

Response of lycopene in treatment of oral submucous fibrosis

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Abstract

Introduction: Oral Submucous Fibrosis (OSF) is a well-known precancerous condition with malignant transformation rate as high as 7.6%. It results in marked rigidity of oral cavity and an eventual inability to open the mouth. Although OSF has a high rate of morbidity but no reliable treatment modality for its management has been developed yet.

Objective: To determine the frequency of positive response of oral lycopene in the treatment of patients with Oral Submucous Fibrosis.

Methods: A descriptive case series of patients with OSF was conducted at our institution for a period of 6 months i.e. 18-11-2014 to 18-05-2015 in the Department of Oral & Maxillofacial Surgery, King Edward Medical University, Lahore. Data was collected by using non-probability sampling technique. After informed consent, all patients were prescribed lycopene 30 mg BD dose for a period of 6 months. Changes in mouth opening (IO) was measured every month for each patient. Data was entered and analyzed using SPSS 20.

Results: A total number of 100 cases were selected for this study. Mean age of the patients was 27.24±8.22 of which 53(53%) were male and 47(47%) were female cases. Positive response of lycopene was noted in 76(76%) of cases while 24(24%) did not respond to the treatment. No adverse effects reported during the treatment period as well as during follow-up.

Conclusion: It is concluded that the lycopene can and should be used as a first line of treatment in the management of Oral Submucous fibrosis.

Keywords: Oral submucous fibrosis, Precancerous, Lycopene, Red carotene. Beta carotene, Efficacy.

Introduction

Oral Submucous Fibrosis is a precancerous condition⁽¹⁾ with malignant transformation rates as high as 7.6%.^(2,4) It is a chronic debilitating disease of the oral cavity characterized by inflammation and progressive fibrosis of the submucosal tissues (lamina propria and deeper connective tissues). It results in marked rigidity and an eventual inability to open the mouth.^(3,4) This condition affects approximately 0.5% (5 million people) of the population in the Indian subcontinent.⁽⁷⁾ Association of areca nut in the occurrence of Oral Submucous fibrosis has been proved by many studies.⁽⁴⁾ It's been observed that chewing areca nut releases free radicals which in turn lead to the suppression of immunity.

Treatment options include lycopene, iron and multivitamin supplements in addition to a range of therapeutic agents such as intralesional injection of steroids, hyaluronidase, human placental extract, chymotrypsin, pentoxifylline and collagenase.⁽⁸⁾ Surgical release operations for the fibrous bands, jaw muscles and temporomandibular joint have been used for more extreme cases.⁽²⁾

Lycopene is a potent antioxidant present in tomatoes and pink grapefruit. Like beta-carotene, Lycopene belongs to the family of carotenoids. As an antioxidant, it is about twice as powerful as beta-carotene. Review of the various safety studies has shown no adverse effects when administered in high doses even up to 3 g/kg/day of dietary or formulated

lycopene.⁽⁹⁾ Presently, there is no consensus about the precise dosage of Lycopene when administered as a pure compound but various clinical trials suggest a dose ranging from 13 to 75 mg/kg/day.⁽¹⁰⁾ It warrants further studies in the future to help standardize an optimal dosage of the drug. In contrast to other management modalities for OSF, Lycopene offers a noninvasive option that yields significant amelioration of the symptoms and signs of the disease as demonstrated by the improved maximal mouth (inter-incisal distance) opening up to 69.56% (P<0.05).^(4,1) The main focus of research has been the antioxidant property of lycopene.

However, it has also been shown to exert its effect via other mechanisms such as gene function regulation, gap junction communication, hormone and immune modulation, carcinogen metabolism, and modulation of metabolic pathways involving phase 2 drug metabolizing enzymes.^(12,13,14) Lycopene is usually administered as a pill/ tablet per oral. This study was conducted to determine the frequency of positive and negative responses of lycopene in the treatment of oral submucous fibrosis.

Methods

A total number of 100 patients using non-probability consecutive sampling technique were enrolled in our study. Patients suggesting the clinical diagnosis of OSF and matching the inclusion criteria were recruited for the study, from the Department of Oral and Maxillofacial surgery, King Edward Medical

University, Lahore, Pakistan. Permission to conduct the study was obtained through the Research and Ethics Committee of the corresponding Institute. Anonymity of the patients was assured and an informed consent was obtained from each individual patient. Inclusion criteria set for the study was: 1) Both males and females, 18-50 years of age. 2) Patients who agree to stop the use of causative agent (pan/supari). 3) Patients having inter-incisal distance (mouth opening) less than 30 mm assessed clinically using a ruler or Vernier Caliper. 4) Patients with OSF grading from Group I to Group IV A (Annex a). All of the selected patients were given Tab. Lycopene 30 mg twice daily per oral for a period of 06 months. Each patient was assessed every month to measure and record the extent of inter-incisal distance (mouth opening) and signs of progression of the disease. Improvement of at least 03 mm or more in inter-incisal distance (normal range 40-45 mm) using a Vernier calipers after 06 months of treatment. All the data collected was entered and analyzed by using Statistical Package for Social Sciences (SPSS) version 12.0. All the Qualitative variables like gender and positive response was described in terms of frequencies and percentages. Quantitative variables like age was

described in the form of mean +/- Standard Deviation (SD). Data was stratified by age, gender and grades. After stratification of the data, chi-square test was applied keeping a p-value ≤ 0.05 as significant and a power of 80% was chosen as the statistical power of the study.

