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LYCOPENE AND INTRALESIONAL BETAMETHASONE INJECTIONS IN THE MANAGEMENT OF ORAL SUBMUCOUS FIBROSIS

Dr. Md Asad Iqubal[1], Dr. Supriya Singh[2], Dr. Ravindra Kumar Prasad[3], Dr. Rohit Singh[4] and *Dr. Jazib Nazeer[5]

[1]Lecturer, Department of Oral Medicine and Radiology, Patna Dental College & Hospital, Patna, Bihar, India.
[2]Lecturer, Department of Oral Medicine and Radiology.
[3]Tutor, Department of Oral Pathology, Patna Dental College & Hospital, Patna, Bihar, India.
[4]Lecturer, Department of Prosthodontic Crown Bridge and Implantology, Patna Dental College & Hospital, Patna, Bihar, India.
[5]Lecturer, Department of Oral Pathology, Patna Dental College & Hospital, Patna, Bihar, India.

***Corresponding Author: Dr. Jazib Nazeer**
Lecturer, Department of Oral Pathology, Patna Dental College & Hospital, Patna, Bihar, India.

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ABSTRACT

Aims and Objectives: This study was conducted to determine the efficacy of lycopene in the management of oral submucous fibrosis (OSMF) and to compare its efficacy with intralesional betamethasone injections. **Materials and Methods:** 88 patients were divided randomly into two groups. Group I subjects were treated with 10,000 mcg of lycopene (*Lyconex*) daily, in two equally divided doses, for two months. Group II subjects were given intralesional injections of betamethasone. Both the groups were assessed in terms of mouth opening and burning sensation. **Results:** A significant improvement in mouth opening was seen in both the groups and the improvement was better in Group I. The mean improvement in mouth opening in Group I was 37.62% (12 mm) at the end of the study, which was statistically highly significant and weekly evaluation revealed that this high signifi cance was from the third week onward, and Group II patients (only intralesional steroids) showed an average improvement of 13% (3.9 mm) at the final follow-up visit. **Conclusion:** Lycopene (*Lyconex*) is better than intralesional betamethasone injections in improving mouth opening and decreasing burning sensation.

KEY WORDS: lycopene, management, oral submucous fibrosis, intralesional.

INTRODUCTION

Oral sub mucous Fibrosis is a well known clinical entity since the time of sushruta when it was known as Vidari.[1] Oral submucous fibrosis (OSMF) is a premalignant condition of the oral mucosa first described in 1952. Various factors implicated in the etiology of OSMF are environmental agents, and nutritional, genetic, and autoimmune factors. Environmental agents, such as, the allied preparations of betel nut and betel quid have been observed to be associated with OSMF.[2] The potential for malignant transformation in OSMF is high.[3] In the biosynthesis of many carotenoids, lycopene is an important intermediate. Lycopene has been seen to have many anti-carcinogenic and antioxidant properties. It also plays a role in the improvement of precancerous lesions. Studies also suggest that as lycopene inhibits hepatic fibrosis in rats and human fibroblast activity *in vitro*, it appears to be a promising agent in the management of OSMF.[4] So far, studies on the management of OSMF using lycopene are only few.[4] Therefore, a need was felt to conduct a study to determine the efficacy of lycopene in the management of OSMF and to compare this treatment with intralesional betamethasone injections.

MATERIALS AND METHODS

The patients for the study were those who visited the Department of Oral Medicine and Radiology. In the present study, 88 patients who presented with signs and symptoms suggestive of OSMF were enrolled. The sample size was determined based on the number of patients with OSMF attending the department in a month. Each patient was informed about the protocol and was given appropriate instructions after obtaining a written consent. The inclusion and exclusion criteria for the study were as follows:

Inclusion criteria

- Patients who were healthy and well-oriented to place, person, and time
- Patients of either sex aged between 15 and 60 years
- Patients with a history of areca nut chewing and burning sensation on eating spicy food

• Restricted mouth opening and presence of palpable vertical fi brous bands, stiffness and blanching.

Exclusion criteria
• Subjects who had undergone any treatment for OSMF
• Those with any systemic disease

Only clinically diagnosed cases of OSMF were considered for this study, as a biopsy could further decrease mouth opening, due to secondary contractures, which might affect the patient follow-up findings. However, a brush biopsy was done for the patients. Following the establishment of the diagnosis, each patient was educated about the nature of the condition and its precancerous potential, and they were motivated to discontinue the use of areca nut, tobacco or any other abusive habit in any form. The study included patients with OSMF encompassing all the groups based on the Lai DR classification (group A, B, C, and D). Patients with any other pre-malignant disorder, such as leukoplakia, were not included. All the patients of the study were advised oral prophylaxis to remove extrinsic stains. This was done to motivate the patient toward recovery and to know if the patient resumed the habit.

The patients were divided randomly into two groups
Group I: Subjects were treated with 10,000 mcg of lycopene daily in two equally divided doses for two months.

Group II: Subjects were given intralesional injections of betamethasone (1 mL ampule of 4 mg each) where the fibrous bands were palpable, twice weekly for two months.

