

## EFFICACY OF INTRALESIONAL PLACENTAL EXTRACT, DEXAMETHASONE AND HYALURONIDASE IN TREATMENT OF ORAL SUBMUCOUS FIBROSIS: A COMPARATIVE STUDY

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**Abstract:** **Background:** Oral submucous fibrosis is a well-recognized chronic insidious disease, precancerous condition, autoimmune and collagen related disorder which is multifactorial in origin mainly associated with the practice of chewing betel quid containing areca nut, a habit common among lower socio-economic strata of society. Its medical management is still a matter of debate and no definite protocol is standardized yet to achieve a miraculous result. Intralesional injections of drugs like dexamethasone, placental extract and triamcinolone helps to increase the mouth opening by breaking the fibrous bands.  
**Objectives:** In this study we have tried to compare the efficacy of intralesional placental extract, dexamethasone and triamcinolone acetone in clinically diagnosed oral submucous fibrosis patients randomly divided into three groups.  
**Study design:** Comparative case series analysis study with random allocation of 30 patients equally in three groups.  
**Materials & Method:** Oral submucous fibrosis patients were randomly divided in three equal groups with 10 patients each. Group A (n=10) subjects received 2ml intralesional placental extract (Placentrex) mixed with 2ml of 2% lignocaine HCL weekly for an interval of 8 weeks. Group B (n=10) subjects were given intralesional injection of dexamethasone 1.5 ml, mixed with 2 ml of 2% lignocaine HCL injected intralesionally weekly for 8 weeks and Group C patients were administered intralesional Hyaluronidase 1500 IU mixed with 2 ml of 2% lignocaine HCL for same interval weekly. Mouth opening and burning sensation was recorded clinically & subjectively.  
**Result:** Observed data were compared statistically using Student's Paired t test analysis for the efficacy of the drugs used and the results were tabulated. Improvement in mouth opening was observed the maximum with intralesional injection of hyaluronidase followed by placental extract and then dexamethasone. Improvement in burning sensation was observed maximum with intralesional injection of dexamethasone followed by placental extract and comparatively less improvement was seen with hyaluronidase.  
**Conclusion:** Intralesional injection is an effective method of managing oral submucous fibrosis and can possibly eliminate the morbidity associated with surgical management. Intralesional injection of hyaluronidase is comparatively better than intralesional placental extract administration followed by intralesional dexamethasone. Burning sensation reduces with all intralesional injections but comparatively less with hyaluronidase.

**Keywords:** Oral submucous fibrosis, Placental extracts (Placentrex), Dexamethasone, Hyaluronidase

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**INTRODUCTION:**

Oral submucous fibrosis is a precancerous condition, first described by Schwartz in 1952 as atropica idiopathica (tropica) mucosae oris<sup>1,2</sup>. It is also known as idiopathic scleroderma of the mouth, idiopathic palatal fibrosis, sclerosing stomatitis, diffuse oral submucous fibrosis and submucous fibrosis of the palate and pillars.<sup>3</sup> It is a chronic, insidious disease affecting the oral cavity and sometimes pharynx. It originates with vesicle formation and is always associated with juxtaepithelial inflammatory reaction followed by fibro elastic changes in the lamina propria with epithelial atrophy<sup>4</sup>. It is characterized by the progressive build up of constricting bands of collagen in the cheeks and adjacent structures of the mouth, which can cause problems with speech and swallowing and severely restrict mouth opening and tongue movement leading to difficulty in eating<sup>5,6</sup>. OSMF has been documented in the Indian population since the time of Sushruta- a renowned Indian physician (circa sixth century BCE) as Vidari, the features of which simulate Oral Submucous Fibrosis, and is more oftenly seen in South Asian countries<sup>7,8</sup>. In recent years the prevalence rate reported in India is up to 6.42% with predominance in males of age 20-40 years<sup>9</sup>.

