



Evaluation of Therapeutic Efficacy of Different Treatment Modalities in Oral Submucous Fibrosis: A Comparative Study

¹Beenakumary TP, ²Anju Gopinathan T, ³Megha Varghese, ⁴Rekha Raghavan, ⁵Muhammed Najeer VM, ⁶Alen Pius

ABSTRACT

Aim: Aim of this study was to assess the efficiency of different treatment modalities for oral submucous fibrosis.

Materials and methods: Sixty patients were included in the study, which was diagnosed as stage II oral submucous fibrosis (OSMF) based on habitual history and clinical findings. Three groups were made after randomization, i.e., group 1: capsule lycopene group, group 2: capsule lycopene and injection dexamethasone, group 3: injection dexamethasone and hyaluronidase group. Symptom severity was done by visual analog scale (VAS) scoring system viz burning sensation/pain in the patients; patient satisfaction was assessed. Vernier calipers were used to measure patients' maximum mouth opening at day 1, 1st month, 2nd month, 3rd month.

Results: Male and female had the mean age of 28.20 ± 4.26 and 39.34 ± 2.12 in group 1, in group 2 was 27.88 ± 7.12 and 40.92 ± 7.16 , in group 3 was 28.90 ± 8.69 and 40.10 ± 6.22 , respectively. There was no statistically significant difference between treatment modalities based on satisfaction. On 2nd month, maximum patients with no pain were more in group 3 followed by group 2, and this was statistically significant. At a 3rd month, the maximum reduction in pain was in group 3 followed by group 2 and group 1. Mouth opening was improved in the group 3 followed by groups 2 and 1, respectively. On 3rd

month statistically significant difference was observed between the study groups.

Conclusion: The present study concludes that the treatment with dexamethasone + hyaluronidase group showed better results in improvement in mouth opening in OSMF patients than lycopene, lycopene and dexamethasone groups. Improvement in mouth opening, reduced burning sensation in OSMF patients was also shown by lycopene. Hence lycopene can be considered as a good alternative for treatment for OSMF when dexamethasone is contraindicated due to different reasons.

Clinical significance: Any oral cavity part can be affected by OSMF including the pharynx. It is a potentially malignant disorder. So early recognition and initiation of the effective regimen for the treatment in both early and advanced cases of OSMF are necessary.

Keywords: Burning sensation, Lycopene, Mouth opening, Oral submucous fibrosis.

How to cite this article: Beenakumary TP, Gopinathan AT, Varghese M, Raghavan R, Najeer MVM, Pius A. Evaluation of Therapeutic Efficacy of Different Treatment Modalities in Oral Submucous Fibrosis: A Comparative Study. J Contemp Dent Pract 2019;20(3):390-394.

Source of support: Nil

Conflict of interest: None

¹Department of Oral Medicine and Radiology, PSM College of Dental Science and Research, Thrissur, Kerala, India

²Department of Oral and Maxillofacial Surgery, PSM College of Dental Science and Research, Thrissur, Kerala, India

^{3,5}Department of Periodontics, PSM College of Dental Science and Research, Thrissur, Kerala, India

⁴Department of Periodontics, Educare Institute of Dental Sciences, Chattiparamba, Kerala, India

⁶Department of Conservative Dentistry and Endodontics, PSM College of Dental Science and Research, Thrissur, Kerala, India

Corresponding Author: Beenakumary TP, Department of Oral Medicine and Radiology, PSM College of Dental Science and Research, Thrissur, Kerala, India, Phone: +919746398593, e-mail: drbeenajithmds@gmail.com

INTRODUCTION

Oral submucous fibrosis (OSMF) is an insidious, chronic, potentially malignant well recognized oral disease condition. It is characterized by inflammation, progressive fibrosis of the connective tissue including lamina propria and deeper tissues. The inflammatory reaction of juxtepithelial tissue along with vesicle formation leads to lamina propria elasticity, followed by atrophy of the epithelial tissue, later causes oral mucosal stiffness and trismus, making the mastication difficulty.¹

Asians have higher prevalence, especially more in India. Nepal, China, Thailand, and South Vietnam have more cases of OSMF.² There are multiple etiologies like chilli consumption, nutritional deficiency states, areca

nut chewing, genetic susceptibility, autoimmunity and collagen disorders have been suggested to be involved in the pathogenesis of the condition. Arecoline present in are canut is proved to be the main causative agent of OSMF.³

