

# CLINICAL OUTCOMES OF LYCOPENE WITH BETA-CAROTENE IN PREMALIGNANT LESIONS OF ORAL CANCER

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## Abstract:

Oral cancer is often preceded by precancerous or premalignant lesions and conditions such as leukoplakia, erythroplakia and oral submucosal fibrosis. These premalignant conditions are easy to diagnose but difficult to manage. This study is to compare the clinical outcomes of lycopene with beta carotene in premalignant lesions of oral cancer. The study included 125 patients with oral premalignant stage attending Sai Sree cancer hospital, Warangal. These patients were then treated with lycopene with beta carotene and a set of signs and symptoms including mouth opening were examined prior and after therapy. After the treatment with lycopene with beta carotene for a period of 2-3 months clinical improvement of mouth opening, signs and symptoms in patients were observed.

**CONCLUSION:** This work is showing that lycopene with beta carotene is overall favorable for early cases of oral premalignant state and conditions to cease and delay the disease progress.

**Key words:** Lycopene, Beta carotene, Oral cancer, Premalignant, Leukoplakia, Erythroplakia and oral submucosal fibrosis.

## INTRODUCTION:

Oral cancer is a major problem in the Indian subcontinent where it ranks among the top three types of cancer in the country and is eighth most common cancer world wide <sup>[1]</sup>. It is often preceded by precancerous or premalignant lesions and conditions such as leukoplakia, erythroplakia and oral submucosal fibrosis<sup>[2]</sup>. WHO defined leukoplakia as a white patch or plaque that cannot be characterized clinically or pathologically as any other disease and is not associated with any other physical or chemical causative agent<sup>[3]</sup>.

WHO defined Erythroplakia as a fiery red patch that cannot be characterized clinically or pathologically as any other definable disease. It is much less common than leukoplakia but it has the greatest potential for malignant transformation. Erythroplakia is often flat with a smooth or granular surface<sup>[4]</sup>. Oral submucosal fibrosis (OSMF) is a chronic disorder characterized by fibrosis of the mucosal lining of the upper digestive tract involving the oral cavity, oropharynx and frequently the upper third of the oesophagus<sup>[5]</sup>.

**Table 1. Signs and symptoms of OSMF**

Early forms	Late presentation
<ul style="list-style-type: none"> <li>▪ Burning sensation, exacerbated by spicy food</li> <li>▪ Vesiculation</li> <li>▪ Blanching of mucosa</li> <li>▪ Leathery mucosa</li> </ul>	<ul style="list-style-type: none"> <li>▪ Fibrous bands within mucosa</li> <li>▪ Limitation of mouth opening</li> <li>▪ Narrowing of oropharyngeal orifice with distortion of uvula</li> <li>▪ Woody changes to mucosa and tongue</li> </ul>

The major risk factors are tobacco (both smoked and smokeless forms), betel quid chewing and alcohol. More than 4000 different chemicals are found in tobacco and tobacco smoke. More than 60 of these chemicals are known to cause cancer<sup>[6]</sup>.

Antioxidants may be regarded as those substances which will significantly delay or inhibit the oxidation of a substance and protect the body against oxidative damage. Insufficient levels of antioxidants or inhibition of antioxidant enzymes causes oxidative stress and damage or kill the cells.

The antioxidants act by

- ❖ breakage of chain reaction,
- ❖ reducing concentration of reactive oxygen species,
- ❖ scavenging initiating radicals,
- ❖ chelation of transition metal catalyst<sup>[6]</sup>.

**Lycopene:** It is a major carotenoid found in tomato which has potent anticancer activity in many types of cancer. The antioxidant properties of lycopene are thought to be primarily involved in its preventive effects in chronic diseases. It also has potent benefits in oral potentially malignant lesions. Because of its high number of conjugated dienes, lycopene is one of the most potent antioxidants, with a singlet oxygen quenching ability twice as high as that of  $\beta$ -carotene and 10 times higher than that of  $\alpha$ -tocopherol<sup>[7]</sup>.

