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Oral Submucous Fibrosis, OSMF: A Novel Therapeutic Approach

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Abstract

Oral Submucous Fibrosis (OSMF) is a chronic, progressive, scarring disease associated with chronic areca nut consumption, representing a generalized pathological state of the oral mucosa that significantly increases the risk of cancer. This study aims to evaluate the effectiveness of Tab. Colchicine 0.5 mg along with Intralesional Inj. Placentrex 1500 IU 2 ml in the management of OSMF.

Methodology

A total of 26 patients clinically diagnosed with Grade II (15) and Grade III (11) OSMF were divided into two groups (Group I and Group II). Group I patients were treated by administering Tab. Colchicine 0.5 mg twice daily with Intralesional Inj. Placentrex 1500 IU (2 ml) at a weekly interval for 12 weeks. Group II patients were treated with Intralesional Inj. Placentrex 1500 IU (2 ml) at a weekly interval for 12 weeks

Results

The results showed an overall significant improvement in burning sensation, mouth opening, and buccal mucosal flexibility in Group I compared to Group II, indicating the efficacy of the combined regimen of Tab. Colchicine 0.5 mg and Intralesional Inj. Placentrex 1500 IU 2 ml.

Conclusion

This study suggests that the use of 0.5mg Tab. Colchicine with Intralesional Inj. Placentrex 1500 IU 2ml is valuable in treating OSMF, showing superior outcomes without any side-effects. Future research with larger sample sizes and histological assessments is recommended to confirm these findings.

Keywords

OSMF-Oral Submucous Fibrosis; Colchicine 0.5 mg; Placentrex 1500 IU

Abbreviation

OSMF- Oral Submucous Fibrosis, Tab.-Tablet, Inj.- Injection, mg- milligram.

Introduction

Oral submucous fibrosis (OSMF) was first reported by Schwartz in 1952 as “atrophia idiopathica mucosae oris [1-3]. The WHO defines Oral Submucous Fibrosis as a “precancerous oral condition”—a widespread pathological state of the oral mucosa associated with a significantly increased risk of cancer [4]. The use of areca nut is the primary etiological agent associated with the development of OSMF [1-3,5]. The main alkaloid found in areca nuts is arecoline. Arecaidine, arecoline, guvacoline, and guvacine are other alkaloids found [6]. The aetiology of OSMF also involves other factors such genetic predisposition, nutritional inadequacies, immunological problems, lime, chilies, and collagen abnormalities [1-3,5]. The main objectives in the treatment of OSMF are to improve the signs and symptoms, stop disease progression, and reduce the propensity for malignant transformation [3,7]. Many therapies, including physical therapy, medication, surgery, and habit modification (i.e., cessation of areca nut usage), have been recommended for the treatment of OSMF. However, none have been able to demonstrate the condition's complete regression. Thus, the search for an effective therapeutic approach continues [1, 8, 9]. In the course of disease treatment, convenience of drug administration is one of the factors for successful management of disease. Since oral drug administration is more convenient than intralesional drug administration, it would be ideal to have an oral alternative for managing OSMF [2]. Colchicine is an alkaloid derived from the crocus-like plant Colchicum autumnale, chemically known as colchicum-N-(5,5,7,9-tetrahydro-1,2,3,10-tetramethoxy-9-oxobenzo [alpha] heptalen-7-yl) acetamide. Numerous studies have confirmed the role of colchicine as antifibrotic agent by inhibiting collagen synthesis and increasing collagenolytic activity. Besides, it also has some anti-inflammatory properties. This anti-inflammatory property is related to the drug’s effect on polymorphonuclear leukocytes and monocyte chemotaxis, as well as leukocyte adhesiveness, and also its effect on prostaglandin E, which suppresses the leukocyte function [1]. Colchicine is toxic in doses greater than 0.1 mg/kg. The most

commonly reported toxic side effect of long-standing colchicine therapy is nausea, vomiting, diarrhoea, and abdominal pain due to its effect on the rapidly proliferating epithelial cells of the gastrointestinal tract. These symptoms are especially common at dosage levels of 2–3 mg/day, although they are entirely reversible by appropriate symptomatic management. The side effects are minimal when doses are less than or equal to 1 mg/day [1,5,9-11]. Till date vary few studies have reported the use of colchicine in the management of OSMF. This study is planned to determine the effectiveness of Tab. Colchicine 0.5 mg along with Intralesional Inj. Placentrex 1500 IU 2 ml in the management of OSMF.

