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RESEARCH ARTICLE

Comparative Study of Intralesional Triamcinolone Acetonide and Hyaluronidase *vs* Placental Extract in 60 Cases of Oral Submucous Fibrosis

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ABSTRACT

Background: Oral submucous fibrosis (OSMF) is a common premalignant condition caused by chewing arecanut, betel quid and gutkha with tobacco. Its medical treatment is not yet fully standardized, although the optimal doses of its medical treatment is in the form of triamcinolone acetonide combined with hyaluronidase or intralesional placental extract.

Objectives: We compared the efficacy of intralesional triamcinolone acetonide combined with hyaluronidase in group A *vs* placental extract in group B.

Design: Comparative case series analysis series study with random allocation of 60 patients equally into two groups.

Materials and methods: Patients of OSMF (60) were randomly allocated into two groups A and B. Group A (n = 30) patients received combination of triamcinolone acetonide (10 mg/ml) + hyaluronidase (1,500 IU) at weekly intervals for 8 weeks. Group B (n = 30) patients received 2 ml of placentrex injection intralesionally at weekly interval for 8 weeks. Treatment outcome was evaluated on the basis of improvement in trismus, oral mucosal pattern and reduction in burning sensation.

Results: Trismus improvements in group A with combination of triamcinolone acetonide + hyaluronidase were significantly better to that in group B where placentrex was used. No significant difference in results in the two groups were observed as far as improvement in oral mucosal pattern and burning sensation were compared in the two groups.

Conclusion: Combination of triamcinolone acetonide and hyaluronidase intralesionally is more effective than placental extract intralesionally in treatment of OSMF. But placental extract injections are cost-effective. No side effects were seen in both study groups.

Keywords: Oral submucous fibrosis, Triamcinolone acetonide, Placentrex injection, Hyaluronidase injection, Trismus.

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INTRODUCTION

Oral submucous fibrosis (OSMF) is a chronic insidious premalignant condition of the oral mucosa.[1-3] It is an insidious, chronic change in fibroelasticity, characterized by a burning sensation in the oral cavity, blanching and stiffening of the oral mucosa and oropharynx and trismus.[4]

Schwartz coined the term atrophica idiopathica mucosa oris to describe an oral fibrosing disease as he discovered in five Indian women from Kenya.[5] Joshi subsequently termed the condition OSMF.[5]

It is clinically and histopathologically characterized diffusely blanched mucosa, presence of fibrous bands, depapillated tongue, erosions in the mucosa, where the patients chiefly complains of burning mouth and inability to take spicy food.[1,2] Juxtaepithelial inflammatory reaction, fibroelastic changes in the lamina propria and epithelial atrophy leading to stiffness of oral mucosa, trismus and inability to eat.[1,2]

It is a precancerous condition common in the Indian subcontinent.[6] The incidence varies from 0.2 to 0.5% in India with a higher percentage being found in southern areas.[6] The exact etiology is still obscure, but many factors, such as betel nut, tobacco, smoking, pan masala and chillies, have been thought to be contributory. If untreated, the risk of malignant change in advanced cases of OSMF is relatively high.[6]

The clinical diagnosis is done on the basis of (a) difficulty to take hot and spicy foods, (b) difficulty in opening mouth, (c) inability to protrude the tongue, (d) blanching of oral mucosa, (e) reduced elasticity and mobility of tissues (f) presence of fibrous bands on palpation.[6]

Treatment includes intralesional injections of placental extract which act as biogenic stimulant and use is based on the tissue therapy method.[6] Also used are intralesional corticosteroid injections with hyaluronidase.[7]

MATERIALS AND METHODS

This is a comparative case series analysis study of 60 OSMF patients managed under two different treatment schedules in Department of ENT Head and Neck surgery done during the study period of 56 months from March 2007 to November 2011. Institutional ethical committee scrutinized the study and clearance was obtained.

