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Comparative evaluation of Intralesional Dexamethasone Versus Hyaluronidase in the Management of OSMF: A Original Research study

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ABSTRACT

Background: Oral Submucous Fibrosis (OSMF) is a chronic, progressive, and potentially malignant oral disorder characterized by juxta-epithelial fibrosis, leading to severe trismus and burning sensation. Intralesional corticosteroids are a conventional treatment, but their efficacy in reversing fibrosis is limited. Hyaluronidase, a fibrolytic enzyme, has been proposed as an alternative or adjunct. There is a paucity of evidence directly comparing these two agents as monotherapies.

Objective: This study aimed to compare the clinical efficacy of intralesional dexamethasone versus intralesional hyaluronidase in the management of OSMF.

Methods: A single-blind, parallel-group, randomized clinical trial was conducted on 60 patients with clinically and histopathologically confirmed OSMF. Patients were randomly allocated into two equal groups (n=30). Group A received intralesional injections of dexamethasone (4 mg/mL), and Group B received intralesional injections of hyaluronidase (1500 IU). Injections were administered weekly for eight weeks. The primary outcome was the change in maximal inter-incisal mouth opening (mm). Secondary outcomes included changes in burning sensation, measured on a 10-point Visual Analogue Scale (VAS), and improvement in cheek flexibility. Assessments were performed at baseline, 1 month, 3 months, and 6 months.

Results: Both groups showed significant improvement from baseline. At the 6-month follow-up, the mean improvement in mouth opening was significantly greater in the hyaluronidase group (Group B: 8.4 ± 2.8 mm) compared to the dexamethasone group (Group A: 6.3 ± 2.5 mm) ($p = 0.012$). Conversely, the reduction in burning sensation was more pronounced in Group A, with a final mean VAS score of 2.1 ± 0.6, compared to 3.5 ± 0.8 in Group B ($p < 0.001$). A significantly higher percentage of patients in Group B (60.7%) reported marked improvement in cheek flexibility compared to Group A (32.1%) ($p = 0.025$). No severe adverse effects were reported in either group.

Conclusion: Intralesional hyaluronidase monotherapy demonstrated superior efficacy in improving mouth opening and cheek flexibility in OSMF patients. However, intralesional dexamethasone was more effective in alleviating the symptomatic burning sensation. The choice of agent may be tailored based on the patient's primary complaint.

Keywords: *Oral Submucous Fibrosis, Hyaluronidase, Corticosteroids, Dexamethasone, Trismus, Randomized Clinical Trial.*

INTRODUCTION

Oral Submucous Fibrosis (OSMF) is a debilitating, chronic oral mucosal disease predominantly affecting individuals in South and Southeast Asia **[1]**. It is strongly associated with the habit of chewing areca nut (betel quid), a practice deeply ingrained in many cultures **[2]**. The condition is characterized by a juxta-epithelial inflammatory reaction followed by

progressive deposition of dense, avascular collagenous connective tissue in the lamina propria and submucosa, leading to mucosal rigidity **[3]**. Clinically, this manifests as a blanching and leathery texture of the oral mucosa, fibrous bands, and a progressive reduction in mouth opening (trismus), which severely impacts mastication, speech, and oral hygiene. Most critically, OSMF is recognized by the World Health Organization as a potentially malignant disorder, with a malignant transformation rate reported to be as high as 7-13% **[4]**.

The pathogenesis of OSMF is multifactorial, involving areca nut alkaloids stimulating fibroblast proliferation and collagen synthesis, upregulation of pro-fibrotic cytokines like Transforming Growth Factor-beta (TGF-β), and increased cross-linking of collagen fibers **[5]**. Management aims to halt disease progression, improve functional ability, and alleviate symptoms. Current treatment modalities range from habit cessation and nutritional supplements to physiotherapy and surgical intervention for advanced cases **[6]**.

