RESEARCH PAPER

An In-Vivo Comparative Evaluation of the Effectiveness of Intralesional Placentrex and Hyaluronidase for the Safe Treatment of Oral Submucous Fibrosis: A Clinical (Original Research) Study

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ABSTRACT

Aim:

This study aims to evaluate the effectiveness of intralesional placentrex and hyaluronidase for the safe treatment of oral submucous fibrosis.

Materials and Methods:

This study examined 80 patients with symptoms like restricted mouth opening, burning sensations, cheek stiffness, limited tongue movement, and dry mouth. A subset of 40 patients (ages 20-45) was identified, all diagnosed with Grade II oral submucous fibrosis (OSMF) and characterized by a maximum inter-incisal mouth opening of just 21 mm and the presence of fibrous bands in the buccal mucosa. Forty participants were randomly assigned to two groups: Group I received intralesional injections of 2 mL of placentrex to promote tissue healing, while Group II received a combination of dexamethasone (4 mg) and hyaluronidase (1500 IU) via intralesional injection to reduce inflammation and increase tissue flexibility. Outcomes were assessed based on improvements in mouth opening and burning sensations, measured using a visual analog scale (VAS) at 2, 4, and 6-weeks post-treatment.

Statistical Analysis and Results:

To measure treatment effectiveness, we assessed mouth opening capacity and burning sensations on a visual analogue scale (VAS) at 2, 4, and 6 weeks. Initial evaluations showed a mean mouth opening of 21 mm and a VAS score of 7 for both groups. Results at 2 weeks indicated Group I had a mean mouth opening of 23.45 mm and a VAS score of 6.5, whereas Group II showed a mean mouth opening of 25.06 mm and a VAS score of 6.2. At 4 weeks, Group I's mouth opening increased to 26.25 mm (VAS 5.8) and Group II's to 29.12 mm (VAS 5.2). By 6 weeks, Group I reached 28.07 mm (VAS 3.4), and Group II achieved 31.05 mm (VAS 3.2). One-way ANOVA was employed for a statistical analysis of treatment efficacy across groups.

Conclusion:

This study concluded that both treatments were effective in alleviating stage II OSMF symptoms, with the combination of hyaluronidase and dexamethasone showing slightly better results in improving mouth opening and reducing burning sensation after six weeks.

Keywords: Oral Submucous Fibrosis, Intralesional Placentrex, Hyaluronidase, Pre-Malignant Condition, Burning Sensation, Cheek Stiffness

