

## Comparative evaluation of Lycopene-Hyaluronidase combination and Lycopene alone in the treatment of OSMF

Devleena Bhowmick<sup>1</sup>, Shubham Kumar<sup>2</sup>, Saba Nasreen<sup>3\*</sup>, Raunaque Saba<sup>4</sup>,  
Haider Iqbal<sup>5</sup>, Love Kumar Bhatia<sup>6</sup>

<sup>1</sup>Senior Lecturer, Department of Oral Medicine & Radiology, PDM Dental College & Research Institute, Bahadurgarh, Jhajjar, Haryana, India

<sup>2</sup>Senior Resident, Department of Dentistry, Sri Krishna Medical College & Hospital, Muzaffarpur, Bihar, India

<sup>3</sup>Senior Resident, Department of Dentistry, Sri Krishna Medical College & Hospital, Muzaffarpur, Bihar, India

<sup>4</sup>Senior Resident, Department of Dentistry, JawaharLal Nehru Medical College & Hospital, Bhagalpur, Bihar, India

<sup>5</sup>Department of Oral Medicine & Radiology, Sardar Patel Post Graduate Institute of Dental & Medical Sciences, Lucknow, Uttar Pradesh, India

<sup>6</sup>Department of Prosthodontics, Sardar Patel Post Graduate Institute of Dental & Medical Sciences, Lucknow, Uttar Pradesh, India

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### Abstract

**Introduction:** OSMF is a common potentially malignant disorder found in India caused by chewing gutkha with tobacco. Many studies have proven the beneficial effect of antioxidants in the management of osmf. **Aim:** The aim of the present study is to compare the efficacy of antioxidant Lycopene alone and in combination with intralesional Hyaluronidase injection in the treatment of OSMF patients. **Material and Method:** 50 diagnosed OSMF patients (Stage-2) were included in the study and were divided randomly into two groups. Group-A patients received 8 mg capsule of lycopene daily in two equally divided dose while Group-B patients received 8 mg capsule of lycopene daily in two equally divided dose in combination with intralesional injection of hyaluronidase 1500 IU twice weekly for 3 month. The clinical parameters (inter-incisal mouth opening & VAS for burning) were evaluated at baseline & at the completion of treatment on 90th day. **Results:** By the completion of study, inter-icisal mouth opening increased significantly ( $p < 0.05$ ) from  $25.20 \pm 3.01$  mm to  $29.36 \pm 3.17$  mm &  $24.58 \pm 3.90$  mm to  $32.41 \pm 3.22$  mm for Group-A & Group-B patients respectively. Changes in VAS for burning sensation decreased significantly ( $p < 0.05$ ) from  $7.16 \pm 0.96$  to  $0.88 \pm 0.72$  &  $6.47 \pm 1.10$  to  $0.20 \pm 0.12$  for Group-A & Group-B patients respectively. Also, Group-B patients witnessed statistically significant changes in clinical parameters at 90th day compared to Group-A patients.

**Conclusion:** Lycopene in combination with intralesional hyaluronidase is more effective in treating the patients with OSMF than lycopene alone.

**Keywords:** OSMF, Lycopene, Hyaluronidase, Antioxidant

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### Introduction

Oral Sub Mucous Fibrosis (OSMF) is a common premalignant condition found in India caused by tobacco/aeca nut chewing which is characterized by difficulty in mouth opening due to progressive sub-mucosal inflammation and fibrosis[1]. "Vidari" a condition described by "Susrutha" in ancient medicine has similar characteristics of OSMF. Schwartz (1952) described an oral mucosal condition as "Atrophiaiidiopathica Mucosa Oris", and later the term OSMF was given by Joshi (19530[2].OSMF is known to have high potential for malignant transformation, and it affects persons of all ages and sexes across the South East Asian population. Presence of multiple etiological factors (areca nut chewing, chilli consumption, nutritional deficiency states, genetic susceptibility and collagen disorders) and debatable pathogenesis, makes the management