Sixty patients, both males and females, were randomly allocated into two groups of 30 each, i.e. group A (n = 30) and group B (n = 30).

All patients in the present study are arecanut, betel quid, gutkha and tobacco chewers in various combinations (Table 1).

Table 1: Improvement of mouth opening during the course of treatment

	0 week	*1st week*	*2nd week*	*3rd week*	*4th week*	*6th week*	*8th week*	*p-value at 8th week b/w groups A and B*
Group A	16.266	18.6	22.4	26.2	28.8	34.2	35.9	0.000
Group B	15.83	19.2	24.2	26.4	29.4	32.1	33.8	—

Diagnosis of OSMF were done on clinical criteria and no biopsy was done. Lesions suggestive of other diseases clinically were excluded from the study. SPSS 17 program were used to analyze the data.

The selected patients included both males and females of all age groups and socioeconomic status. Youngest was 11-year-old boy and oldest 52-year-old man. There were 47 males and 13 females in our study. The average age was 27.4 years in group A and 28.2 years in group B. Most of the patients were young manual laborers who easily had access to gutkha (flavored arecanut with tobacco) cheaply (Graph 1).

Apart from the baseline investigations mouth opening, color and burning sensation of the oral mucosa were recorded in groups A and B before and after infiltration of triamcinolone acetonide (10 mg/ml) + hyaluronidase (1500 IU) in group A and 2 ml of placentrex injection in group B. Intralesional injections were given in the soft palate and in the fibrous bands formed anterior to anterior pillars (at multiple sites bilaterally).

The mouth opening was recorded using a graduated vernier gauge to measure the distance between the upper and lower central incisal edges at maximal unaided mouth opening (IID—interincisal distance; Fig. 1). IID of 40 mm and above was considered as normal mouth opening score (grade 0, no trismus), 30 to 39 mm (grade 1, trismus), 20 to 29 mm (grade 2, trismus), 10 to 19 mm (grade 3, trismus) and 0 to 9 mm (grade 4, trismus).

The color of oral mucosa was assessed in natural light and scored as normal pink (0), red or deep pink (1), pale white (2) and blanched white (3) (Figs 2 and 3). Increased burning sensation of mouth to chilies or spicy foods is graded

