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OSMF: LONG TERM STUDY OF TREATED PATIENTS

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ABSTRACT

Background and Objective: Oral Submucous fibrosis (OSMF) is a chronic debilitating disease and a well recognized premalignant condition of oral cavity. The exact pathogenesis is not well established but the cause is believed to be multifactorial. The most commonly used treatment regimen is combination of Hydrocortisone acetate or Triamcinolone Acetonide with hyaluronidase and recently oral Pentoxifylline, but studies of its long term effect are lacking. The present study was therefore conducted to evaluate the long term effectiveness of afore said drugs.

Material & methods: In the present study 60 previously treated patients of OSMF were registered. Out of which 34 patients had received Inj. Hydrocortisone acetate (1.5ml) mixed with Hyaluronidase (1500 I.U.) at weekly interval for 22 weeks, 15 patients had received Inj. Triamcinolone Acetonide (10mg/ml) mixed with Hyaluronidase (1500 I.U.) at biweekly interval for 22 weeks and 11 patients were given Tab Pentoxifylline (Trental) 400mg three times daily for a period of 7 months. Long term outcome was evaluated on the basis of symptom score and sign score.

Results: There was statistically significant improvement between long term follow up score and immediate Post-treatment symptom score (p value < 0.05)

Interpretation and Conclusion: It was concluded that the improvement in symptoms and signs following treatment increased further or maintained in long term follow up.

KEYWORDS

Oral Submucous fibrosis, Hydrocortisone acetate, Hyaluronidase, Pentoxifylline, Long term effects.

Introduction-

Oral submucous fibrosis (OSMF) is a chronic debilitating disease and a well recognized potentially malignant condition of oral cavity associated with areca nut chewing and characterized by generalized fibrosis of oral soft tissue resulting in marked rigidity and progressive inability to open the mouth.[1-3] This disease is mainly confined to South East Asian countries especially in Indian subcontinent. Pathogenesis is not yet established but it is believed to be due to multifactorial causes such as hereditary predisposition[4], Vitamin A and B complex deficiency[3], collagen synthesis disorder[3,4], areca nut and tobacco chewing[5]. An allergic reaction to innocuous substances has also been suggested as a possible cause of OSMF[3,6]. The disease initially presents as burning sensation in oral cavity, stomatitis including erythematous mucosa, vesicles and mucosal ulcers. In later stages, it is characterized by inability to open mouth (trismus) because of widespread fibrosis and scarring. Various medical and surgical treatment modalities has been employed for its management. The most common mode of medical treatment has been different forms of corticosteroid injections with or without hyaluronidase. Local injection of 1500 IU of Hyaluronidase mixed with 1.5 ml (37.5 mg) Hydrocortisone acetate has been used at our centre for the last 20 years with satisfactory clinical results and without any significant side effects. Combination of Triamcinolone acetonide (10 mg / ml) & Hyaluronidase 1500 IU has been used with equal efficacy[7]. Tab Pentoxifylline (trental) 400mg three times daily for a period of 7 months was also used in some patients with good results. In afore said studies long term follow up was lacking, so this study was planned to see the long term effectiveness of our previously treated patients.

Aims and objective:

This study was conducted to evaluate the long term effectiveness of the various forms of medical treatment of Oral Submucous Fibrosis given at our centre.

Material & Methods-

This study was done on 60 previously diagnosed and treated cases of oral submucous fibrosis that have already completed their full course of treatment. Out of these 60, 34 patients had received Injections Hydrocortisone acetate 1.5 ml (37.5 mg) mixed with 1500 IU of Hyaluronidase at weekly interval for 22 weeks, 15 patients had received Injections Triamcinolone Acetonide (10 mg / ml) mixed with 1500 IU Hyaluronidase at biweekly interval for 22 weeks and 11 patients had been treated by Tab Pentoxyphylline 400 mg three times a day for a period of 7 months. These patients were properly explained about the study and their consent was taken. The study was cleared by Institutional Ethics committee.

The symptoms and signs were noted on a working proforma. Scoring of symptoms like burning sensation in mouth upon consumption of spicy or hot foods, repeated vesicles or ulcer formation, reduced opening of mouth and difficulty in cheek blowing was done according to verbal complaint rating scale of 0-10 points where 0 means no symptom and 10 means most severe symptom as perceived by the patient subjectively. Signs were scored from 0 to 10 points according to following criteria. Trismus was scored as 0 for no trismus where interincisor distance was 5.25cms or more in males and 4.75cms or more in females, scored as 2 or grade I where interincisor distance was more than 3cms but less than normal, scored as 5 or grade III where interincisor distance was 2-3cms and scored as 10 where interincisor distance was less than 2cms. Ankyloglossia was scored as 5 when protrusion of tongue was partial and scored 10 when there was inability to protrude out the tongue. Vesicles or ulcers in oral cavity were scored 2 when they were unilateral single, scored 4 when bilateral single, scored 6 when unilateral multiple and scored 10 when bilateral multiple. Areas of fibrosis were scored 2 for each area – soft palate including uvula, right or left anterior faucial pillar including tonsil, right or left buccal mucosa including gingivobuccal sulcus, right or left retro molar trigone, tongue or floor of mouth. Colour of mucosa scored as 0 for pink, 5 for partially white and 10 for complete white.