Materials and Method

In this study, 26 patients in the age range of 20 to 40 years who visited the oral medicine and radiology department between 2022 and 2023 and were clinically diagnosed with OSMF (Grade II and III) were included. The study protocol received approval from the Institutional Ethical Committee. All ethical guidelines were followed, and written informed consent was obtained from the selected patients who participated in the study. (The identification of various clinical Grades of OSMF was based on Kerr et al.'s clinical criteria.) [12].

Inclusion criteria involved patients with clinical Grade II and Grade III OSMF, ages ranging from 20 to 40 years of both genders. Patients who have habits of betelnut, pan-masala, gutkha, or mixed habits and present complaints like burning sensation, reduced mouth opening, and restricted tongue movement were involved. Conversely, the exclusion criteria entailed individuals unwilling to participate, those already undergoing or having received treatment for OSMF, and those experiencing difficulty in mouth opening unrelated to OSMF. Additionally, immunocompromised individuals with systemic diseases, pregnant females, individuals on immunosuppressants, and those with drug allergies.

A detailed case history, including their habits (type, frequency per day, and duration), was taken, and a clinical examination was done. All the obtained data was recorded on the standard proforma. After selecting patients based on inclusion and exclusion criteria, all the patients in OSMF (Grade II and III) went for routine blood investigations, including a complete blood count, a liver function test, and a kidney function test. Based on the investigatory findings, patients with OSMF were divided into two groups: Group I and Group II. This investigation was repeated once per month for Group I.

Group I

Patients were prescribed with Tab. Colchicine 0.5mg twice daily orally. Placentrex 1500 IU 2ml was injected using a 26-gauge needle insulin syringe intralesionally in oral mucosa and pterygomandibular raphe once per week.

Group II

Placentrex 1500 IU 2ml was injected using a 26-gauge needle insulin syringe intralesionally in oral mucosa and pterygomandibular raphe once per week.

In the OSMF patients, the following parameters were measured:

1. The intensity of the burning sensation using a Numerical Rating 10-point Visual Analogue Scale (VAS).

- The interincisal mouth opening between the mesioincisal edge of the upper-right central incisor to the mesioincisal edge of the lower right central incisor with the help of a vernier caliper, (Figure 1).

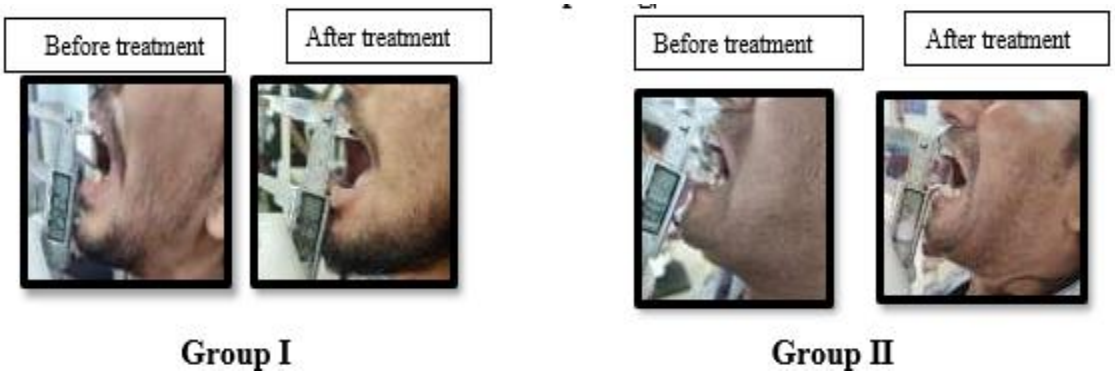

Figure 1: Measurement of the mouth opening.

