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To determine the efficacy of colchicine as a monotherapy in Oral Submucous Fibrosis (OSMF) Patients

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Abstract---Introduction: Oral submucous fibrosis (OSMF) is a potentially malignant disorder of oral mucosa affecting mainly population in South and Southeast Asia. Oral submucous fibrosis (OSMF) condition results in scars, fibrosis of the tissues, and develops precancerous lesions in some long-term individuals most frequently affecting the buccal mucosa. This study is aimed to determine the effectiveness of colchicine in the management of OSMF along with examination of clinical conditions such as burning sensation, buccal mucosal flexibility, interincisal distance, and protrusion of tongue. Materials and Methodology: Group A: Study participants who were getting treatment with 0.5 mg colchicine tablets twice daily for 3 months. Group B: Treatment with intralesional injection of 2 mL dexamethasone, hyaluronidase 1,500 IU with 2 mL lignocaine twice a week for 4–6 weeks. Periodic reassessment of all the participants on certain selected parameters was done after 3 and 6 months. All the data obtained were subjected to statistical analysis at the end of the study. The statistical analysis was performed by using the SPSS 17.0 version for Windows (Chicago, IL, USA). Results: The mean values of burning sensation, mouth opening, cheek flexibility, and tongue protrusion in group A and group B before the treatment were $6.4 \pm$

1.6, 28.9 ± 1.8 , 10.4 ± 3.92 , 30.9 ± 2.9 and 6.6 ± 1.7 , 29.9 ± 2.4 , 10.36 ± 4.2 , 31.6 ± 4.8 respectively as shown in table - 1. There was no statistically significant difference observed in the flexibility of buccal mucosal and tongue protrusion at all the time intervals between both the groups. Conclusion: The management of OSMF with colchicine can be one of the effective treatment modalities in patients in whom steroids are strictly contraindicated due to medical conditions as a steroid-sparing agent.

Keywords---colchicine, OSMF, areca nut.

Introduction

Oral Submucous Fibrosis (OSMF) is considered as one of the chronic conditions affecting most of the Indians and to some extent affecting other Asiatic people. However, numerous immigrations of population from the Indian subcontinent, dentist encounter this disease in developed countries.¹ Oral submucous fibrosis (OSMF) condition results in scars, fibrosis of the tissues, and develops precancerous lesions in some long-term individuals most frequently affecting the buccal mucosa.² Most common pathological findings of this disease are chronic inflammation, increased collagen deposition in the connective tissues which are present below the oral mucosal epithelium, inflammation of the lamina propria or inflammation of the deep connective tissues, and other degenerative changes affecting the muscles. A severe burning sensation of the mouth after intake of spicy foods is often noticed in OSMF patients. Dry mouth, pain, taste sensation disorders, limited tongue mobility, stiffness of the jaw (trismus), dysphagia, and altered tone of voice are the other common symptoms of OSMF condition. A higher mortality rate of OSMF ranges from 1.5 to 15 % due to its malignancy transformation.³ There are various treatment options available for OSMF which includes drug administration, surgical excision, and physiotherapy but still none of them cures the disease. Colchicinum-N- (5,5,7,9-Tetrahydro-1,2,3,10-tetramethoxy-9-oxobenzo [alpha] heptalen-7-yl) acetamide, colchicine an alkaloid which is an antifibrotic agent found to inhibit collagen synthesis and higher collagenolytic activity apart from this it has anti-inflammatory properties. The anti-inflammatory property is due to the colchicine drug acting on the PMNL's (polymorphonuclear leukocytes) and chemotaxis, adhesiveness of leukocytes and prostaglandin E.

Colchicine is found to be effective in the treatment of conditions like gout, recurrent aphthous stomatitis, and oral lichen planus and lowering the fibrosis in liver and kidney diseases.^{6,7} There are only few studies conducted on colchicine in the management of OSMF. Daga D et al⁸ and Krishnamoorthy B et al⁹ stated that administration of intralesional injection of hyaluronidase along with colchicine are effective in the treatment of OSMF which aids in widening of mouth opening and reduction of burning sensation without causing any side effects. This study is aimed to determine the effectiveness of colchicine in the management of OSMF along with examination of clinical conditions such as burning sensation, buccal mucosal flexibility, interincisal distance, and protrusion of tongue.