In initial phase of disease, mucosa feels leathery with palpable fibrotic bands. In advanced stage the oral mucosa loses its resiliency and becomes blanched and stiff. Other features of disease include xerostomia, recurrent ulceration and pigmentation of oral mucosa, dryness of mouth, burning sensation, decreased mouth opening and tongue protrusion<sup>10</sup>. Histopathological examination shows subepithelial fibrosis and chronic inflammation accompanied by hyalinization and loss of vascularity, squamous hyperplasia with parakeratosis<sup>11</sup>. Its precancerous nature was first described by Paymaster in his study of 650 Indian patients and he found that one third of patients had onset of slowly growing squamous cell carcinoma<sup>12</sup>. It causes significant morbidity (in terms of loss of mouth function) and mortality (when transformation into squamous cell

carcinoma occurs)<sup>13</sup>. The term oral submucous fibrosis was finally given by Joshi in 1953<sup>14</sup>. Its medical management is still a matter of debate and no definite protocol is standardized yet to achieve a miraculous result. Intralesional injections of drugs like dexamethasone, placental extract, triamcinolone acetonide and hyaluronidase have shown remarkable results in course of medical line of treatment.

**MATERIAL & METHODS**

This randomized single blinded comparative study was done on 30 cases of clinically diagnosed oral submucous fibrosis with age range from 16 to 60 years, during June 2013 to April 2014. Out of 30 patients 22 were males and 8 female patients were part of the study. Clinical diagnosis of OSMF was based on symptom of burning sensation in mouth upon consumption of spicy or hot foods, repeated vesiculation or ulceration in oral cavity, and on obvious signs of blanched oral mucosa, palpable fibrous bands and difficulty in mouth opening. After assured diagnosis staging of cases were evaluated based on study by Pindborg 1989<sup>15</sup>. Patients were informed about the nature of study and written consent was obtained. Interincisal distance was measured from mesioincisal edge of the upper left Central incisor to the mesioincisal edge of the lower left central incisor with the help of Vernier Callipers (Figure 1). The burning sensation was assessed using visual analogue scale marked from 0 to 10 where 0 indicates no burning sensation and 10 indicates maximum burning sensation.

**Inclusion Criteria :**

Patients with positive history of chewing of the areca nut and any form of tobacco with difficulty in mouth opening (Only stage II), swallowing and chewing, and burning sensation on eating spicy foods were included in the study.

**Exclusion Criteria**

Patients having any Systemic illness, undergone any previous surgery of oral cavity or under any drug therapy were excluded. Patients with Trismus due to any other cause like TMJ problems, Pericoronitis of lower third molars etc were excluded. Even patients diagnosed with

stage I & stage III were not included in the study.

All 30 patients were randomly divided in three equal groups with 10 patients each. Group A (n=10) subjects received 2ml intralesional placental extract (Placentrex) mixed with 2ml of 2% lignocaine HCL weekly for an interval of 8 weeks. Group B (n=10) subjects were given intralesional injection of dexamethasone 1.5 ml, mixed with 2 ml of 2% lignocaine HCL injected intralesionally weekly for 8 weeks and Group C patients were administered intralesional Hyaluronidase 1500 IU mixed with 2 ml of 2% lignocaine HCL for same interval weekly (Figure 2). All intralesional injections were given at various sites of fibrous bands and repeated injection was avoided to decrease mechanical insult of tissue (Figure 3). Patients were advised to do mouth opening exercise for 30 minutes daily without any dropouts; all the 30 cases were observed for 2 months.

**RESULTS:**

The study group consisted of 30 patients. Male to female ratio was 2.75:1. The age range was between 16-60 years with a mean age of 37.5 years. In Group A (Placental Extract) average improvement in mouth opening was 8.02 mm with definite reduction in burning sensation (Table 1). In Group B (Dexamethasone) the average improvement in mouth opening was 7.28 mm with maximum reduction in burning sensation (Table 2) whereas in Group C (Hyaluronidase) improvement in mouth opening was 9.20 mm with moderate reduction in burning sensation (Table 3). Paired t-test results comparing improvement in mouth opening before and after treatment is shown in Table 4 with Paired t-test results comparing improvement in burning sensation is shown in Table 5.