To improve the mouth opening in OSMF, many surgical and medical treatment modalities were tried previously. Lycopene is known to be the safe antioxidant of utmost importance, which is a phytochemical bright red carotenoid and carotene pigment present in red colored fruits and vegetables like red carrots, tomatoes, papayas, and watermelons. Profound benefits of lycopene were demonstrated in leukoplakia, a precancerous lesion because of its potent properties of anti-carcinogenic and antioxidant.⁴ For the past several decades, steroids such as glucocorticoid were used extensively in the treatment of OSMF initially due to its anti-inflammatory property. The surgical management offers less promising disease management because of the recurrence of fibrosis postoperatively.⁵

Relief from the condition is attained by fibrous bands breakage and dissolution by hyaluronidase. The intracellular cement substance's viscosity is decreased by the breaking down of the connective tissue ground substance called hyaluronic acid. Hyaluronic acid's role in the collagen formation is prevented by hyaluronidase. Hyaluronidase may have the capability to have better results against restricted mouth opening.⁶

As there is no evidence to prove the best treatment modality for OSMF, this study was conducted to evaluate the efficacy of different treatment modalities.

MATERIALS AND METHODS

The prospective study was conducted in the department of Oral Medicine and Radiology, PSM College of Dental Science and Research, Kerala. Ethical approval for the study taken from the institutional review board and

Informed consent was obtained from all the participants. Sixty patients (40 male and 20 female), aged around 20–45 years were included in the study, who were reported to the Department of Oral Medicine and radiology and which was diagnosed as stage II OSMF based on habitual history and clinical findings (Figs 1 and 2).

History of burning sensation on intake of hot and spicy foods and beverages, limitation in tongue protrusion, gradual decrease in mouth opening, and palpable fibrous bands were inclusion criteria for the study and those who had past history of radio/chemotherapy, patients with other comorbid disorders, temporomandibular disorder, or pericoronitis and stage III with ulcerations and other mucosal diseases were the exclusion criteria for the study.

Sixty patients were randomly distributed under three groups depending on treatment modalities.

- *Group 1—Capsule lycopene group:* Lycopene capsule of 2 mg per day (Lycored™ Jagsonpal Pharmaceuticals Ltd., New Delhi, India) was given. The Capsule contains 100% natural lycopene of 2000 microgram in each capsule, taken twice daily orally for 3 months.
- *Group 2—Capsule lycopene and injection dexamethasone:* Lycopene capsule of 2 mg per day for 3 months and intralesional injection of 0.5 mL of local anesthesia with 2 mL of dexamethasone twice weekly.
- *Group 3—Injection dexamethasone and hyaluronidase group:* Intralesional injection of 0.5 mL of local anesthesia with 2 mL of dexamethasone and 1500 I.U of hyaluronidase biweekly was administered.

All the patients underwent the clinical examination of the oral cavity. The severity of symptoms was measured by VAS scale, viz burning pain/sensation in the patients, with the score ranged from a numerical 0 (no pain or discomfort) to 10 (severe most pain/discomfort). Patient satisfaction was evaluated. Vernier calipers were used to measure patients' maximum mouth opening at day 1, 1st month, 2nd month, 3rd month.



Fig. 1: Patient with oral submucous fibrosis



Fig. 2: Intraoral clinical condition of oral submucous fibrosis



Fig. 3: Mouth opening: Intra incisal width measurement

The measurement of the distance between the center of incisal edges of maxillary and mandibular central incisor at maximum opened mouth position was used to measure mouth opening (Fig. 3). The interalveolar distance along the midline was measured in edentulous patients.