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Introduction

A precancerous condition, often referred to as a precancerous lesion, comprises a cluster of abnormal cells that exhibit a higher-than-average risk of developing into cancer, serving as a critical "warning sign" for potential future malignancy. Although these cells are not classified as cancerous at present, they possess the potential to progress to cancer if left unmonitored and untreated. The medical terms used to describe these abnormal cellular changes include dysplasia and hyperplasia.[1,2] Various types of precancerous conditions exist, including cervical dysplasia, which affects the cervix; adenomatous colon polyps, commonly found in the colon; actinic keratosis, which develops on sun-exposed skin; and oral leukoplakia, a condition presenting with white patches in the mouth. Oral submucous fibrosis (OSMF) is a long-lasting and progressively worsening condition that can increase the risk of cancer. It is primarily linked to the habitual chewing of areca nut, often referred to as betel nut, as well as the use of various tobacco products.[3,4] This debilitating condition leads to the development of fibrous tissue in the oral mucosa, which can cause a range of troubling symptoms. Individuals with OSMF often experience a marked stiffness in the oral tissues, making it difficult and painful to move the mouth. Additionally, they may endure a persistent burning sensation in the oral cavity, along with trismus, which is a significant restriction in the ability to open the mouth. These symptoms can severely impact daily activities such as eating and speaking, ultimately affecting the quality of life.[5,6] OSMF is often recognised as a precancerous condition, with studies suggesting a risk of 7–9% that it may progress to oral cancer over time. Managing Oral Submucous Fibrosis involves a multifaceted approach, with the primary focus on the cessation of harmful habits such as areca nut chewing and tobacco use. Diagnosing OSMF typically relies on observing clinical symptoms, which may include burning sensations in the mouth, restricted mouth opening, and the presence of a distinctive white, fibrous mucosa.[7,8] A biopsy may also be performed to confirm the diagnosis. Treatment strategies are varied and may include nutritional supplements to support healing, intralesional injections of steroids or hyaluronidase to reduce inflammation and promote tissue elasticity, physiotherapy to improve mobility of the oral tissues, and surgical intervention for cases of advanced fibrosis.[9,10] One promising treatment for early-stage (Stage II) Oral Submucous Fibrosis is the use of Intralesional Placentrex is a treatment derived from a carefully processed aqueous extract of human placenta, showcasing its potential as a biogenic stimulator. This innovative therapy has been recognized for its safety and efficacy, particularly in alleviating the debilitating symptoms associated with Oral Submucous Fibrosis (OSMF). Clinical studies have demonstrated that administering Intralesional Placentrex can lead to significant improvements in mouth opening and can relieve the discomfort of burning sensations.[11] This therapeutic effect is likely attributed to Placentrex's ability to modulate collagen production within the affected tissues, facilitating better healing and flexibility. Another valuable treatment option for managing OSMF is Hyaluronidase, a potent proteolytic enzyme. Its primary role involves breaking down hyaluronic acid, a key component found in connective tissues. By doing so, Hyaluronidase reduces the viscosity of fibrous bands, subsequently improving accessibility to the tissues and enhancing overall mobility. Typically administered through intralesional injections, Hyaluronidase is often used in conjunction with corticosteroids like dexamethasone. This combination not only aids in increasing mouth opening but also alleviates discomfort associated with burning sensations. Together, these therapeutic modalities create a comprehensive approach to addressing the complex challenges posed by OSMF, ultimately aiming to enhance the quality of life for individuals affected by this condition.[12,13] This study aims to evaluate the effectiveness of intralesional placentrex and hyaluronidase for the safe treatment of oral submucous fibrosis

Materials and Methods

This study focused on a total of 80 patients who presented with a variety of symptoms, primarily restricted mouth opening, burning sensations, stiffness in the cheeks, restricted tongue movement, and dryness of the mouth. Following thorough clinical examinations, a subset of 40 patients, comprising both males and females aged between 20 and 45 years, was

identified. These patients exhibited a notably limited inter-incisal mouth opening, typically restricted to just 21 mm. Furthermore, the examination revealed the presence of palpable vertical fibrous bands within the buccal mucosa, as well as blanching of the oral mucosa, resulting in a distinctive marble-like appearance. These findings confirmed a diagnosis of Grade II oral submucous fibrosis (OSMF). Inclusion criteria for this study mandated a clinical diagnosis of Grade II OSMF, which was based on measurements of mouth opening, the presence of fibrous bands, and reported symptoms. Additionally, a history of areca nut or gutkha chewing, as well as related products was necessary for participation. Conversely, patients were excluded if they had oral or oropharyngeal cancers (Grades 4/5), known systemic disorders that could lead to restricted mouth opening—such as scleroderma or temporomandibular joint ankylosis—other oral potentially malignant disorders like severe leukoplakia, any previous treatments for OSMF, or if they were currently taking antioxidants or multivitamin supplements. Informed consent was obtained from all participants. The study aimed to evaluate the effectiveness of two different treatment modalities for patients diagnosed with Grade II Oral Submucous Fibrosis (OSMF). A total of 40 patients participated in the study who was randomly assigned to one of two treatment groups, each consisting of 20 individuals. In Group I, patients received intralesional injections of 2 mL of placentrex, a treatment believed to promote tissue healing and regeneration. The injections were carefully administered using a 2 mL syringe paired with a 26-gauge needle. Prior to the injections, the treating physician palpated the affected areas to identify the fibrous bands characteristic of OSMF, ensuring that the injections were delivered to the most pertinent sites for maximum therapeutic effect. Group II, on the other hand, was treated with a combination therapy of dexamethasone (4 mg), an anti-inflammatory agent, and hyaluronidase (1500 IU), an enzyme that enhances the absorption and distribution of injected fluids, which was also delivered via intralesional injection. This dual approach aimed to reduce inflammation and promote flexibility in the fibrous tissue. To assess the outcomes of these treatment strategies, the researchers focused on two primary parameters: improvements in mouth opening and the intensity of burning sensations experienced by the patients. The severity of these symptoms was evaluated using a visual analog scale (VAS), which allows patients to grade their discomfort on a continuum, providing a quantifiable measure of their condition. Assessments were carried out at three intervals: 2 weeks, 4 weeks, and 6 weeks after the initiation of treatment. Throughout the entire treatment period, all patients were advised to engage in consistent mouth opening exercises. These exercises were crucial, as they aimed to enhance oral mobility and prevent the recurrence of fibrosis, thereby complementing the effects of the injected therapies. Data related to various clinical parameters, including mouth opening measurements and pain intensity were meticulously collected every two weeks. This systematic approach allowed for a thorough examination of the efficacy and safety of both intralesional placentrex and the combination of dexamethasone and hyaluronidase, contributing valuable insight into the management of oral submucous fibrosis.

