Original Article

Indian Journal of Dental Education
Volume 9 Number 3, July - September 2016
DOI: https://dx.doi.org/10.21088/ijde.0974.6099.9316.2

Comparative Evaluation of Curcumin Extracts and Lycopene in Leukoplakia

Shivakumar G.C.*, Sahana.S., Nishat Fatima***, Akhilanand Chaurasia******

Abstract

Objective: Oral precancerous lesions are one of the most prevalent lesions worldwide today. Leukoplakia is the commonest premalignant lesion, which if neglected can be fatal. Several therapeutic agents have been tried to intervene. Of which, Lycopene has been tried, tested and accepted as a conventional form of treating leukoplakia. Curcumin, [1,7-bis-(4-hydroxy-3-methoxyphenyl)-1,6- heptadiene-3,5-dione] is regarded as the most organically active ingredient of the spice turmeric, consisting 2–8% of most turmeric preparations. It has anti-oxidant, anti-inflammatory and pro-apoptotic activities. The purpose of the study was to compare the anti-precancerous activities of lycopene with curcumin. *Methodology*: A randomized clinical trial was designed with 20 patients, equally distributed into Group A and Group B. Group A was administered lycopene while Group B patients were treated with Curcumin. The study subjects were followed up for three months, regularly at 15 days intervals, during which they were counselled to quit the habit. *Results*: A significant improvement was noted in both the groups in terms of decrease in size of lesions and cure of lesions. *Conclusion*: Curcumin can be used to treat oral leukoplakia as effectively as lycopene.

Keywords: Oral Leukoplakia; Lycopene; Curcumin; Anti-Cancer; Oral Precancerous Lesion.

Introduction

There has been considerable public and scientific interest in the use of phytochemicals derived from dietary components to combat or prevent human diseases, especially the two commonest killers in the developed world: cardiovascular disease and cancer. The dried ground rhizome of the perennial herb Curcuma longa Linn has been used in Asian medicine since the second millennium BC. Its utility is referred to in the ancient Hindu scripture, the Ayurveda. Oral Cancer is the most common type of cancers of the head and neck region with an yearly incidence of greater than 3,00,000 cases. The severity of the disease is such that it has both higher rates for mortality and morbidity, with a survival rate of less than 50% [1]. The best way to prevent this disease from occurring is by early detection. Leukoplakia, the most common premalignant lesion of the oral cavity presents with 60% chance of developing into oral squamous carcinoma [2]. This lesion is also recognised as a risk marker for oropharyngeal cancer [3]. Leukoplakia refers to a clinical entity which is defined by the World Health Organization (WHO) " a white patch or plaque that cannot be characterised clinically or histologically as any other disease." In practice, the definition becomes complete by including the observation that it cannot be removed by simple scraping and hence distinguishing it from pseudomembranous candidiasis [4]. The incidence of the disease is higher in habitual smokers and alcoholics. Various antioxidants like retinol, retinoid, carotenoids, vitamin C and vitamin E are used currently as effective chemo preventive agents in the treatment of leukoplakia. Lycopene is a carotenoid present in tomatoes and red coloured fruits and vegetables is a potent antioxidant with singlet oxygen quenching ability twice that of beta carotene. It increases the gap junctional communication (GJC) between the cancer cells and also improves the resistance of lymphocytes to oxidative stress [5]. Lycopene can be considered as the gold standard

Author's Affiliation: *Professor, Oral Medicine & Radiology, **Reader, Public Health Dentistry, BBD College of Dental Sciences, BBD University, Lucknow. ***Natural Products Research Lab, Department of Biochemistry, ****Assistant Professor, Department of Oral Medicine & Radiology, Faculty of Dental Sciences, King George's Medical Unniversity Lucknow. King George's Medical University, Lucknow.

Reprints Requests: Akhilanand Chaurasia, Assistant Professor, Department of Oral Medicine & Radiology, Faculty of Dental Sciences, King George's Medical Unniversity, Lucknow, Uttar Pradesh 226003.