very challenging and controversial. This condition predominantly affects Type-I collagen fibres with variable amounts of other types of collagen[3]. Pathologically it is characterized by increased synthesis of new collagen fibres by myofibroblasts, which exceeds the rate at which it is degraded. This results in increase in the total amount of collagen synthesis over time. This resultant fibrosis is characterized by progressive difficulty in mouth opening and burning sensation of the oral mucosa. The prevalence of OSMF in Indian population has increased from 0.03% to 6.42% over the past 40 years with malignant transformation rate of 7-30% [4]. Habit cessation with medication has been the fore runner of conservative management of OSMF, however no single satisfactory cure has been found because of irreversible nature of the disease. Carotenoids have been known to decrease the incidence of oral premalignant lesions and condition. Lycopene is an effective plant derived carotenoid with highly effective antioxidant properties. Documented papers have established its potent anti-carcinogenic and anti-oxidant properties and have been advocated in conservative management of precancerous lesions and conditions such as leukoplakia and OSMF[5].

Hyaluronidase, an enzyme that works by degrading hyaluronic acid (the ground substance in connective tissue) has also been studied and

\*Correspondence

**Dr. Saba Nasreen**

Senior Resident, Department of Dentistry, Sri Krishna Medical College & Hospital, Muzaffarpur, Bihar, India.

E-mail: [drsabanareen@gmail.com](mailto:drsabanareen@gmail.com)

successfully used for management of OSMF[6]. The present study would try to ascertain the role of lycopene alone and in combination of hyaluronidase in the conservative management of OSMF.

#### Materials and Method

This clinical prospective study was conducted in the Department of Dentistry, Sri Krishna Medical College & Hospital, Muzaffarpur, Bihar in accordance with revised Helsinki Declaration of 1975 after obtaining approval from the institutional ethical committee. After clinical examination of the lesion, a total of 50 male patients aged between 25 to 40 years with stage 2 OSMF[7] were included in the study. Patients with psychiatric problems, cardiac problems, gastrointestinal and metabolic disorders were excluded from the study. Detailed family and medical history with a history of associated habits (areca nut/gutkha/pan masala chewing, smoking and alcohol intake) was recorded. All patients were properly explained about the study and their written consent was taken. The patients were randomly divided into two equal groups:

GROUP-A patients were given Cap Lycored™ (Jagsonpal Pharmaceuticals Limited, New Delhi, India), containing 100% natural Lycopene, Zinc & Selenium, 8mg daily in two equally divided dose for 3 months.

GROUP-B patients were given Cap Lycored™ (Jagsonpal Pharmaceuticals Limited, New Delhi, India) 8 mg daily in two equally divided dose along with intralesional injection of Hynidase (Shreya Life Sciences Private Limited, Aurangabad, Maharashtra, India) containing 1500 IU of Hyaluronidase weekly for 3 months. Mouth opening exercise and cessation of the habit were common to all groups.

The clinical parameters evaluated during the study included improvements in mouth opening measured as interincisal distance in millimeters and burning sensation by Visual Analog Scale (VAS) from 1 to 10. The parameters were recorded at baseline (day 1) and at the completion of the study (day 90). All the results were recorded in Microsoft Excel Sheet and were analysed by Statistical package for the social sciences (SPSS) version 21 (IBM Corp., Chicago, Illinois, USA). Student t-test was used for evaluation of level of significance. A two-tailed p value less than 0.05 ( $p < 0.05$ ) was considered statistically significant.

#### Results

50 male patients aged between 20 to 40 years (mean age 28.6 years) participated in our study with 25 patients in each group-A & group-B. Average baseline mouth opening in group-A patients was  $25.20 \pm 3.01$  mm while that for group-B patients was  $24.58 \pm 3.90$  mm. At the end of the study (day 90) mouth opening was  $29.36 \pm 3.17$  mm and  $32.41 \pm 3.22$  mm in both the groups respectively (Table-1, Figure 1). Intragroup comparison revealed a significant increase in interincisal mouth opening for both the groups from baseline to 90th day. However, intergroup comparison at baseline was non-significant while it was significantly higher for Group-B patients at 90th day.

