

Original Research Article

Efficacy of local and systemic corticosteroid and hyaluronidase therapy in oral submucous fibrosis: a histopathological study

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ABSTRACT

Background: As the etiopathogenesis of OSMF is not well established, a myriad of different medical and surgical modalities of treatment are reported however studies on histopathological changes after treatment are very sparse. There are reports on various regimens of steroids using different molecules, doses and routes of administration and their combination with other drugs. These were the driving factors to conduct this study. This histopathological study was conducted to know the efficacy of various forms of steroid therapy in various combinations.

Methods: This prospective randomized single blinded outcome based study was conducted in the department of Otorhinolaryngology (ENT) and Pathology in a tertiary care medical college hospital. The 150 clinically diagnosed patients were divided into 5 groups: A, B, C, D and E. Each group was treated differently with different modes of administration of steroids with and without combinations of other medicines. To study histopathological changes before and after treatment, biopsy was taken in 100 patients who gave their consent for the same.

Results: The various histopathological changes observed in the tissues taken after the treatment in 100 patients, were in terms of changes in the epithelium towards normalisation, decrease in fibrous tissue in the submucosa, decrease in the cellular infiltration, appearance of new capillaries, restoration of glandular activity and decrease in the fibrosis of muscles. The calculated Chi square value ($p > 0.05$) was found less than table value.

Conclusions: Local and systemic corticosteroid and hyaluronidase therapy in patients with OSMF were found effective. However, histopathologically, it was not found statistically significant whether corticosteroids are given locally and/or systemic with or without injection hyaluronidase.

Keywords: Oral submucous fibrosis, Corticosteroids, Hydrocortisone, Hyaluronidase

INTRODUCTION

The presenting clinical features of oral submucous fibrosis (OSMF), which is prevalent throughout the Indian subcontinent, are intolerance to spicy foods, blanching and stiffness of oral mucosa and difficulty in opening the mouth and protruding out the tongue.^{1, 2} The etiopathogenesis of OSMF is yet not established but the factors incriminated are: race and religion, genetic, malnutrition and poor dental hygiene, excessive spicy foods, habits of chewing betel nuts, betel leaves and tobacco.³⁻⁷ Some considers it collagen disorder and

precancerous lesion due to its frequent association with cancer of oral cavity.⁸⁻¹¹ The reported histopathological changes are fibroelastotic transformation of the connective tissues in the lamina propria, round cell infiltration with less vascularity, associated with epithelial atrophy, acanthotic and paracanthotic changes.^{1, 7} The incidence of OSMF and oral cancers is very high in India.^{5, 11}

As the etiopathogenesis of OSMF is not well established³, a myriad of different medical and surgical modalities of treatment are reported¹ however studies on histo-

pathological changes after treatment are very sparse.¹² This was the driving force to conduct this study.

Cessation of habits of chewing incriminating substances (arecanut, tobacco, betel quid and other local irritants like MISI and Mava), addictions of alcohol and smoking and taking spicy and hot food and, constitute the important aspect of medical treatment. Though the steroid therapy in OSMF is supported by many workers, other methods of medical remedies reported with varying benefits are: injection of placental extract, collagenase, elastase, trypsin, and hyaluronidase, interferon- γ (IFN- γ), pentoxifylline, lycopene, curcumin and turmeric oil, and oral zinc.^{1,12-18}

There are reports on various regimens of steroids using different molecules, doses and routes of administration and their combination with other drugs.¹¹⁻¹³ The aim of this cohort prospective histopathological study was to study the efficacy of local and systemic corticosteroid with and without hyaluronidase.

METHODS

This prospective randomized single blinded outcome based study was conducted in 150 clinically diagnosed patients with OSMF in the department of Otorhinolaryngology (ENT) PBM Group of Hospitals Bikaner from March 1979 to February 1981. The 150 clinically diagnosed patients were divided into 5 groups: A, B, C, D and E. All these patients were given vitamins and minerals, dental treatment, and instructed to give up betel nuts and leaves and tobacco. To study histopathological changes before and after treatment, biopsy was taken in 100 patients who gave their consent for the same. The pathologist evaluating post-treatment biopsies was not aware of the treatment group. OSMF patients with oral and pharyngeal cancer were not included in this study.

The 50 patients of group A, who had mild disease, were not given corticosteroids. Biopsy before and after treatment, was taken in 30 patients in this group. The remaining 100 OSMF patients were treated with corticosteroids therapy in 4 forms and designated as Group B, C, D and E, which were adopted according to the severity of the disease. The severity of OSMF was judged by the measurement of the interdental space of the opened mouth at central incisors.