Both the groups were assessed in terms of mouth opening and burning sensation before the treatment, weekly during the treatment period of two months, and the final evaluation was done two months after the completion of the treatment. The complete period of the study was four months. This was a prospective, randomized, and blinded controlled study, in which the patients were selected through a chit system. Chits of Group I and Group II were placed in a box and patient was asked to blindly pick a chit according to which the patients were divided into Group I or II.

Mouth opening: This was assessed as the interincisal distance measured from the mesioincisal edge of the upper left central incisor tooth to the mesioincisal edge of the lower left central incisor tooth. The measurement was made using a vernier caliper and was recorded in millimeters.

Burning sensation: The intensity of the burning sensation was determined using a Visual Analog Scale (VAS) of 0-10, where 0 indicated no burning sensation and 10 indicated the worst possible burning sensation. This was recorded at baseline and weekly intervals. It was recorded based on the patient's response.

Statistical analysis: All the relevant data were entered in a proforma. It was then sorted, tabulated, and statistically analyzed to draw a conclusion. All quantified variables in the study, that is, mouth-opening measurements, age, quantity, and duration of habit, were subjected to statistical analysis.

All these values were analyzed for mean (or median as applicable), standard deviation, errors, and range. The unpaired *t*-test was used for evaluation of the statistical significance of mouth-opening values between groups.

The paired *t*-test was used for evaluation of the statistical significance of mouth-opening values between weeks in the same group. The *P*-value was set at 0.05 and was considered highly significant at <0.01 and very highly significant at <0.001.

RESULTS

Age and sex distribution: In the present study 88 OSMF patients were included and were randomly divided into two groups. The mean age of subjects in Group I was 30.40 ± 9.11 years, while the mean age of Group II subjects was 24.49 ± 6.98 years. In Group I, 54.5% of the patients were above 25 years of age, while in Group II, 59.1% of the subjects were below 25 years of age. Statistically, there was no significant difference in terms of age between the two groups ($P = 0.365$). The majority of subjects in both the groups were males. Statistically, there was no significant difference in terms of gender between the two groups ($P = 0.680$, Table 1).

Table 1: Age-group distribution

Age group (years)	Group I (n = 44) No.	Group I (n = 44) (%)	Group II (n = 44) No.	Group II (n = 44) (%)
<25	20	45.5	26	59.1
>25	24	54.5	18	40.9
Mean age±SD	30.40±9.11	30.40±9.11	24.49±6.98	24.49±6.98

Mouth opening
Pretreatment
Group I had a more consistent range of mouth opening (range 2.4-4.5 mm) with a mean of 3.19 ± 0.55 mm, while Group II had a relatively wide range (1.3-4.6 mm) a mean of 3.00 ± 0.82 mm. Comparison of data in the two groups did not reveal a statistically significant intergroup difference ($P = 0.382$).

Post-treatment
The average mouth opening in Group I was 4.39 + 0.29 mm and in Group II it was 3.39 ± 0.63 mm.

Change in mouth opening and statistical analysis

Group I: At baseline (pretreatment), the mean mouth opening was 3.19 ± 0.55 mm, which remained unchanged at week one, but thereafter, it started showing a gradual increase. At the end of the treatment, there was a 37.62% increase in mouth opening, which was very highly significant as compared to the baseline.

Group II: At baseline (pretreatment), the mean mouth opening was 3.00 ± 0.82 mm, which remained unchanged at week one, but thereafter, started showing an increase. At the end of the treatment, a 13% improvement in mouth opening was seen showing a statistically highly significant difference from baseline.

Burning sensation

Group I: At baseline (pretreatment), the burning sensation was 50.82 ± 24.08. At the end of treatment a 94.5% reduction in burning sensation was seen, which was statistically very highly significant ($P < 0.001$). Group II: At baseline (pretreatment), the burning sensation was 49.55 ± 24.15. At the end of treatment a 54.1% reduction in burning sensation was seen and it was very highly significant ($P < 0.001$). No significant association between the percentage reduction in burning sensation, percentage increase in mouth opening, and duration of symptom of burning sensation as well as mouth opening was observed in either group, independently or collectively.

DISCUSSION

Lycopene is a powerful antioxidant obtained from tomatoes. Studies also suggest that lycopene inhibits hepatic fibrosis in rats and human fibroblast activity *in vitro*. Therefore, it can be beneficial in the management of OSMF.