**Beta-carotene:** Beta-carotene is a vitamin A precursor commonly found in dark green, orange or yellowish fruits and vegetables, such as spinach, carrots, sweet potato, mango, papaya, and oranges. The main actions of beta carotene include:

- Antioxidant and free radical scavenging
- Immunomodulation, stimulation of increase in cell mediated immune response (T- helper, NK cells and cells with IL-2 receptors) due to increased monocyte expression and increased activity of tumor necrosis factor alpha.
- Inhibition of mutagenesis.
- Inhibition of cancer cell growth <sup>[8]</sup>.

#### MATERIAL AND METHODS:

154 patients who presented with clinical signs and symptoms of Premalignant stages of oral cancer were included in the study. Among them 29 patients were excluded (5 patients expired, 13 did not come for follow up, 2 posted for radiation and 9 for surgery). A distribution of number of patients included according to different stages are shown in table 2.

**Table 2. Distribution of patients according to disease stage.**

Disease stage	No. of patients
<i>Premalignant lesions</i>	
Leukoplakia	45
Erythroplakia	26
<i>Premalignant condition</i>	
Oral submucosal fibrosis	52
Leukoplakia with OSMF	2

Institutional Human Ethics Committee was sought and the number is (MGM/VCOP/PHARM D/V/2017/016). Informed consent was explained and obtained from all the patients. They were explained about the disease condition and its premalignant potential. A detailed personal and social history of the patient was recorded after the clinical diagnosis was done, a set of clinical signs and symptoms and mouth opening were studied in individual patient prior to and after lycopene with beta carotene therapy using digital Vernier callipers.

#### RESULTS

In the present study out of 125 patients, there were 94 males and 31 females. The age incidence amongst 125 cases was shown in table.3 It is obvious that highest incidence was found between the age groups 31 to 40 and 41 to 50. The various predisposing factors in the patient were identified and chewing of smokeless forms of tobacco majorly gutkha was the most common etiological factor followed by tobacco pan (table 4). Majority of the patients were uneducated that constitute 76% while educated patients percentage was 24% (table 5). The percentage of patients from rural area was 80% to that of from urban area is 20% (table 6). The interincisal distance of  $25.3944 \pm 5.58$  was found prior to lycopene with beta carotene treatment and it was improved to  $28.408 \pm 5.96$  as shown in fig.1. After the treatment with lycopene with beta carotene for a period of 2-3 months, the patients with age group 21-30 have shown an improvement in the mouth opening from  $27.40 \pm 5.86$  to  $30.07 \pm 6.63$  whereas in age group of 31-40,  $26.46 \pm 5.19$  to  $29.71 \pm 5.23$  was observed. The patients with age group of 41-50, 51-60, 61-70 and 71+ shown an improvement of  $24.80 \pm$

4.87 to  $27.8 \pm 5.7$ ,  $23.55 \pm 3.9$  to  $26.91 \pm 3.87$ ,  $24 \pm 5.9$  to  $28.09 \pm 6.2$  and  $26.5 \pm 2.1$  to  $31 \pm 1.4$  respectively as shown in fig.2. The various symptoms as reported by the patients were shown in table 9. 71 patients complained of burning sensation. 53 patients reported difficulty in mouth opening, whereas 67 patients reported difficulty in swallowing. 10 patients reported changes in taste. Dryness of mouth was reported in 26 patients while 14 patients complained of excessive salivation. 44 patients reported difficulty in speaking. Vesicles and ulcers were reported in 41 patients. After the treatment with antioxidants drugs for a period of 2-3 months, symptoms of burning sensation of mouth was relieved in 69.01% of cases. Difficulty in mouth opening was relieved in 77.35% of cases. Symptom of difficulty in swallowing was relieved in 82.09% whereas difficulty in speaking was relieved in 93.18%. Dryness of mouth and excessive salivation are improved in 76.93% and 92.86% respectively. Vesicles and ulcers were cured in 78.05% of cases. This was shown in fig.3. The most common sign observed was presence of fibrous bands, which was reported in 50 patients. Blanching of oral mucosa was reported in 33 patients. 15 patients showed trismus and 33 patients showed restricted tongue movements. Depapillation of tongue was observed in 47 patients shown in table 10. After the treatment with antioxidants drugs for a period of 2-3 months, blanching of oral mucosa was improved in 90.9% patients. The sign presence of fibrous bands was improved in 68% patients. Restriction of tongue movements improved in 87.88% patients whereas trismus improved in 60% patients. Depapillation of tongue is cured in 80% patients while erythematous erosions was improved in 87.1% patients as shown in fig.4.