Group B patients (50) were started with local intra-oral submucosal injection of 50 mg of hydrocortisone twice a week, up to the dose of 500 mg (20 cases), 1000 mg (20 cases) and 1500 mg (10 cases), depending upon the severity and improvement of the disease. Biopsy was taken in 30 patients in this group before and after the finishing of desired hydrocortisone dose.

In group C patients (10), the treatment regime comprised of injection hydrocortisone 50 mg intra-oral submucosal

with injection hyalase 1 ampule (hyaluronidase 1500 IU) dissolved in normal saline at the site of lesion twice a week up to the dose of 1000 mg hydrocortisone. Biopsy was taken in all the ten patients before and after the completion of the treatment.

In group D (20 cases), the treatment was carried out in the form of oral dexamethasone 0.5 mg QID for 1 week, than 0.5 mg TDS for 2 weeks then 0.5 mg BID for 1 week followed by a maintenance dose of 0.5 mg OD for another 2 weeks. Thus 10 patients of this group received total dose of 50 mg in 6 weeks. Another such course was given in 10 patients depending upon the clinical improvement. Biopsy was taken in 15 patients in this group before and after the desired course of treatment.

In group E patients (20), combination therapy of injection hydrocortisone and oral dexamethasone was administered. Ten patients received one course of 50 mg oral dexamethasone in 6 weeks and another 10 patients got 2 such courses (total 100 mg of dexamethasone) similar to group D patients. Along with oral dexamethasone therapy, intra-oral submucosal injection hydrocortisone 50 mg twice a week, of total 500 mg (10 cases) and 1000 mg (10 cases) was also administered. Biopsy was taken in 15 patients in this group before and after the course of treatment. Chi square test was employed for checking the association among the groups.

Biopsy was taken from the most affected area of the oral cavity. Supravital staining (Strong, 1968) by 2% toluidine blue solution was done in patients who were having ulcerations in oral cavity. The biopsy tissue was preserved in buffered 10% neutral formaline solution for 24 hours for fixation. The paraffin microsections of 5 microm thickness were cut and subjected for haematoxyline and eosine staining.

RESULTS

The various histopathological changes seen in 100 patients with OSMF before treatment are shown in the Figure 1-6. The main histopathological changes noticed in the present study were atrophied or hypertrophied mucosa with keratosis or parakeratosis, fibrosis of submucosa, cellular infiltration, narrowed or dilated blood vessels, atrophied glands and fibrosis of muscles.

The submucosa showed fibrosis in almost all the patients which was marked, moderate and mild in approximately 1/3rd of the patients. The cellular infiltration of occasional eosinophils and lymphocytes was seen in half the cases and marked cellular infiltration of plasma cells, eosinophils and lymphocytes was found in about 1/3rd of the cases. No cellular infiltration was seen in 13% of the cases. The blood vessels were observed narrowed in 71% cases, dilated in 8% and normal in 21% of the cases. In about half the number of cases, glands were obliterated.

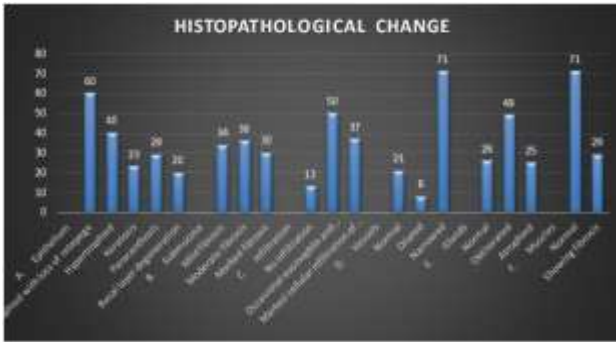


Figure 1: Bar graph showing histopathological changes in 100 patients with OSMF.



Figure 5: Microphotograph (H and E 80X) showing hyperkeratosis of the epithelium in a patient with OSMF.



Figure 2: Microphotograph (H and E 80X) showing atrophied mucosa and fibrosed submucosa with remnants of the glandular tissue in a patient with OSMF.



Figure 6: Microphotograph (H and E 80X) showing atrophy of the epithelium with submucosal fibrous and collagen tissue in a patient with OSMF.



Figure 3: Microphotograph (H and E 80X) showing fibrosis around the alveoli of glandular entities to the extent that some of them appear slit like, suggesting their disappearance in a patient with OSMF.



Figure 4: Microphotograph (H and E 80X) showing atrophy of the epithelium with involvement of the muscle fibres in a patient with OSMF.

The various histopathological changes observed in the tissues taken after the treatment in 100 patients, were in terms of changes in the epithelium towards normalisation, decrease in fibrous tissue in the submucosa, decrease in the cellular infiltration, appearance of new capillaries, restoration of glandular activity and decrease in the fibrosis of muscles (Figure 7 and 8). The degrees of improvement were labelled as mild, moderate, and marked (Table 1). The analytic comparison among the groups did not reveal statistically significant difference ($p > 0.05$). Chi square test was employed for checking the association among the groups. The calculated Chi square value was found less than the table value. It shows that there is no association between the groups and observed histopathological changes. The patients, who showed moderate to marked improvement histopathologically, also showed a desired improvement by subjective and objective means and they were not given further treatment.



