Original Article

Efficacy of hyaluronidase and dexamethasone intralesional injections in the management of oral submucous fibrosis

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Abstract

Objective: To evaluate the efficacy of intralesional injections of dexamethasone and hyaluronidase in the treatment of oral submucous fibrosis (OSMF).

Materials and Methods: The present study included 180 patients with OSMF who were divided into four groups and 45 healthy individuals who were included in the control group. The OSMF subjects were injected with hyaluronidase 1,500 IU mixed in 1.5 ml of dexamethasone and 0.5 ml of lignocaine HCL intralesionally twice a week for one month along with a basic physiotherapy regimen consisting of mouth exercises two times daily. Individuals in the control group were administered placebo capsules. Treatment was carried out for 4 weeks, the burning sensation and mouth opening were evaluated before and after treatment.

Results: A significant improvement in the mouth opening and reduction in burning sensation was noted in mild to moderate cases of OSMF after treatment.

Conclusion: In this study, intralesional injection of hyaluronidase with dexamethasone is showed to be an effective method to manage the signs and symptoms in mild to moderate cases of OSMF

INTRODUCTION

Oral submucous fibrosis (OSMF) is 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 fibroelastic change of the lamina propria, with epithelial atrophy leading to stiffness of the oral mucosa, trismus, and inability to eat". Other terms of OSMF mentioned in the literature are "diffuse oral submucous fibrosis," "idiopathic scleroderma of the mouth," "idiopathic palatal fibrosis," "sclerosing stomatitis and "juxta-epithelial fibrosis".1

Multifactorial pathogenesis is implicated in the development of OSMF.2-5 These include chewing of areca nuts, nutritional deficiencies, and autoimmune disorders. However, leaching of compounds from areca nuts remains the main etiology of oral submucous fibrosis. Other predisposing factors like chillies, bacterial infections and salivary changes have also been mentioned.6

As the disease a progress, the oral mucosa becomes blanched and slightly opaque white fibrous bands appear. Whitening often occurs in spots such that the mucosa acquires a marble-like appearance. Fibrous bands in the buccal mucosa run in a vertical direction and fibrosis is sometimes so marked that the cheeks are almost immovable. The lips are often affected and upon palpation, a circular band can be felt around the entire rima oris. Clinically, these changes were marked on the lower lip. The circular fibrosis may cause obliquity of the rima oris and atrophy of the vermilion border.7

The main purpose of treating OSMF is to address the signs and symptoms of patients, such as burning of the mucosa, pain, ulceration, vesicles, difficulty in chewing, limited jaw opening, and improving the quality of life of the patient. OSMF is a progressive disease and is recognized as a premalignant condition. Timely management of this disease aids in preventing its progression and malignant transformation.8-12

Several treatment strategies have been attempted to manage OSMF with a range of success, including pharmacological approaches, surgical treatment, and physiotherapy, but none have been successful in curing this condition to date. The objective of the present study was to evaluate the efficacy of intralesional injections of dexamethasone and hyaluronidase in the treatment of oral submucous fibrosis.

Material and methods

The present prospective, case-control study was conducted after obtaining approval from the institutional ethical committee. The study group included 180 patients with clinically diagnosed OSMF and the control group comprised 45 healthy individuals. Patients with infections and inflammatory causes responsible for trismus, intra-articular causes of trismus, myofascial pain dysfunction syndrome, trauma to the maxillofacial skeleton, dermatomyositis, myositis ossificans, temporomandibular joint arthritis, arthralgia, scleroderma, systemic disease, gingivitis and periodontitis, parafunctional habits, and previous treatment history for OSMF were excluded from the study. A detailed history of the patients was recorded with special reference to the habit of chewing betel nuts with or without tobacco. Patients were asked about the type of betel nut and tobacco consumed, duration of habit, and amount of tobacco or betel nut consumed per day as per structured proforma. The subjects were informed of the study procedure, and informed consent was obtained from all participants. All patients were examined for the presence of clinical signs or symptoms of OSMF. The patients were inquired burning sensation was recorded on a visual analogue scale (VAS)

The VAS was a 10 cm line without calibrations drawn with one extreme negative and one extreme positive end. The patient was instructed to mark one point on the VAS, depicting their current burning sensation status. At the second visit, the previous markings on the VAS scale were not shown to the patient to prevent bias. The jaw opening of all participants was documented using a Vernier caliper to measure the distance between the upper and lower central incisor edges at the maximum unaided mouth opening.