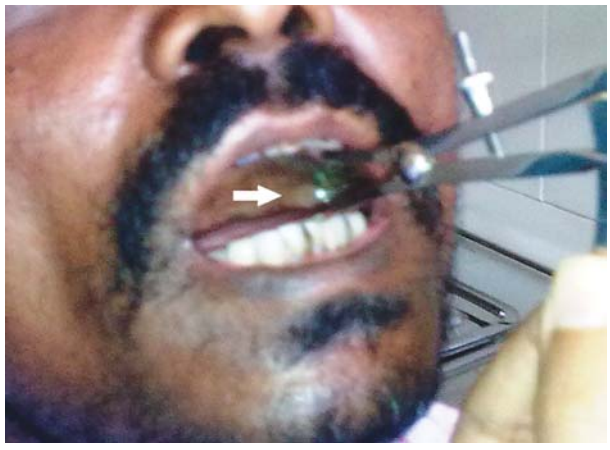


Fig. 2: Blanched oral mucosa seen

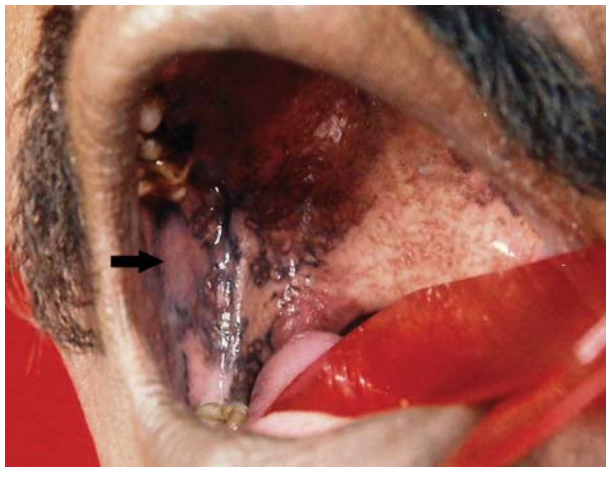


Fig. 3: Fibrosed mucosa with tobacco staining seen

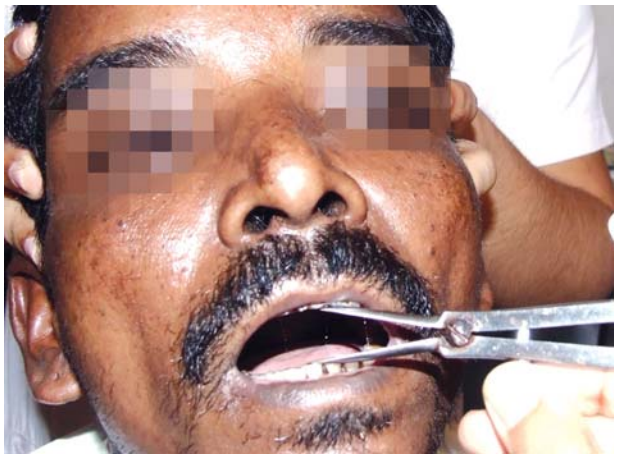


Fig. 1: Trismus measured using calipers

Fig. 4: Intralesional injections being given

according to the severity of burning as; no burning sensation (0), minimal burning sensation (1), moderate burning sensation (2) and severe burning sensation (3). The infiltrations were done submucosally 1 ml on each side of the palate and pillars. The infiltrations were done every week in groups A and B and the three parameters IID, color of oral mucosa and burning sensation noted (Fig. 4).

RESULTS

All the 60 patients were in the grade 3 trismus at the time of diagnosis. The average IID improved from 16.266 to 35.9 mm in group A and from 15.83 to 33.8 mm in group B after 8 weeks of treatment (Fig. 5 and Table 2).

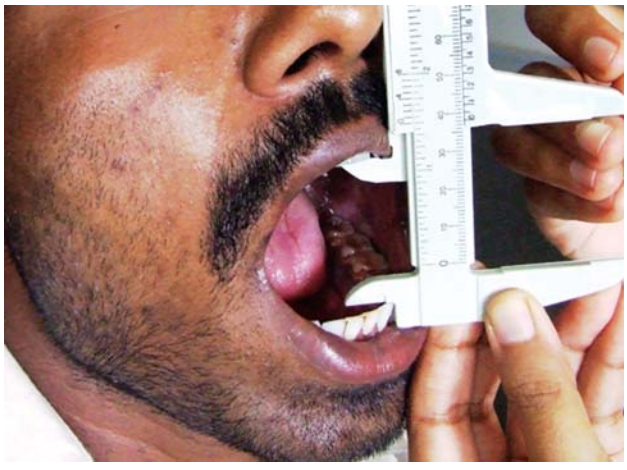


Fig. 5: IID measured after 8 weeks of successful treatment

A significant improvement were seen in both the groups in all the three parameters.

The difference in mouth opening score at 8 weeks were significant with group A patients showing better results compared to group B (Graph 2).

The difference of scores in improvement of burning sensation and oral mucosal pattern at 8th week were not significant when groups A and B were compared.

All the group A and B patients had relief from grade 3 to grade 1 trismus after 8 weeks of treatment.

Significant reduction in burning sensation was seen from the 2nd week itself in both groups (Table 3 and Graph 3).

Color of the oral mucosa improved from blanched white to normal pink in most of the cases (Table 4 and Graph 4).

No reactions to the injections or complications were seen in both study groups. All the patients were given multivitamins, iron folic acid tablets and antioxidants after 8 weeks. No analgesics were given to the patients as 26 gm needle was used during the procedure which was virtually painless. Pearson's Chi-square test was used to test significance of the results in the two groups and the values were tabulated using Levene's test for equality of variances (Tables 5 to 7).