The pre-treatment and immediate post-treatment symptom and sign scores were taken from previous records of medically treated patients. In the long term follow up symptom and sign scores were noted by thorough history and examination as done earlier. The response to treatment and long term effectiveness of treatment was assessed by noting subjective improvement in symptom scores and objective improvement in sign scores between immediate post treatment scores and long term follow up scores. Long term follow up means observation of effects after a minimum of 6 months of stopping treatment.

Results and analysis-

Majority of patients of OSMF were in 3rd decade (40%) followed by 4th decade (18.3%). Youngest patient was 16 years and oldest was aged 70

years. Male to female ratio was 4.45:1. 53.3% were in the habit of using pan masala/ gutkha, 20% were using areca nut/ tobacco while 23.3% were using both. Out of them 20% were smokers.

Table I shows pretreatment, immediate post-treatment and long term follow up symptoms and sign scores. There was 61.7 % improvement in immediate post-treatment total symptom score, which improved further to 67.9 % in long term follow up. There was 40.6% improvement in immediate post-treatment total sign score, which improved further to 46.9% on long term follow up.

Table – I ***Shows Pre-treatment symptom scores, sign scores and improvement in these scores immediately after treatment and on long term follow up***

	Pre treatment score	Immediate Post treatment score	%Improvement	Long term Follow Up score	%Improvement	Difference of % improvement (Long term –immediate post treatment)
Symtoms						
Burning sensation in mouth	394	114	71.1%	93	76.4%	5.3%
Vesicle/Ulceration of oral cavity	286	78	74.8%	34	88.1%	13.0%
Difficulty in mouth opening	384	191	50.3%	185	51.8%	1.5%
Difficulty in cheek blowing	227	112	50.7%	103	54.6%	3.9%
Total symptom scores	**1291**	**495**	**61.7%**	**415**	**67.9%**	**6.2%**
Signs						
Trismus	369	188	49.1%	174	52.8%	3.7%
Ankyloglossia	190	85	55.3%	80	57.9%	2.6%
Vesicle/Ulceration of oral mucosa	296	78	73.6%	32	89.2%	15.0%
Area of Fibrosis	558	432	22.6%	408	26.9%	4.3%
Color of mucosa	385	285	25.9%	260	32.5%	6.6%
Total sign scores	**1798**	**1068**	**40.6 %**	**954**	**46.9%**	**6.3%**

The results were compared statistically by using paired 't' test. Table II Shows Mean, Standard Deviation and P Value. Comparison between the pre-treatment scores and immediate post-treatment scores shows statistically significant improvement ($p< 0.05$) in all symptoms and signs scores.

Table - II ***Mean, Standard Deviation and P Value of pretreatment, post treatment and long term follow up scores***

	Mean & Std Deviation of Pre treatment score (a)	Mean & Std Deviation of Immediate Post treatment score (b)	P value (a&b)	Mean & Std Deviation of Long term Follow Up score (c)	P value (b&c)
Symtoms					
Burning sensation in mouth	6.57±2.40	1.90±1.34	<0.0001	1.55±0.83	0.0433
Vesicle/Ulceration of oral cavity	4.77±2.98	1.30±1.72	<0.0001	0.57±1.69	0.0026
Difficulty in mouth opening	6.40±1.92	3.18±1.57	<0.0001	3.08±1.66	0.4715
Difficulty in cheek blowing	3.78±3.58	1.87±2.26	<0.0001	1.72±2.12	0.0949
Total symptom scores	**21.52±6.57**	**8.25±4.47**	**<0.0001**	**6.92±4.15**	**0.0004**
Signs					
Trismus	6.15±2.31	3.13±1.83	<0.0001	2.90±1.81	0.2038
Ankyloglossia	3.17±3.18	1.42±2.27	<0.0001	1.30±2.20	<0.0001
Vesicle/Ulceration of oral mucosa	4.93±3.40	1.30±1.72	<0.0001	0.53±1.37	0.0009
Area of Fibrosis	9.30±1.42	7.20±1.53	<0.0001	6.80±1.44	0.0130
Color of mucosa	6.42±2.27	4.75±2.14	<0.0001	4.33±2.15	0.1992
Total sign scores	**30.00±7.22**	**17.8±6.13**	**<0.0001**	**15.90±5.26**	**0.0005**

In the long term follow up there were further improvement in all symptom and sign score. Statistical significance was found in the improvement of scores of burning sensation in mouth , vesicle/ulceration of oral cavity, ankyloglossia and area of fibrosis ($p< 0.05$), however no such significance was noted in scores of difficulty in cheek blowing, trismus and color of mucosa ($p> 0.05$).