Materials and Methodology

This study is conducted in the Department and after getting prior approval from Institutional Ethical Committee under the guidelines provided by the World Medical Association Declaration of Helsinki on ethical principles for medical research involving humans for studies. The duration of the study was opted for 6 months. A total of 40 participants were employed in the current study based on the previous study by Daga D et al.⁸

Patients who were clinically diagnosed as OSMF of stages I, II, III were informed about the study protocol and were recruited based on their interest to take part in the study and readiness to accept regular follow-up protocol. There are few exclusion criteria which included patients who are already receiving other treatment for OSMF, stage IV patients in whom oral carcinoma is present along with OSMF, pregnant patients, patients receiving immunosuppressant drugs, patients with difficulty and restricted mouth opening due to reasons other than OSMF and patients having fibrotic lesions other than OSMF. Group A: Study participants who were getting treatment with 0.5 mg colchicine tablets twice daily for 3 months. GroupB: Treatment with intralesional injection of 2 mL dexamethasone, hyaluronidase 1,500 IU with 2 mL lignocaine twice a week for 4–6 weeks.

All the clinical examinations were basically performed by a single trained and well-calibrated examiner. The selection of the areas of injection was generally dependent on clinical judgment. The baseline intensity of the burning sensation, interincisal mouth opening, flexibility of buccal mucosal and tongue protrusion values was recorded periodically. This was followed by full-mouth oral prophylaxis and certain therapeutic intervention was provided to the participant according to the group assigned. Periodic reassessment of all the participants on certain selected parameters was done after 3 and 6 months. All the data obtained were subjected to statistical analysis at the end of the study. The statistical analysis was performed by using the SPSS 17.0 version for Windows (Chicago, IL, USA). The normality of the data was subjected to be tested using the Shapiro–Wilk test. In order to test the association between the groups, the Chi-square test was used. And to test the mean difference between two groups, a Student's t-test (paired sample t-test and independent sample t-test) was used. All the P values which are less than 0.05 were considered statistically significant.

Results

A total of 40 participants, 20 in each group with 14 males, 6 females in group A and 12 males, 8 females in group B, and mean age of 42.72 ± 11.62 were comprised into the study. The mean values of burning sensation, mouth opening, cheek flexibility, and tongue protrusion in groupA and groupB before the treatment were 6.4 ± 1.6 , 28.9 ± 1.8 , 10.4 ± 3.92 , 30.9 ± 2.9 and 6.6 ± 1.7 , 29.9 ± 2.4 , 10.36 ± 4.2 , 31.6 ± 4.8 respectively as shown in table - 1. Intragroup comparisons of the patients receiving colchicine displayed significant enhancement in burning sensation and mouth opening at all the follow-up periodic reassessment ($P < 0.05$). The buccal mucosal flexibility and tongue protrusion values were not found to be statistically significant at 1 month to 3 months follow-up. When comparing with group B, significant improvement was

found in mouth opening and tongue protrusion at all the periodic reassessment intervals of follow-up. The values of burning sensation and buccal mucosal flexibility were not found to be significantly altered at 3 months to 6 months follow-up.

As detailed in the table – 2, observing the intergroup comparisons, significant P values were found between both the groups at baseline to 1 month and 3 months to 6 months follow-up visits but from baseline to 6 months, no statistical difference was found between the two groups in burning sensation parameter. Similarly, statistical significance was found between both the groups for mouth opening was seen at baseline to 1 month only. Lastly, there was no statistically significant difference observed in the flexibility of buccal mucosal and tongue protrusion at all the time intervals between both the groups.

Table 1
Intragroup comparisons of study parameters at different intervals of follow-up