## DISCUSSION

In this study we found highest incidence of premalignant stages in 3<sup>rd</sup> and 4<sup>th</sup> decade of life i.e, 75 out of 125 cases (60%) were between age of 30 to 50 years. This corresponds with Rohit *et al.*,<sup>[9]</sup> who recorded 44 out of 64 cases i.e, 68.75% to be in 3<sup>rd</sup> and 4<sup>th</sup> decades. Kamal *et al.*,<sup>[10]</sup> have also reported highest incidence of 43.3% in the 3<sup>rd</sup> decade of life.

Although premalignant stages affects both sexes, male predominance for this condition has been noted in many studies. Males 94 (75.2%) were dominating in this study also. The reason for male predominance is because of easy availability of gutkha and other related products among youngsters. Moreover males are the working gender and money earners among Indian subcontinent. Areca nut/betel quid, gutkha is chewed for variety of reasons such as stress reliever, mouth freshener, improving concentration and digestion after food. Majority of females in our study were addicted to areca nut or betel quid.

Almost all the patients have at least habit of taking either forms of tobacco. In our study we found that most common etiological factor is gutkha chewing seen in 63 out of 125 patients i.e, 50.4%. These findings are in agreement with the reports given by Vanaja *et al.*,<sup>[13]</sup> and Supadminidevi *et al.*,<sup>[14]</sup> Syeda *et al.*,<sup>[15]</sup> they concluded that the occurrence of premalignant condition is faster and more severe in gutkha chewers as compared to other forms of areca nut product chewers.

In this work the patients were treated with lycopene and beta carotene therapy. Improvement or decreasing severity of disease condition was reported. Burning sensation was improved in 49 patients i.e, 69.01%. Our findings were in agreement of publications of Borle *et al.*,<sup>[17]</sup> who observed 58.18% relief from this symptom in their cases. Our study also bear significant resemblance to Rohit *et al.*,<sup>[9]</sup> whose study findings showed 70% improvement of symptom burning sensation post antioxidant therapy.

We found lycopene with beta carotene is more efficacious in improving mouth opening with an improvement of  $3.013 \pm 0.38$ mm similar findings were observed in Niranzena *et al.*,<sup>[7]</sup> of about  $4.92 \pm 2.5$ mm.

**Table.3 Distribution of sample based on age incidence**

S. No	Age group (years)	Total Cases	
		Number	Percentage
1.	21-30	19	15.2
2.	31-40	41	32.8
3.	41-50	34	27.2
4.	51-60	18	14.4

5.	61-70	11	8.8
6.	71+	2	1.6

Table.4 Predisposing factors in patients

Etiological/ Predisposing factors	Number of cases	Percentage
Chewing only	41	32.8
Chewing + Smoking	45	36
Chewing + Smoking + Alcohol	26	20.8
Sharp tooth	5	4
Dentures	4	3.2
Spicy food	4	3.2