- Buccal mucosal flexibility according to Bailoor and Nagesh [12, 13]. V2 = is marked at 1/3rd the distance from the angle of the mouth on a line joining the tragus of the ear and the angle of the mouth and V1 = the subject is then asked to blow his cheeks, and the distance measured between the two. Buccal mucosal flexibility = V1-V2, (Figure 2).

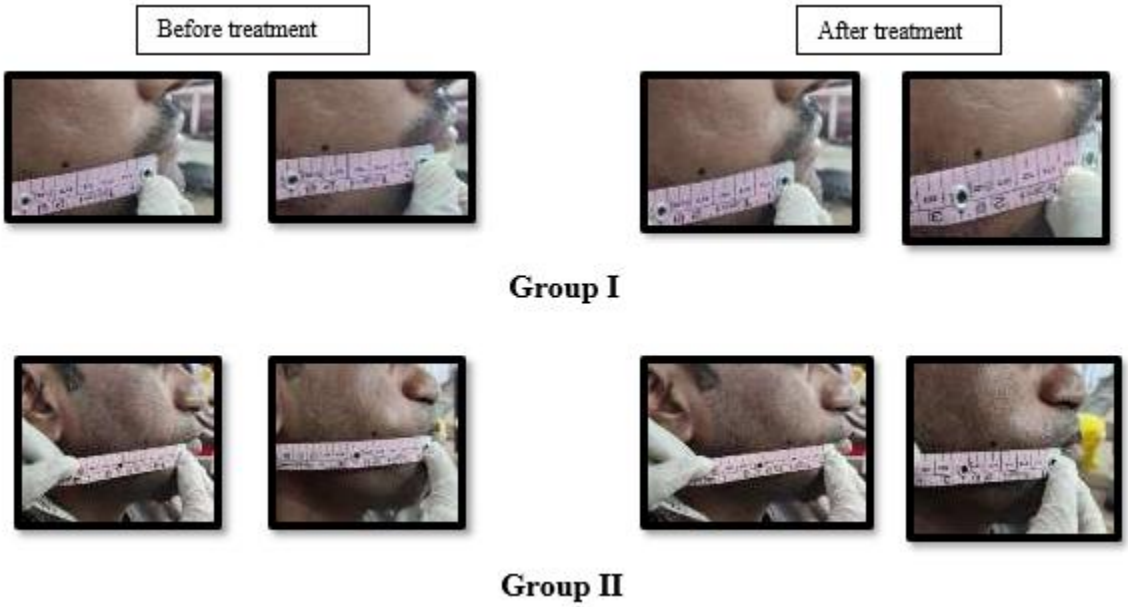

Figure 2: Measurement of buccal mucosal flexibility.

- Tongue protrusion with the scale from the normal mesioincisal angle of the upper central incisor to the tip of the tongue when maximally extended with mouth wide open [9], (Figure 3).