E-mail-chaurasiaakhilanand49@gmail.com

therapeutic agent to leukoplakia considering its positive results in several studies [6,7,8]. Curcumin (diferuloyl methane) is a yellow pigment present in turmeric powder which exhibits anti inflammatory, antioxidant, anti carcinogenic and pro-apoptotic activities. It has been linked with the suppression of mutagenesis and is used as a chemopreventive agent in variety of cancers including oral cavity. The spice is common to the Indian cuisine and will prove to be a cost effective measure in leukoplakia treatment [9]. The present study intended to identify the comparative effect of both curcumin and lycopene on leukoplakia.

Aims and Objectives

1. To compare the efficacy of curcumin extracts and lycopene in homogenous leukoplakia patients.
2. To clinically determine the systemic effect of curcumin on homogenous leukoplakia patients.
3. To clinically determine the systemic effect of lycopene on homogenous leukoplakia patients.

Methodology

A Randomized control trial was conducted on 20 patients who were diagnosed with leukoplakia, both clinically and histopathologically. The informed consent of the patients was obtained before the trial after briefing them about the risks and benefits of the study. The patients were taken into the study based on the following eligibility criteria. Inclusion criteria was the presence of clinically and histopathologically diagnosed leukoplakia, those who had not taken any form of treatment for leukoplakia in the last 6 months, patients with willingness to quit the adverse habits(smoking tobacco, chewing tobacco and alcohol) and those who were ready for a 6 months follow up. Patients with any systemic diseases, who are already diagnosed with carcinoma and pregnant and lactating mothers were excluded. A proforma was filled which elicited a thorough personal history, habits history and dental history.

Patients were randomly allocated into either of the two groups. A double blind study was undertaken to minimize any bias occurring in the association of cause and effect. The patients and the analyst were not informed as to which group they belonged.

Group A (Curcumin group): 10 patients were given with 1g of curcumin capsules orally in 2 divided doses daily for a period of three months.

Group B (Lycopene group): 10 patients were treated with 6 mg of lycopene for 3 months.

Follow up: Both the groups were evaluated fortnightly for a period of 3 months. In every visit patients were reinforced to refrain from the habits. The patients were instructed to report immediately if an untoward reaction was noted. At the end of 3 months, the clinical response was noted and was coded as;

1. Complete remission of lesion
2. Partial improvement or decrease in the size of the lesion more than 50%.
3. A stable or no response when size reduction is less than 50%.
4. Progression or appearance of a new lesion.

The size of the lesion was also noted at every visit. Statistical analysis was done to compare the data using the students paired t test.

Results

The study participants consisted of 13 males and 7 females. In Group A, 6 were males and 4 were females. In Group B, 7 were males and 3 were females. Overall a definite male predominance was noted. The mean age of the participants in Group A was 35.4 years with the oldest participant being 57 years and youngest participant of 21years (Table 1).

Table 1: Distribution of study participants according to gender

	Group A	Group B	Total
Males	6(60%)	7(70%)	13(65%)
Females	4(40%)	3(30%)	7(35%)
Total	10	10	20

Table 2: Location of the lesions in the oral cavity, group wise

The mean age of the participants in Group B was 35.1 years with the oldest participant being 53 years and youngest participant of 17years. Both the groups were comparable in terms of age and gender. None of the patients reported with any toxic effects or allergy. The most common site involved was the buccal

mucosa in 12 (60%) patients, followed by4 (20%) in tongue, 2(10%) in gingiva and 2(10%) in the palate (Table 2). 14 of the cases presented with homogenous type of leukoplakia and the rest with verrucous type of leukoplakia.