Parameters	Time (months)	Group A		Group B	
		Mean $\pm$ SD	P	Mean $\pm$ SD	P
Burning sensation	Baseline vs 1	6.4 $\pm$ 1.6vs5.2 $\pm$ 1.7	0.00	6.6 $\pm$ 1.7vs4 $\pm$ 1.7	0.00
	1 vs 3	5.2 $\pm$ 1.6vs4.1 $\pm$ 1.9	0.001	4 $\pm$ 1.7vs3.8 $\pm$ 1.7	0.462
	3 vs 6	4.1 $\pm$ 2vs2.3 $\pm$ 1.9	0.00	3.8 $\pm$ 1.7vs3.7 $\pm$ 1.3	0.671
	Baseline vs 6	6.4 $\pm$ 1.6vs2.3 $\pm$ 1.9	0.00	6.6 $\pm$ 1.7vs3.6 $\pm$ 1.3	0.00
Mouth opening	Baseline vs 1	28.9 $\pm$ 1.8vs30.1 $\pm$ 1.8	0.004	29.9 $\pm$ 2.4vs33.3 $\pm$ 2.7	0.00
	1 vs 3	30 $\pm$ 1.8vs30.8 $\pm$ 1.8	0.023	33.3 $\pm$ 2.6vs33.6 $\pm$ 2.6	0.05
	3 vs 6	30.1 $\pm$ 1.7vs31.7 $\pm$ 1.9	0.012	33.6 $\pm$ 2.6vs33.9 $\pm$ 2.5	0.058
	Baseline vs 6	29 $\pm$ 1.8vs31.7 $\pm$ 1.9	0.00	29.9 $\pm$ 2.4vs34.0 $\pm$ 2.5	0.00
Buccalmucosa flexibility	Baseline vs 1	10.4 $\pm$ 3.92vs10.6 $\pm$ 3.7	0.252	10.3 $\pm$ 4.2vs10.7 $\pm$ 3.8	0.112
	1 vs 3	10.7 $\pm$ 3.7vs10.8 $\pm$ 3.8	0.099	10.7 $\pm$ 3.8vs11.5 $\pm$ 4.5	0.031
	3 vs 6	10.8 $\pm$ 3.8vs11 $\pm$ 3.6	0.019	11.5 $\pm$ 4.5vs11.4 $\pm$ 3.7	0.813
	Baseline vs 6	10.4 $\pm$ 3.9vs11 $\pm$ 3.7	0.023	10.4 $\pm$ 4.1vs11.4 $\pm$ 3.7	0.001
Tongue protrusion	Baseline vs 1	30.9 $\pm$ 2.9vs31.2 $\pm$ 3.8	0.392	31.6 $\pm$ 4.8vs32.2 $\pm$ 4.9	0.014
	1 vs 3	31.2 $\pm$ 3.8vs31.8 $\pm$ 3.8	0.275	32.2 $\pm$ 4.9vs33 $\pm$ 4.8	0.002
	3 vs 6	31.7 $\pm$ 3.8vs32 $\pm$ 3.8	0.437	32.8 $\pm$ 4.9vs34.2 $\pm$ 4.4	0.014
	Baseline vs 6	31 $\pm$ 3vs32 $\pm$ 3.8	0.084	31.6 $\pm$ 4.8vs33.7 $\pm$ 4.4	0.00

Table 2
Intergroup comparisons of study parameters at different intervals of follow-up

Parameter	Time	Mean difference $\pm$ SD		P - value
		Group A	Group B	
Burning sensation	Baseline vs 1	1.2 $\pm$ 0.09	2.61 $\pm$ 0.05	0.003
	1 vs 3	1.2 $\pm$ 0.39	0.33 $\pm$ 0.03	0.025
	3 vs 6	1.82 $\pm$ 0.01	0.15 $\pm$ 0.35	0.001
	Baseline vs 6	4.13 $\pm$ 0.52	2.94 $\pm$ 0.54	0.077
Mouth opening	Baseline vs 1	1.15 $\pm$ 0.03	3.47 $\pm$ 0.19	0.00
	1 vs 3	0.79 $\pm$ 0.05	0.38 $\pm$ 0.02	0.127
	3 vs 6	0.84 $\pm$ 0.23	4.2 $\pm$ 0.05	0.139
	Baseline vs 6	2.75 $\pm$ 0.23	0.39 $\pm$ 0.11	0.021
Buccal mucosa flexibility	Baseline vs 1	0.29 $\pm$ 0.27	0.39 $\pm$ 0.37	0.667
	1 vs 3	0.19 $\pm$ 0.09	0.99 $\pm$ 0.72	0.119
	3 vs 6	0.20 $\pm$ 0.03	0.23 $\pm$ 0.85	0.521
	Baseline vs 6	0.71 $\pm$ 0.22	1.18 $\pm$ 0.55	0.239
Tongue protrusion	Baseline vs 1	0.42 $\pm$ 0.83	0.66 $\pm$ 0.18	0.642
	1 vs 3	0.49 $\pm$ 0.03	0.83 $\pm$ 0.02	0.475
	3 vs 6	0.39 $\pm$ 0.07	1.14 $\pm$ 0.55	0.159
	Baseline vs 6	1.19 $\pm$ 0.88	2.45 $\pm$ 0.44	0.105

