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Randomized controlled trial to evaluate the efficacy of lycopene in combination with vitamin E and selenium in the treatment of leukoplakia

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Abstract

Aims and Objectives: A randomized controlled study was carried out to evaluate the efficacy of lycopene in combination with vitamin E and selenium in the treatment of leukoplakia in patients visiting dental college Jharkhand.

Materials and Methods: Forty patients of leukoplakia were randomly categorized (irrespective of size and severity of the lesions) in two groups: Group A and B. Group A consisting of 20 patients were administered combination of lycopene (3 mg), vitamin E (200 I.U.) and selenium (100 mcg) twice daily and group B consisting of 20 patients were given placebo capsules once daily for a period of 4 months. Post-treatment follow-up period was 3-4 months. The product used in the study was LYC-O-MATO soft gels, manufactured by Mano pharmaceuticals, Chennai, India. The treatment outcome was evaluated both clinically and histologically and the results were statistically evaluated using Student's unpaired '*t*' test.

Results: The results showed that the patients receiving lycopene in combination with vitamin E and selenium have statistically significant improvements both clinically and histologically as compared to those receiving placebo and with no side effects.

Conclusion: The study results proved that the efficacy and safety of lycopene along with selenium and vitamin E in the management of oral leukoplakia.

Keywords: lycopene, oral leukoplakia, selenium, vitamin E

1. Introduction

Cancer is the most formidable health problem faced by mankind in today's world. Cancer of the oral cavity is the eighth most common cancer and accounts for 2% cancer deaths worldwide Unlike the other cancers, oral cancer shows signs and symptoms before developing. These signs and symptoms are broadly termed as potentially malignant disorders (PMD's) of oral cavity Where premalignant lesions are said to be localized, premalignant conditions are generalized states, both having increased potential for malignant transformation as compared to their normal counterparts [1].

Leukoplakia is by far the most common oral premalignant lesion representing 85% of such lesions. Oral leukoplakia is associated with tobacco habit and cannot be characterized as any other lesion [2]. The main purpose of early identification of leukoplakia is early interception and management to prevent its malignant transformation. Early neoplastic or paraneoplastic lesions can be treated through "cancer chemoprevention" before development of clinically apparent signs and symptoms in overt malignancies wherein the carcinogenic steps can be arrested or reversed through pharmacological treatments [3].

Lycopene is a red colored, fat-soluble pigment synthesized by plants and microorganisms. Millardet first discovered it in 1876. The name Lycopene was given by Schunck [4]. It is a carotenoid mainly present in red fruits and vegetables. The greatest known dietary source of lycopene is tomato. Lycopene can also be derived from other red fruits and vegetables e.g. pink grapefruits, watermelons, pink guavas, apricots etc. Other than these, it is present in certain fungus and algae [1].

The inverse relationship between high tomato consumption and upper aero-digestive tract cancers like cancers of oral cavity, pharynx, larynx and esophagus has been proved in several studies. One such study suggested that lycopene can be effectively and safely used for the management of oral leukoplakia. Also there are many previous studies, showing the efficacy of the vitamin E and selenium, in the treatment of leukoplakia [5].

This study has done to evaluate the efficacy of lycopene in combination with vitamin E and selenium in the management of oral leukoplakia.

2. Materials and Methods

A total of 40 patients, who visited the Department of Oral Medicine and Radiology at the Dental college Garhwa (Jharkhand), were selected for the study, where oral leukoplakia was confirmed both clinically and histologically. An ethical clearance was obtained from the ethical committee of the hospital.

The aim and purpose of the study was explained to each patient thoroughly and written consent was obtained. Also the habits like tobacco, Pan masala chewing usage were assessed

on each visit and the patients were encouraged to discontinue the same. These 41 patients were randomly categorized (irrespective of the size and severity of the lesions) in two groups:

- Group-A (Study group): Twenty-one patients were treated with 6 mg of lycopene + vitamin E (400 I.U.) + selenium (200 mcg) in two equally divided doses. The product used in the study was LYC-O-MATO soft gels, manufactured by Mano pharmaceuticals, Chennai, India.
- Group-B (Placebo group): Twenty patients were given placebo capsules once daily.

  After recording the pre-treatment clinical and histological findings, all the patients were evaluated at a regular interval of 15 days for a period of 4 months of active treatment and once in a month for another 4 months of post-treatment follow-up. In case of any untoward reaction such as rash, allergy, etc., the patients were asked to report immediately. The clinical response was noted down carefully and was classified as following:
- Complete remission of lesion (100%).
- Partial improvement or decrease in the size of the lesion more than (75%).
- A stable or no response when size reduction is less than 50% (no response).
- Progression (Prog) or appearance of a new lesion (–25%).

Post-treatment biopsy was taken after the completion of 4 months of treatment period. Statistical analysis was done and results were compared using Student's (unpaired) 't' test

3. Result

In this study, the majority *i.e.*, 38 (92.6%) were males. There were 19 males and 2 female's in-group A and 19 males and one female in-group B. Thus, the male predominance over females was as high as 12:1 [Tables 1 and 2]. Of the 41 patients in the two groups (group A + group B), the average age was found to be 47 years. Most of the patients were in the middle age (31-50 years). The youngest patient in this study was 26 years old and the oldest was 65 years old.