The mean size of the lesion before the initiation of the therapy was comparable. The mean size of the lesion in Group A was 17.544, while the Group B mean size of the lesion was 17.503before treatment. The Group A mean size of the lesion was 3.12, while

Table 2: Location of the lesions in the oral cavity, group wise

Site	Group A	Group B	Total (%)
Upper lip	-	-	0 (0)
Lower lip	-	-	0 (0)
Left Buccal mucosa	5	4	9 (45%)
Right buccal mucosa	1	2	3(15%)
Gingiva	1	1	2(10%)
Palate	1	1	2(10%)
Tongue	2	2	4(20%)
Floor of the mouth	-	-	0(0)

Table 3: Size of lesions (in cm2) before and after treatment with curcumin therapy

Pre Treatment	Post treatment
18.23	3.45
16.25	4.5
20.1	3.56
13.78	2.78
17.89	1.9
15.45	2.76
13.86	3.45
21	4.65
22.23	2.55
16.75	1.6

t test value– 15.614 ($p < 0.0001$)

Table 4: Size of lesions (in cm2) before and after treatment with lycopene therapy

Pre Treatment	Post Treatment
19.3	3.45
21.47	2.3
23.56	3.9
22.56	4.14
14.5	1.2
13.48	2.2
15.2	4.2
12.6	2.34
17.36	2.7
15	1.2

t test value – 13.48($p<0.0001$)

Table 5: Clinical improvement in lesions in both groups

Improvement	Group A – patient numbers	Group B – patient numbers
Complete improvement	4	5
Partial improvement	3	3
Stable response	3	2
Progression	0	0
Mean	80%	82%
S.D	27.1548	28.6981

the Group B mean size of the lesion was 2.763 after treatment (Table 3 and 4). The t test value at p level lesser than 0.0001 and degrees of freedom at 9 for Group A is 15.614, which shows there is a significant improvement with curcumin therapy. The t test value at p level lesser than 0.0001 and degrees of freedom at 9 for Group B is 13.48, which depicts a significant improvement of the lesion with lycopene therapy. It can be noted that the size of the lesion reduced drastically both in the study and control group, suggesting that curcumin had equivalent tumor suppressing property as that of lycopene (Table 5).

Discussion

The present study was conducted on 20 patients. There was no loss to follow up. All the subjects exhibited a significant reduction in size. The Student's t test which was used to compare the pre-treatment and post treatment results in both groups. Clinically significant improvements in terms of decrease in size and clinical response were seen in both groups. The positive aspect of curcumin is it does not exhibit any activity in cells of non-affected areas thereby making it a toxic free intervention [10]. Literature evidence supports the role of anti cancer effect of Lycopene. Bhuvenaswari et al [11] assessed the chemopreventive efficacy of lycopene on 7,12-dimethyl benzanthrecen (DMBA)- induced hamster buccal pouch carcinogenesis and found lycopene to be effective in preventing neoplasia. Mohit pal singh etal [12] conducted a study to evaluate two different doses of lycopene on 58 patients and found that administration of 8mg lycopene /day gave the best results. Curcumin derived from turmeric (Curcumin longa has been used for thousands of years in the orient as a healing agent for variety of illnesses. Research over the last few decades has shown that curcumin is a potent antiinflammatory agent with strong therapeutic potential against a variety of cancers. Curcumin has been shown to suppress transformation, proliferation, and metastasis of tumors. These effects are mediated through its regulation of various transcription factors, growth factors, inflammatory cytokines, protein kinases, and other enzymes. Curcumin has been shown to have protective and therapeutic effects against cancers of the blood, skin, oral cavity, lung, pancreas, and intestinal tract, and to suppress angiogenesis and metastasis in rodents. Curcumin's ability to affect gene transcription and to induce apoptosis in preclinical models is likely to be of particular relevance to cancer chemoprevention and chemotherapy in patients[13,14]. It was proved in a study that curcumin increases significantly the local and systemic antioxidant status and the levels of Vitamin C and E in patients affected with oral precancerous lesions [15].The male predominance in the study is in concordance to several other studies [14,16,17]. Curcumin known for its extensive therapeutic properties is used by physicians of various specialities. What needs to be borne in mind is that curcumin is rapidly metabolised and reaches therapeutic levels without causing any side effects. The possible role of Curcumin on periodontal health is studies by Guimareaes etal [18]. This suggests that this natural compound has multiple benefits when used. Though the study results suggested that both lycopene and curcumin were effective chemopreventive agents. It is recommended that the study be conducted on a larger sample size and longer follow up to assess their effect more accurately. The authors are of opinion that using genetic markers like EGFR, P-53 helps to specifically assess the efficacy of these therapeutic agents on molecular level.

