

Comparison of Therapeutic Efficacy of Placental Extract with Dexamethasone and Hyaluronic Acid with Dexamethasone for Oral Submucous Fibrosis - A Retrospective Analysis

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ABSTRACT

Introduction: Oral Submucous Fibrosis (OSMF) is a potentially malignant disease of the oral cavity associated with betel nut chewing. The management of OSMF has been a subject of controversy and no definitive and widely accepted treatment is currently available for this condition.

Aim: To retrospectively evaluate the therapeutic efficacy of two treatment regimens (placental extract with dexamethasone and hyaluronic acid with dexamethasone) for the treatment of OSMF.

Materials and Methods: The records of the patients diagnosed with OSMF were obtained from the departmental archives. A total of 25 records were selected and divided into two study groups based on the treatment regimens, as Group A (placental extract + dexamethasone) and Group B (hyaluronidase + dexamethasone). The records were studied for improvement in

mouth opening and reduction in burning sensation. Descriptive statistics, paired t test and student's t test were used for statistical analysis.

Results: In Group A and Group B, the average increase in mouth opening from baseline record to 8th week of treatment was 3.53 ± 1.26 mm and 3.65 ± 1.42 mm respectively and average decrease in burning sensation, noted by VAS scale, was 5.13 ± 1.13 and 4.90 ± 1.29 respectively. The pre- and post-treatment differences were found to be statistically significant for both the groups ($p < 0.001$) and for both the treatment outcomes. When the average difference of the treatment outcomes was compared between the two study groups, no statistically significant difference was noted ($p > 0.05$).

Conclusion: The results of the present study indicate that both the treatment regimens studied are equally effective in the treatment of oral submucous fibrosis.

Keywords: Areca nut, Burning sensation, Intralesional injections, Mouth opening

INTRODUCTION

OSMF is a potentially malignant disease of the oral cavity associated with areca nut chewing [1]. It is considered as a disorder of collagen metabolism and is characterized by increased production and decreased degradation of collagen fibers [2]. It is a chronic debilitating condition with high rate of morbidity as it causes progressive inability to open the mouth, resulting in difficulty in eating and thereby causing nutritional deficiencies [1].

The management of OSMF has been a subject of controversy [3]. Several therapeutic and surgical methods have been tried in the treatment of OSMF. These treatment modalities use antioxidants, iron supplements, curcumin, steroids, placental extract, fibrinolytic agents and also include surgical elimination of the fibrotic bands [1]. However, no definitive and widely accepted treatment is currently available for this condition [2].

The main goal of the treatment of OSMF is to reduce trismus and burning sensation [4]. One of the important therapeutic modalities is intralesional injection therapy. The most commonly used intralesional agents are placental extract, corticosteroids and hyaluronidase. The mechanism of action and therapeutic efficacy vary from one drug to another and their combinations used [4].

Placental extract contains growth factors and anti-inflammatory agents and also has antiplatelet activity [5]. It has biogenic stimulator action and is used on the basis of tissue therapy method. It stimulates metabolism, increases the vascularity and promotes

regeneration and recovery of the tissue, upon implantation into the body [3,5].

Steroids have anti-inflammatory action which helps to provide symptomatic relief. It also has antifibrotic activity and prevents fibrosis by decreasing fibroblastic proliferation and deposition of collagen [6].

Hyaluronidase causes breakage and dissolution of fibrous bands thus providing relief from the condition. It acts by breaking down hyaluronic acid, the ground substance of connective tissue, thereby decreasing the viscosity of intracellular cement substance. Moreover, the role of hyaluronic acid in collagen formation is also prevented by the use of hyaluronidase. It is postulated that, hyaluronidase may be capable of providing better results in patients with restricted mouth opening [7].

Based on the available literature, there is no definitive evidence of the best treatment modality for OSMF. Hence, we embarked on this study to retrospectively evaluate the therapeutic efficacy of two drug regimens namely placental extract with dexamethasone and hyaluronidase with dexamethasone for the treatment of OSMF.

MATERIALS AND METHODS

This retrospective study was conducted in the Department of Oral Medicine and Radiology, K. M. Shah Dental College and Hospital, Sumandeep Vidyapeeth University, Piparia, Vadodara, Gujarat, India, after obtaining the permission from the Institutional

Ethics Committee (SVIEC/ON/DENT/SRP/15094). The records of the patients diagnosed with OSMF were obtained from the departmental archives for a one year period from 1st January 2014 to 31st December 2014. The records of the OSMF patients who have completed eight sessions of injection therapy were included in the study. The records of the OSMF patients who had received only oral drugs, referred for surgical treatment or who had any previous history of OSMF treatment were excluded.

A total of 25 records were selected according to these inclusion and exclusion criteria and further analyzed. All the selected records were of the patients having Stage III OSMF according to More et al., classification [8]. The selected records were divided into two study groups according to the treatment regimen used - Group A: placental extract (2ml) + dexamethsone (4mg/ml) and Group B: hyaluronidase (1500 IU) + dexamethsaone (4mg/ml). Group A comprised of 15 patients and Group B comprised of 10 patients. As there is difference in the cost of placental extracts and hyaluronidase and as there is no evidence in available literature regarding superior efficacy of one over the other, the choice of the medication was based on the patient's preference.