Overall intralesional triamacinolone acetonide and hyaluronidase is better than placental extract in treating

Table 2: Burning sensation in the oral cavity improved during the course of treatment

	0 week	*1st week*	*2nd week*	*3rd week*	*4th week*	*6th week*	*8th week*	*p-value at 8th week b/w groups A and B*
Group A	2.36	2.20	2.03	1.70	1.46	1.26	0.96	0.167
Group B	2.56	2.36	2.16	1.93	1.60	1.23	0.86	—

Table 3: Improvement in the color of the oral mucosa during the course of treatment

	0 week	*1st week*	*2nd week*	*3rd week*	*4th week*	*6th week*	*8th week*	*p-value at 8th week b/w groups A and B*
Group A	2.733	2.466	2.266	2.033	1.466	1.133	0.833	0.960
Group B	2.633	2.366	2.233	2.066	1.533	1.100	0.866	—

Table 4: Paired samples statistics

Group			*Mean*	*N*	*Std. deviation*	*Std. error mean*
1.00	Pair 1	@0_week	16.2667	30	2.03306	0.37118
		@8th_week	35.9000	30	1.93605	0.35347
	Pair 2	@0_Cweek	2.3667	30	0.49013	0.08949
		@8th_Cweek	0.9667	30	0.18257	0.03333
	Pair 3	@0_Bweek	2.7333	30	0.44978	0.08212
		@8th_Bweek	0.8333	30	0.37905	0.06920
2.00	Pair 1	@0_week	15.8333	30	1.93129	0.35260
		@8th_week	33.8000	30	1.51771	0.27709
	Pair 2	@0_Cweek	2.5667	30	0.50401	0.09202
		@8th_Cweek	0.8667	30	0.34575	0.06312
	Pair 3	@0_Bweek	2.6333	30	0.49013	0.08949
		@8th_Bweek	0.8667	30	0.34575	0.06312

Table 5: Paired sample's correlations

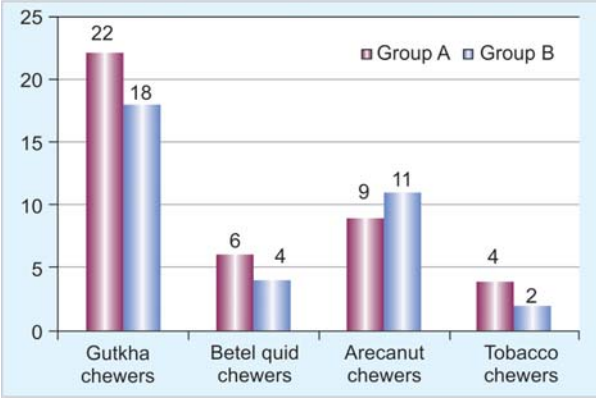
Group			N	Correlation	Sig.
1.00	Pair 1	@0_week & @8th_week	30	0.121	0.525
	Pair 2	@0_Cweek & @8th_Cweek	30	–0.244	0.194
	Pair 3	@0_Bweek & @8th_Bweek	30	–0.270	0.150
2.00	Pair 1	@0_week & @8th_week	30	0.059	0.758
	Pair 2	@0_Cweek & @8th_Cweek	30	–0.145	0.444
	Pair 3	@0_Bweek & @8th_Bweek	30	0.312	0.093

