

Assessment of the Efficacy of Orally Administered Lycopene in Improving the Mean Maximum Incisal Opening in Individuals Suffering from Oral Submucous Fibrosis

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ABSTRACT

Objective: To compare the effectiveness of orally administered lycopene versus a placebo in increasing mean maximum incisal opening in patients with oral submucous fibrosis (OSF).

Methodology: This randomized controlled trial, conducted at the Oral and Maxillofacial Surgery Department of Lahore Medical and Dental College from January to July 2020, enrolled 68 eligible patients. Two groups were formed: Group 1 (received oral lycopene) and Group 2 (received placebo). A block size of 4 was utilized for patient allocation, alternating between groups until the sample size was met. Both groups underwent a comprehensive 3-month treatment plan, including habit cessation and daily physiotherapy involving tongue spatula insertion between teeth (with spatula replacement). Only Group 1 received an additional 40mg oral lycopene daily. Follow-up appointments occurred monthly for 3 months, measuring maximal incisal opening with a Vernier Caliper.

Results: Baseline incisal opening was 25.39 ± 2.92 mm in Group 1 and 25.23 ± 3.03 mm in Group 2. At the 3-month mark, Group 1 showed an incisal opening of 31.71 ± 2.84 mm, while Group 2 had 28.31 ± 2.98 mm. The mean change in incisal opening was 6.32 ± 0.96 mm for Group 1 and 3.08 ± 0.90 mm for Group 2. Group 1 exhibited a significantly higher mean change in incisal opening compared to Group 2 ($p < 0.001$).

Conclusion: Lycopene administration is more effective than a placebo in improving mouth opening in OSF patients. Therefore, lycopene should be considered as a treatment option to enhance maximal incisal opening and improve the quality of life for individuals with OSF.

Keywords: Maximum incisal opening, Oral submucous fibrosis, Lycopene orally, Nutt eating

Authors' Contribution:

^{1,2}Conception; Literature research; manuscript design and drafting; ^{3,4}Critical analysis and manuscript review; ^{5,6}Data analysis; Manuscript Editing.

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Introduction

Oral submucous fibrosis (OSF) is a debilitating, multifactorial disease of the oral cavity characterized by inflammation and fibrosis of the submucosal tissues.¹ The data released by the World

Health Organization (WHO) in 2022 indicated a global OSF prevalence of 4.96%, accompanied by a 95% confidence interval spanning from 2.28% to 8.62%.² Presently, OSF is primarily concentrated in the Indian subcontinent, encompassing countries like India and Pakistan in Southeast Asia.² In China,

its predominant occurrence is in regions such as Hunan, Hainan, and Taiwan.³ While OSF can manifest at any age, it is most frequently diagnosed in adolescents and adults below the age of 35. Although the majority of the literature highlights a heightened incidence of OSF in females, some sources suggest that it is most prevalent in men aged 20 to 40 years.⁴ A decade-long follow-up study conducted by researchers revealed a noteworthy rise in OSF cases in eastern India, particularly among the male population.³ Consuming pepper, smoking cigarettes, and drinking alcohol have all been linked to an accelerated progression of oral squamous cell carcinoma.⁵ According to the findings of a study that was conducted in Taiwan, drinking alcohol was found to be connected with an increased risk of OSF, which in turn increased the total risk of malignant transformation of OPMD by 23%.⁶ According to research, there are over 5000 different compounds that can be found in tobacco smoke. N-nitrosamine is the component that is primarily responsible for the genotoxic effect of tobacco smoke.⁷ N-nitrosamine has the ability to directly generate cytotoxic effects on keratinocytes and fibroblasts,⁸ as well as to trigger oxidative stress and inflammation, and to activate immunological cells, such as macrophages, lymphocytes, and B cells.⁷ When a person smokes, a huge amount of reactive oxygen species, also known as ROS, are produced and released into the body. These ROS act on intracellular lipid, protein, polypeptide, nucleic acid, and other biological macromolecules, causing alterations in the structural and functional properties of proteins as well as damage to nucleic acid.⁹ In turn, the accumulation of oxidative damage can cause cell senescence, which can further increase the generation of ROS, thus creating a vicious cycle. IL-1, IL-6, and GRO-, all of which are part of the senescence-associated secretory phenotype (SASP), cause double-strand DNA breaks and promote genetic instability in keratinocytes.¹⁰ Long-term inflammation from persistent mechanical stimulation of the oral mucosa leads to atrophy of