Patients with OSMF were categorized into four groups based on inter-incisal mouth opening according to Lai et al.13

- Group A (mouth opening more than 35 mm)
- Group B (mouth opening between 30-35 mm)
- Group C (mouth opening between 20-30 mm)
- Group D (mouth opening less than 20 mm)

The OSMF individuals were administered intralesional injections of hyaluronidase 1,500 IU mixed in 1.5 ml of dexamethasone and 0.5 ml of lignocaine HCL twice a week for one month along with a basic physiotherapy regimen consisting of mouth exercises twice a day. The participants in the control group were administered placebo capsules. The treatment was carried out for 1 month, and the participants were reevaluated for burning sensation and mouth opening. The entire patients was advised and encouraged to quit their deleterious habits.

Statistical analysis was carried out using Statistical Package for Social Sciences (SPSS), IBM Statistics version 21.0. Values are presented as number, mean, and standard deviation (SD). Student’s t-test, paired t-test, one-way analysis of variance (ANOVA), and Tukey’s post-hoc test were performed. For all tests, a P-value of 0.05 or less was considered statistically significant.

Results

Male and female distribution

Table 1 shows gender wise distribution of the study participants. In the present study, there were 43 males and 2 females in groups A and B, 44 males and 1 female in groups C and d, 39 males and 6 females in control group

Table 1: Male and female distribution in five study groups

Groups	Male	%	Female	%	Total
Group A	43	95.56	2	4.44	45
Group B	43	95.56	2	4.44	45
Group C	44	97.78	1	2.22	45
Group D	44	97.78	1	2.22	45
Control	39	86.67	6	13.33	45
Total	213	94.67	12	5.33	225

Distribution of the subjects according to the habits

The distribution of the subjects according to the habits and side used is represented in table 2. In this study we did not observe any significant difference regarding the different habits mong the various study groups.

Table 2: Distribution of the subjects according to the habits

Groups	Areca nut		Gutka		Pan masala		Combination		Total	p-value
	n	%	n	%	N	%	n	%		
Group A	11	24.4	12	26.7	12	26.7	10	22.2	45	0.714
Group B	13	28.9	12	26.7	11	24.4	9	20.0	45	0.121
Group C	10	22.2	11	24.4	12	26.7	12	26.7	45	0.246
Group D	12	26.7	10	22.2	10	22.2	13	28.9	45	0.128
Control	0	0	0	0	0	0	0	0	0	-

Comparison with respect to mean age, packets per day and no of years (Table 3)

A non significant difference was observed between five groups with mean age of the study participants. The mean age was maximum in group B and minimum in control group. Upon pair wise comparisons, no significant was observed between the groups with respect to age.

A significant difference was observed between five groups with mean packed per day ($F=337.2852$, $p=0.0001$) at 5% level of significance. It means that, the mean packets consumed by participants were different. Another words, the mean packed per day is maximum in Group 3 and minimum in group A followed by other study groups. Upon pair wise comparison, a significant difference was observed between, when the mean packed per day of group D is compared with group A, group B, and group C ($p<0.05$). But in control group is control, no one gave history of habit.

A significant difference was observed between the study groups with mean number of years ($F=281.1934$, $p=0.0001$) of habits at 5% level of significance. The mean number of years is maximum in Group D and minimum in group A followed by other

study groups. Upon pair wise comparison, a significant difference was observed between, when the mean number of years of group D is compared with group A, group B, and group C ($p<0.05$). But in control group, no one has the history of any habits.

Table 3: Comparison of five study groups with respect to mean age, packets per day and no of years

Groups	Age (Years)		Packets per day		No of years	
	Mean	SD	Mean	SD	Mean	SD
Group A	37.18	4.97	5.27	1.10	5.56	1.78
Group B	39.69	4.85	8.58	1.22	7.04	1.51
Group C	37.87	5.60	11.96	2.87	9.04	1.19
Group D	38.27	5.15	7.58	1.50	10.91	2.65
Control	36.44	7.35	-	-	-	-
Total	38.89	6.12	6.68	4.29	6.51	4.08
F-value	10.4522		337.2852		281.1934	
p-value	0.0001*		0.0001*		0.0001*	
Pair wise comparison of groups						
Group A vs Group B	p=0.0888		p=0.0001*		p=0.0001*	
Group A vs Group C	p=0.5637		p=0.0001*		p=0.0001*	
Group A vs Group D	p=0.6128		p=0.0001*		p=0.0001*	
Group A vs Control	p=0.5388		-		-	
Group B vs Group C	p=0.1267		p=0.0035*		p=0.0001*	
Group B vs Group D	p=0.0427		p=0.0001*		p=0.0001*	
Group B vs Control	p=0.0833		-		-*	
Group C vs Group D	p=0.0601		p=0.0001*		p=0.0001*	
Group C vs Control	p=0.4579		-		-	
Group D vs Control	p=0.0971		-		-	