Statistical Analysis

In this study, all statistical analyses were conducted utilizing SPSS version 31.0, a robust software suite specifically designed for statistical computing and data analysis in the social sciences. This powerful tool enables researchers to efficiently manage and interpret complex data sets, facilitating insightful conclusions and enhancing the overall understanding of the research findings.

Results

This study involves a cohort of 40 patients; all diagnosed with grade II oral submucous fibrosis, with ages ranging from 20 to 45 years. The sample includes both males and females, specifically featuring 22 males and 18 females, as depicted in Table 1, which provides a detailed statistical breakdown of age and gender among the participants. To visualize the demographic distribution and relevant characteristics, Graph 1 is included, offering an insightful illustration of the study population. For the treatment protocol, the participants were systematically divided into two distinct groups. Group I consisted of 20 patients who were administered intralesional injections of 2 mL of Placentrax, a therapeutic agent intended to promote effective tissue healing. These injections were performed with precision, utilizing a 26-gauge needle, as the physician carefully palpated the affected regions to ensure optimal placement of the treatment. In contrast, Group II, also comprising 20 patients, received an alternative treatment regimen consisting of a combination of dexamethasone (4 mg) and hyaluronidase (1500 IU). This duo, delivered via

intralesional injections, was specifically targeted at reducing inflammation while enhancing tissue flexibility. To evaluate the effectiveness of the treatments, various outcome measures were employed. Improvements in mouth opening capacity were documented, alongside assessments of burning sensations experienced by the patients, which were measured using a visual analog scale (VAS). These evaluations took place at predetermined intervals of 2, 4, and 6 weeks following the intervention, allowing for a comprehensive analysis of the treatment outcomes. Table 2 provides insights into the clinical data of Group I (N=20) patients with grade II oral submucous fibrosis. The treatment involved administering the specified intralesional injections of Placentrax. To evaluate the effectiveness of the treatment, we assessed the patients' mouth opening abilities and recorded their VAS scores prior to the intervention. A thorough statistical analysis of preoperative data revealed that the mean mouth opening was 21 mm, accompanied by a VAS score of 7. Similarly, Table 3 details the demographic and clinical profiles of Group II (N=20) patients who received hyaluronidase injections. Preoperative assessments, including mouth opening capabilities and VAS scores, were performed to determine the effectiveness of the treatment approach. The findings indicated that the mean mouth opening was also 21 mm, with a VAS score of 7. Subsequent tables document the progress made at various time intervals post-treatment. Table 4 presents data for Group I at 2 weeks post-injection, indicating a mean mouth opening increased to 23.45 mm and a reduction in VAS scores to 6.5. In Table 5, the results for Group II are displayed, showing a mean mouth opening of 25.06 mm and a VAS score of 6.2 at the same 2-week interval. The improvements continued over time, as illustrated in Table 6 for Group I, reporting a mouth opening of 26.25 mm and a VAS score of 5.8 at the 4-week mark. Table 7 shows Group II's advancements, with a mean mouth opening of 29.12 mm and a VAS score of 5.2 at 4 weeks post-treatment. As noted in Table 8, further progress was observed in Group I at the 6-week follow-up, with a mean mouth opening reaching 28.07 mm and VAS scores dropping significantly to 3.4. Lastly, Table 9 encapsulates the results for Group II, with the final assessments revealing a mean mouth opening of 31.05 mm and a VAS score of 3.2 at the 6-week evaluation. To summarize the overall findings across both groups, Table 10 employs one-way ANOVA to provide a statistical estimation, reflecting the treatment efficacy and outcomes across the studied groups.