the injured mucosa and the development of ulcers. Inflammatory mediators such as interleukin-1 (IL-1), IL-6, IL-8, tumor necrosis factor- (TNF-), and transforming growth factor (TGF-) are secreted to initiate the inflammatory reaction.³ Mucosal ulceration causes the coagulation system to be activated and stimulates fibroblast proliferation. TGF-1 activation in buccal mucosal fibroblasts (BMFs) may be stimulated by thrombin.¹¹⁻¹² Integrins alphavbeta1 (v1), v3, and v5 are responsible for mediating this activation. Connective tissue growth factors (CTGFs) are the end outcome of this process. For OSMF, a variety of treatment options have been suggested, including stopping the use of betel nut, physiotherapy, medication, and surgery.¹³ Despite the many treatments that OSMF sufferers have attempted, there is still no cure for symptom alleviation.¹⁴ Since OSMF is a chronic illness and a premalignant condition that is quite common, it is important to investigate and find an alternate, efficient treatment.¹⁵ In several in-vivo and in-vitro experiments, lycopene, a powerful antioxidant derived from tomato extract, has been shown to be the most efficient radical scavenger. In addition to being used to treat OSMF, its antioxidant qualities have also been studied in the treatment of other health-related disorders.¹⁶ Since there is a lack of locally collected evidence to support Lycopene as a viable treatment option for OSF, the purpose of this study is to attain tangible evidence to support the rationale of this drug as a mainstay treatment for OSF in Pakistan and to determine whether such a treatment produces acceptable results in the given population. Considering the adverse effects and the expenses involved in surgery and of intralesional dugs, treatment with Lycopene is a new avenue worth discovering.

Methodology

This randomized controlled trial, conducted at the Oral and Maxillofacial Surgery Department of Lahore Medical and Dental College from January to

July 2020, enrolled 68 eligible patients, i.e. those cases positively diagnosed with OSF, age ranged 20-70 years, with maximal incisal opening between 20 – 30 mm, and those who have not received any prior treatment for the condition were included in the study. Whereas those who did not give consent to be included, with mouth opening restriction due to other causes e.g., Myofacial pain, Disc displacement disorders, TMJ ankylosis, history of mandibular and maxillary trauma/fractures, facial space infections, neoplasms of the head and neck, etc, having degenerative joint, psychiatric or gastrointestinal diseases and those with low compliance and irregular follow up were excluded from the trial.

After taking both, verbal and written consent from the patient, demographic history (name, age, contact number) and history associated with the habits was taken and the proforma dully filled. The patients were then clinically assessed intraorally and extra orally. Patients were counseled regarding the premalignant nature of OSF and encouraged to break the habit of areca nut and supari chewing. Two groups were formed: Group 1 (received oral lycopene) and Group 2 (received placebo). Block size of 4 was chosen, where the first two patients were assigned to group 1 and next two into group 2, until sample size is achieved. Patients in both groups were given a comprehensive 3-month treatment plan including complete cessation of habit and five times daily physiotherapy by interpositioning tongue spatulas between teeth and adding a new spatula every 5- 10 day.

