



## Efficacy of conservative versus intralesional therapy in OSMF – A comparative study

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### Abstract

**Background and Objectives:** Oral submucous fibrosis (OSMF) is a potentially malignant lesion of the oral cavity and successful management remains a challenge. Our study aims to compare the efficacy of three commonly used modalities of treatment, namely (i) non-invasive therapy like physiotherapy only, (ii) physiotherapy in combination with antioxidants, and (iii) invasive therapy like intralesional therapy. It aimed to ascertain the most effective treatment modality among the three which one of them helped improve the maximum mouth opening (MMO) and reduce oral sensitivity to spicy food as measured on numeric analog scale (NAS).

**Materials and Methods:** This randomized multilabel study was conducted on 49 patients visiting the outpatient Department of Oral Medicine and Radiology, over a 2-year period. A detailed history of burning sensation in the mouth and the severity was recorded using NAS. A Vernier caliper was used for the measurement of MMO. The symptom of burning sensation and MMO was evaluated on the 15<sup>th</sup>, 30<sup>th</sup>, 45<sup>th</sup>, and 90<sup>th</sup> days.

**Results:** Findings from the study showed that physiotherapy alone was not effective in alleviating neither burning sensation nor did it significantly improve the MMO. The percentage decrease in burning sensation was highest in the interventional group receiving an intralesional injection (87.4% at 45 days and 100% at 90 days). Physiotherapy with antioxidant group showed almost similar percentage decrease in burning sensation as the interventional group (80.8% at 45 days and 96.8% at 90 days). For MMO, physiotherapy with antioxidant group showed better MMO at 90 days (34.2% vs. 26.8%).

**Conclusion:** A non-invasive treatment modality of physiotherapy with antioxidant treatment modality is as effective as an invasive intralesional injection, in the management of patients with OSMF. The findings suggest that non-invasive modality of physiotherapy with antioxidant treatment can be considered as standard care for the management of OSMF.

### Introduction

Oral submucous fibrosis (OSMF) is a potentially malignant condition affecting the oral cavity and the pharynx. Initially, it presents as a juxta-epithelial inflammatory reaction followed by fibroelastic changes in the submucosa and epithelial atrophy manifesting as the stiffness of the oral mucosa and trismus.<sup>[1-3]</sup> It is associated with areca nut (betel nut) chewing and the incidence further increases when betel chewing is combined with tobacco use.<sup>[3,4]</sup> There are no standardized treatment options available for OSMF and it is managed symptomatically and empirically. Pharmacological treatment

includes anti-inflammatory drugs such as corticosteroids, oxygen radical scavengers such as vitamins, micronutrients, and antifibrotic agents such as HMG-CoA inhibitors.<sup>[4,5]</sup> Various other agents such as lycopene and isoxsuprine have also been evaluated. The other treatment options include physiotherapy and surgery. OSMF is predominantly seen in the Asian countries such as India, Pakistan, Sri Lanka, and Bangladesh. However, with the increasing availability of various areca nut products in other countries in recent times, the incidence of OSMF is set to increase.<sup>[4,6]</sup>

There are very few studies that are available on the management of OSMF. The paucity of studies regarding the

management of OSMF as well as lack of standardized treatment is attributable to the lack of understanding of the exact etiology of this disease.<sup>[7-9]</sup> The different modes of management are conservative, medical, and surgical. However, a cure for OSMF is yet indefinable and the debilitating effects of the disease are difficult to control. The invasive methods such as surgical modalities and intralesional injections of hyaluronidase and corticosteroids have provided relief for short periods; however, they are associated with more scarring and fibrosis in the long term.

We conducted a multiphase, randomized open-label study comparing common treatment modalities of physiotherapy alone; physiotherapy combined with antioxidants; and intralesional therapy in patients with OSMF. In the present study, burning sensation which is a subjective measure and reduced interincisal distance, the most objective criteria for evaluation of improvement in OSMF were used as primary parameters for assessing the efficacy of the three treatment modalities. Subjects in the group comprising physiotherapy with antioxidants were administered lycopene supplements. Studies documented in 2007 and more recently in 2012 suggest lycopene used as the first line of treatment for OSMF was effective in ameliorating burning sensation as well as improving mouth opening.<sup>[10,11]</sup>

### Aims of the study

The aims of this study were as follows:

- I. To assess the efficacy of non-invasive therapies, namely physiotherapy alone and physiotherapy with antioxidants in improving maximum mouth opening (MMO) and reducing oral sensitivity to spicy food as measured on numeric analog scale (NAS) in patients with OSMF.
- II. To assess whether invasive treatment modality does intralesional therapy improve the MMO and helps in reducing oral sensitivity to spicy food as measured on NAS in patients with OSMF.
- III. To compare if the non-invasive modalities such as physiotherapy and antioxidants with physiotherapy are as effective as invasive therapy such as intralesional therapy in managing burning sensation and improving MMO.

