

## A Study of the Efficacy of Oral Colchicine in the Treatment of Oral Submucous Fibrosis

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### Abstract

**Background & Objectives:** Oral submucous fibrosis (OSF) is characterized by abnormal deposition of collagen and is considered to be a potentially malignant disorder by World Health Organization (WHO). It is a precancerous disorder and transforms into malignancy in 1.5 – 15% of all cases. It manifests with wide variety of symptoms like restriction in mouth opening, ulceration, xerostomia and burning sensation. Since it greatly interfere with the quality of life of the patients, proper treatment with primary focus on relieving the symptoms of OSF is necessary. The management of OSF has been a subject of controversy and no definite and widely accepted treatment is available. The aim of this study is to assess the efficacy of oral colchicine in the treatment of OSF.

**Methods:** 60 patients presenting with OSF between December 2020 and May 2022 were included in the study. A detailed history was recorded. A thorough ENT and general examinations were performed. After investigating the patients for their Liver Function Tests and COVID-19 Rapid Antigen Testing, these patients were assessed for their mouth opening using vernier calipers and Visual Analogue Scale (VAS) was used to assess the burning sensation sensed by the patient and recorded. Then these patients were given oral colchicine therapy. The patients were followed up for a period of 6 months. They were reassessed and the results were recorded.

**Results:** Majority of the patients were of less than 40 years, with a male predominance among those presenting with OSF. In this study, gutka was the substance mostly abused. Significant improvement in mouth opening and symptomatic relief from burning sensation in buccal mucosa was seen with oral colchicine therapy.

**Interpretation & Conclusion:** Patients presenting with OSF need appropriate treatment. In our study, we found that early interventions gave better results. Oral colchicine could be a major leap in the treatment of OSF.

**Keywords:** Oral Submucous Fibrosis, Colchicines, Mouth Opening, Burning Sensation.

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### Introduction

Oral submucous fibrosis (OSF), reported in 1952 by Schwartz as “atrophia idiopathica mucosae oris” [1] is a potentially malignant disease that leads to progressive juxtaepithelial fibrosis of the oral soft tissues, affecting mainly the South and Southeast Asian population [2]. There is an increased prevalence of squamous cell carcinoma in patients with OSF. The highest malignant transformation rate of OSF of about 7.6% was reported from India as per International Agency for Research on Cancer monograph on OSF [3].

The etiology of OSF is multifactorial. Areca nut chewing is considered the most important etiologic factor [4], but other factors such as nutritional

deficiency, altered salivary constituents, collagen disorders and genetic susceptibility are also involved in the causation of OSF [5]. The constituents of areca nut including arecoline and tannin, interfere with normal collagen metabolism by increasing the synthesis of collagen and decreasing its breakdown. This results in increased collagen deposition and thus resulting in fibrosis of oral tissues [4].

Various treatment modalities including drug therapy, surgical therapy and physiotherapy have been proposed for the management of OSF. Various drugs with antifibrotic, anti-inflammatory and antioxidant activity have been used in the

management of OSF but with unpredictable results and incomplete remission. No single drug has been reported to be effective in treatment of OSF. Hence, a combination of drugs has been used for the same.

Colchicine is an alkaloid chemically known as colchicinum-*N*-(5,5,7,9-Tetrahydro-1,2,3,10-tetramethoxy-9-oxobenzo [ $\alpha$ ] heptalen-7-yl) acetamide [6]. Various studies have established the role of colchicine as an antifibrotic agent by inhibiting collagen synthesis and increasing collagenolytic activity [7]. It has been used in reducing fibrosis in liver and kidney diseases [8]. Besides, it also has some anti-inflammatory properties. This anti-inflammatory property is related to drug's effect on polymorphonuclear leukocytes and monocyte chemotaxis, leukocyte adhesiveness and also its effect on prostaglandin E, which suppresses the leukocyte function [9].

#### Aims and Objectives

1. To find the efficacy of Oral Colchicine therapy in OSF.
2. To assess the symptomatic relief from Oral Colchicines therapy.
3. To assess the improvement in mouth opening and relief from burning sensation in buccal mucosa in OSF patients with Oral Colchicine therapy.