Table.5 Distribution of sample based on educational status

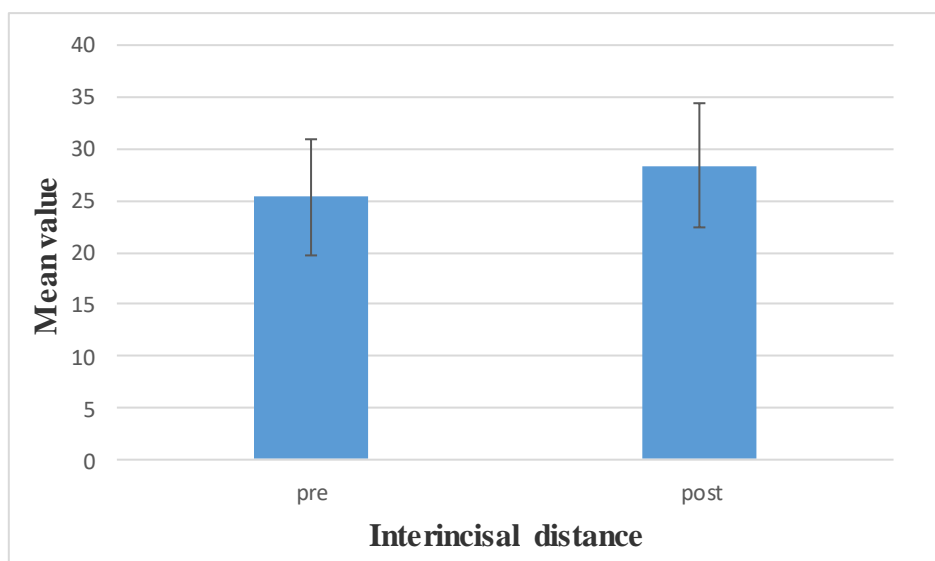
Educated		Uneducated	
No. of cases	Percentage	No. of cases	Percentage
30	24	95	76

Table.6 Distribution of sample based on locality

Rural		Urban	
No. of cases	Percentage	No. of cases	Percentage
100	80	25	20

Table.7 Effect of lycopene with beta carotene on mouth opening premalignant lesions of oral cancer

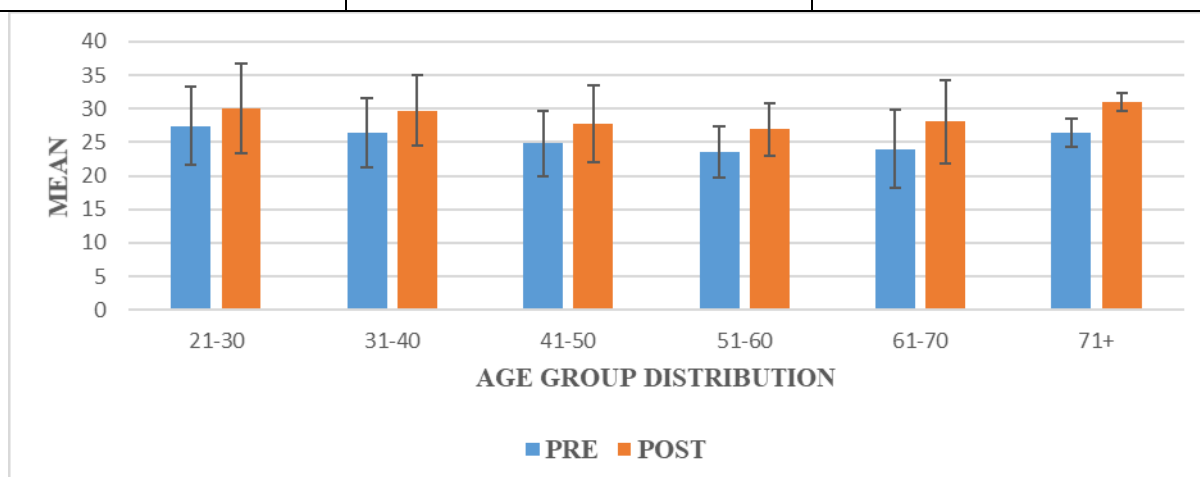
	Prior to lycopene with beta carotene therapy (Mean±Standard deviation)	Post lycopene with beta carotene therapy (Mean±Standard deviation)
Interincisal distance	25.3944 ± 5.58	28.408 ± 5.96



**Fig.1 Improvement in mouth opening in patients with premalignant lesions of oral cancer**

**Table.8 Effect of lycopene with beta carotene on mouth opening according to age distribution in patients with premalignant lesions of oral cancer**