### Materials and Methods

The study was conducted following approval from the Institutional Review Board. A total of 85 patients visiting the outpatient Department of Oral Medicine and Radiology, over a 2-year period were evaluated for study participation. Among them, 54 patients were screened for the study. Of the screened patients, 49 who satisfied the study criteria and were willing to participate in the study were enrolled.

### Inclusion criteria

The following criteria were included in the study:

- Patients with a history of burning sensation and MMO <35 mm and >20 mm

- Patients who were not on any treatment at the time of screening
- Patients who were willing for the study procedures such as biopsy and hematological examination
- Patients who were histopathologically diagnosed with OSMF.

### Exclusion criteria

The following criteria were excluded from the study:

- Patients with temporomandibular joint disorders
- Patients suffering from any other systemic diseases.

At the initial visit, a comprehensive habit history was elicited and the data were recorded in a pre-designed pro forma. Patient's habit history for the use of various forms of areca nut products was recorded.

A detailed history of burning sensation of the mouth and its severity was recorded using the NAS. A Vernier caliper was used for measuring the MMO and two recordings per visit were determined passively. The MMO was measured between the left maxillary and mandibular central incisors, if absent the adjacent appropriate teeth were selected.

All the 54 Stage II OSMF patients were counseled individually and educated about the harmful effects of the areca nut, gutka chewing, or other proprietary preparations. The subjects were motivated to quit the habit and were explained about the benefits and treatment modalities. An informed consent was obtained from the patient before enrollment into the study. The required blood investigations – hemoglobin levels, peripheral blood smear clotting, and bleeding time were performed.

### Study procedure

The patients who satisfied the study criteria were willing to participate and signed the informed consent document were enrolled in the study. A total of 49 patients were finally enrolled into the study and were randomized into three treatment arms [Table 1].

Group I consisted of physiotherapy only, Group II consisted of physiotherapy combined with antioxidant (lycopene), and Group III consisted of intralesional injections. MMO and burning sensation symptom were evaluated on the 15<sup>th</sup>, 30<sup>th</sup>, and 45<sup>th</sup> days during the treatment and at the 3<sup>rd</sup> month (Day 90). Subjects in Group II were given 8 mg lycopene capsules supplement for the same duration.

**Table 1:** Gender- and age-wise distribution of the participants in the study

Distribution of demographic characteristics among the study participants				
Variables	Categories	Group A	Group B	Group C
		n (%)	n (%)	n (%)
Sex	Males	14 (93.3)	15 (87.5)	16 (94.1)
	Females	1 (6.7)	2 (12.5)	1 (5.9)
Age	Mean±SD	32.3±7.5	31.1±5.4	30±6.4

Blood investigations revealed reduced hemoglobin levels in all study patients. Hence, ferrous sulfate 200 mg and folic acid 5 mg daily were advised for 3 months for all study participants.

Subjects in Group I (physiotherapy only) were advised to perform jaw opening exercises with Hister’s appliance. Subjects were advised to perform the exercise 5 times per session and to do five sessions per day. The appliance was held for 1 min on each occasion and unwinding of the screw of the Hister’s appliance was done, unless discomfort persisted. In case of severe discomfort and pain, subjects were advised to take paracetamol (250 mg), 30 min before performing the exercise.

Subjects in the Group II (antioxidant with physiotherapy) were given lycopene supplements and were advised to perform the same physiotherapy regimen as the patients in the physiotherapy only group.

Subjects receiving physiotherapy in the study were advised to maintain a daily diary for the assessment of compliance to treatment.

Subjects in the Group III (intralesional therapy) received biweekly submucosal injections, for 7 weeks duration. A combination of hyaluronidase (Hyalase 1500 I.U) and dexamethasone (Dexona 4 mg/mL) was given to the subjects.

After each session of respective therapy, the following jaw opening exercise was to be performed by all the study subjects. The exercises were taught at the time of study visit(s):

- Wide mouth opening and maintaining it for 5 s – 10 repetitions.
- Lateral deviation of the mandible to right and left side – 10 repetitions.
- Protrusion of mandible – 10 repetitions.
- Gradual mouth stretching by placing the left thumb over the upper incisor and right index finger over the lower incisor and maintaining it for 5 s – 10 repetitions.