#### Materials and Methods

This study included patients with clinically diagnosed OSF, who attended the OPD of Department of E.N.T of Jawaharlal Nehru Medical College and Hospital during the period December 2020 to May 2022. A detailed case history, including their habits was taken and clinical examination was done. Clinical diagnosis was based on reduced mouth opening, burning sensation in mouth, blanching of mucosa, presence of vesicles or ulcerations in oral cavity.

**Burning sensation** - Burning sensation in buccal mucosa was recorded before the start of treatment

as a baseline. It was recorded then at intervals of 3 weeks, 6 weeks, 3 months and 6 months during treatment, using a Visual Analog Scale (VAS). Scoring was done from 0 to 10 based on patient's response (Score 0: No pain; Score 10: Severe pain).

**Mouth Opening:** The distance between the mesioincisal edge of right upper central incisor till the mesioincisal edge of right lower central incisor was measured for the assessment of mouth opening. In case of missing teeth, left central incisor was taken for measurement. Baseline measurement was taken before the start of treatment and then measurements were taken subsequently at intervals of 3 weeks, 6 weeks, 3 months and 6 months.

Clinical examination of oral mucosa for blanching of the mucosa and presence of ulceration was done.

**Sample size:** A total of 60 patients, clinically diagnosed with oral submucous fibrosis, who attended the ENT OPD during the study period were included in this study.

**Inclusion criteria:** Patients with clinically diagnosed OSF were included in the study.

#### Exclusion criteria

- Medically compromised patients.
- Those who had received previous treatment were excluded from the study.
- Other accompanying mucosal disorders, if present.
- Persons with a history of drug allergy to colchicines.
- Pregnant females.

After investigating the patients for their Liver Function Tests and COVID-19 Rapid Antigen Testing, these patients were assessed for their mouth opening using vernier calipers and Visual Analogue Scale was used to assess the burning sensation perceived by the patient and recorded.

The patients were treated by administering tablet Colchicine 0.5 mg twice daily for 12 weeks and were asked to discontinue their habits. The patients were followed up for a period of 6 months. They were reassessed for their mouth opening and burning sensation. The efficacy of the treatment modalities were assessed by:

1. Improvement in mouth opening by measuring interincisal distance.
2. Improvement in burning sensation (improvement in VAS scores)

The results were recorded and tabulated.

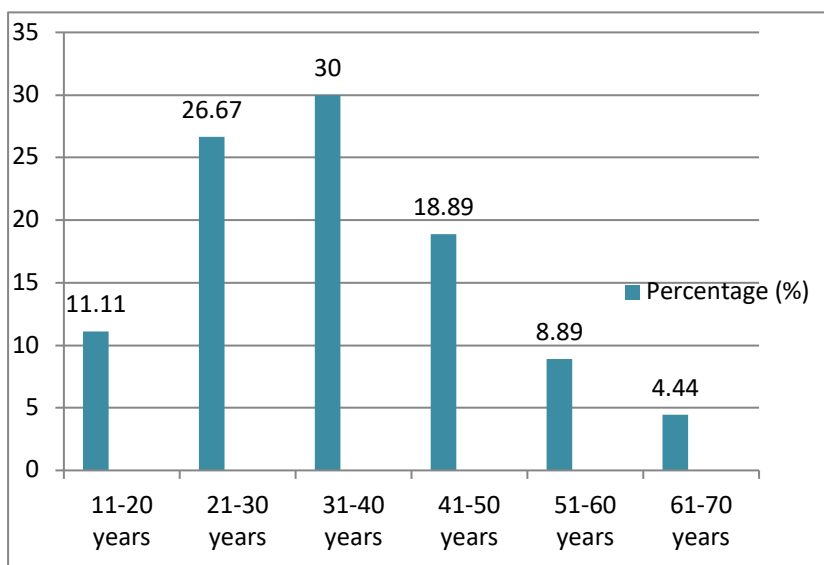
**Results**

The present study consisted of 60 cases, which were clinically diagnosed with OSF, studied between December 2020 to May 2022 in the department of ENT, Jawaharlal Medical College, Bhagalpur.