**DISCUSSION**

A myriad of literature reflects that many therapeutic and surgical methods have been tried in the past for treatment of this high risk



Figure 1: Measurement of mouth opening by Vernier caliper



Figure 2: Armamentarium for procedure



Figure 3: Intralesional injection in fibrous bands



PATIENTS	AGE	MOUTH OPENING IN (mm)			BURNING SENSATION VAS SCALE		
		BRFORE	AFTER	DIFFERENCE	BEFORE	AFTER	DIFFERENCE
1	32	19.5	27.3	7.8	9	4	5
2	27	18.6	25.5	6.9	8	3	5
3	22	16.4	25.7	9.3	10	4	6
4	18	20.3	29.1	8.8	8	2	6
5	54	21.4	29.5	8.1	8	3	5
6	34	18.7	26.6	7.9	7	2	5
7	38	15.1	23.4	8.3	6	4	2
8	29	19.3	27.2	7.9	7	3	4
9	25	17.5	24.1	6.6	9	2	7
10	36	18.1	26.7	8.6	8	4	4

TABLE 1: GROUP I (PLACENTAL EXTRACT)

Average improvement in mouth opening was 8.02 mm with marked reduction in burning sensation

PATIENTS	AGE	MOUTH OPENING IN (mm)			BURNING SENSATION VAS SCALE		
		BRFORE	AFTER	DIFFERENCE	BEFORE	AFTER	DIFFERENCE
1	35	14.1	21.6	7.5	10	2	8
2	33	16.1	24.2	8.1	9	3	6
3	48	17.4	25.5	8.1	9	2	7
4	42	21.2	29.1	7.9	8	2	6
5	59	20.1	27.5	7.4	9	1	8
6	31	16.8	24.6	7.8	10	3	7
7	22	15.3	23.4	8.1	7	2	5
8	19	17.1	24.2	7.1	9	1	8
9	47	14.8	20.1	5.3	8	2	6
10	26	18.2	23.7	5.5	8	2	6

TABLE 2: GROUP II (DEXAMETHASONE)

Average improvement in mouth opening was 7.28 mm with maximum reduction in burning sensation

PATIENTS	AGE	MOUTH OPENING IN (mm)			BURNING SENSATION VAS SCALE		
		BRFORE	AFTER	DIFFERENCE	BEFORE	AFTER	DIFFERENCE
1	27	13.2	22.8	9.6	9	6	3
2	16	14.6	23.6	9.0	8	5	3
3	43	12.8	22.7	9.9	9	5	4
4	39	18.5	27.4	8.9	7	4	3
5	34	20.2	28.9	8.7	10	7	3
6	60	21.2	30.2	9.0	9	6	3
7	22	17.5	27.2	9.7	10	6	4
8	28	16.9	25.9	9.0	8	5	3
9	47	15.4	24.1	8.7	8	6	2
10	33	19.1	28.6	9.5	9	5	4

TABLE 3: GROUP III (HYALURONIDASE)

Average improvement in mouth opening was 9.20 mm with moderate reduction in burning sensation

THERAPY	DURATION	MOUTH OPENING	DIFFERENCE	t value	p value
		Mean + SD	Mean + SD		
PLACENTREX	BEFORE	18.49(+/-) 2.75	8.02(+/-) 0.45	18.18	0.0014
	AFTER	26.51(+/-) 4.10			
DEXAMETHASONE	BEFORE	17.11(+/-) 3.15	7.28(+/-) 1.02	12.56	0.0005
	AFTER	24.39(+/-) 4.43			
HYALURONIDASE	BEFORE	16.94(+/-) 2.45	9.20(+/-) 1.33	25.82	0.0001
	AFTER	26.14(+/-) 3.05			

TABLE 4: Paired T-Test results comparing improvement in mouth opening before and after treatment

precancerous condition, but no definitive and universal treatment protocol is currently available. Symptomatic relief and improvement in the oral opening with medicinal treatment such as local injections of cortisone, hyaluronidase and placental extract has been observed.