Conclusion

Curcumin can be used to treat oral premalignant lesions like leukoplakia effectively and safely along with the likes of carotenoids and lycopene. It will be the most cost effective method as India produces nearly the whole world's turmeric crop.

References

1. Greenlee RT, Murray T, Bolden S, Wingo PA. Cancer statistics 2000. CA Cancer J Clin. 2000; 50: 7-33.
2. Mithani SK, Mydlarz WK, Grumbine FL, Smith IM, Califano JA. Molecular genetics of premalignant oral lesions. Oral Diseases. 2007; 13: 126-33.
3. Lippman SM, Hong WK. Molecular markers of the risk of oral cancer. N Engl J Med. 2001; 344: 1323–6.
4. Pindborg JJ, Reichart P, Smith CJ, Van der waal I. World Health Organization: histological typing of cancer and precancer of the oral mucosa. Berlin: Springer–Verlag; 1997.
5. Patel JS, Umarji HR, Dhokar AA, Sapkal RB, Patel SG, Panda AK. Randomized controlled trial to evaluate the efficacy of oral lycopene in combination with vitamin E and selenium in the treatment of oral leukoplakia. J Indian Acad Oral Med Radiol. 2014; 26: 369-373.
6. Agarwal S, Rao AV. Tomato Lycopene and its role in human health and chronic diseases. CMAJ. 2000; 163: 739-744.
7. Giovannucci E. Tomatoes, tomato based products, lycopene and cancer: Review of the epidemiologic literature. J Natl Cancer Inst. 1999; 91: 317-331.
8. Singh M, Krishnappa R, Bagewadi A, Keluskar V. Efficacy of oral lycopene in the treatment of oral leukoplakia. Oral Oncol. 2004; 40: 591-560.
9. Maciej Michalak, Micha Paulo, Kamil Pudo. Therapeutic significance of curcumin and its role in cancer treatment. Journal of Pre-clinical and Clinical Research. 2012; 6(2): 73-76.
10. Syng-Ai C, Kumari AL, Khar A. Effect of curcumin on normal and tumor cells: role of glutathione and bol-2. Mol Cancer Ther. 2004; 3: 1101-1108.

11. Bhuvenaswari V, Velmurugan B, Balasenthil S, Ramachandran CR, Nagini S. Chemopreventive efficacy of lycopene on 7,12 – Dimethyl benz[a]anthracene induced Hamster buccal pouch carcinogenesis. Fitoterpia. 2001; 72(8): 865-874.
12. Mohitpal Singh, R.Krishnappa, Anjana Bagewadi, Vaishali Keluskar. Efficacy of oral lycopene in the treatment of oral leukplakia. Oral Oncol. 2004; 40: 591-596.
13. A.Pramela Rani and V.Saikishore. The potential role of curcumin in cancer prevention and treatment. Research and reviews: Journal of Pharmacy and Pharmaceutical Sciences.
14. Cheng AL, Hsu CH, Lin JK. Phase I clinical trial of curcumin, a chemopreventive agent, in patients with high-risk or pre-malignant lesions. Anticancer Res. 2001; 21(4): 2895-2900.
15. Balwant Rai, Jasdeep Kaur, Reinhilde Jacobs, Jaipaul Singh. Possible action mechanism for curcumin in precancerous lesions based on serum and salivary markers of oxidative stress. Journal of Orofacial sciences. 2010; 52(2): 251-256.
16. Waldron CA, Shafer WG. Current concepts of oral leukoplakia. Int Dent J. 1960; 10: 352-367.
17. Patel JS, Umarji HR, Dhokar AA, Sapkal RB, Patel SG, Panda AK. Randomised controlled trial to evaluate the efficacy of oral lycopene in combination with vitamin E and selenium in the treatment of oral leukoplakia. J Indian Acad Oral Med Radiol. 2014; 26: 369-373.
18. Guimareaes MR, Coimbra LS, de Aquino SG. Potent anti-inflammatory effects of systemically administered curcumin modulate periodontal disease in vivo. J Periodont Res. 2011; 46: 269-279.