The mean VAS score for burning sensation recorded at baseline was  $7.16 \pm 0.96$  for Group-A patients and  $6.47 \pm 1.10$  for Group-B patients. The mean VAS scores recorded at the end of the study were  $0.88 \pm 0.72$  and  $0.20 \pm 0.12$  for both the groups respectively (Table-2, Figure 2). Intragroup comparison revealed a significant decrease in burning sensation for both the groups from baseline to 90th day. However, intergroup comparison at baseline was non-significant while it was significantly lower for Group-B patients at 90th day.

#### Discussion

Oral submucous fibrosis (OSMF) is defined by Pindborg and Sirsat as an insidious chronic disease affecting any part of the oral cavity and sometimes pharynx. Although occasionally preceded by and/or associated with vesicle formation, it is always associated with juxtaepithelial inflammatory reaction followed by fibro elastic

changes in the lamina propria, with epithelial atrophy leading to stiffness of the oral mucosa causing trismus and inability to eat[8]. The role of various pathophysiological and predisposing factors makes the prompt diagnosis and management of OSMF patients a challenging one. Areca nut and associated products are the most established etiological factor. These nuts contain arecoline, arecaine & tannins which interfere with fibroblast proliferation and dysregulate collagen synthesis. Burning sensation associated with OSMF is mainly due to epithelial atrophy, which is a sequel of juxtaepithelial inflammation causing vascular compression[9].

OSMF is one such potentially hazardous malignant disease which apart from being chronic and insidious, also has a high rate of malignant transformation. Various interventions (medicinal and non-medicinal) have been tried in OSMF and use of lycopene in this condition is not new[10]. Lycopene is a major carotenoid which is found in tomato have antioxidant and chemopreventive properties against potentially malignant disorders. It plays a key role in reduction of this inflammatory process and fibrosis, thus leading to epithelial regeneration and reduction of burning sensation[11,12].

Hyaluronidase, an enzyme is considered as "spreading factor" as it decomplexes Hyaluronic Acid which is an essential component of the extracellular matrix<sup>13</sup>. The use of hyaluronidase as intra-lesional injection in OSMF patients has been extensively reviewed in literatures and is known to present symptomatic relief in mucosal stiffness by softening and diminishing of fibrous tissues/bands.

In the present study, both the treatment modalities were effective in bringing out significant increase in mouth opening and significant reduction in burning sensation at completion of 90 days after the commencement of treatment. Also, by completion of 90 days, Group-B (Lycopene-Hyaluronidase combination) patients witnessed significantly greater reduction in burning sensation and significantly higher increase in mouth opening compared to Group-A (Lycopene alone) patients. Selvam & Dyanand (2012) suggested a combination of lycopene with intralesional steroids and hyaluronidase to be highly efficacious in reducing the symptoms and increase in mouth opening of OSMF patients[14]. Karemore & Motwani (2012) also suggested that lycopene was highly efficacious in relieving sign and symptoms of OSMF[15]. However, a recent meta-analysis reported non-significant differences between lycopene and other interventions used in the treatment of OSMF[16].

Kakaret. al. (1985) reported that patients treated with hyaluronidase witnessed quick improvement in symptoms but a combination of dexamethasone gave better and long lasting results<sup>17</sup>. In a study, intralesional injection of Hyaluronidase with Dexamethasone was found to be effective in management of Grade-III OSMF, thereby deferring the surgical intervention and its associated morbidity. Also, a recent meta-analysis reported weak evidences of additional clinical benefits with corticosteroid with hyaluronidase therapy in OSMF patients over control drugs (lycopene, pentoxifylline, aloe vera, dexamethasone, Turmix and isoxsuprine) therapy[18-20].

The newer approaches to management of OSMF include use of placental extracts and physical therapy by ultrasound waves[21]. In the present study, a significant improvement in mouth opening and reduction in burning sensation was evidenced for Group-B patients compared to Group-A patients at the completion of the study. However, the authors recommend more high-quality, multi-centric randomized controlled trials with larger sample size and extensive follow up periods to further access its effectiveness.

#### Conclusion

Combination of Lycopene with intralesional injection of Hyaluronidase has great benefits in alleviating the symptoms of OSMF patients and can be tried out as the first line of treatment in selected patients.