However, only Group 1 was advised an additional management of 40mg lycopene to be taken orally once a day. Patients in both groups were called for follow up after every month for three months. Maximal incisal opening was measured, using Vernier Caliper, and recorded at the follow-ups. All the data were collected through a pre-designed proforma. All the records and the data were collected by the same operator. We calculated the frequency and percentage for qualitative variables

such as gender, and for quantitative variables like age and maximum incisal opening, we computed the mean and standard deviation. To account for potential effect modifiers, we stratified the data based on age, gender, and baseline incisal opening due to areca nut chewing. For each group, we determined mouth opening after three months and calculated the overall mean increase in maximum incisal opening, which we subsequently compared. To assess significance, we applied a post-stratification t-test with a significance threshold set at P-value ≤ 0.05 . Additionally, we compared the mean increase in incisal opening between both groups using an independent sample t-test, where again, a P-value ≤ 0.05 was considered statistically significant.

Results

The mean age of all cases was 31.43 ± 9.24 years. The mean age of patients in Lycopene group was 30.53 ± 8.43 years and in placebo group was 32.32 ± 10.03 years. There were 20(58.8%) male and 14(41.2%) female cases in each group. In lycopene group there were 34(100%) cases that had history of areca nut chewing and in placebo group there were 34(100%) cases had history of areca nut chewing. The mean incisal opening at baseline in Lycopene group was 25.39 ± 2.92 mm and in placebo group was 25.23 ± 3.03 mm. The mean incisal opening at 3rd month in Lycopene group was 31.71 ± 2.84 mm and in placebo group was 28.31 ± 2.98 mm. The mean change in incisal opening in Lycopene group was 6.32 ± 0.96 mm and in placebo group was 3.08 ± 0.90 mm. The mean change in incisal opening in Lycopene group was statistically higher as compared to placebo group, p-value < 0.001 .(Table I)

Discussion

In the current study, all the patients had a positive history of consuming areca nuts in one form or the other. This is supported by the literature as areca nut being a proven cause of OSF.

Table I: Comparison of Change in Incisal Opening MM at 3rd (MM) month in Both Groups

Variables		Study groups	Change in incisal opening mm				p-value
			Mean	S. D	Minimum	Maximum	
Age(years)	20-49	Lycopene	6.29	1.01	6.29	1.01	<0.001
		Placebo	2.97	0.89	2.97	0.89	
	50-70	Lycopene	6.37	0.92	6.37	0.92	<0.001
		Placebo	3.30	0.92	3.30	0.92	
Gender	Male	Lycopene	6.42	4.90	7.70	6.42	<0.001
		Placebo	3.14	1.20	4.50	3.14	
	Female	Lycopene	6.16	4.70	7.90	6.16	<0.001
		Placebo	2.99	1.50	4.60	2.99	
Incisal opening (baseline)	20-25 mm	Lycopene	6.55	0.90	5.10	7.90	<0.001
		Placebo	3.23	0.88	1.50	4.60	
	25.1-30 mm	Lycopene	6.08	0.99	4.70	7.70	<0.001
		Placebo	2.94	0.91	1.20	4.50	

In the writer's experience majority of the patients give history of paan chaalia and supari chewing as a form of areca nut consumption, however, a study done by Selvam et al in Chennai, India deduced Ghutka as the predominant form of areca nut chewing among the patients of OSF.¹⁷ The difference in these two findings is perhaps due to geological differences in culture and habits. Other habits of smoking, alcohol consumption, tobacco chewing was inconsistently present in the patients and not assessed. A study done by Karemore et al., deduced that the patients who had a short term OSF displayed a much better response to Lycopene as opposed to those who suffered from OSF for longer periods.¹⁸ In the present study all patients despite having a positive history of areca nut chewing, differed in the duration of sustaining this habit. Therefore, the study included patients with both short and long-standing disease, without distinction. This aspect was not observed and compared among the patients and can be considered as a shortcoming of this study. In this study there is a Male to Female

ratio of 10: 7 with a male predominance, which is supported by the study done by Ranganathan et al., that found the ratio to be 9.9:1.¹⁹ In the current study a range of age groups between 20 to 70 years were included. It was found that a majority (39 out of 68 patients or 57%) of the patients were 30 years and below. This finding was in lieu with the studies done by Selvam et al and Maher et al who both found 60% and 70% of their patients under the age of 30 years, respectively.¹⁷ None of the patients in the present study experienced any side effects to Lycopene. There is a lack of evidence on the adverse effects of Lycopene in humans. There was a case study done on a 61-year-old woman who demonstrated a harmless side effect known as Lycopopenemia, which resolved after a Lycopene free diet in 3 weeks.²⁰ Another study reported that consuming natural or formulated Lycopene results in no side effects.²¹ The evaluation of the effectiveness of Lycopene was a measured value in terms of mouth opening and hence, non-subjective. All readings and measurements were taken by a single operator.