Table 6: Group statistics

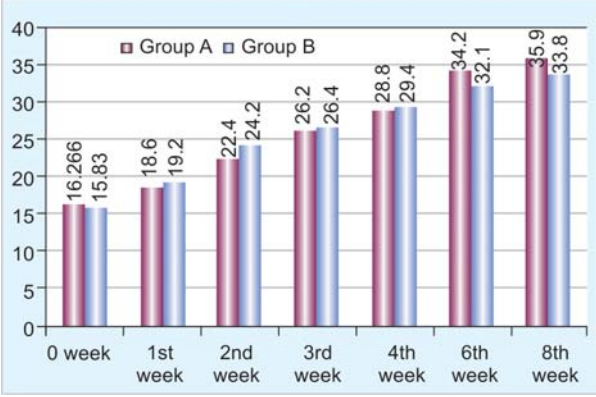
	Group	N	Mean	Std. deviation	Std. error mean
@0_week	1.00	30	16.2667	2.03306	0.37118
	2.00	30	15.8333	1.93129	0.35260
@8th_week	1.00	30	35.9000	1.93605	0.35347
	2.00	30	33.8000	1.51771	0.27709
@0_Cweek	1.00	30	2.3667	0.49013	0.08949
	2.00	30	2.5667	0.50401	0.09202
@8th_Cweek	1.00	30	0.9667	0.18257	0.03333
	2.00	30	0.8667	0.34575	0.06312
@0_Bweek	1.00	30	2.6333	0.66868	0.12208
	2.00	30	2.6333	0.49013	0.08949
@8th_Bweek	1.00	29	0.8621	0.35093	0.06517
	2.00	30	0.8667	0.34575	0.06312

Table 7: Levene's test for equality of variances

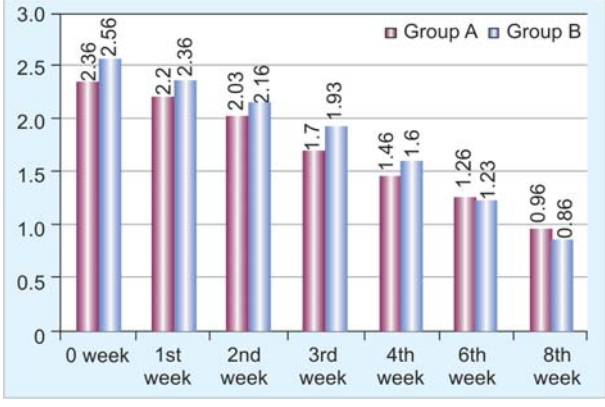
	Levene's test for equality of variances	t-test for equality of means								
		F	Sig	t	df	Sig. (2-tailed)	Mean difference	Std. error difference	95% confidence interval of the difference	
		Lower	Upper	Lower	Upper	Lower	Upper	Lower	Upper	Lower
@0_week	Equal variances assumed	0.015	0.901	0.846	58	0.401	0.43333	0.51196	–0.59147	1.45814
	Equal variances not assumed	—	—	0.846	57.848	0.401	0.43333	0.51196	–0.59153	1.45820
@8th_week	Equal variances assumed	1.272	0.264	4.676	58	0.000	2.10000	0.44914	1.20095	2.99905
	Equal variances not assumed	—	—	4.676	54.872	0.000	2.10000	0.44914	1.19986	3.00014
@0_Cweek	Equal variances assumed	0.988	0.324	–1.558	58	0.125	–0.20000	0.12836	–0.45693	0.05693
	Equal variances not assumed	—	—	–1.558	57.955	0.125	–0.20000	0.12836	–0.45694	0.05694
@8th_Cweek	Equal variances assumed	8.930	0.004	1.401	58	0.167	0.10000	0.07138	–0.04289	0.24289
	Equal variances not assumed	—	—	1.401	44.006	0.168	0.10000	0.07138	–0.04387	0.24387
@0_Bweek	Equal variances assumed	0.374	0.543	0.000	58	1.000	0.00000	0.15137	–0.30299	0.30299
	Equal variances not assumed	—	—	0.000	53.182	1.000	0.00000	0.15137	–0.30358	0.30358
@8th_Bweek	Equal variances assumed	0.010	0.920	–0.051	57	0.960	–0.00460	0.09070	–0.18623	0.17703
	Equal variances not assumed	—	—	–0.051	56.861	0.960	–0.00460	0.09073	–0.18628	0.17709