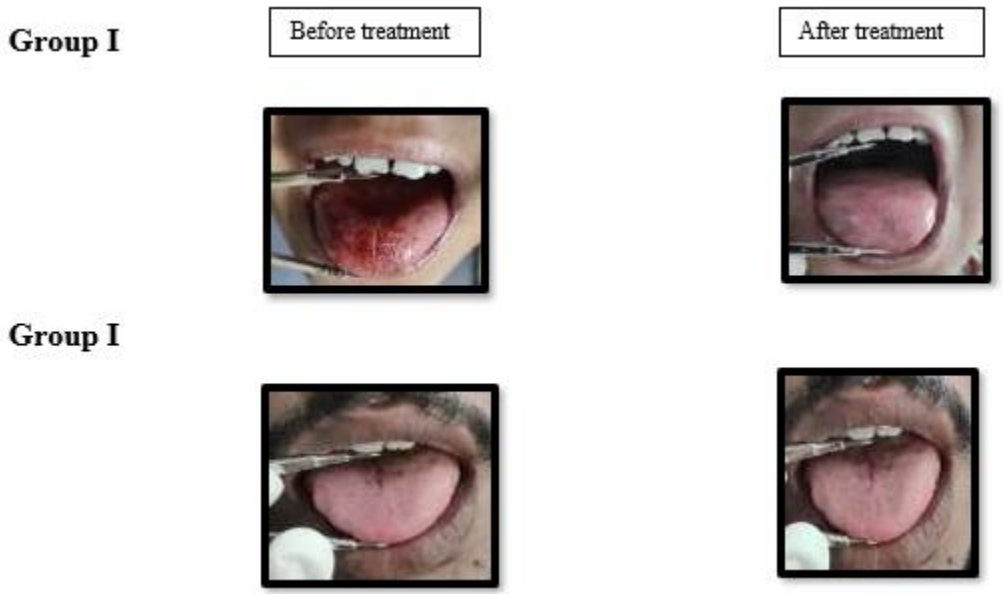

Figure 3: Measurement of the tongue movement.

Patients in both the groups were asked to discontinue their habits and were treated for 12 weeks. Patients were instructed to observe for any local allergy symptoms, such as itchiness, redness, or ulcerations at the injection site, as well as any developing constitutional problems, and to report them right away. Such patients' treatments were discontinued, and they were directed to receive treatment for the same. The outcome assessment was compared between the first visit and 3 months after the first visit. All the clinical examinations were performed by a single trained examiner. All data obtained were subjected to statistical analysis at the end of the study.

Results

In this study, there were a total of 26 patients, 13 in each group, with 25 males and only 1 female. 11 patients had Grade III OSMF, and 15 had Grade II OSMF. All the patients had the habit of arecanut chewing, either in the form of betel nuts or other commercially available products like gutkha and pan masala. Out of the 26 patients, only 15 attended follow-up sessions until the 12-week mark, of which 8 were in Group I and 7 were in Group II.

Intergroup comparison (Table 1):

On observing the intergroup comparison (Table 1), at the base line, a significant difference was found only for the mouth opening. For other parameters, it was not significant. After 12 weeks, a statistically significant difference was found for the mouth opening and buccal mucosal flexibility. For the mouth opening and tongue movement, no significant P value was found for both the groups (Group I and Group II), (Table 1).

At Baseline (Pretreatment) (n=26)			
Variables	**Group I (n=13)**	**Group II (n=13)**	**P Value**
Burning mouth	8.23 ± 1.59	4.85 ± 3.48	0.01*a
Mouth opening (mm)	20.69 ± 4.53	20.30 ± 4.24	0.82b
Cheek flexibility (cm)	0.50 ± 0	0.50 ± 0	-
Tongue movement (cm)	2.96 ± 0.91	3.27 ± 0.56	0.31b
After 3 months (post-treatment) (n=15)			
Variables	**Group I (n=8)**	**Group II (n=7)**	**P Value**
Burning mouth	2.13 ± 1.13	5.00 ± 2.94	0.07[a]
Mouth opening (mm)	32.06 ± 6.30	26.18 ± 3.22	0.04*[b]
Cheek flexibility (cm)	0.94 ± 0.18	0.50 ± 0	<0.001**[b]
Tongue movement (cm)	3.94 ± 0.65	3.59 ± 0.73	0.34[b]

Table 1: Comparison of clinical parameters between two treatment Groups (Intergroup).