Steroids stop the proliferation of fibroblasts resulting in reduction in the number of collagen fibers and also help in release of cellular proteases in the connective tissue extracellular compartment which in turn activate the collagens and zymogen that ingest the insoluble collagen stimulating the rate of collagen breakdown. They also act by inhibiting the inflammatory response<sup>16</sup>. The initial symptomatic relief could be due to the anti-inflammatory action of the steroids, which helps in clearing the juxtaepithelial inflammation<sup>17</sup>. It is a common practice in India to treat OSMF patient using intralesional dexamethasone injection. Submucosal administration of aqueous extract of healthy human placental extract (Placentrex) has shown marked improvement of the condition and the rationale behind using it is its anti-inflammatory nature with less mucosal damage. Placentrex accelerates cellular metabolism, aids in absorption of exudates, and stimulates regenerative process, increases physiological function of organs, produces significant enhancement of wound healing. Filatov in 1933 stated a theory that animal and vegetable tissue, when severed from parent body and exposed to conditions unfavorable but not mortal to their existence undergo biological re-adjustments leading to development of substance in state of survival to ensure their vitality such tissue are the extract, implanted or injected in to the body after resistance to pathogenic factors stimulate the metabolic or regenerative processes, thereby favoring recovery. It has no contra indications and results are obtained to be lasting<sup>18</sup>. The rationale behind using hyaluronidase is it acts by breaking down hyaluronic acid, lowers the viscosity of intracellular substances and decreases collagen formation<sup>19</sup>. It breaks down

hyaluronic acid (ground substance of connective tissue), lowers the viscosity of intracellular cement substance i.e. hyaluronidase decreases cell formation by virtue of its action on hyaluronic acid, which plays an important role in collagen formation<sup>20</sup>. By virtue of its specific action on hyaluronic acid, which plays an important role in the formation of collagen, hyaluronidase may be responsible for the better results in patients with restricted mouth opening.

Reduction of burning sensation and improvement in mouth opening were the basis of our treatment regimen. In our study we found that improvement in mouth opening was observed the maximum with intralesional injection of hyaluronidase followed by placental extract and then dexamethasone. Improvement in burning sensation was observed maximum with intralesional injection of dexamethasone followed by placental extract and comparatively less improvement was seen with hyaluronidase. The aim of our study was to compare the efficacy of single drug regimen in the treatment of oral submucous fibrosis as every drug regimen has different mechanism of action so different regimen should be used for a patient as per need.

#### CONCLUSION

Intralesional injection is an effective method of managing oral submucous fibrosis and can possibly eliminate the morbidity associated with surgical management. Intralesional injection of hyaluronidase is comparatively better than intralesional placental extract administration followed by intralesional dexamethasone in patients with much reduced mouth opening. Burning sensation reduces with all intralesional injections but comparatively less with hyaluronidase and much better with dexamethasone and placental extract.

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THERAPY	DURATION	BURNING SENSATION	DIFFERENCE	t value	p value
		Mean + SD	Mean + SD		
PLACENTREX	BEFORE	8.00(+/-)0.65	4.90(+/-)0.75	17.66	0.0004
	AFTER	3.10(+/-)1.05			
DEXAMETHASONE	BEFORE	8.70(+/-)1.05	6.70(+/-)0.71	23.27	0.0000
	AFTER	2.00(+/-)0.35			
HYALURONIDASE	BEFORE	8.70(+/-)0.65	3.20(+/-)0.45	12.11	0.0002
	AFTER	5.50(+/-)1.01			

TABLE 5: Paired T-Test results comparing improvement in burning sensation before and after treatment

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