**Results**

A total of 49 patients completed the study. The burning sensation was assessed before the start of study treatment using one-way ANOVA test [Table 2]. Following study initiation, the efficacy parameters – burning sensation, were assessed at intervals of 15, 30, and 45 days [Tables 3 and 4] using one-way ANOVA test followed by Bonferroni’s *post hoc* analysis. The comparative mean score of burning sensation and MMO at 90 days using independent Student’s *t*-test was performed. Findings from the study showed that efficacy parameters – reduction in burning sensation and MMO for the antioxidant with physiotherapy group are the same as that in the interventional group receiving intralesional injection [Table 5]. The percentage decrease in burning sensation was highest in the interventional group receiving an intralesional injection, 87.4% at 45 days and 100% at 90 days. However, the physiotherapy with antioxidant group showed almost similar percentage decrease in burning sensation in the interventional group, 80.8% at 45 days and 96.8% at 90 days [Table 6]. Increase in mouth opening, i.e., the MMO

scores were also comparable between the two groups, but the physiotherapy with antioxidant group showed better MMO at 90 days, 34.2% versus 26.8% [Table 6]. The findings from

**Table 2:** The baseline NAS values of burning sensation and mouth opening measurements at the start of the study

Comparison of mean NAS of burning sensation and mouth opening distance during pre-Rx between three study groups using one-way ANOVA test

Variables	Groups	N	Mean±SD	F	P value
Burning sensation	Group A	15	4.9±1.2	1.361	0.27
	Group B	17	5.1±1.1		
	Group C	17	5.6±1.2		
Mouth opening	Group A	15	28.5±4.6	0.672	0.52
	Group B	17	28.7±5.2		
	Group C	17	26.9±4.3		

NAS: Numeric analog scale, ANOVA: Analysis of variance, SD: Standard deviation

**Table 3:** Comparative NAS values of burning sensation at 15, 30, and 45 days

Comparison of mean NAS of burning sensation at various post Rx periods between three study groups using one-way ANOVA test followed by Bonferroni’s *post hoc* analysis

Time (days)	Groups	N	Mean±SD	F	P value	Sig. diff	P value
15	Group A	13	5.0±1.2	4.475	0.02*	A versus B	0.29
	Group B	16	4.2±1.5			A versus C	0.01*
	Group C	17	3.6±1.1			B versus C	0.56
30	Group A	13	4.9±1.0	20.463	<0.001*	A versus B	<0.001*
	Group B	15	2.7±1.4			A versus C	<0.001*
	Group C	15	2.1±1.2			B versus C	0.54
45	Group A	13	4.9±1.2	53.831	<0.001*	A versus B	<0.001*
	Group B	15	1.1±1.4			A versus C	<0.001*
	Group C	15	0.8±0.9			B versus C	1.00

Statistically significant\*, NAS: Numeric analog scale, ANOVA: Analysis of variance, SD: Standard deviation

**Table 4:** Comparative mean scores of MMO at 15, 30, and 45 days

Comparison of mean distance of mouth opening at various post Rx periods between three study groups using one-way ANOVA test

Time (days)	Groups	N	Mean±SD	F	P value
15	Group A	13	28.5±4.1	0.587	0.56
	Group B	16	30.0±5.1		
	Group C	17	28.5±3.8		
30	Group A	13	29.8±3.9	1.241	0.30
	Group B	15	31.5±5.0		
	Group C	15	29.3±3.2		
45	Group A	13	31.1±3.6	2.153	0.13
	Group B	15	33.4±4.9		
	Group C	15	30.6±3.0		

MMO: Maximum mouth opening

**Table 5:** Comparison of mean NAS burning sensation and mouth opening measurements using Bonferroni *post hoc* analysis

Time	Group B		Group C		Group B		Group C	
	Mean diff	P value	Mean diff.	P value	Mean diff.	P value	Mean diff.	P value
	T0 versus T1	0.9	0.02*	2.0	0.001*	-1.5	<0.001*	-1.7
T0 versus T2	2.2	<0.001*	3.5	0.001*	-3.3	<0.001*	-2.8	0.008*
T0 versus T3	3.9	<0.001*	4.7	<0.001*	-5.3	<0.001*	-4.1	0.003*
T0 versus T4	4.9	<0.001*	5.4	<0.001*	-8.4	<0.001*	-6.8	<0.001*
T1 versus T2	1.3	0.005*	1.5	0.02*	-1.8	0.002*	-1.1	0.30
T1 versus T3	3.0	<0.001*	2.7	<0.001*	-3.8	<0.001*	-2.4	0.02*
T1 versus T4	4.0	<0.001*	3.4	0.004*	-6.9	<0.001*	-5.1	<0.001*
T2 versus T3	1.7	<0.001*	1.2	0.04*	-2.0	<0.001*	-1.3	0.004*
T2 versus T4	2.7	<0.001*	1.9	0.01*	-5.1	<0.001*	-4.0	<0.001*
T3 versus T4	1.0	0.17	0.7	0.94	-3.1	<0.001*	-2.7	0.001*

