, Singh K, Ghosh S, Gupta S. Comparison of therapeutic response of lycopene and curcumin in oral submucous fibrosis: a randomized controlled trial. *Oral Dis*. 2019;25:73-79.
28. Jain N, Annigeri RG, Pipalia PR. Efficacy of garlic in conjunction with pentoxifylline in the management of oral submucous fibrosis—a preliminary study. *Int J Pharm Sci Res*. 2016;7:5017-5023.
29. Yadav M, Aravinda K, Saxena VS, et al. Comparison of curcumin with intralesional steroid injections in oral submucous fibrosis—a randomized, open-label interventional study. *J Oral Biol Craniofac Res*. 2014;4:169-173.
30. Pipalia PR, Annigeri RG, Mehta R. Clinicobiochemical evaluation of turmeric with black pepper and *Nigella sativa* in management of oral submucous fibrosis—a double-blind, randomized preliminary study. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2016;122:705-712.

Reprint requests:

Dr. Aditi Chandrashekar, MDS
Department of Oral Medicine and Radiology
College of Dental Sciences, Pavilion Road
Davangere- 577004
Karnataka
India
Aditi212121@gmail.com