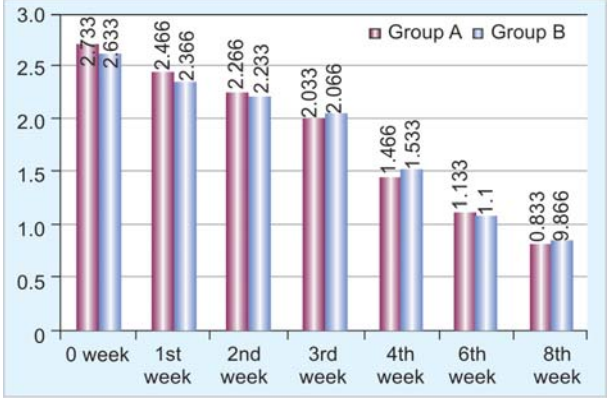
Graph 1: Habits seen in patients in both groups



Graph 2: Improvement of mouth opening during the course of treatment



Graph 3: Burning sensation in the oral cavity improved during the course of treatment



Graph 4: Improvement in the color of the oral mucosa during the course of treatment

trismus of OSMF but give equal results when parameters of burning sensation and improvement in oral mucosal color is concerned.

DISCUSSION

Oral submucous fibrosis is a widely prevalent oral mucosal lesion in Indian population and considering its premalignant potential and severe clinical manifestations many studies are done by many authors regarding various aspects of this condition such as etiology pathogenesis and treatment. Etiology and pathogenesis of OSMF is obscure.[8,9] Arecoline of *Areca catechu* is mostly attributed as the causative factors in addition to pan and tobacco in different combinations.[8,9]

Arecoline, an active alkaloid found in betel nuts, stimulates fibroblasts to increase production of collagen by 150%.[10] Arecoline was found to elevate the mRNA and protein expression of cystatin C, a nonglycosylated basic protein consistently up regulated in a variety of fibrotic diseases, in a dose-dependent manner in persons with OSMF.[11]

Arecoline is an inhibitor of metalloproteinases and a stimulator of tissue inhibitor of metalloproteinases, thus decreasing the overall breakdown of tissue collagen.[12] Keratinocyte growth factor-1, insulin-like growth factor-1 and IL-6 expression, which have all been implicated in tissue fibrogenesis, were also significantly up regulated in persons with OSMF due to areca quid chewing and arecoline may be responsible for their enhanced expression.[13,14] Flavanoid, catechin and tannin in betel nuts cause collagen fibers to cross-link, making them less susceptible to collagenase degradation.[15] This results in increased fibrosis by causing both increased collagen production and decreased collagen breakdown.[16]

OSMF remains active even after cessation of the chewing habit, suggesting that components of the arecanut initiate OSMF and then affect gene expression in the fibroblasts, which then produce greater amounts of normal collagen.[17] Chewing areca quid may also activate NF-kappa-B expression, thereby stimulating collagen fibroblasts and leading to further fibrosis.[18]

Arecanuts have a high copper content and chewing areca-nuts for 5 to 30 minutes significantly increases soluble copper levels in oral fluids. This increased level of soluble copper supports the hypothesis that copper acts as an initiating factor in OSMF by stimulating fibrogenesis through up regulation of copper-dependent lysyl oxidase activity.[19] Other factors attributed are immunological, nutritional, allergy, viral and candidal infections.[19]

The disease initially presents as burning sensation in oral cavity. It is clinically divided into three stages.[20] In stage 1 there is stomatitis, erythematous mucosa, vesicles, mucosal ulcers, melanotic mucosal pigmentation and mucosal petechiae.[21,22] In stage 2, fibrosis occurs in ruptured vesicles and ulcers when they heal. There is blanching of oral mucosa.[21,22] Vertical and circular palpable fibrotic bands are seen in buccal mucosa.[21,22] Specific findings include trismus, stiff and small tongue, blanched and leathery floor of mouth, fibrotic and depigmented gingiva, rubbery soft palate with decreased mobility, blanched and atrophic tonsils, shrunken band-like uvula and sinking of cheek not commensurate with age or nutritional status.[21,22] In stage 3, there are sequelae in the form of leukoplakia in about 25% of cases, speech and hearing deficits because of involvement of tongue, palate and eustachian tubes.[21,22]