T0: Baseline, T1: 15 days, T2: 30 days, T3: 45 days, T4: 90 days Statistically significant\*. NAS: Numeric analog scale

**Table 6:** Percentage decrease of burning sensation and increase in MMO at 45 days and 90 days

Time	Percentage decrease in the burning sensation (%)			Percentage increase in the mouth opening (%)		
	Group A	Group B	Group C	Group A	Group B	Group C
45	7	80.8	87.4	13.5	17.6	15.4
90		96.8	100.0		34.2	26.8

MMO: Maximum mouth opening

the study indicate that conservative therapy of antioxidants combined with physiotherapy is as effective as invasive intralesional injection therapy. Considering that conservative therapies are more acceptable to patients, antioxidants combined with physiotherapy are a suitable treatment option for patients with OSMF.

## Discussion

OSMF is a poorly understood disease, the etiology and the pathogenesis remain elusive till date. However, most studies point toward an association between consumption of areca nut products and OSMF. Studies have also indicated a higher incidence of OSMF in patients with combined habits of tobacco and areca nut use.<sup>[12-14]</sup> In line with the findings from these studies, in the current study also, all the subjects enrolled in the study gave a positive history of the use of areca nut in variable forms. These findings further reaffirmed the etiological role of areca nut in OSMF.

In the present study, among 49 patients, 45 were male, suggestive of male preponderance. This is supported by findings from various studies which have shown that OSMF is predominantly seen in males.<sup>[4]</sup> Lai *et al.* reported that 96.67% of those affected with OSMF were male.<sup>[15]</sup> Most of the patients were in the age group of 20–30 years. This was similar to the reports of Borle and Borle and other studies that it predominantly occurs in the 3<sup>rd</sup> decade.<sup>[4]</sup>

The results of the present comparative study depict that physiotherapy as a solo mode of treatment is not effective in alleviating burning sensation and does not significantly improve MMO. This is in contrast with the results of a study conducted in 54 Nepali patients, which showed that physiotherapy improved was effective in increasing mouth opening compared with patients treated with local injection of hyaluronidase with steroids.<sup>[7]</sup> Cox and Zollinger showed in their study that physiotherapy is effective in increasing MMO.<sup>[7]</sup> Similarly, studies have shown that lycopene is beneficial in improving MMO as well as burning sensation in OSMF. Kumar *et al.* in their study showed that lycopene alone and lycopene with intralesional steroid injection resulted in a 3.4 mm and 4.6 mm increase in MMO, respectively. Karemore *et al.* also showed that lycopene significantly improved MMO.<sup>[10,11]</sup>

The current study showed that a combination of physiotherapy with antioxidants resulted in a significant reduction in burning sensation as well as improvement in MMO when compared with physiotherapy alone. Studies have also shown that intralesional injections of dexamethasone and hyaluronidase are highly effective in the management of OSMF.<sup>[3]</sup> The findings from the current study also showed intralesional injections of dexamethasone and hyaluronidase significantly reduced the burning sensation and improved the MMO.<sup>[16]</sup> The current study is unique as it compared the efficacy of physiotherapy alone, antioxidant along with physiotherapy, and intralesional injection. Analysis of the study results showed that the improvement seen in the antioxidants with physiotherapy group was comparable to that seen in the intralesional therapy group. The finding showed that conservative management is as effective as an interventional therapy in the management of OSMF. Conservative management is beneficial in the management of OSMF and can be considered as a suitable first-line treatment option.

However, the drawback of the current study is the small sample size as well as the absence of staging of OSMF. A larger

study with more number of patients, in patients with different stages of OSMF, needs to be conducted so that the efficacy of antioxidant plus physiotherapy can be better evaluated and established.

## Conclusion

From the findings of the present study, it can be concluded that physiotherapy alone does not provide relief for burning sensation, which is the primary subjective criteria of patients with OSMF. Physiotherapy with antioxidant therapy as well as intralesional therapy, both provide good results in relieving burning sensation and improving mouth opening. A non-invasive treatment modality of physiotherapy with antioxidants is effective in the management of patients with OSMF.

Further research with a larger number of patients is required to establish the efficacy of antioxidant plus physiotherapy as the preferred treatment option for OSMF.

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