Intragroup Comparison (Table 2):

The mean values for burning sensation, mouth opening, buccal mucosal flexibility, and tongue movement for Group I were 8.38 ± 1.51, 22.01 ± 2.76, 0.50 ± 0, 3.18 ± 0.79, respectively. After 3 months, all the parameters were statistically significant, but for mouth opening and buccal mucosal flexibility, they were highly significant. For Group II, a significant difference was found for the mouth opening and for the tongue movement, while for the other parameters, it was not significant.

Group I (n=8)			
Variables	**Baseline (Pretreatment)**	**After 3 months (post-treatment)**	**P Value**
Burning mouth	8.38 ± 1.51	2.13 ± 1.13	0.01*[a]
Mouth opening (mm)	22.01 ± 2.76	32.06 ± 6.30	<0.001**[b]
Cheek flexibility (cm)	0.50 ± 0	0.94 ± 0.18	<0.001**[b]
Tongue movement (cm)	3.18 ± 0.79	3.94 ± 0.65	0.02*[b]
Group II (n=7)			
Variables	**Baseline (Pretreatment)**	**After 3 months (post-treatment)**	**P Value**
Burning mouth	5.43 ± 3.55	5.00 ± 2.94	0.79
Mouth opening (mm)	19.85 ± 3.92	26.18 ± 3.22	<0.001**[b]
Cheek flexibility (cm)	0.50 ± 0	0.50 ± 0	-
Tongue movement (cm)	3.24 ± 0.64	3.59 ± 0.73	0.001*[b]

Table 2: Baseline and after 3 months comparison of clinical parameters within Group (Intragroup).

Discussion

Oral submucous fibrosis (OSMF) is a condition with potential for malignancy in the oral cavity characterized by juxtaepithelial inflammatory reactions and progressive fibrosis of the lamina propria and deeper connective tissues of the upper digestive tract, involving the oral cavity and upper part of the

digestive tract. 6,8 The etiology of OSMF is multifactorial. Areca nut chewing is considered the most important etiologic factor, but other factors such as nutritional deficiency, changes in salivary components, collagen abnormalities, and genetic predisposition are also factors involved in the etiopathogenesis of OSMF. 1-4 The abrasive nature of the areca nut continuously causes local trauma and irritation to the oral mucosa, which could eventually lead to cellular and morphological changes. The active alkaloid found in betel nuts is arecoline, which stimulates fibroblasts to increase production of collagen at a higher rate than normal, leading to progressive fibrosis of the oral mucosa. Also, a high amount of copper content is found in areca nut, which, on chewing it for 5–30 minutes, increases soluble copper levels in oral fluids, which is an initiating factor in OSMF [1, 14]. According to the literature, OSMF is a disease of middle age, with peak incidence occurring in the second to fourth decade of life, with male predominance. 5,7 The present study shows similar findings. This is probably due to the fact that teenagers and young adults are getting attracted to consuming commercially available areca nut products like gutkha and pan masala due to the marketing, publicity, and easy availability of such products. Males are the working gender in the Indian subcontinent and are more likely to develop abusive habits when compared to females. Areca nut and gutkha are chewed for various reasons, as they act as stress relievers and mouth fresheners [9,14].

Various treatment modalities have been tried to treat patients suffering from OSMF. Medical interventions comprise dietary supplementation with vitamins, antioxidants, corticosteroid therapy, proteolytic agents (hyaluronidase, placental extracts, and anticytokines), physiotherapy, and surgical therapy, but till date there has been no treatment found that completely cures the disease, so the search for other treatment modalities for the management of the OSMF continues [9, 15]. Placentrex is an aqueous extract of the human placenta that contains nucleotides, enzymes like alkaline and acid phosphatase, vitamins (E, A, B1, B2, B4, B6), pantothenic acid, nicotinic acid, P-aminobenzoic acid, folic acid, essential and non-essential amino acids, and certain trace elements. Vitamin A slows, delays, arrests, or even reverses the invasive malignant potential, while Vitamin E improves the mucosal color, mouth opening, and reduces fibrous bands. Local injection of Placentrex is safe, cheap, and effective in OSMF without any significant side effects or contra indication [16,17,18].