Discussion

The South Asian countries namely India, Sri Lanka, Pakistan, China, and Bangladesh recorded the predominant numbers of patients affected with oral submucous fibrosis, apart from its presence being observed among the people of Indian origin in South Africa and a few parts of America. The major factors that could attribute to the OSMF are consumption of excessive red chilies, chewing of areca nut, nutritional deficiencies, genetic susceptibility, autoimmunity and collagen disorders are commonly involved in the pathogenesis of OSMF. Teenagers and young adults are mostly getting attracted to consume the commercially available areca nut products like gutka and paan masala basically because of its marketing strategies, publicity and easy availability of such products.¹⁰ The mean age of the OSMF patients that was observed in this study is like the mean age of OSMF patients stated by *Sadaksharam J et al* and *Yadav M et al*.^{11,12} In the current study, gutka chewers were more common than betel quid chewers and other forms of smokeless tobacco. Identical findings were seen in the studies by *Ali et al*¹³ and *Reichart et al*¹⁴ about gutka and other areca nut products. This shows that the people having areca nut as gutka are more likely to have the new cases of OSMF.

The abrasive nature of the areca nut continuously causes local trauma and irritation to the oral mucosa which could eventually lead to morphological changes.¹⁵ Though the contributory factors in the pathogenesis of OSMF are well-documented, the management of this condition is still not very successful. Various surgical treatments have been carried out to cure OSMF but there seems to be no definitive or widely accepted treatment that is currently available till date. The essential primary step before commencing any treatment procedure is discontinuation of the habit.¹⁶ Intralesional injections with steroids have been

used predominantly to treat OSMF. The mechanism of action of the steroids is by directly opposing the action of soluble factors that are generated by sensitized lymphocytes after its activation by specific antigens. Steroids also act as immunosuppressive drug and could suppress various inflammatory reactions. Hence this prevents fibrosis by reducing the fibroblastic proliferation and collagen deposition.^{17,18}

Various studies observed the potent beneficial effects of colchicine in treating certain disorders like gout in animals and human beings. A few authors have also claimed that colchicine as an effective agent to treat Behcet's syndrome, recurrent aphthous stomatitis and oral lichen planus with positive results.¹⁹ Daga D et al⁸ reported that the intralesional injection of hyaluronidase along with oral colchicine gave better results in the management of OSMF without any notable side effects. A history of burning sensation was observed in all the patients at the start of the study. The decrease in the severity of burning sensation was rapid in group A than in group B which concludes the usefulness of colchicine in the management of OSMF. This might probably be because of the anti-inflammatory effect of colchicine by its destabilizing action on the microtubules. Group B patients had significant enhancement only during the administration of intralesional injections. Group A patients reported a sustained increase in the mouth opening even after the cessation of treatment. But, the overall improvement in the mouth opening was found to be greater in the group B patients. The improvement in the mouth opening in group A can be attributed to colchicine's anti-fibrotic effect as it effectively inhibits procollagen secretion, reduces collagen synthesis and thus downregulates fibroblast proliferation. It also helps in preventing the extrusion of collagen fibres from the fibroblast and increases collagenolytic activity. Buccal mucosal flexibility or cheek flexibility directly indicates the suppleness and elasticity of the buccal mucosa. In the present study, a negotiable difference in the comparison of cheek flexibility in both group A and group B with 5.99 and 9.97% respectively was found which indicate the positive role of colchicine. The increase in cheek flexibility might be due to decreased fibrinogenesis in both the groups. The current study results were in concordance with a study done by Yadav M et al¹² in the patients who are receiving a weekly intralesional injection of 4 mg dexamethasone and 1,500 IU hyaluronidase. In the present study, interventional drugs were well-tolerated by patients in both groups.

Conclusion

The management of OSMF with colchicine can be one of the effective treatment modalities in patients in whom steroids are strictly contraindicated due to medical conditions as a steroid-sparing agent. Since there was no statistically significant difference between both the groups in reducing the signs and symptoms but clinically there was a quite rapid improvement in reducing burning sensation, improvement in buccal mucosal flexibility and tongue protrusion in patients receiving colchicine. Because of the easy availability of colchicine, cost-effectiveness and good patient compliance, colchicine can be used as an adjuvant treatment modality in the management of OSMF.

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