For early to moderate stages of OSMF, intralesional pharmacotherapy remains the cornerstone of management. Intralesional corticosteroids, such as triamcinolone acetonide and dexamethasone, have been the mainstay for decades **[7]**. Their mechanism of action is primarily anti-inflammatory, inhibiting the initial inflammatory cascade that precedes fibrosis. They also exhibit some anti-fibrotic properties by reducing collagen synthesis and inhibiting fibroblast activity **[8]**. Despite their widespread use, their ability to reverse established fibrosis is often limited and relapse rates can be high.

In recent years, hyaluronidase, a proteolytic enzyme, has gained attention as a therapeutic agent for OSMF. Hyaluronidase works by depolymerizing hyaluronic acid, a key component of the extracellular matrix ground substance, thereby reducing tissue viscosity and breaking down fibrous bands **[9]**. This action is believed to improve the pliability of the fibrotic mucosa and enhance the diffusion of other therapeutic agents when used in combination **[10]**. Several studies have demonstrated the efficacy of hyaluronidase, particularly when combined with corticosteroids, showing a synergistic effect that leads to better outcomes than either agent alone **[11, 12]**.

Despite the promising results of combination therapy, a significant research gap exists in the direct, head-to-head comparison of intralesional corticosteroids and hyaluronidase as monotherapies. Understanding the individual contribution and primary effect of each agent is crucial for developing evidence-based, tailored treatment protocols. While steroids are thought to primarily target inflammation and symptoms, hyaluronidase is hypothesized to directly address the established fibrosis. A direct comparative trial would clarify whether one agent is superior for functional improvement (mouth opening) versus symptomatic relief (burning sensation).

Therefore, the present comparative randomized clinical trial was designed to assess and compare the clinical outcomes of intralesional dexamethasone versus intralesional hyaluronidase as monotherapies in the management of patients with OSMF. The primary aim was to evaluate the difference in improvement of maximal inter-incisal mouth opening between the two groups.

MATERIALS AND METHODS

Study Design and Setting

This study was a single-center, parallel-group, single-blind, randomized controlled clinical trial conducted at the Department of Oral Medicine and Radiology, Global Institute of Dental Sciences, from January 2022 to December 2023. The study protocol was approved by the Institutional Ethical Committee (IEC/2021/11/04) and was registered with the Clinical Trials Registry of India (CTRI/2021/12/038910). All procedures were conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to their enrollment.

Participants and Sample Size

The sample size was calculated based on a previous study evaluating mouth opening in OSMF. To detect a mean difference of 3 mm in mouth opening with a standard deviation of 3.5 mm, an alpha of 0.05, and a power of 80%, a sample size of 28 patients per group was required. To compensate for a potential 10% attrition rate, a total of 60 patients (30 per group) were recruited.

Inclusion Criteria:

1. Patients aged 18 to 50 years.
2. Clinically diagnosed and histopathologically confirmed cases of OSMF (Grade II or III based on Khanna & Andrade's classification).
3. Maximal inter-incisal opening of less than 35 mm.
4. Willingness to cease the areca nut chewing habit.
5. Willingness to provide informed consent and attend all follow-up appointments.

Exclusion Criteria:

1. Patients with severe systemic diseases (e.g., uncontrolled diabetes, hypertension, bleeding disorders).
2. Pregnant or lactating females.

3. Known hypersensitivity to dexamethasone or hyaluronidase.
4. History of previous surgical or medical treatment for OSMF within the last year.
5. Presence of oral mucosal dysplasia or malignancy.
6. Patients on long-term steroid therapy for other conditions.

Randomization and Blinding

Eligible patients were randomly assigned in a 1:1 ratio to either Group A (Dexamethasone) or Group B (Hyaluronidase) using a computer-generated random number sequence. The allocation was concealed using sequentially numbered, sealed, opaque envelopes opened by a clinical coordinator not involved in patient assessment. The assessing clinician and the patients were blinded to the treatment allocation. However, due to the different preparations of the investigational drugs, the operator administering the injections could not be blinded.