Colchicine is an alkaloid found in the crocus-like plant Colchicum autumnale. Numerous studies have confirmed that colchicine acts as an antifibrotic agent by inhibiting collagen synthesis and enhancing collagenolytic activity. It has been used to reduce fibrosis in liver and kidney diseases. Besides, it also has some anti-inflammatory properties [1-3, 5, 8, 9]. This antifibrotic and anti-inflammatory effect can be used in the management of OSMF. Up to our knowledge, only a limited number of studies have reported the use of colchicine in OSMF, and this is the first study to evaluate the effectiveness of Tab. Colchicine 0.5mg with Intralesional Inj. Placentrex 1500IU 2 ml in the management of OSMF. In the present study, burning sensation, mouth opening, and buccal mucosal flexibility were considered as parameters to compare the efficacy of both regimens. A statistically significant improvement was observed in all the parameters (burning sensation, mouth opening, and buccal mucosal flexibility) with the use of Tab. Colchicine and Placentrex combination (Group I), indicating the efficacy of this regimen in the management of OSMF. Whereas in Group II statistically, significant improvement was noted for mouth opening and tongue movement while burning sensation, and for buccal mucosal flexibility, it was not significant (Tables 1 and

2). These results indicate that both medication regimens are useful in treating OSMF, while Tab. Colchicine with Placentrex appears to provide more significant improvement. The findings were similar to the study conducted by Dipti Daga, et al., Neupane GP, et al., Dr. Nishant, et al., kaluram khande, et al., Somisetty V, et al., Krishnamoorthy, et al., Dr. Jasmohan Singh Sidana, et al.

In the study by Ankur N. Dhanani, et al. patients with OSMF received 1 ml of placental extract once a week for 8 weeks. At the end of the study, they found that placental extract effectively relieves burning sensation. These findings were also similar to other studies [15, 16]. In the study conducted by Somisetty V. et al., they found a reduction in the burning sensation, which might be due to the anti-inflammatory effect of colchicine's destabilising action on the microtubules. In the present study, the combined anti-inflammatory effect of Tab. Colchicine and Placentrex led to a reduction in burning sensation.

Progressive fibrosis leads reduction in the mouth opening, tongue movement and buccal mucosal flexibility. In the present study mouth opening, buccal mucosal flexibility, and tongue movement group I showed better response than the group II. These findings were similar to the other studies [1,2,5,8,9,11, 14]. Colchicine has shown to inhibit collagen synthesis thereby reduce fibrosis. Because of antifibrotic and anti-inflammatory effect of Colchicine, it is used in other disease like cardiovascular and liver diseases as well [20,21]. Till date very few studies have been reported for the use of Colchicine in OSMF. At the dose of 0.5mg, no side effects were noted. Besides, addition of Colchicine with other drug gives the advantage of low dose of colchicine used and thus reduced toxicity [1, 2].

Conclusion

OSMF primarily affects middle-aged and young adult males, with a peak incidence between the 2nd and 4th decades of life. In both treatment groups, there was a notable improvement in burning sensation, mouth opening, tongue movement, and buccal mucosal flexibility. Significantly, Group I (Tab. Colchicine + Intralesional inj. of Placentrex) exhibited superior responses in burning sensation, mouth opening, and buccal mucosal flexibility for both Grade II and Grade III. This suggests that Group I have a significant role in improving OSMF without any side effects.

Limitation and Future Prospect

The study is limited by a small sample size, high loss to follow-up attributed to factors like lack of awareness, motivation, and the addictive nature of areca nuts, along with socioeconomic considerations. Histological assessment for patients with OSMF was not done because the study was based on the clinical classification provided by Kerr et al [12]. A Group of patients who are only receiving a Tab. Colchicine 0.5 mg should be included to determine its effectiveness in the OSMF. Multicentric studies involving a larger sample size and proper follow-up would help confirm the true efficacy of colchicine.

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