The present study was designed to evaluate the efficacy of lycopene-10,000 mcg (*Lyconex*) in the management of OSMF and to compare this treatment with intralesional betamethasone injections (1 mL ampule of 4 mg each). In the present study 88 subjects with OSMF were in the age range of 17-50 years, with a mean age of 28 years. This was comparable to the mean age of 28 years observed by Kumar *et al*.[3] and 28.8 years observed by Hazarey *et al*.[5] Among the 88 OSMF subjects, 74 (84%) were male and 14 (16%) were female, thus showing extreme male predominance, with a ratio of 5.25:1. A similar male predominance was reported by Sinor *et al*. (58 out of 60 were men, 29:1) and Pindborg (81 out of 118 were male, 2.2:1). The male predominance could be due to easy accessibility for males to use these products more frequently than females in our society.[6,7]

Restriction of mouth opening is a major disability associated with OSMF. An improvement of a few millimeters has been reported. In our study a significant improvement was seen in both the groups. The mean improvement in mouth opening in Group I (lycopene group) was 37.62% (12 mm) at the end of the treatment and it was very highly significant ($P < 0.001$). There are very few published studies on evaluating the effectiveness of lycopene in OSMF. Kumar *et al*. also conducted a similar study in 2007, on efficacy of lycopene in the management of OSMF. They reported that the mouth opening was increased by 3.4 mm in patients receiving 16 mg of lycopene and 4.6 mm in patients receiving 16 mg of lycopene along with biweekly intralesional steroid injections.[3] In our study there was more improvement in mouth opening as compared to the study by Kumar *et al*., which could be due to the drug *Lyconex* (which was used in our study) also containing Vitamin A, C, E, and B. These vitamins help to enhance the immune system, encourage cell growth and division, and boost the metabolism. Studies have also been done using antioxidant supplements and have shown good results. Gupta *et al*.[8] reported a 50% improvement in mouth opening in six of their patients treated with *Antoxid*.

The mean improvement in mouth opening in Group II (only intralesional steroids) was 13% (3.9 mm) at the end of the treatment, which was a statistically highly signifi cant difference from the baseline ($P = 0.018$). Canniff *et al*., in 1986, found that only intralesional steroids were not very useful in the management of OSMF.[3] In another study done by Borle and Borle, in which intralesional injections of triamcinolone were combined with hyaluronidase, there was no improvement in mouth opening.[9] In our study there was 13% improvement with only intralesional steroids.

A burning sensation when eating spicy food or even normal food is common among OSMF patients, due to which they switch over to a bland diet, which is generally not nutritionally adequate. Although the exact mechanism causing the burning sensation is not clear, intolerance to spices could be due to the atrophic and permeable epithelium. In our study, patients treated with lycopene (Group I) had a reduction in burning sensation by 94.2% at the end of the therapy and it was very highly significant ($P < 0.001$). Similar findings were reported in a study done by Kumar *et al*., in which burning sensation was reduced effectively in patients taking lycopene and lycopene with intralesional steroids.[3]

Patients treated with intralesional steroid injections (Group II) had a reduction in burning sensation by 54.1% at the end of the treatment. The change in burning sensation was very highly significant ($P < 0.001$). Borle and Borle found that treatment of OSMF with intralesional injections of hyaluronidase and corticosteroids (triamcinolone acetonide) reduced burning sensation by 86.84%.[9] Katharia *et al*. observed that in the treatment of OSMF, with intralesional placental extracts the burning sensation improved by 40.2% and Haque *et al*. noticed that the burning sensation reduced by 54-60% with IFN γ.[10] When the results of both the groups were compared the mean burning sensation in Group I was very highly significant

as compared to Group II ($P < 0.001$). The results of the present study indicate that lycopene (*Lyconex*) is more effective than intralesional steroid injections in improving the mouth opening and burning sensation in patients with OSMF. The reasons for this effi cacy may be.

• Lycopene prevents free radical damage to cells. Studies have shown that it reduces the susceptibility of lymphocyte DNA to oxidative damage, inactivates hydrogen peroxide (H2O2) and nitrogen oxide (NO), and protects cells from NO-induced membrane damage and cell death. Lycopene has both physical and chemical antioxidant properties, in which physical quenching in much better than chemical quenching.[11]

• Lycopene inhibits hepatic fibrosis in rats and human fibroblast activity *in vitro*. Thus, it can be beneficial in the management of OSMF (Kitade *et al*.[12]). This also suggests inhibition of the stellate cell activity. There were no associated side effects with the use of lycopene (*Lyconex*). There were a few limitations to this study. The duration of follow up was only two months; a longer follow-up study should be done to rule out any long-term effects of lycopene. The *Lyconex* capsule that was used in the study also contained vitamin A, B, C, and E, in addition to lycopene, so the improvement observed in the study could be the combined effect of all these and it could not be attributed to lycopene alone. From our study, it could be inferred that lycopene in combination was better than intralesional betamethasone injections for improving mouth opening and decreasing the burning sensation in patients with OSMF. Further studies, with a larger sample size, and with longer follow-up periods are required to determine the longterm effect of lycopene (*Lyconex*) in OSMF.

CONCLUSION

A positive response was seen in Group I in our study when compared with Group II. Group I patients were given capsules of *Lyconex*, which also contained Vitamins A, B, C, and E, in addition to lycopene. Thus, the improvement observed in the study could be the combined effect of all these, which was better than betamethasone. Lycopene in combination was effi cacious as well as a safe and reliable drug in the management of OSMF. It was a noninvasive option for the management of OSMF, which helped in the improvement of the signs and symptoms of the condition. This combination could, therefore, be used as a first-line drug of treatment in patients with this debilitating disease. Further trials in this regard should be carried out, to investigate the probable mechanism by which this combination exerts the beneficial effect.

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