The mouth opening measured with Vernier's caliper, burning sensation recorded using VAS scale and the adverse effects, if any during each session of injection therapy were retrieved from the selected records for analysis.

The data was then statistically analyzed by using SPSS version 19.0. Descriptive statistics, paired t test and Student's unpaired t tests were applied for statistical analysis. The level of significance was set at p-value of <0.05.

RESULTS

The mean age of the patients in the present study was 40.13 ±12.78 years, with the minimum age of 23 years and maximum age of 67 years. The male to female ratio was 7.33:1 [Table/Fig-1]. On analyzing the harmful oral habit, 21 patients had the habit of chewing gutka (comprising of areca nut, tobacco, catechu, paraffin wax, slaked lime, flavoring agents), three patients had the habit of chewing areca nut and one patient had the habit of chewing pan (comprising of betel leaf, tobacco, areca nut, catechu, slaked lime).

Mouth Opening: At baseline, the average mouth opening in Group A and Group B were 26.5±6.52 mm and 21.7±6.29 mm respectively. In Group A and Group B, the average increase in mouth opening from baseline to 8th week was 3.53±1.26 mm and 3.65±1.42 mm respectively. When the average mouth opening values at baseline and at 8th week of treatment were compared, the differences were found to be statistically highly significant for both the groups (p<0.001) [Table/Fig-2].

Study Group	Age (Years)			Sex		
	Mean Age	Minimum	Maximum	Male	Female	Total
A	44.07 ± 13.97	23	67	13	02	15
B	33.00 ± 6.93	23	42	09	01	10
All participants	40.125 ± 12.78	23	67	22	03	25

[Table/Fig-1]: Distribution of study participants according to age and sex.

Mouth Opening (mm)				
Study Group	Pre-treatment	Post-treatment	Difference	p-value
Group A	26.5 ± 6.52	30.03 ± 6.42	3.53 ± 1.26	<0.001
Group B	21.7 ± 6.29	25.35 ± 7.11	3.65 ± 1.42	<0.001
Burning Sensation (VAS)				
Group A	6.67 ± 0.97	1.53 ± 0.99	5.13 ± 1.13	<0.001
Group B	6.40 ± 1.17	1.50 ± 1.71	4.90 ± 1.29	<0.001

[Table/Fig-2]: Intra-group pre and post treatment analysis of improvement in mouth opening and burning sensation.

	Group A	Group B	p-value
Improvement in mouth opening (mm)	3.53±1.26	3.65±1.42	0.735
Improvement in burning sensation	5.13±1.13	4.90±1.29	0.759

[Table/Fig-3]: Inter-group comparison of treatment outcomes. (Unpaired t test).

Burning Sensation: At baseline, the average burning sensation as noted by VAS scale in Group A and Group B were 6.67±0.97 and 6.40±1.17 respectively. The average decrease in burning sensation noted by VAS scale scores from baseline to 8th week was 5.13±1.13 in Group A and 4.90±1.29 in Group B. When the average VAS scores at baseline and at 8th week of treatment were compared, the differences were found to be statistically highly significant for both the groups (p<0.001) [Table/Fig-2].

Intergroup Comparison: When the average differences of mouth opening and burning sensation from baseline to 8th week of treatment were compared for Group A and Group B, no statistically significant difference was found for both the treatment outcomes (p>0.05) [Table/Fig-3].

Adverse Effects: Out of the 25 patients, 21 patients did not have any adverse effects while four of them reported mild local pain following the injections.

DISCUSSION

OSMF is a chronic debilitating condition with a high risk of malignant transformation. It is a chronic disease and differs in symptoms and severity at every stage [9]. Many surgical and therapeutic treatments have been tried for the cure of OSMF, but still no definitive or widely accepted treatment is currently available [2].

Intralesional injections of drugs like dexamethasone, triamcinolone, hyaluronidase and placental extract have shown relief from the symptoms and improvement in the mouth opening in patients with OSMF. Various combinations of drug regimens have been used in the treatment of OSMF and each drug has a different mechanism of action [2].

In both our study groups, males outnumbered the females. This finding was similar to the study conducted by Sharma et al., and Kumar et al., [10,11]. The mean age of the patients having OSMF was 40.13±12.78 years. This finding was similar to that of More et al., [12] who reported a mean age of 36.67±13.35 years in their patients but was not in accordance with Kumar et al., [11] and Selvam et al., [13] who found lower mean ages in their patient groups.

In habit analysis, it was noted that most of the patients were having the habit of chewing gutka (n=21) followed by areca nut (n=03) and pan (n=01). This finding was similar to that of Sharma et al., [10] and Selvam et al., [13]. This finding emphasizes the role of areca nut as the main etiologic factor for OSMF.