Figure 7: Microphotograph (H and E 80X) showing mucosal hypertrophy, rarefaction of submucous fibrous tissue and increased vascularity after treatment in a patient with OSMF.



Figure 8: Microphotograph (H and E 80X) showing conversion of epithelium towards normal and vascularisation of submucosal fibrous tissue after treatment in a patient with OSMF.

Table 1: Showing histopathological improvement in groups A, B, C, D and E after treatment in 100 patients with OSMF.

Groups (cases)	Degrees of improvement	Histopathological changes observed in						Statistical analysis	
		Epithelium N (%)	Sub-mucosa N (%)	In-filtration N (%)	Vessels N (%)	Glands N (%)	Muscles N (%)	Chi-square	P value
A (30)	Mild	7 (23)	5 (17)	5 (17)	8 (27)	8 (27)	6 (20)	12.29	0.13
	Moderate	7 (23)	9 (30)	13 (43)	10 (33)	12 (40)	2 (7)		
	Marked	6 (20)	6 (20)	2 (7)	2 (7)	-	-		
B (30)	Mild	6 (20)	5 (17)	5 (17)	7 (23)	6 (20)	-	3.73	0.95
	Moderate	4 (13)	6 (20)	4 (13)	6 (20)	6 (20)	1 (3)		
	Marked	10 (33)	9 (30)	11 (37)	7 (23)	8 (27)	2 (7)		
C (10)	Mild	2 (20)	2 (20)	2 (20)	3 (30)	3 (30)	-	2.6	0.98
	Moderate	3 (30)	4 (40)	2 (20)	3 (30)	3 (30)	1 (10)		
	Marked	5 (50)	4 (40)	6 (60)	4 (40)	4 (40)	1 (10)		
D (15)	Mild	3 (20)	3 (20)	3 (20)	3 (20)	3 (20)	2 (13)	5.86	0.82
	Moderate	4 (27)	4 (27)	6 (40)	6 (40)	7 (47)	3 (20)		
	Marked	3 (20)	3 (20)	1 (7)	1 (7)	-	1 (7)		
E (15)	Mild	5 (33)	5 (33)	3 (20)	4 (27)	7 (47)	2 (13)	9.38	0.49
	Moderate	5 (33)	5 (33)	5 (33)	4 (27)	3 (20)	2 (13)		
	Marked	-	-	2 (13)	2 (13)	-	-		

DISCUSSION

It was hypothesized that intraoral injections of hydrocortisone alone and with oral tablets of dexamethasone would give better results than only oral tablets of dexamethasone, however present histopathological study could not confirm the hypothesis.

The epithelium was found atrophied with loss of retepege in 60% cases, hypertrophied in 40% cases and keratosis, paracanthosis, and basal layer degeneration in about one-fourth of the patients. Other studies have reported similar observations.^{2,7,19,20} The fibrosis of muscles was seen in only 29% cases. Our findings are supported by other workers.^{3,5,8} The earlier reports on the histopathology of OSMF also reported the involvement of muscles in few cases.²⁰

After the treatment in group A patients, mucosa showed marked improvement towards normalization in 30% cases and moderate improvement in 35% cases. Marked rarefaction of fibrous tissue in submucosa was seen in 30% cases, and moderate in 45% cases. Marked reduction of cellular infiltration was noticed in only 10% cases and moderate in 65% cases. After the treatment group B patients showed marked improvement of mucosa in 50% cases, while 20% had moderate improvement. Marked rarefaction of submucosal fibrous tissue was found in 45% patients and moderate in 30%. More than half (55%) patients showed marked reduction of cellular infiltration while it was moderate in 20%. Appearance of new capillaries was markedly seen in 35% cases and moderately in 30% cases. Restoration of glandular activity was seen in 40% patients while it was found moderate in 30%. Marked reduction of muscle fibrosis was found only in 10% patients. Our findings are similar to other report.²¹

In group C, 50% cases showed marked improvement towards normalization in epithelium, rarefaction of fibrosis was seen in 40% patients. The infiltration was markedly reduced in 60% patients and in 40% patients developed new vessels and restoration of glandular activity. Two patients of group C having injections hyaluronidase developed abscess at the site of injections. In group D, only 20% patients showed marked improvement while 50% patients had moderate improvement. Group E patients had only mild to moderate improvement histopathologically.