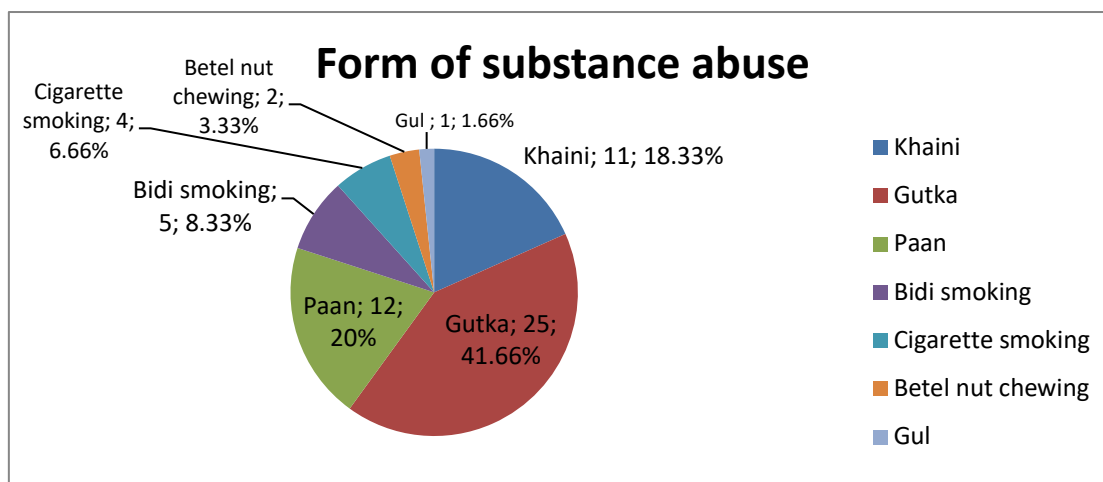
In this study, the age of the patients ranged from 18 to 65 years. The age distribution of patients in different age group is presented in table 1.

The youngest patient was 18 years old while the oldest was of 65 years.

In the present study, there is a peak incidence in the 3<sup>rd</sup> and 4<sup>th</sup> decades.



**Graph 1: Age Distribution**



**Graph 2: Forms of substance abused**

Gutka was found to be the most common substance abused by patients in our study followed by Paan. IBM SPSS Version 26 was used to calculate the mean, SD and to analyze the significance level of association between various variables involved in this study and the results were derived accordingly.

**Table 1: Comparison of mean scores of mouth opening & burning sensation at diagnosis and 6 months after treatment using paired 't'-test, with confidence interval = 95%**

Variable	Total (N)	Mean (pre-treatment)	Mean (post-treatment)	Mean of difference	SD of difference	p- value for pre-treatment vs post-treatment (t value)
Mouth opening	60	21.20mm	26.41mm	5.21mm	0.46	0.000(-61.387)
VAS Scores for burning sensation	60	6.20	3.17	3.03	0.81	0.000 (20.544)

Mean increase in mouth opening after interventions were assessed and was found to be  $5.21 \pm 0.46$  mm improvement with Oral Colchicine therapy.

Mean decrease in VAS scores were calculated for burning sensation after intervention. It was found to be 3.03.

Relative decrease in VAS scores for burning sensation were also calculated and was found to be 52.86%.

**Table 2: Improvement in VAS scores for burning sensation after intervention.**

Mean decrease in VAS scores for burning sensation after intervention	Relative decrease in VAS scores for burning sensation after intervention
3.03±0.81	52.86%

## Discussion

According to a review article, OSF is mainly a disease of Indian sub-continent where arecanut chewing is rampant. Thus there is an urgent need to initiate public health education measures to educate people about the debilitating, oral premalignant condition before it is too late. Till date, no definitive and widely accepted treatment is currently available [10].

The interventions in the treatment of OSF include a wide spectrum of medications, which include dietary supplements (antioxidants and vitamins), anti-inflammatory agents (corticosteroids), proteolytic agents (hyaluronidase and placental extracts), vasodilators, immunomodulators and anti-cytokines. These treatment modalities may be administered via different routes, such as oral, topical or submucosal injections. There is no standardized protocol regarding the number and precise sites of intralesional injections. Surgical interventions have been used for management of advanced cases of OSF. Physical therapy acts

synergistically with other treatment modalities or may be used alone to manage OSF patients.