**Table 1: Inter-incisal mouth opening (in mm) within Group A & Group-B patients at different time intervals**

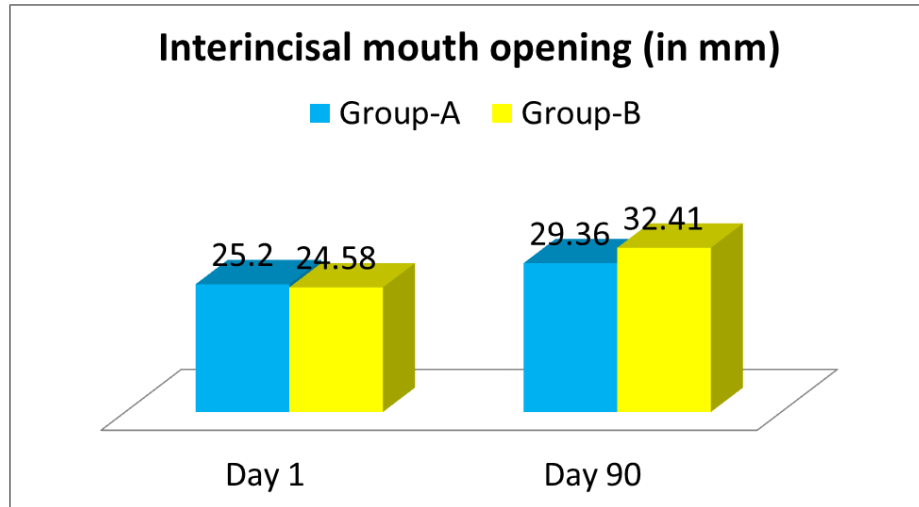
| Time Interval | Group A(n=25) | Group-B(n=25) | p       |
|---------------|---------------|---------------|---------|
| Day 01        | 25.20 ± 3.01  | 24.58 ± 3.90  | 0.5322  |
| Day 90        | 29.36 ± 3.17  | 32.41 ± 3.22  | 0.0015* |
| p             | < 0.0001*     | < 0.0001*     |         |

(\* - significant, p<0.05)

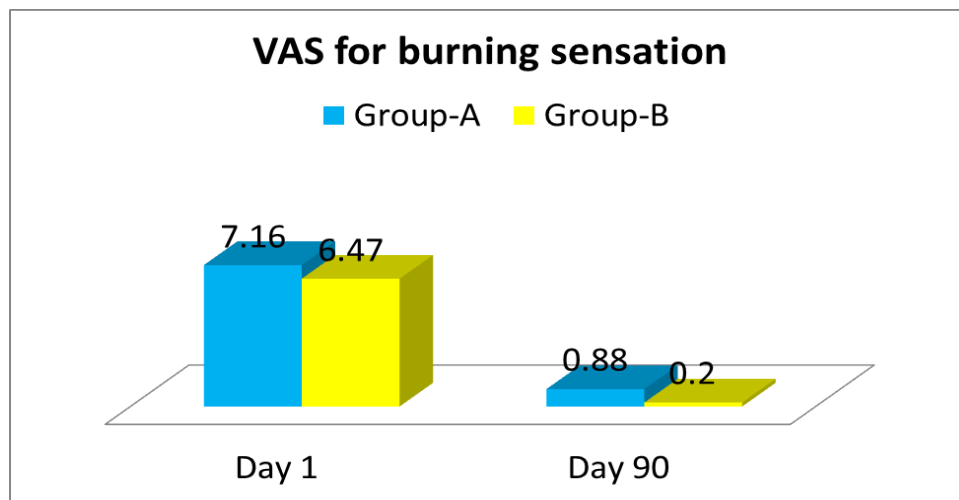
**Table 2: VAS for burning sensation within Group-A & Group-B patients at different time intervals**

| Time Interval | Group A(n=25) | Group-B(n=25) | p         |
|---------------|---------------|---------------|-----------|
| Day 01        | 7.16 ± 0.96   | 6.47 ± 1.10   | 0.0222    |
| Day 90        | 0.88 ± 0.72   | 0.20 ± 0.12   | < 0.0001* |
| p             | < 0.0001*     | < 0.0001*     |           |

(\* - significant, p<0.05)



**Fig 1: Graph comparing Interincisal mouth opening (in mm)**



**Fig 2: Graph comparing VAS for burning sensation**

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