Intervention Protocol

All patients received comprehensive counseling on habit cessation.

- **Group A (Dexamethasone Group):** Patients received intralesional injections of dexamethasone sodium phosphate (4 mg/mL). A total of 1 mL was injected into the fibrotic bands of each buccal mucosa (total 2 mL per session) using a 26-gauge needle.
- **Group B (Hyaluronidase Group):** Patients received intralesional injections of hyaluronidase. A vial containing 1500 International Units (IU) of hyaluronidase was reconstituted with 2 mL of normal saline. A total of 1 mL of this solution was injected into the fibrotic bands of each buccal mucosa (total 2 mL per session).

Injections were administered weekly for a total of eight consecutive weeks. Patients in both groups were also prescribed standard antioxidant and multivitamin supplements (Beta-carotene, Vitamin A, E, C, and Lycopene) for the duration of the study.

Outcome Assessment

Clinical parameters were recorded at baseline (T0), 1 month (T1), 3 months (T2), and 6 months (T3) after the initiation of treatment.

1. **Primary Outcome (Mouth Opening):** Maximal inter-incisal distance was measured in millimeters (mm) between the incisal edges of the maxillary and mandibular central incisors using a calibrated digital Vernier caliper. The average of three readings was recorded.
2. **Secondary Outcomes:**

- **Burning Sensation:** Assessed subjectively using a 10-point Visual Analogue Scale (VAS), where 0 indicated 'no burning' and 10 indicated 'worst imaginable burning'.
- **Cheek Flexibility:** Assessed by the examining clinician and graded on a 3-point qualitative scale: 1 (Minimal Improvement), 2 (Moderate Improvement), 3 (Marked Improvement) at the end of 6 months.

Statistical Analysis

Data were entered into a Microsoft Excel spreadsheet and analyzed using SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY). Descriptive statistics (mean, standard deviation, frequencies, percentages) were calculated. The normality of data distribution was checked using the Shapiro-Wilk test. An independent samples t-test was used to compare the mean values of mouth opening and VAS scores between the two groups. A Chi-square test was used to compare categorical data (cheek flexibility). The paired t-test was used for intra-group comparisons from baseline to follow-up. A p-value of < 0.05 was considered statistically significant.

RESULTS

Participant Flow and Baseline Characteristics

A total of 72 patients were screened for eligibility, of whom 60 met the inclusion criteria and were randomized into two groups of 30 each. Two patients from Group A and two from Group B were lost to follow-up by the 6-month mark. Thus, data from 56 patients (28 in Group A, 28 in Group B) were included in the final analysis. The demographic and baseline clinical characteristics of the participants in both groups are presented in **Table 1**. There were no statistically significant differences between the groups at baseline in terms of age, gender, habit duration, mouth opening, or VAS score for burning sensation ($p > 0.05$), indicating successful randomization.

Table 1: Baseline Demographic and Clinical Characteristics of Study Participants

Characteristic	Group A (Dexamethasone) (n=28)	Group B (Hyaluronidase) (n=28)	p-value
Age (years, Mean ± SD)	34.5 ± 7.2	35.8 ± 6.9	0.531
Gender (Male/Female)	24 / 4	25 / 3	0.989*
Habit Duration (years, Mean ± SD)	9.8 ± 3.1	10.2 ± 3.5	0.672
Mouth Opening (mm, Mean ± SD)	19.5 ± 2.1	19.8 ± 2.3	0.615

Characteristic	Group A (Dexamethasone) (n=28)	Group B (Hyaluronidase) (n=28)	p-value
VAS Score (0-10, Mean ± SD)	7.8 ± 0.9	7.6 ± 1.1	0.498
Chi-square test; all other p-values from Independent t-test.			