The mild and moderate categories of the patients with OSMF, whether treated with steroids or not, have some chances of reversal, though complete reversal cannot be assured. In patients with advanced degree of OSMF, pathology is irreversible. Therefore OSMF is still a challenging pathology for both the clinicians and pathologists. Treatment regimens of group A and D were more convenient to the patients as they did not have to come for intraoral and submucosal injections and so became economical too. There were no side effects in groups A, B, D and E. The main shortcoming of present study was lack of long term follow up after the completion of therapy.

CONCLUSION

It is evident from our study that mild and moderate category of the patients with OSMF whether treated with steroids or not, have some chances of reversal though complete reversal seems unlikely. In patients with advanced degree of OSMF, pathology is irreversible. Therefore OSMF is still a challenging pathology for both the clinicians and pathologists. The local and systemic corticosteroid therapy with or without hyaluronidase was found effective histopathologically in patients with OSMF however there was no statistically significant difference in the outcome among the different groups treated without corticosteroids, with local and/or systemic corticosteroids with or without hyaluronidase.

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REFERENCES

1. Bansal M. *Diseases of Ear, Nose and Throat with Head and Neck Surgery.* 2nd ed. New Delhi: Jaypee Brothers Medical Publishers (P) Ltd; 2018: 407-409.

2. Angadi PV, Rekha KP. Oral submucous fibrosis: a clinicopathologic review of 205 cases in Indians. *Oral Maxillofac Surg.* 2011;15(1):15-9.
3. Tilakaratne WC, Ekanayaka RP, Warnakulasuriya S, Oral submucous fibrosis: a historical perspective and a review on etiology and pathogenesis. *Oral Surg Oral Med Oral Pathol Oral Radiol.* 2016;122(2):178-91.
4. Joshi SG. Submucous fibrosis of palate and pillars. *Ind J Otol.* 1953;4:110.
5. Wahi PN, Kapur VL, Luthra UK, Srivastava MC. Submucous fibrosis of oral cavity: studies on epidemiology. *Bull WHO.* 1966;35:793.
6. Desa JV. Submucous fibrosis of palate and cheek. *Annals of Otol.* 1957;66:1143.
7. Sirsat SM, Khanolkar VR. "Histological, electron microscope and enzyme studies of submucous fibrosis of the palate. *J Pathol Bacteriol.* 1960;79:53-8.
8. Rao ABN. Idiopathic palatal fibrosis. *Br J Surg.* 1962;50:23.
9. Bansal M. *Essentials of Ear, Nose and Throat.* 1st ed. New Delhi: Jaypee Brothers Medical Publishers (P) Ltd. 2016: 262-264
10. Pindborg JJ, Mehta PS, Daftary DK. Occurrence of epithelial atypia in 51 Indian villagers with oral submucous fibrosis. *Br J Cancer.* 1970;24:253.
11. Pindborg JJ. Oral submucous fibrosis: a review. *Ann Acad Med Surg.* 1989;18:603-7.
12. Singh M, Niranjana HS, Mehrotra R, Sharma D, and Gupta SC. Efficacy of hydrocortisone acetate/hyaluronidase vs triamcinolone acetonide/hyaluronidase in the treatment of oral submucous fibrosis. *Indian J Med Res.* 2010;131:665-9.
13. Kakar PK, Puri RK, Venkatachalam VP. Oral submucous fibrosis- treatment with hyalase. *J Laryngol Otol.* 1985;99:57-9.
14. Haque MF, Meghji S, Nazir R, Harris M. Interferon gamma (IFN -gamma) may reverse oral submucous fibrosis. *J Oral Pathol Med.* 2001;30:12-21.
15. Rajendran R, Rani V, Shaikh S. Pentoxifylline therapy: new adjunct in the treatment of oral submucous fibrosis. *Indian J Dent Res.* 2006;17:190-8.
16. Kerr AR. Efficacy of oral lycopene in the management of oral submucous fibrosis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2007;103:214-5.
17. Das DA, Balan A, Sreelatha KT. Comparative study of the efficacy of curcumin and turmeric oil as chemopreventive agents in oral submucous fibrosis: a clinical and histopathological valuation. *J Indian Acad Oral Medi Radiol.* 2010;22(2):88-92.
18. Kumar A, Sharma SC, Sharma P, Chandra OM, Singhal KC, Nagar A. Beneficial effect of oral zinc in the treatment of oral submucous fibrosis. *Indian J Pharmac.* 1991;23:236-41.
19. Su IP. Idiopathic scleroderma of the mouth. *Arch Otol.* 1954;59:330.

20. Paymaster JC. Cancer of buccal mucosa: clinical study of 650 cases in Indian patients. *Cancer.* 1956;9:431.
21. Pindborg JJ, Sirsat MS. Oral submucous fibrosis. *Oral Surg.* 1966;22:764.

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