Age groups	Prior to lycopene with beta carotene therapy (Mean ± Standard deviation)	Post lycopene with beta carotene therapy (Mean ± Standard deviation)
21-30	27.40 ± 5.86	30.07 ± 6.63
31-40	26.46 ± 5.19	27.71 ± 5.23
41-50	24.80 ± 4.87	27.80 ± 5.71
51-60	23.55 ± 3.9	26.91 ± 3.87
61-70	24 ± 5.9	28.09 ± 6.2
71+	26.5 ± 2.1	31 ± 1.4



**Fig.2 Effect of lycopene with beta carotene on mouth opening according to age groups in patients with premalignant lesions of oral cancer**

S. No	Symptoms	Number of cases	Percentage	Lycopene with beta carotene therapy			
				Improvement		No improvement	
				Number	Percentage	Number	Percentage
1	Burning sensation	71	56.8	49	69.01	22	30.98
2	Pain in mouth	73	58.4	50	68.49	23	31.50
3	Difficulty in mouth opening	53	42.4	41	77.35	12	22.64
4	Taste change	10	8	8	80	2	20
5	Dryness of mouth	26	20.8	20	76.93	6	23.07
6	Loss of sensory function of tongue	14	11.2	13	92.86	1	7.14
7	Excessive salivation	14	11.2	13	92.86	1	7.14
8	Lack of salivation	19	15.2	18	94.74	1	5.26
9	Difficulty in speaking	44	35.2	41	93.18	3	6.82
10	Difficulty in swallowing	67	53.6	55	82.09	12	17.91
11	Hearing difficulty	14	11.2	14	100	0	0
12	Nasal twang	3	2.4	1	33.33	2	66.67
13	Vesicles and ulcers	41	32.8	32	78.05	9	21.95

Table.9 Effect of lycopene with beta carotene on symptoms in patients with premalignant lesions of oral cancer.