Of the 60 patients included in this study, 54(90%) were males and 6(10%) were females. This was in concurrence with earlier studies conducted by Kumar et al, which showed 100% male predominance and that by Lai et al, which also showed a similar finding of 96.67% male predominance. This predominance of males may be due to the habit of arecanut chewing, gutka, paan consumption being more in males.

Majority of the patients in this study, i.e. about 67.78% were less than 40 years old. This again was similar to the findings of a study conducted by Mohd Saalim et al, in which 66.67% cases were less than 40 years of age. Similar observations were observed in earlier studies of Kumar et al and Maher et al, where 70.69% and 70% of cases were less than 40 years of age.

In India, tobacco has been abundantly consumed in its various forms and betel nut chewing has also been in practice since times. The presenting

complaints of OSF patients were mainly their restricted mouth opening and intolerable burning sensation in their buccal mucosa on ingestion of spicy and hot food items.

The present study showed that there was a mean improvement of  $5.21 \pm 0.46$  mm in the mouth opening and a relative improvement of 52.86% in the VAS scores for burning sensation in the buccal mucosa following ingestion of hot and spicy foods.

In a study conducted by Neupaane et al, Colchicine did show statistically significant improvement in mouth opening and, decrease in burning sensation in OSF patients. For this reason, it is concluded that Colchicine is a good alternative treatment for OSF in patients in whom dexamethasone is contraindicated or those who cannot make frequent visits for intralesional injections due to disability, far reaching places or any other reason. In such patients it is better to substitute Colchicine therapy rather than not to treat at all [11].

Colchicine inhibits collagen synthesis and increases collagenolytic activity and has found to be of use in OSF. In a study by Krishnamoorthy *et al.* reported that 0.5 mg colchicine orally, twice daily along with intralesional 0.5 ml hyaluronidase 1500 IU gives significant improvement in burning sensation and mouth opening [12].

In a study conducted by Dipti Daga et al, patients with OSF took 0.5 mg oral colchicine twice daily and received injections of 1500 IU hyaluronidase into each buccal mucosal lesion once weekly. By the second week, the burning sensation was alleviated, mouth opening increased, and histological parameters were reduced. The aforementioned dosages combined with 0.5 mL lignocaine hydrochloride once weekly improved mouth opening and reduced the burning sensation in patients with grade II OSF after 12 weeks [13].

In a study conducted by Bhuvana Krishnamurthy et al, the effectiveness in improving the mouth opening by the systemic use of colchicine is well noted [14].

In the present study of treatment modalities of OSF, most of the time patients presented with burning sensation of oral mucosa on ingestion of spicy food and restricted mouth opening. Many also presented with recurrent ulceration in oral cavity. Tobacco usage and betel nut chewing is very common among Indians. Any oral ulcerations or growths in such patients should be treated with great suspicion and full-on effort should be made to examine the oral cavity in patients with restricted mouth opening. Any referred pain should not be neglected in such patients. Timely diagnosis and early treatment will decrease the burden of morbidity and mortality in these patients.

### Conclusion

Clinical diagnosis is easy and any oral mucosal growths may require repeated biopsies. Management of these patients is challenging due to lack of a definite protocol and their failure to quit their habit of such abuses, which they have been fond of since their adolescence.

Based on the observations of our study, the following conclusions can be drawn:

- The age predilection of occurrence of OSF is in those less than 30 years of age.
- There is a strong male predominance among those presenting with OSF.
- Efficacy of Oral Colchicine in improving mouth opening is very much appreciable.
- Efficacy of Oral Colchicine in reducing burning sensation in buccal mucosa is statistically significant.

Colchicine is a good alternative treatment for oral submucous fibrosis in patients in whom dexamethasone is contraindicated or those who cannot make frequent visits for intralesional

injections due to disability, far reaching places or any other reason. In such OSF patients it is better to substitute Colchicine therapy rather than not to treat at all.

The encouraging results should prompt a clinical trial on more number of OSF patients to broaden the therapeutic usefulness and applications of one of our most ancient treatment agents. This baseline study gives scope for further studies with the systemic use of Colchicine alone in the treatment of OSF and also for research in the use of the drug as a formulation that can be administered locally into the fibrous bands to confirm the above result.

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