*$p<0.05$

Burning sensation scores (Tables 4 and 5)

A significant difference was observed between five groups with mean burning sensation scores at before treatment ($p=0.0001$) at 5% level of significance. It means that, the burning sensation scores of the participants in the five study groups were different. The mean burning sensation scores before treatment was minimum in Group A and maximum in group D followed by other study groups. Further, to know the pair wise comparison showed that, a significant difference was observed between all the groups ($p=0.0001$) before treatment. Where as a non significant difference was observed between all the groups after treatment ($p>0.05$).

Table 4: Comparison of five study groups (1, 2, 3, 4 and5) with respect to mean burning sensation scores before and after treatment

Groups	Before		After		Mean	% of	t-value	P-value
	Mean	SD	Mean	SD	difference	mean change		
Group A	6.30	0.63	2.06	0.62	4.24	67.31	14.656	0.0001*
Group B	7.23	1.10	2.22	0.60	5.01	69.30	16.241	0.0001*
Group C	7.77	0.97	2.48	1.11	5.30	68.14	10.399	0.0001*

Group D	8.34	0.78	2.53	0.70	5.81	69.63	21.757	0.0001*
Control	0.00	0.00	0.00	0.00	0.00			
F-value	826.9858		101.4126					
p-value	0.0001*		0.0001*					

*p<0.05

Table 5: Inter-group comparisons of burning sensation before and after treatment

Comparisons	Before		After	
	Mean difference	P value	Mean difference	P value
Group A Vs Group B	-0.93	p=0.2807	-0.77	p=0.0005*
Group A Vs Group C	-1.47	p=0.1412	-1.06	p=0.0001*
Group A Vs Group D	-2.04	p=0.3077	-1.57	p=0.0001*
Group A Vs Control	-	p=0.0601	-	p=0.0001*
Group B Vs Group C	-0.54	p=0.0849	-0.29	p=0.1961
Group B Vs Group D	-1.11	p=0.0873	-0.8	p=0.0008*
Group B Vs Control	-	p=0.1241	-	p=0.0001*
Group C Vs Group D	-0.57	p=0.6969	-0.51	p=0.0196*
Group C Vs Control	-	p=0.3417	-	p=0.0001*
Group D Vs Control	-	p=0.2412	-	p=0.0001*

Comparison of five study groups (1, 2, 3, 4 and5) with respect to mean mouth opening before and after treatment (Tables 6 and 7)

A significant difference was observed between five groups with mean mouth opening scores before treatment (p=0.000) at 5% level of significance. It means that, the mean mouth opening of the participants in the five study groups was different. The mean mouth opening scores before treatment was maximum in Group A and minimum in group D followed by other groups. Further, pair wise comparison showed, a significant difference between all the groups (p=0.000).

A significant difference was observed between five groups with mean mouth opening scores after treatment (p=0.000) at 5% level of significance. Further pair wise comparison showed a significant difference was observed between all the groups (p=0.000).

Table 6: Intra-group comparisons of mouth opening (mm) before and after treatment

Groups	Before		After		Mean difference	% of mean change	t value	P value
	Mean	SD	Mean	SD				
Group A	37.82	1.50	40.07	1.01	2.25	5.95	12.454	0.000*
Group B	33.13	1.41	36.38	1.51	3.25	9.81	20.354	0.000*
Group C	24.76	2.36	28.33	3.01	3.57	14.42	10.960	0.000*
Group D	17.80	0.97	18.04	1.04	0.24	1.35	1.914	0.062
Control	50.16	2.25	50.18	2.30	0.02	0.04	0.092	0.927
F-value	2200.222		1769.639					
p-value	0.000*		0.000*					

*p<0.05

Table 7: Inter-group comparisons of mouth opening before and after treatment

Comparisons	Before		After	
	Mean difference	P value	Mean difference	P value
Group A Vs Group B	4.69	0.000*	3.69	0.000*
Group A Vs Group C	13.06	0.000*	11.74	0.000*
Group A Vs Group D	20.02	0.000*	22.03	0.000*
Group A Vs Control	12.34	0.000*	10.11	0.000*
Group B Vs Group C	8.37	0.000*	8.05	0.000*
Group B Vs Group D	15.33	0.000*	18.34	0.000*
Group B Vs Control	17.03	0.000*	13.80	0.000*
Group C Vs Group D	6.96	0.000*	10.29	0.000*
Group C Vs Control	25.40	0.000*	21.85	0.000*
Group D Vs Control	32.36	0.000*	32.14	0.000*

*$p<0.05$

Discussion

Of the 225 participants in the present study, 213 were male and 22 were female. Male predominance was similar to previous studies and the reasons behind this fact were hypothesized, and the severity is related to increased frequency and amount of chewing areca nut among males than females due to occupational stress. Second, because of its stimulant or euphoric properties, increased salivary stimulation, psychotropic action, parasympathetic effect, its role in digestion, hunger satisfaction, and its action as a breath sweetener, it results in more severe disease in younger cohorts of males in comparison with older groups and females.