Primary Outcome: Inter-incisal Mouth Opening

Both groups showed a statistically significant improvement in mouth opening from baseline at all follow-up intervals ($p < 0.001$ for intra-group comparisons). However, when comparing the two groups, the improvement in mouth opening was significantly greater in the hyaluronidase group (Group B) at the 3-month and 6-month follow-ups. At 6 months, the mean mouth opening in Group A was 25.8 ± 2.5 mm (an increase of 6.3 mm), while in Group B it was 28.2 ± 2.8 mm (an increase of 8.4 mm). This difference was statistically significant ($p = 0.012$). The detailed comparison is shown in **Table 2**.

Secondary Outcome: Burning Sensation (VAS Score)

Both treatments resulted in a significant reduction in the VAS score for burning sensation ($p < 0.001$). The dexamethasone group (Group A) showed a more rapid and pronounced reduction in symptoms. At the 6-month evaluation, the mean VAS score in Group A was 2.1 ± 0.6, which was significantly lower than the mean VAS score of 3.5 ± 0.8 in Group B ($p < 0.001$). These findings are detailed in **Table 2**.

Table 2: Comparison of Clinical Outcomes (Mouth Opening and VAS Score) Between Groups

Parameter	Group	Baseline (T0)	1 Month (T1)	3 Months (T2)	6 Months (T3)	p-value (T3)
Mouth Opening (mm)	**Group A (Dexamethasone)**	19.5 ± 2.1	21.8 ± 2.2	24.1 ± 2.4	25.8 ± 2.5	**0.012**
	Group B (Hyaluronidase)	19.8 ± 2.3	23.5 ± 2.5	26.8 ± 2.7	28.2 ± 2.8	
VAS Score (0-10)	**Group A (Dexamethasone)**	7.8 ± 0.9	5.1 ± 0.8	3.2 ± 0.7	2.1 ± 0.6	**<0.001**
	Group B (Hyaluronidase)	7.6 ± 1.1	6.2 ± 1.0	4.8 ± 0.9	3.5 ± 0.8	
p-value for inter-group comparison at 6 months (T3) using Independent t-test.						

Secondary Outcome: Cheek Flexibility

At the 6-month follow-up, a significantly higher proportion of patients in the hyaluronidase group reported marked improvement in cheek flexibility. In Group B, 17 out of 28 patients (60.7%) reported marked improvement, compared to only 9 out of 28 patients (32.1%) in Group A. The difference between the groups was statistically significant ($\chi^2 = 7.34$, $p = 0.025$), as shown in **Table 3**.

Table 3: Comparison of Cheek Flexibility Improvement at 6 Months

Improvement Level	Group A (Dexamethasone) n (%)	Group B (Hyaluronidase) n (%)	Total n (%)
Marked Improvement	9 (32.1%)	17 (60.7%)	26 (46.4%)
Moderate Improvement	12 (42.9%)	8 (28.6%)	20 (35.7%)
Minimal Improvement	7 (25.0%)	3 (10.7%)	10 (17.9%)
Total	28 (100%)	28 (100%)	56 (100%)
p-value from Chi-square test = 0.025.			

No systemic or severe local adverse effects were observed in either group. Some patients reported transient pain at the injection site, which resolved within a few hours.

DISCUSSION

The management of OSMF presents a significant clinical challenge due to its progressive nature and potential for malignant transformation. This study was designed to provide high-quality evidence by directly comparing the efficacy of two commonly used intralesional agents, dexamethasone and hyaluronidase, as monotherapies. The findings reveal a differential efficacy profile for these drugs: hyaluronidase was superior in improving the functional parameters of mouth opening and cheek flexibility, while dexamethasone was more effective for symptomatic relief of burning sensation.