Therefore, there were no risks of compromise to the results. The present study showed a mean increase in mouth opening in Lycopene group of 6.32 ± 0.96 mm and in placebo group of 3.08 ± 0.90 mm. It is worthy to note that an improvement in mouth opening occurred in the placebo group as well, in which the patient's observed cessation of habit and mouth opening exercises. This increase in mouth opening, without the use of Lycopene, suggests both, cessation of habit and exercise, have a positive effect. This is an important finding and should be considered as a part of treatment management of OSF. This is further supported by the literature that suggests mere cessation of areca nut chewing should be the first step of treatment.²² In the present study, the mean change in incisal opening was the only measured value. This value within the Lycopene group was found to be statistically higher as compared to placebo group, p -value < 0.001 . However, other related symptoms of OSF were not observed. A similar local descriptive, case series was performed to determine the efficacy of Lycopene on both, burning sensations and mouth opening in patients of Oral submucous fibrosis. A majority of 69.3% of the patients had a habit of pan chewing, which was similar to the present study where the P value of 0.00001 (statistically significant) was used to compare the effectiveness of lycopene for burning sensations before and after therapy. Similarly, the mouth opening was compared and P value was found to be 0.002 (statistically significant). Thus, they determined that Lycopene was effective in not just symptomatic relief but also in increasing mouth opening.²³

The effectiveness of lycopene in enhancing maximal mouth opening and other clinical symptoms in individuals with oral submucous fibrosis (OSF) was extensively evaluated in another meta-analysis. Although the study found that lycopene increased maximal mouth opening in OSF patients, it found no statistically significant changes between the lycopene and control groups in terms of burning sensation, discomfort associated with lesion, or

tongue protrusion.²⁴ Another research compared the effectiveness of the newer antioxidant lycopene to a placebo in the treatment of OSMF, both in addition to the elimination of the offending behavior. In a study involving 92 people, 46 received lycopene while the other 46 received a placebo. Patients in the lycopene group took 8 mg of Lycored TM daily, split between two 4 mg doses, whereas those in the placebo group had a placebo pill twice a day. The primary results demonstrated that lycopene was considerably effective in reducing OSMF symptoms. As measured by a significant increase (69.56%) in maximum mouth opening ($P0.05$), it was beneficial in lowering objective indications of OSMF. This leads us to the conclusion that free radicals, also known as reactive oxygen molecules, are a substantial contributor to both premalignant and malignant states. The results of the current investigation suggest that the antioxidant lycopene may be useful in the treatment of OSMF.²⁵ The results of the present study suggest Lycopene as an effective line of management for OSF. Moreover, another study was done to evaluate the efficacy of oral lycopene therapy in patients with oral submucous fibrosis and to compare these effects with intralesional corticosteroids and a placebo. They reported that mouth opening values for the patients showed an average increase of 3.4 mm with Lycopene only, 4.6 mm with Lycopene and steroids and 0.0 mm for patients on a placebo. These values were statistically found to be highly significant. So, the observed effects suggested that lycopene is not just effective on its own, but has a synergistic effect when paired with intralesional corticosteroids.²⁶ The present study was, however, limited to the use of Lycopene alone and an addition of a third group with both measures of treatment would have produced a more comparative result.

Conclusion

The study's findings indicate that lycopene is more effective than a placebo in enhancing mouth

opening. Therefore, it is advisable to consider lycopene as a treatment option for oral submucous fibrosis to achieve the best possible incisal opening and enhance the quality of life for patients.

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