Table 1: Age & gender based statistical description of contributing patients

Age Group (Yrs)	Male	Female	Total	P value
20-25	5	4	9	0.04
26-30	4	3	7	0.50
31-35	6	4	10	0.02*
36-40	4	4	8	0.70
41-45	3	3	6	0.60
Total	22	18	40	*Significant
*p<0.05 significant				

Graph 1: Patients demographic distribution and associated details

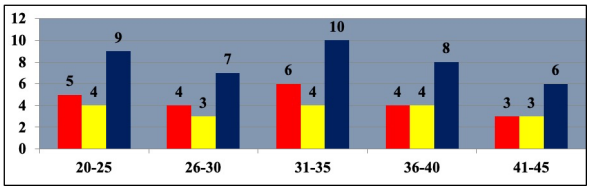

Table 2: Group 1 (N=20) Patients diagnosed with grade II oral submucous fibrosis. The treatment approach involved administering intralesional injections of Placentrax. To assess the effectiveness of the management, we measured mouth opening capabilities and evaluated the VAS (Visual Analog Scale) scores prior to the intervention. Additionally, a thorough statistical analysis was conducted to analyze the preoperative data

Variables	Value	Stat. Mean	Std. Dev.	Std. Error	95% CI	Pearson Chi-Square Value	df	p value
Mouth opening	21	1.14	1.21	1.22	1.23	1.02	1.0	0.09
VAS score	7	1.03	1.04	1.02	1.01	1.05	1.0	0.03
*p<0.05 significant								

Table 3: Group 2 (N=20) Patients diagnosed with grade II oral submucous fibrosis. The treatment approach involved administering intralesional injections ofhyaluronidase. To assess the effectiveness of the management, we measured mouth opening

capabilities and evaluated the VAS (Visual Analog Scale) scores prior to the intervention. Additionally, a thorough statistical analysis was conducted to analyze the preoperative data

Variables	Value	Stat. Mean	Std. Dev.	Std. Error	95% CI	Pearson Chi-Square Value	df	p value
Mouth opening	21	1.14	1.21	1.22	1.23	1.02	1.0	0.09
VAS score	7	1.03	1.04	1.02	1.01	1.05	1.0	0.03
*p<0.05 significant								

Table 4: Group 1 (N=20) Patients diagnosed with grade II oral submucous fibrosis. The treatment approach involved administering intralesional injections of Placentrax. To assess the effectiveness of the management, we measured mouth opening capabilities and evaluated the VAS (Visual Analog Scale) scores 2 weeks to the intervention. Additionally, a thorough statistical analysis was conducted

Variables	Value	Stat. Mean	Std. Dev.	Std. Error	95% CI	Pearson Chi-Square Value	df	p value
Mouth opening	23.45	1.14	1.94	1.15	1.16	1.21	1.0	0.02*
VAS sco re	6.5	1.09	1.0	1.05	1.0	1.08	1.0	1.06
*p<0.05 significant								

Table 5: Group 2 (N=20) Patients diagnosed with grade II oral submucous fibrosis. The treatment approach involved administering intralesional injections of hyaluronidase. To assess the effectiveness of the management, we measured mouth opening capabilities and evaluated the VAS (Visual Analog Scale) scores 2 weeks to the intervention. Additionally, a thorough statistical analysis was conducted to analyze