Table III shows difference of percentage improvement in symptom and sign scores (long term – immediate post treatment) of the patients who had taken different types of medical treatment. This showed inferior long term results of Tab Pentoxyphylline as compared to Injections Hydrocortisone acetate mixed with Hyaluronidase and Injections Triamcinolone acetonide mixed with Hyaluronidase.

Table-III ***Difference of percentage improvement (Long term –immediate post treatment) in symptom and sign scores of different treatment groups***

	Difference of % improvement (Long term –immediate post treatment) of different treatment groups		
Treatment regimen	**Inj. Triamcinolone acetonide + Hyaluronidase n=15**	**Tab Pentoxyphylline n=11**	**Inj. Hydrocortisone acetate + Hyaluronidase n=34**
Symptoms			
Burning sensation in mouth	6.1%	0.0%	6.8%
Vesicle/Ulceration of oral cavity	13%	11.7%	17%

Difficulty in mouth opening	3.1%	-1.7%	1.8%
Difficulty in cheek blowing	5.1%	3.1%	3.4%
Total symptom scores	**6.9%**	**2.0%**	**7.7%**
Signs			
Trismus	3.4%	0.0%	4.8%
Ankyloglossia	1.7%	0.0%	4%
Vesicle/Ulceration of oral mucosa	13%	13.4%	17%
Area of Fibrosis	4.2%	4.0%	4.4%
Color of mucosa	14%	-15.4%	9.3%
Total sign scores	**7.4%**	**-0.8%**	**7.7%**

In our study one patient developed squamous cell carcinoma of buccal mucosa even after completion of treatment. This shows that there was chance of malignancy even after medical treatment.

Discussion-

OSMF had been a troublesome and debilitating disease for ages in our subcontinent. Pathogenesis is not yet established but it is believed to be due to multifactorial causes[4-6]. The disease initially presents as burning sensation in oral cavity. It is clinically divided into three stages[8]. In stage 1 there is stomatitis, erythematous mucosa, vesicles, mucosal ulcers, melanotic mucosal pigmentation and mucosal petechiae. In stage 2, fibrosis occurs in ruptured vesicles and ulcers when they heal. There is blanching of oral mucosa. Vertical and circular palpable fibrotic bands are seen in buccal mucosa. Specific findings include trismus, stiff and small tongue, blanched and leathery floor of mouth, fibrotic and depigmented gingiva, and 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. 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.[9,10]. The precancerous nature of OSMF was first mentioned by Paymaster (1956)[11] who found the development of slow growing squamous cell carcinoma in one third of his patients of OSMF.

Most important aspect of medical treatment is cessation of habit of eating betel quid, areca nut, other local irritants, spicy and hot food, alcohol and smoking. The most common mode of medical treatment had been the use of steroids in its various forms [12-16]. Intralesional injections of hyaluronidase[16], placental extract[17], Interferon-γ (IFN-γ) [18] are also used for treatment of OSMF. Oral zinc[19], Pentoxifylline[20], lycopene[21] were also showed good efficacy in OSMF.

In a study done at our center[7], we compared efficacy of hydrocortisone acetate/hyaluronidase vs triamcinolone acetonide/hyaluronidase in the treatment of oral submucous fibrosis and found similar treatment result of both treatment regimens. The follow up period was three month after completion of treatment.

In the study of PK Kakar et al.[16] the follow up period was varied from 3 months to 2 year but they did not compare immediate post treatment and long term result. M. F. Haque et al.[18] followed up patients up to 6 months and taken 6 month score as net improvement in their study. In the study of R Rajendran et al.[20] follow up period ranges from 6 months to one year after cessation of active medication, but the results are mentioned at the end of the trial period.

The shortcomings of most of the previous studies were lack of long term follow up. The follow up in these studies were up to the completion of treatment. So the present study was planned to see the long term effect of above mentioned drugs for the treatment of OSMF. In the present study our aim is to evaluate the long term result of the treatment which was given in our centre. From the observation it is clear that there was significant subjective and objective improvement after the completion of treatment and this improvement is maintained or increased in long term follow up (up to 2 years).

The shortcomings of the present study were unequal number of patients in different treatment group, limited duration of follow up (only up to 2 years).

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