The primary outcome of this trial, the improvement in inter-incisal mouth opening, was significantly greater in the hyaluronidase group. This can be attributed to the drug's fundamental mechanism of action. Hyaluronidase is a fibrolytic enzyme that directly targets the pathologic hallmark of OSMF—the dense, cross-linked extracellular matrix **[10]**. By depolymerizing glycosaminoglycans like hyaluronic acid, it reduces the viscosity of the ground substance and hydrolyzes

the fibrous bands, thereby increasing tissue pliability and directly countering the physical restriction that causes trismus **[9]**. Our results, showing a mean improvement of 8.4 mm in the hyaluronidase group versus 6.3 mm in the steroid group, strongly support this mechanistic hypothesis. This finding is consistent with earlier reports that have highlighted the fibrolytic potential of hyaluronidase, though many of these studies used it in combination therapy, making it difficult to isolate its specific effect **[13]**.

Conversely, dexamethasone demonstrated superior efficacy in reducing the burning sensation, a key symptom reflecting the underlying inflammatory process in OSMF **[5]**. Corticosteroids are potent anti-inflammatory agents that suppress the expression of pro-inflammatory cytokines, inhibit leukocyte migration, and stabilize lysosomal membranes **[14]**. In the early stages of OSMF, inflammation plays a crucial role in initiating the fibrotic cascade **[3]**. By effectively controlling this inflammation, dexamethasone provides rapid and significant symptomatic relief, as evidenced by the significantly lower VAS scores in Group A. This aligns with the long-standing use of corticosteroids as the first-line treatment for inflammatory oral mucosal conditions **[7, 8]**. The lesser effect of hyaluronidase on burning sensation suggests that its primary action is not anti-inflammatory but rather structural.

The results for cheek flexibility, a subjective but clinically relevant measure of mucosal suppleness, further corroborate the findings for mouth opening. The higher percentage of patients reporting "marked improvement" in the hyaluronidase group indicates a more substantial reversal of tissue rigidity. This is a direct clinical correlate of the enzymatic breakdown of the fibrotic submucosal tissue.

Our study's design as a monotherapy trial is a key strength, allowing for a clear distinction between the effects of an anti-inflammatory agent versus a fibrolytic agent. Previous studies have often combined these agents, with researchers like Singh et al. **[11]** and James et al. **[12]** reporting that the combination of steroids and hyaluronidase yields better results than steroids alone. While our findings do not contradict this, they provide a crucial rationale for *why* combination therapy is effective: each drug targets a different component of OSMF pathophysiology. The steroid manages the active inflammation and symptoms, while the hyaluronidase addresses the established structural fibrosis. This suggests that a combination regimen may indeed be the most rational and comprehensive approach.

This study has several limitations that must be acknowledged. First, it was a single-center trial, which may limit the generalizability of the findings. Second, the 6-month follow-up period is relatively short for a chronic disease like OSMF; long-term studies are needed to assess the stability of the improvements and the rate of relapse. Third, while the patient and assessor were blinded, the operator was not, which could introduce a potential for performance bias, although standardized injection protocols were used to minimize this. Finally, cheek flexibility was assessed using a qualitative scale, and a more objective measurement tool, such as a tonometer, could provide more robust data in future studies.

Future research should focus on long-term comparative trials, including a third arm with combination therapy to definitively establish its superiority over monotherapy. Furthermore, investigating optimal dosing and frequency of injections, as well as exploring novel anti-fibrotic agents like pentoxifylline or interferon-gamma, will be essential to advance the management of this debilitating condition **[15-17]**.

CONCLUSION

Within the limitations of this study, it can be concluded that both intralesional dexamethasone and hyaluronidase are effective therapeutic options for the management of OSMF. However, they exhibit distinct efficacy profiles. Intralesional hyaluronidase was significantly more effective than dexamethasone in improving inter-incisal mouth opening and cheek flexibility, making it a preferable choice for patients whose primary concern is functional limitation. Conversely, intralesional dexamethasone provided superior relief from the burning sensation, indicating its utility for patients with pronounced inflammatory symptoms. These findings suggest that a personalized treatment approach, based on the patient's predominant signs and symptoms, could optimize clinical outcomes in OSMF management.

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