Results

A total number of 100 patients participated in the study. Mean age of the patients was 27.24 (SD \pm 8.22) of which 53(53%) were male and 47(47%) were female cases. Positive response of lycopene was noted in 76(76%) of cases while 24(24%) did not responded to the treatment. A total number of 43(43%) patients were in grade 2, 39(39%) in grade 3 and 18(18%) in grade 4 (see Table 1). Positive response was noted in 42(55.3%) of cases in male and 34(44.7%) of female without significant difference i.e. p-value=0.486 (see Table 2). Moreover majority of the patients 34(44.7%) who responded to the treatment belonged to grade 2 category. There was approximately same positive response to the treatment in all age groups as the p-value was non-significant (Table 3).

Table 1: Treatment Responses according to the Grading system for OSF

| | Grade 2 N(%) | Grade 3 N(%) | Grade 4 N(%) | Total N(%) |
|-------------------|-----------------|-----------------|-----------------|---------------|
| Positive Response | 34 (44.7%) | 27(35.5%) | 15(19.7%) | 76(100%) |
| Negative Response | 9(37.5%) | 12(50%) | 3(12.5%) | 24(100%) |
| Total | 43(43%) | 39(39%) | 18(18%) | 100(100%) |
| p-value | 0.421 | | | |

Table 2: Treatment Responses according to the Gender

| | Positive Response | Negative Response | Total |
|---------|-------------------|-------------------|-----------|
| Male | 42(55.3%) | 11(45.8%) | 53(53%) |
| Female | 34(44.7%) | 13(54.2%) | 47(47%) |
| Total | 76(100%) | 24(100%) | 100(100%) |
| P-value | 0.486 | | |

Table 3: Treatment Responses according to the age groups

| | 18-20 yrs N(%) | 21-30 yrs N(%) | 31-40 N(%) | 41-50 yrs N(%) | Total N(%) |
|-------------------|-------------------|-------------------|---------------|-------------------|---------------|
| Positive Response | 26(34.2%) | 23(30.3%) | 22(28.9%) | 5(6.6%) | 76(100%) |
| Negative Response | 7(29.2%) | 9(37.5%) | 7(29.2%) | 1(4.2%) | 24(100%) |
| Total | 33(33%) | 32(32%) | 29(29%) | 6(6%) | 100(100%) |
| p-value | 0.893 | | | | |

Discussion

Oral submucous fibrosis is a rising threat in Southeast Asia. Oral submucous fibrosis is incurable. As explained in this study a much safer and simpler treatment modality, along with habit restriction, is essential to restrict the progression of Oral and Submucous fibrosis and to provide adequate relief to the patient.

Potentially harmful and/or costly treatment modalities e.g. surgery, submucosal steroid injections, placental extracts and hyaluronidase injections should be avoided and replaced by much more pragmatic means. Gowda et al. 2011, studied 12 oral submucous fibrosis patients and evaluated the clinicopathological response to lycopene: A carotenoid antioxidant and improvement was seen after the treatment with lycopene, 2000 µg, twice daily, for three months, with no significant toxicity.⁽¹⁵⁾ Similarly in our study we used lycopene, 30mg twice daily, for a period of 6 months, and found no significant toxicity in any of the patients. In our study we experienced that patients who showed a positive response not only gained an increase in mouth opening but also a cessation of the progression of the disease. Review of the various safety studies has shown no adverse effects when administered in high doses even up to 3 g/kg/day of dietary or formulated lycopene.⁽⁹⁾

The results of this study are similar to those of another study on OSMF, performed by Haque et al, in which he reported a positive result in OSMF cases using a treatment modality used for liver fibrosis (lycopene). Lycopene also upregulates the lymphocyte resistance to stress and suppresses the inflammatory response.⁽¹⁶⁾

Results of previous studies are reassuring. The one common feature that underlies this disease is oxidative damage. So, antioxidants can influence or prevent seemingly unrelated conditions.⁽¹⁷⁾

It is evident that a protracted treatment is required, if there is to be any significant impact in the management of oral and submucous fibrosis. Lycopene, being a more potent and less toxic retinoid, seems to be the more logical and pragmatic choice. Lycopene has

also shown to inhibit various cancers and premalignant conditions such as oral leukoplakia, where it inhibits dysplasia. Due to its nontoxic nature lycopene can be easily supplemented in the patient's diet.

Conclusion

Oral submucous fibrosis being an untreatable condition is difficult to manage. Costly, extensive and more morbid surgical procedures have not proven to be any useful with a penultimate recurrence. Other medical treatments though still being studied are to some extent useful, but they themselves have their associated morbidities and side effects. Lycopene being a potent antioxidant proves to be, as our study has shown, a viable modality for treatment due to its next to none toxicity, ease of use and ease of availability with good patient compliance. The observed results show that lycopene can and should be used as a first line treatment modality in management of Oral and submucous fibrosis.

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