Treatment protocol for OSMF is not standardized. Most important aspect of medical treatment is quitting chewing betel quid, arecanut, other local irritants, spicy and hot food, alcohol and smoking.[2,3] The various modalities of treatments include: Intralesional corticosteroid injections with hyaluronidase, intralesional injections of placental extract, systemic administration of corticosteroids, lycopene,[23] pentoxifyline therapy[24] and surgical excision of fibrous bands is being tried with various degrees of success.

Placental extract contains growth factors and anti-inflammatory agents[6] and also antiplatelet activity.[6] The action of placenta extract is essentially biogenic stimulation and use is based on the tissue therapy method.[6] According to this theory when animal and vegetable tissues are severed from the parent body and exposed to unfavorable conditions, but not mortal to their existence, undergo biogenic readjustment leading to development of substance in the state of their survival to ensure their vitality biogenic stimulators.[6] Such tissues or their extract when implanted or injected into the body after resistance of pathogenic factors stimulates metabolic or regenerative process thereby favoring recovery.[6]

Triamcinolone acetonide suppresses immune system by reducing activity and volume of lymphatic system.[7,16] It heals inflammatory mucosal lesions that are responsive to steroids. Decreases inflammation by suppressing the migration of polymorphonuclear leukocytes and by reversing capillary permeability.[7,16] It is a better corticosteroid for intralesional injection as it has better local potency, longer duration of action and lesser systemic absorption.[7,16]

Hyaluronidase is an enzyme which reduces the viscosity of ground substance, thus making the tissues more permeable to injected corticosteroid triamcinolone acetonide.[7,16] It stimulates hydrolysis of hyaluronic acid, one of the chief ingredients of tissue cement, which offers resistance to diffusion of liquids through tissues.[7,16] It facilitates distribution and absorption of locally injected substances.[7,16] It also promotes resorption of excess fluids and extravasated blood in the tissues.[7,16]

Sinha et al in his 36 cases study has inferred that injection hydrocortisone is five times more effective than placentrex in qual doses.[25]

Kaushal et al used 2 mg collagenase in 1 ml distilled water with good symptomatic relief.[26] Kakar et al in theirs 96 cases study using dexamethasone 4 mg, hyaluronidase 1,500 IU, hyaluronidase 1,500 IU + dexamethasone 4 mg and 2 ml placental extract in four separate groups found hyaluronidase 1,500 IU + dexamethasone 4 mg more effective than the rest.[27] According to study by Deepak Gupta et al chymotrypsin, hyaluronidase and dexamethasone are more effective than placentrex.[8] Chaturvedi et al treated 103 patients with combination of 1 ml hydrocortisone and 1,500 IU hyaluronidase with good results.[28]

Borle et al found in his 326 cases study lesser relapses with oral formulation of vitamin A 50,000 IU + $FeSO_4$ 200 mg + beclomethasone drops/6th hourly for 3 weeks than compared to injection triamcinolone + hyaluronidase.[29] Katharia et al noted drastic improvement in symptoms and fibrous bands with 2 ml placentrex in his 22 case study.[6] Lai et al in their study over 10 years concluded that dexamethasone 4 mg + hyaluronidase 1,500 IU weekly for 20 weeks better than surgical treatment.[30]

CONCLUSION

Intralesional infiltrations with placental extract and triamcinolone with hyaluronidase are equally effective in treating trismus of OSMF. No difference in treatment efficacy was seen in placental extract group or with triamcinolone with hyaluronidase group. But placental extract injections are cost-effective. No side effects were seen in both study groups.

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