The site involved in the majority of patients was buccal mucosa. Thirty-five (87.5%) patients out of 40 in general (group A + B) had lesions on buccal mucosa followed by the gingiva/ridge (12.5%), tongue (10%), lips (7.5%) and palate (2.5%) [Table 3]. The most common clinical type of leukoplakia observed in patients was homogenous followed by non-homogenous and verrucous type.

Table 1: Age & Sex Distribution in Group – A

Age group(in years)	Male	Female	Total
11-20	-	-	0
21-30	1	-	1
31-40	4	1	5
41-50	7	-	7
51-60	4	-	4
61-70	2	1	3
Total	18	2	20

Table 2: Age and Sex Distribution in Group B

Age group(in years)	Male	Female	Total
11-20	-	-	0
21-30	1	-	1
31-40	7	1	8
41-50	5	1	6
51-60	3	-	3
61-70	2	-	2
Total	18	2	20

Table 3: Site distribution of the lesion

Site	Group A	Group B	Total
Upper lip	-	-	0
Lower lip	3	-	3(7.5%)
Right buccal mucosa	9	11	20(50%)
Left buccal mucosa	7	8	15(37.5%)
Gingiva	2	3	5(12.5%)
Palate	1	-	1(2.5%)
Tounge	2	2	4(10%)

Table 4: Clinical improvement in percentage (%)

Improvement	Number of patients (Group A)	Number of patients (Group B)
Complete improvement (100%)	5	0
Partial improvement (>50%)	13	3
Stable response (<50%)	2	17
Progression (25%)	0	0
Mean	84%	16%
S.D.	24.77	24.78

t value = 8.85, P=0.0051

On statistical evaluation, the patients in-group A (lycopene + vitamin E + selenium) showed a mean improvement of 84% with a standard deviation of 24.77 and in group B, it was 16% with a standard deviation of 24.78. Five patients showed complete (100%) improvement (CI), 13 showed partial (>50%) improvement (PI) and 2 showed stable response (<50%) or no improvement (SR) in group A while in group B only three patients showed partial improvement, 17 showed no improvement or stable response, and not a single patient showed complete improvement. The response was highly significant when group A was compared with group B [T able 4].

4. Discussion

Oral leukoplakia (OL) is one among important potentially malignant disorders of the oral mucosa. Leukoplakia may occur anywhere on the oral mucosa, and its prevalence varies from 0.2% to 5.2% of the Indian population. The tobacco chewing habit both in smoking and smokeless form is the most common cause for OL. Many oral squamous cell carcinomas develop from potentially malignant disorders [6].

In our study, 95% of patients were above 30 years, while the mean age was 47 years. Also, the male to female ratio was 12:1 indicating a high male predominance. Various other investigators like Waldron [7], and more recently Mohitpal

Singh *et al*. [8] also reported male predominance.

In the present study it was found that lycopene in combination with vitamin E and selenium was effective in improving bitterly both clinical and histopathologic ally in the patients of leukoplakia and the response was statistically significant as compared to the placebo group. The first clinical response noted was thinning of the leukoplakia lesion, followed by decrease in the size of the lesion. Histological response in patients receiving lycopene was significant and was marked by a reversal of various dysplastic changes followed by decrease in the size of the lesion and the appearance of Pink mucosa.

Mohitpal Singh *et al*., in 2004, [8] assessed the efficiency of lycopene in 58 cases of leukoplakia. In their study, the patients were divided into three groups, and received 8 mg/day, 4 mg/day, and a placebo for a period of 3 months. The study suggested that lycopene could be effectively and safely used for the management of oral leukoplakia. Also, the 8-mg regime showed better results than the 4-mg regime. The efficacy of lycopene as a potent antioxidant in the treatment of other oral precancerous lesions like oral submucous fibrosis has also been proved in many studies [9, 10].

Other similar chemo preventive drugs like retinoids and beta-carotene also have been successfully used in the treatment of leukoplakia but the biggest drawback was toxic reactions like cheilitis, dryness, peeling of skin or headaches related to their provitamin A activity. Lycopene lacks the beta-ionone ring structure and is therefore devoid of pro-vitamin A activity and related side effects [11]. In our study, during the period of active treatment of 4 months, no patient reported with undesirable side effects proving the safety of drug in the management of leukoplakia.

5. Conclusion

Major aim of this research is the chemoprevention. Numerous clinical study have been made in understanding the role of various chemo preventive agents, particularly carotinoids and micronutrients in the treatment of oral cancer. Although the present this study clearly proves that lycopene in combination with vitamin E and selenium is a very effective and safe chemo preventive. The chemo preventive agents must possess minimal toxicity for long-term therapy. Further studies can also be carried out using genetic markers like EGFR, P-53, to assess the efficacy of chemo preventive agents more accurately.

Hence, it is recommended that a similar study utilizing a larger sample size, longer follow-up should be carried out to establish the chemo preventive action of lycopene**.**

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