Variables	Value	Stat. Mean	Std. Dev.	Std. Error	95% CI	Pearson Chi-Square Value	df	p value
Mouth opening	25.06	2.17	1.16	1.13	1.12	1.24	1.0	0.07
VAS score	6.2	1.02	1.02	1.06	1.04	1.03	1.0	0.01*
*p<0.05 significant								

Table 6: Group 1 (N=20) Patients diagnosed with grade II oral submucous fibrosis. The treatment approach involved administering intralesional injections of Placentrax. To assess the effectiveness of the management, we measured mouth opening capabilities and evaluated the VAS (Visual Analog Scale) scores 4 weeks to the intervention. Additionally, a thorough statistical analysis was conducted

Variables	Value	Stat. Mean	Std. Dev.	Std. Error	95% CI	Pearson Chi-Square Value	df	p value
Mouth opening	26.25	1.16	1.23	1.55	1.24	1.31	1.0	0.02*

VAS score	5.8	1.05	1.04	1.01	1.03	1.06	1.0	0.07
*p<0.05 significant								

Table 7: Group 2 (N=20) Patients diagnosed with grade II oral submucous fibrosis. The treatment approach involved administering intralesional injections of hyaluronidase. To assess the effectiveness of the management, we measured mouth opening capabilities and evaluated the VAS (Visual Analog Scale) scores 4 weeks to the intervention. Additionally, a thorough statistical analysis was conducted to analyze

Variables	Value	Stat. Mean	Std. Dev.	Std. Error	95% CI	Pearson Chi-Square Value	df	p value
Mouth opening	29.12	2.12	1.056	1.059	1.38	1.32	1.0	0.06
VAS score	5.2	1.05	1.02	1.01	1.03	1.02	1.0	0.05*
*p<0.05 significant								

Table 8: Group 1 (N=20) Patients diagnosed with grade II oral submucous fibrosis. The treatment approach involved administering intralesional injections of Placentrax. To assess the effectiveness of the management, we measured mouth opening capabilities and evaluated the VAS (Visual Analog Scale) scores 6 weeks to the intervention. Additionally, a thorough statistical analysis was conducted

Variables	Value	Stat. Mean	Std. Dev.	Std. Error	95% CI	Pearson Chi-Square Value	df	p value
Mouth opening	28.07	2.19	2.08	1.056	1.18	1.06	2.0	0.06
VAS score	3.4	1.08	1.04	1.04	1.03	1.02	1.0	0.04*
*p<0.05 significant								

Table 9: Group 2 (N=20) Patients diagnosed with grade II oral submucous fibrosis. The treatment approach involved administering intralesional injections of hyaluronidase. To assess the effectiveness of the management, we measured mouth opening capabilities and evaluated the VAS (Visual Analog Scale) scores 6 weeks to the intervention. Additionally, a thorough statistical analysis was conducted to analyze

Variables	Value	Stat. Mean	Std. Dev.	Std. Error	95% CI	Pearson Chi-Square Value	df	p value
Mouth opening	31.05	2.18	2.66	2.45	2.52	2.28	1.0	1.08
VAS score	3.2	1.05	1.04	1.03	1.05	1.02	.01	0.04*
*p<0.05 significant								

Table 10: Estimation amongst all studied groups using one-way ANOVA

Variables	Degree of Freedom	Sum of Squares ∑	Mean Sum of Squares m∑	F	Level of Sig. (p)
Between Groups	6	3.783	2.054	1.2	0.01*
Within Groups	18	3.862	1.361	-	
Cumulative	784.23	81.672	*p<0.05 significant		