Counseling to quit the habit was a part of the study period. The mouth opening was assessed, and symptoms were compared to the lesions graded on VAS during every clinical evaluation. Patients were tested for serum urea, creatinine and liver function tests to evaluate any existing hepatic or renal pathology of the baseline and every month repeated once during the study period to rule out any other comorbidities. Patients were instructed to report immediately any constitutional symptoms or

Table 1: Mean age distribution among study groups

Groups	N	Age		p value
		Male (Mean \pm SD)	Female (Mean \pm SD)	
1	20	28.20 \pm 4.26	39.34 \pm 2.12	<0.001***
2	20	27.88 \pm 7.12	40.92 \pm 7.16	<0.001***
3	20	28.90 \pm 8.69	40.10 \pm 6.22	<0.001***

*** Highly significant

Table 3: Evaluation of Burning sensation/pain (VAS) between study groups

Duration and groups		No pain	Mild pain	Moderate pain	severe pain	Fischer exact test
Day 1	Group 1	0	4	6	10	$\chi^2 = 5.220$ $p = 0.324$
	Group 2	0	3	7	10	
	Group 3	0	4	5	11	
1st month	Group 1	0	4	8	8	$\chi^2 = 8.378$ $p = 0.110$
	Group 2	0	7	6	7	
	Group 3	0	6	6	8	
2nd month	Group 1	0	7	9	4	$\chi^2 = 10.984$ $p = 0.021^*$
	Group 2	2	9	7	2	
	Group 3	4	9	6	1	
3rd month	Group 1	6	13	1	0	$\chi^2 = 7.436$ $p = 0.388$
	Group 2	7	13	0	0	
	Group 3	14	6	0	0	

*Significant

adverse reactions. Mouth opening and VAS scale were recorded at monthly follow-up visits.

Statistical Analysis

The results after the inferential and descriptive statistical analysis, continuous measurement is presented as mean \pm SD. The study analysis was done for all the three groups to know the study significance between them by analysis of variance (ANOVA) and qualitative data were analyzed using the Fischer exact test.

RESULTS

The mean age distribution among study groups is depicted in Table 1. In group 1, 28.20 \pm 4.26 and 39.34 \pm 2.12 was the mean age of male and female, in group 2 27.88 \pm 7.12 and 40.92 \pm 7.16, in group 3 was 28.90 \pm 8.69 and 40.10 \pm 6.22, respectively. There was a significant difference noted in all three groups (<0.001).

Patient satisfaction by a grading scale in Table 2 reveals that the results for the satisfaction of the different treatment modalities were almost similar in all the groups with no statistically significant difference.

Table 3 depicts the severity of burning sensation/pain recorded using VAS score where the study group

Table 2: Assessment of patient's satisfaction of the treatment modalities

Patient satisfaction grade	Group 1 (n = 20)	Group 2 (n = 20)	Group 3 (n = 20)	p value
Very satisfied	2 (10.0%)	4 (20.0%)	3 (15.0%)	0.435 NS
Fairly satisfied	10 (50.0%)	7 (35.0%)	8 (40.0%)	
Fairly unsatisfied	8 (40.0%)	9 (45.0%)	9 (45.0%)	
very unsatisfied	0	0	0	

p > 0.05, NS–Nonsignificant

did not have statistical significance differences on day 1. But patients in group 3 had a number of patients with severe pain. There was a slight reduction in the number of study subjects with severe pain in group 2 on the 1st month when compared with group 1 and 3. Study subjects with no pain were more in group 3 followed by group 2 on 2nd month, and this was found to be statistically significant. At a 3rd month, the maximum reduction in pain was in group 3 followed by group 2 and group 1.

In group 3, the mouth opening had improved more in the 1st month, 2nd month, 3rd month (22.18 ± 0.86 , 23.14 ± 1.09 , 26.43 ± 0.22) followed by group 2 (21.98 ± 0.73 , 22.65 ± 0.89 , 25.12 ± 0.91) and group 1 (21.64 ± 1.01 , 22.12 ± 1.82 , 23.88 ± 0.66), respectively. On 3rd month, a statistically significant difference was observed between the study groups (Table 4).

DISCUSSION

The practice of chewing *gutka* and betel quid is the most important association factor for the potentially malignant disorder OSMF. Since the time of Sushruta, it has been encrypted in the Indian literature as 'Vidari'. In the year 1952, the first case was reported by Schwartz and its precancerous nature was identified by Paymaster in 1956. Definition of OSF as was given by Pindborg and Sirsat, in 1966 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 juxtepithelial inflammatory reaction followed by fibroelastic changes in the lamina propria, with epithelial atrophy leading to stiffness of the oral mucosa causing trismus and inability to eat."⁷

In the treatment of OSMF, various categories of drugs have been used, but their effectiveness leaves much to be desired and definitive cure has not been afforded by any treatment.⁸ Increased potential for side effects is high while oral administration as it limits the concentration of drugs in lesional tissue and significant mechanical injury and noncompliance on the patient's part is high with intralesional injections due to the accompanying discomfort and pain.⁹ The health of the consumers has been compromised immensely by the use of arecanut in different forms with or without tobacco as it has unfortunately permeated the ordinary household. The major fatal sequel to their usage is the onset of OSMF and cancer of the oral cavity and India is the globally leading country in this.