The treatment regimens studied in our patient groups are the commonly prescribed regimens in our department based on patient preferences with regard to their cost, as there is no evidence supporting a superior efficacy of one over the other.

In the present study, increase in mouth opening and reduction in burning sensation were considered as two basic parameters to compare the efficacy of both the regimen. In Group A, statistically significant improvement was observed both in mouth opening and burning sensation with the use of placental extract and dexamethasone combination indicating the efficacy of this regimen in the treatment of OSMF. Statistically significant improvement was noted in mouth opening and burning sensation in Group B as well, with the use of hyaluronidase and dexamethasone combination stating the usefulness of the regimen in the treatment of OSMF.

But when the therapeutic efficacy of both the regimens was compared, the difference was statistically not significant for both the parameters. Even though the average baseline mouth opening of both the groups were different, our study analyzed the average increase in mouth opening at the end of 8 weeks irrespective of the severity of reduced mouth opening at baseline. Thus, we state that both the regimens are equally effective in the treatment of OSMF.

Singh et al., conducted a study to evaluate effectiveness of placental extract injections in the treatment of OSMF and favorable treatment outcomes were noted [14]. James et al., evaluated the efficacy of hyaluronidase and dexamethasone combination in the treatment of OSMF and definite reduction in burning sensation and improvement in mouth opening was observed [15]. These findings are similar to our study.

Steroid plays an important role in the treatment of OSMF and is a commonly used treatment measure for medical management of OSMF. Various studies have demonstrated the successful use of various steroids for the treatment of OSMF [9,16]. In the present study as well, both the regimens included steroid with desirable treatment outcomes.

The combination of the drugs studied in the present study is unique in a way that, in available literature, there is no comparison made of these two treatment regimens. So outcome of the present study establishes the therapeutic efficacy of these combinations and provides scope to further explore the results of our study in future researches.

Various researchers have compared the efficacy of intralesional injections in combination with other treatment modalities. Krishnamoorthy et al., studied therapeutic efficacy of colchicine in combination with intralesional hyaluronidase injections, whereas, Rao et al., evaluated treatment outcomes by alpha lipoic acid in combination with intralesional steroid and hyaluronidase [17,18]. Selvam et al., compared effectiveness of lycopene and antioxidants in combination with intralesional steroid and hyaluronidase injections [13]. All the studies demonstrated favorable treatment outcomes in terms of mouth opening and burning sensation. The outcomes of these studies are similar to our study in a way that improvement of mouth opening and reduction in burning sensation was observed with intralesional steroids and hyaluronidase injections with or

without other treatment modalities. The outcomes of the studies have been summarized in [Table/Fig-4].

In the present study, majority of participants (n=21) did not demonstrate any adverse effects related to injection therapy of OSMF. Only four (2 from Group A and 2 from Group B) participants reported mild pain after injection. This finding was in contrast to the studies conducted by Singh D et al., and Singh M et al., in which no significant side effects were noted [14,16]. In the studies conducted by Goswami et al., and Vani et al., post-injection pain was noted, similar to our study [19,20].

LIMITATION

The limitations of the present study include smaller sample size and retrospective study design. The lack of awareness and motivation, the addiction potential of areca nut and the socioeconomic background of our patient population attributes to a high rate of loss to follow-up. These have led to the smaller sample size and influenced our study design. We encourage future researchers to study larger sample size with a prospective randomized controlled study design to further explore the findings of the present study.

CONCLUSION

The findings of the present study suggest that both the treatment regimens comprising placental extract with dexamethasone and hyaluronic acid with dexamethasone are equally effective for the treatment of OSMF, both in terms of improvement of mouth opening and reduction of burning sensation.

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S.N.	Author	Drug /Combination Studied	Mouth Opening	Burning Sensation
1.	Singh D et al., [14]	Placental extracts 2 ml	↑	↓
2.	James et al., [15]	Dexamethasone 1.5ml + Hyaluronidase 1500IU	↑	↓
3.	Singh M et al., [16]	Hydrocortisone acetate 1.5ml + Hyaluronidase 1500IU and Triamcinolone acetonide 10mg/ml + Hyaluronidase 1500IU	↑ by both the regimen	↓ by both the regimen
4.	Krishnamoorthy et al., [17]	Colchicine 0.5mg + Hyaluronidase 1500IU and Hyaluronidase 1500IU + Hydrocortisone acetate 25mg/ml	↑ by both the regimen	↓ by both the regimen
5.	Rao et al., [18]	Betamethasone 1ml + Hyaluronidase 1500IU + Alpha lipoic acid	↑ by both the regimen	↓ by both the regimen
6.	Selvam et al., [13]	Lycopene 16mg + Dexamethasone 1.5ml + Hyaluronidase 1500IU and Antioxidants + Dexamethasone 1.5ml + Hyaluronidase 1500IU	↑ by both the regimen	↓ by both the regimen

[Table/Fig-4]: Summary of treatment outcomes in various similar studies.

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