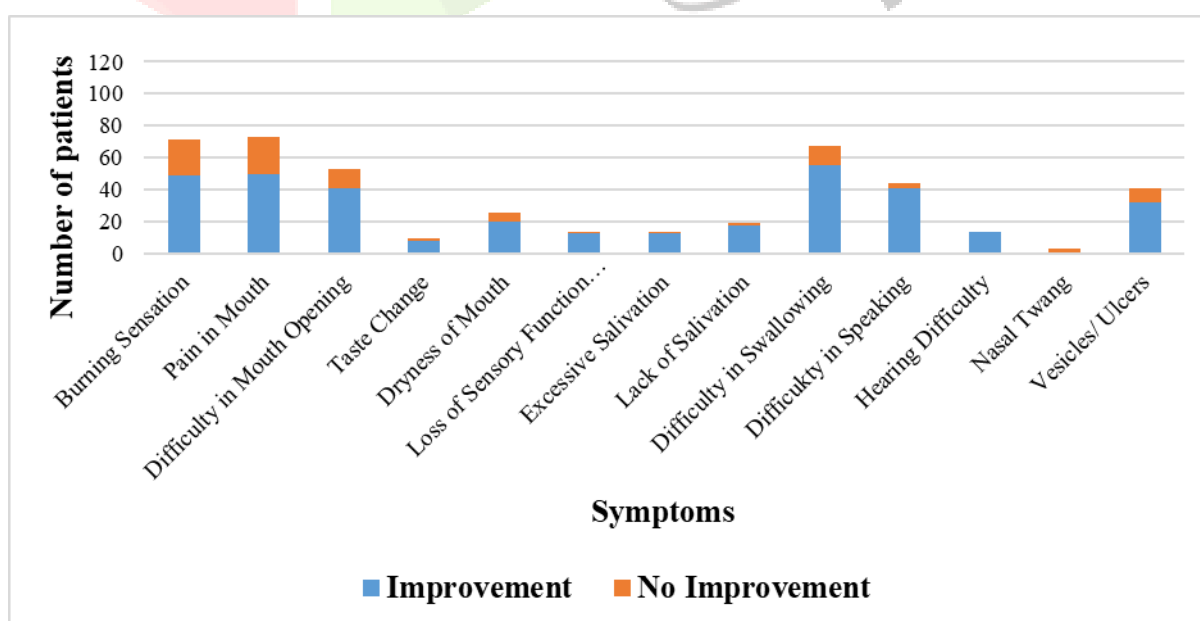
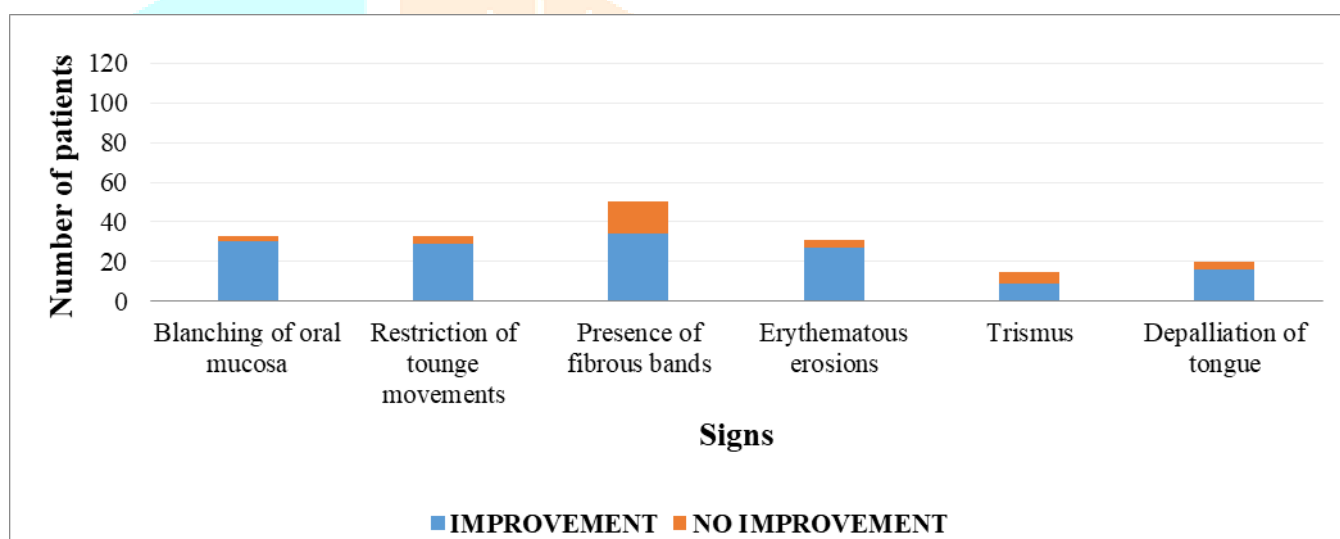


Fig.3 Improvement in symptoms in patients with premalignant lesions of oral cancer

**Table.10 Effect of lycopene with beta carotene on clinical signs in patients with premalignant lesions of oral cancer**

S. No	Clinical Signs	Number of cases	Percentage	Lycopene with beta carotene therapy			
				Improvement		No improvement	
				Number	Percentage	Number	Percentage
1	Blanching of oral mucosa	33	26.4	30	90.9	3	9.09
2	Restriction of tongue movements	33	26.4	29	87.88	4	12.12
3	Presence of fibrous bands	50	40	34	68	16	32
4	Erythematous erosions	31	24.8	27	87.1	4	12.9
5	Trismus	15	12	9	60	6	40
6	Depapillation of tongue	20	16	16	80	4	20

**Fig.4 Improvement in clinical signs in patients with different stages of oral cancer****CONCLUSION**

A set of clinical signs and symptoms were examined prior and post lycopene with beta carotene therapy. Substantial improvement and decrease in disease severity was observed in patients. Thus our work is showing that antioxidants are overall favorable for early cases of oral premalignant lesions and conditions to cease and delay the disease progress. It offers non invasive option that yields significant improvement. So we conclude that antioxidant therapy should be coupled with cessation of predisposing factor to improve patient's disease condition.

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**Conflict of interests**

All authors report no conflict of interest.

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