The signs and symptoms of OSMF have been treated using various pharmacotherapeutic approaches. Corticosteroids (topical and intralesional), various enzymes, interferon-gamma, antioxidants, derivatives of methylxanthine, placental extracts, immune milk, turmeric, colchicine, tea pigments, aloe vera, and spirulina are some of these pharmaceuticals. Hydrocortisone, triamcinolone, and dexamethasone are corticosteroids that decrease inflammatory response and reduce fibrosis. To increase the efficacy of the regimen, enzymes such as hyaluronidase, chymotrypsin, and collagenase are used either alone or in conjunction with additional medicines. Placental extracts aid in the treatment of OSMF by stimulating biogenesis and promoting metabolic regeneration.2

Interferon-gamma has been demonstrated to be superior to other treatments in its ability to correct symptoms. Its function is to modify the production of collagen. Antioxidants are thought to alleviate symptoms by shielding cells from free-radical damage. The antioxidant capabilities of substances, including lycopene, spirulina, turmeric, aloe vera, and green tea, are thought to help alleviate symptoms. Colchicine, immune milk, and pentoxifylline are other medications that have been found to relieve OSMF symptoms. In addition to medication, physiotherapy and surgical procedures are helpful in the management of OSMF.2

In the present study, a notable reliance on the burning sensation and improvement in mouth opening was noted among mild and moderate cases of OSMF. This could be attributed to the treatment regime followed by the patients such as patients were advised to cessate their habit, administration of intralesional injection of corticosteroids and hyaluronidase. It has been reported that corticosteroids suppress inflammatory reactions, thereby preventing fibrosis by decreasing fibroblastic proliferation, subregulating collagen synthesis, and downregulating collagenase production. Hyaluronidase commonly acts by breaking down hyaluronic acid, which leads to the inhibition of sensitized lymphocytes following activation by specific antigens, and by preventing or suppressing inflammatory reactions. Corticosteroids and hyaluronidase are thought to be responsible for the prevention of trismus and fibrous band formation. Therefore, it helps reduce masticatory stress and resistance against functions. Another reason is attributed to physiotherapeutic muscle stretching exercises for the mouth, which were advised to the patient. This aids in preventing limitation of mouth movements and the forceful mouth opening with the help of ballooning of mouth is thought to put pressure on the fibrous band.14-16

Leena et al. noted a remarkable improvement in the mouth opening of patients with OSMF along with a reduction in burning sensation, painful ulceration, and blanching of the oral mucosa after intralesionsal injections of dexamethasone1.5 ml, hyaluronidase 1500 IU with lignocaine (0.5 ml lignocaine HCL.17 Guduru et al. evaluated the clinical efficacy of intralesional infiltration dexamethasone along with hyaluronidase, in reducing the signs and symptoms in individuals with OSMF. The authors noted a significant improvement in mouth opening and burning sensation VAS scores before and after 14 days of treatment in individuals with OSMF.18 The observations were similar to the findings of the present study.

Treatment following intralesional injections has been hypothesized to cause considerable trismus and exacerbated fibrosis. Submucosal injections tend to worsen this condition because of the progressive nature of the disease, repeated needle stick injuries to the soft tissues at various sites, clinical irritation caused by the injected drugs, and repeated needle stick injuries to the soft tissues.19 Considering these issues, along with the side effects and adverse effects of dexamethasone, this treatment modality should be approached cautiously.

Conclusion

No therapeutic strategy is effective for the treatment of OSMF. A variety of modern and traditional natural and chemical therapies have shown promise for the treatment of OSMF. The therapeutic procedure must include both physical treatment and behavioral modifications. Intralesional injection of hyaluronidase with dexamethasone is an effective method of managing mild to moderate cases of OSMF. High-quality, longitudinal, multicenter randomized controlled trials with larger sample sizes are required to further evaluate the effectiveness of different pharmacological formulations used in conjunction with physiotherapy in the management of OSMF.

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