Discussion

Odell E et al reviewed in their study that precancerous conditions often go unnoticed due to a lack of symptoms, emphasising the need for regular screenings. Some may show subtle changes like spots or ulcers, as seen in Bowen's disease. These conditions can arise from chronic inflammation, infections (like HPV), or environmental factors such as UV radiation and tobacco use. Examples include actinic keratosis, cervical intraepithelial neoplasia (CIN), adenomatous polyps, leukoplakia, erythroplakia, and monoclonal gammopathy of undetermined significance (MGUS). Regular screenings, such as Pap smears, HPV tests,

colonoscopies, and skin exams, are crucial for early detection, allowing for treatment before cancer develops.[14,15] Mandefro B et al showed in their study that management often involves removing or destroying abnormal tissue, such as excising polyps or freezing skin lesions. One specific precancerous condition is oral submucous fibrosis (OSMF), primarily caused by chronic chewing of areca nut (betel nut), often found in products like gutka or paan. Other contributing factors include spicy foods, smoking, alcohol consumption, and nutritional deficiencies. Symptoms include a severe burning sensation, reduced mouth opening due to stiffness, a pale or white oral appearance from reduced blood flow, and the development of tough fibrous bands in the cheeks. If not addressed early, OSMF can lead to significant functional limitations and is recognised as a precursor to oral squamous cell carcinoma. Management strategies recommend immediate cessation of areca nut or tobacco use as a primary step.[16,17] Alka H et al included in their study that while the condition can be irreversible, early stages may benefit from nutritional supplements and medical treatments, such as steroids and oral care. In severe cases, surgical intervention may be necessary to release the fibrous bands, improving mouth opening and functionality. OSMF is diagnosed primarily through clinical evaluation, supported by patient history and histopathological examination. Clinically, patients may experience an intense burning sensation when consuming spicy foods, reduced mouth opening (trismus), a stiff tongue, and pale, marble-like oral mucosa.[18,19] Hande AH et al reviewed in their study that uring a physical examination, palpable fibrous bands may be detected in the buccal mucosa, lips, or palate. The severity of OSMF is classified into stages based on mouth opening measurements, with Group I indicating no limitation (greater than 35 mm) and advanced stages (Group IV) signifying severe trismus or cancer changes. Management of OSMF varies according to its severity and emphasises improving mouth opening while halting disease progression.[20,21] Nair MV et al reviewed in their study that the most critical initial step is to immediately stop using habits such as areca nut, betel quid, and tobacco. For early stages, medical interventions may include intralesional corticosteroid injections (like dexamethasone or triamcinolone), often paired with hyaluronidase to break down fibrous bands. Nutritional supplements, including antioxidants and vitamins, can aid healing, and immune-modulators may help reduce inflammation. Physiotherapy through specialised mouth exercises can also improve flexibility and mouth opening. In advanced cases, surgical options may be necessary, including the release of fibrous bands, reconstruction and coronoidectomy to enhance mouth opening. Regular follow-up is crucial due to the risk of malignant transformation in OSMF patients, which requires monitoring for signs of dysplasia or squamous cell carcinoma.[22,23] Goyal J et al showed in their study that recent treatment strategies have included the use of Placentrex, which acts as a tissue stimulant to enhance vascularity and reduce fibrosis. It is usually administered as an intralesional injection and has demonstrated significant improvement in symptoms compared to other treatments. Additionally, hyaluronidase is another effective option; by degrading hyaluronic acid, it helps to increase mucosal pliability and improve the effectiveness of corticosteroids when used together. Overall, treatment protocols often combine intralesional injections of hyaluronidase with agents like Placentrex or dexamethasone, yielding better results than steroids alone for managing restrictions in mouth opening.[24,25]

Conclusion

In the context of this study's limitations, the authors sought to evaluate the effectiveness of intralesional injections of placentrex and hyaluronidase as a treatment for oral submucous fibrosis (OSMF). Their findings revealed and concluded that both intralesional placentrex and a combination of hyaluronidase with dexamethasone were effective in alleviating the symptoms associated with stage II OSMF. Notably, the combination of hyaluronidase and dexamethasone demonstrated a slightly greater improvement in mouth opening and a reduction in burning sensation after a treatment period of six weeks. The authors also concluded that while these treatments show promise, further research is necessary to fully understand their benefits and efficacy.

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