In the present study, the subjects were found to be in their second, third and fourth decades of life, including both male and female. Similarly, a peak incidence between the third and fourth decades of life was also found by Nair et al.,¹⁰ Pindborg and Sirsat.¹¹ A rare case of

Table 4: Comparison of mean score mouth opening for different treatment modalities

Duration	Groups	Mean \pm SD	F value	p value and significance
Day 1	Group 1	19.19 \pm 1.80	8.189	0.574
	Group 2	19.22 \pm 1.89		
	Group 3	20.10 \pm 0.66		
1st month	Group 1	21.64 \pm 1.01	10.325	0.312
	Group 2	21.98 \pm 0.73		
	Group 3	22.18 \pm 0.86		
2nd month	Group 1	22.12 \pm 1.82	9.184	0.102
	Group 2	22.65 \pm 0.89		
	Group 3	23.14 \pm 1.09		
3rd month	Group 1	23.88 \pm 0.66	10.165	0.025*
	Group 2	25.12 \pm 0.91		
	Group 3	26.43 \pm 0.22		

* – Significant

OSMF in a 4-year-old Indian girl was reported by Hayes.¹² The disease onset is insidious, gradual, and often of 2–5 years duration. This could be explained as the disease is not distressing to the patient in the early stages. Due to its association with adverse oral habits, many studies have considered betel nut as the only factor responsible for the development of OSMF.

This study used three basic parameters to compare the efficacy of different treatment modalities such as a decrease in burning sensation, increase in the opening of mouth, and satisfaction. At a 3rd month, the treatment has shown statistically significant improvement. The more efficacious of the regimen was dexamethasone + hyaluronidase combination indicated in the treatment of OSMF. Improvement in burning sensation and mouth opening is noted with the use of capsule lycopene, also in capsule lycopene and injection dexamethasone groups.

With dexamethasone + hyaluronidase group showed maximum mouth opening than with capsule Lycopene group, capsule lycopene and injection and this was statistically significant. Definite reduction in burning sensation and improvement in mouth opening was observed by Shah et al.,⁶ Aara et al.¹³ by evaluating the efficacy of the combination of hyaluronidase and dexamethasone in the treatment of OSMF. These findings are in agreement with our study.

Comparison of oral lycopene with placebo to evaluate its efficacy was done by Kumar et al.¹⁴ in patients with OSMF. In that study showed an average increase in 3.4 mm mouth opening noted in patients receiving lycopene while patients administered with a combination of steroids and lycopene revealed 4.6 mm increase but in the present study a maximum improvement of mouth opening was seen in group 3, i.e., around 6 mm, which was statistically significant. Kakar et al.¹⁵ studied that patients receiving hyaluronidase had swift improvement in symptoms but better and long-term results were

noted in the combination with dexamethasone. This observation was similar to our study, as there was a significant improvement in group 3.

Lycopene capsule and injection dexamethasone combination were evaluated in the present study. The intralesional injection's efficacy in combination with other treatment modalities has been compared by various researchers. Combination of alpha lipoic acid with hyaluronidase and intralesional steroid, the treatment outcome was evaluated by Rao.¹⁶ The comparative treatment effectiveness of the combination of lycopene and antioxidants with intralesional steroid and hyaluronidase injections was studied by Selvam and Dayanand.¹⁷ The treatment was proved to be effective in all the studies, with the observed favorable outcomes with respect to restricted mouth opening and burning sensation.

The limitations of the study are the first being, as the patients with stage I was mostly asymptomatic they were reluctant for treatment and not willing to bear the pain of injections and hence only patients with stage II OSMF were evaluated. As most of the patients in stage III have ulcerations and other mucosal diseases, they were not included in the study. Second, the outcome could not be assessed histologically as the study subjects with stage II OSMF were not willing to undergo biopsy.

CONCLUSION

In this study, treatment with dexamethasone + hyaluronidase demonstrated maximum improvement in mouth opening in oral submucous fibrosis patients than lycopene, lycopene and dexamethasone groups. Lycopene also showed reduced burning sensation and improved mouth opening in oral submucous fibrosis patients. Hence we can conclude that in patients in whom dexamethasone is contraindicated [i.e., peptic ulcers, osteoporosis, psychoses, infectious diseases (e.g., herpes simplex, keratitis)], lycopene is a good alternative treatment for oral submucous fibrosis. It can also be used in patients, who cannot make frequent visits for intralesional injections due to disability, and reluctant to use intra-lesion injection.

REFERENCES

1. Shwetha V, Yashoda Devi B K. efficacy and safety assessment of oxitard, a herbal antioxidant in oral submucous fibrosis- an

- observational clinical study. *Indian J Med Res Pharmaceut Sci* 2016;3(7):48-53.
2. Anil S, Beena VT. Oral submucous fibrosis in 12 -year-old girl: case report. *Journal of Paediatric dentistry*.1993;16(2): 120-122.
3. Ekanayaka RP, Tilakaratne WM. Oral Submucous Fibrosis: Review on mechanisms of pathogenesis and malignant transformation. *J Carcinogene Mutagene*.2013;1-11.
4. Goel S, Ahmed J. A comparative study on efficacy of different treatment modalities of oral submucous fibrosis evaluated by clinical staging in population of Southern Rajasthan. *J Can Res Ther*2015;11:113-118.
5. Kumar K, Saraswathi TR, Ranganathan K. Oral submucous fibrosis: A Clinico-histopathologic study in Chennai. *Indian J Dent Res* 2007;18:90-95.
6. Shah PH, Venkatesh R, More CB, VassandacoumaraV. Comparison of Therapeutic Efficacy of Placental Extract with Dexamethasone and Hyaluronic Acid with Dexamethasone for Oral Submucous Fibrosis - A Retrospective Analysis. *J Clin Diagn Res*. 2016;10(10):ZC63-ZC66.
7. Yoithapprabhunath TR, Maheshwaran T, Dineshshankar J, et al. Pathogenesis and therapeutic intervention of oral submucous fibrosis. *J Pharm Bioall Sci* 2013;5(1): 85-88.
8. Borle RM, Borle SR. Management of oral submucous fibrosis: A conservative approach. *J Oral Maxillofac Surg* 1991;49: 788-791.
9. Sinha SN, Jain PK. Intraoral injection of hydrocortisone & placental extract in oral submucous fibrosis. *Indian J Otolaryngol Head Neck Surg* 1978;30:103.
10. Nair DR, Pruthy R, Pawar U, et al. Oral cancer: Premalignant conditions and screening — An update. *J Cancer Res Ther* 2012;8(Suppl 1):S57-66.
11. Pindborg JJ, Sirsat SM. Oral submucous fibrosis. *Oral Surg Oral Med Oral Pathol* 1966;22:764-779.
12. Hayes PA. Oral submucous fibrosis in a 4-year-old girl. *Oral Surg Oral Med Oral Pathol*1985;59:475-478.
13. Aara A, Vani C, Satishkumar GP, et al. Comparative study of intralesional dexamethasone, hyaluronidase, and oral pentoxifylline in patients with oral submucous fibrosis. *Global J Med Res*. 2012;12(7):1-13.
14. Kumar A, Bagewadi A, Keluskar V, et al. Efficacy of lycopene in the management of oral submucous fibrosis. *Oral Surg OralMed Oral Pathol Oral RadiolEndod*2007;103:207-213.
15. Karkar PK, Puri RK, Venkatachalam VP. Oral submucous fibrosis treatment with hyalase. *J LaryngolOtol*1985;99(1): 57-59.
16. Rao PK. Efficacy of alpha lipolic acid in adjunct with intralesional steroids and hyaluronidase in the management of oral submucous fibrosis. *J Cancer Res Thera*. 2010;6(4):508-510.
17. Selvam NP, Dayanand AA. Lycopene in the management of oral submucous fibrosis. *Asian J Pharm Clin Res*. 2013;6(3): 58-61.