NON-SURGICAL MANAGEMENT OF ORAL LEUKOPLAKIA : A REVIEW

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ABSTRACT

At present, evidence based approach for management of oral leukoplakia is lacking. Leukoplakia, a potentially malignant condition of the oral cavity has increased risk for oral cancer. When treated in early stages, the chances of malignant transformation can be reduced. In spite of several treatment options available, there is no specific and appropriate one for reducing the malignant transformation of the leukoplakia. Tobacco and alcohol abuse is associated with increased risk of development of oral leukoplakia. Surgical intervention for management of oral leukoplakia is a promising approach, but minimizing the risk of malignant transformation is uncertain. On the other hand, medical treatment that includes inconclusive use of chemo-preventive agents such as carotenoids, vitamin C & E, polyphenols, bleomycin, photodynamic therapy are more attractive especially in preventing malignant transformation of oral leukoplakia. Non-surgical treatment overweighs surgical approach in terms of non-invasiveness, good aesthetic outcome, tolerance on the part of the patient without considerable side effects and used when surgical approach is denied or contra-indicated. The aim of this review article is to discuss different non-surgical treatment options for oral leukoplakia.

Key Words: Leukoplakia, Antioxidant, Tobacco

INTRODUCTION:

Oral leukoplakia (OL), as defined by the World Health Organization (WHO), is a predominantly white lesion of the oral mucosa that cannot be characterized as any other definable lesion.[1,2,3] Leukoplakia is most commonly associated with tobacco use, although idiopathic forms are also seen.[2,3] An international working group has amended the earlier WHO definition as follows: "The term leukoplakia should be used to recognize white plaques of questionable risk having excluded (other) known diseases or disorders that carry no risk for cancer".[4]

Leukoplakias that are found most commonly are homogeneous and benign. Homogeneous forms are mostly white, are uniform flat & thin in appearance with shallow cracks of surface keratin, and have

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a smooth, wrinkled, or corrugated surface with a consistent texture throughout.[5] Non-homogeneous forms, are also called as speckled leukoplakia or nodular leukoplakia and are mainly white or mixed white and red lesion (erythroleukoplakia) with an irregular texture that may be flat, nodular, exophytic, or papillary/verrucous and more likely to be potentially malignant.[4,6,7] Histologic characteristics of both types of leukoplakia are variable and may include orthokeratosis or parakeratosis of various degrees, mild inflammation, and variable degrees of epithelial dysplasia.[8]

Leukoplakia is different from other forms of white patches such as thrush or lichen planus because it can, in due course, develop into oral cancer. Within 15 years, about 0.3% to 17.5% of people with leukoplakia will develop into malignancy, while the rates of five-year cumulative malignant transformation range from 1.2 to 14.5%. a common type of skin cancer.[9,10] The probability of developing cancer from leukoplakia depends on the size, shape, and appearance of abnormal cells.[11] The aim of this paper is to present a review of the various non-surgical treatments of oral leukoplakia.

Diagnostic & risk factors and diagnostic investigations:

Key diagnostic & risk factors and diagnostic investigations of oral leukoplakia are presented in table 1 and table 2 respectively. [8]

Management of oral leukoplakia:

Several surgical and non-surgical treatments have been described in the literature, but presently there is no agreement about the best treatment for oral leukoplakia. Outcomes of the conditions seem to differ, and long-term follow-up studies are very few. Surgery can include conventional surgery (range from careful consideration to complete resection), electro-cauterization, laser ablation or cryosurgery.[12-15] The main purpose of oral leukoplakia management is to prevent malignant transformation.[16]

Appropriate clinical examination should be performed on the day of reporting of the lesion; type, size and location of lesion should be carefully recorded. [17] Their risk potential i.e. low risk leukoplakia and high risk leukoplakia should be evaluated. [17,18]

Low risk leukoplakia: Leukoplakia lesions with no or mild dysplasia associated with following features is considered as low risk leukoplakia.

a. Site not in high risk area

b. Size less than 200 mm

c. Homogenous clinical form

High risk leukoplakia: A leukoplakia is termed as a high risk if it shows dysplasia associated with following features:

a. Site in high risk area

b. Size greater than 200mm

c. Non homogenous clinical form [17,18]

Clinical examination is again repeated after 2-3 weeks to evaluate the regression in size of lesion in low risk as well as high risk leukoplakia. After 2-3 weeks of habit termination, if there is reduction in the size of the lesion, then follow up is done primarily every three months followed by every 6-12 months.[17] Biopsy is required for low risk lesion that is not regressing in size even after habit cessation or in cases of high risk lesion, in order to assess the degree of epithelial dysplasia.[19] Conservative treatment is advised in case of lesions showing no signs of dysplasia. Whereas, both conservative and surgical treatment are advised in cases of mild, moderate or severe dysplasia.[17] Oral leukoplakia showing low to moderate malignant risk may be either completely or partially removed, considering the other factors such as location, size and, in the case of smokers, the patient's engagement in smoking cessation.[18,19] In the presence of moderate or severe epithelial dysplasia, surgical treatment is recommended.[19] Non-surgical treatment can be considered as a choice of treatment in Homogenous OL cases without dysplasia or as an early treatment in other cases of OL.[20] Non-surgical treatments results in minimal adverse effects, especially in patients with extensive oral leukoplakia that encompasses a large area of the oral mucosa, or in medically compromised patients with high surgical risks, or when patients refuse to undergo surgery.[18,19,21] Additionally, possible advantages of the nonsurgical treatment of OL include relatively low cost and ease of application of medicaments by patient themselves.[18]

Treatment considerations:

Any treatment of oral leukoplakia should commence with removal of risk factors such as tobacco use, alcohol abuse, betel chewing, superimposed candida infection over the lesion etc. The stopping of tobacco use is the first step in case of tobacco related leukoplakia.[16] Up to 60% of leukoplakia regress or totally disappear after stopping the tobacco habit. Leukoplakia induced by smokeless tobacco may resolve if the habit is discontinued.[18] Counselling by physicians and other professionals significantly increases chance of tobacco quitting. Even a brief (3-minute) counselling session to appeal smoker to abandon tobacco results in quit rates of 5-

10%.[17] Some candidal leukoplakia respond, at least somewhat to antifungal drugs (along with quitting the tobacco/smoking habit) and dysplasia may regress. In view of the evidence linking these harmful habits to the development of potentially malignant and malignant oral epithelial lesions, it would seem rational to actively discontinue the habit and, and to focus on a good diet plan and maintaining proper oral hygiene.[18] Conventional medicinal treatment includes use of chemopreventive agents such as vitamins (vitamins A, C, E), fenretinide (Vitamin A analogue), carotenoids (beta-carotene, lycopene), bleomycin, protease inhibitor, anti-inflammatory drugs, green tea, curcumin etc.[17,21] The use of photodynamic therapy has been also stated.[21] Careful and routine follow-up examinations of leukoplakia are required along with with elimination of any risk-associated behavior or habits.[18] In case of no improvement, more invasive treatment should be opted.[20]

Non-surgical treatment of oral leukoplakia:

A. Carotenoids: Carotenoids are a group of highly hydrophobic molecules that are little soluble or insolubile in water.[18,21]

1. Beta-carotene: Beta-carotene are recommended in the prevention and treatment of OL and possibly oral cancer. Anti-oxidant action of beta-carotene is significant in order to protect against cancer. This purpose is accomplished through a ligation between betacarotene and oxygen, which is an unstable reactive molecule, thus lessening the detrimental effects of free radicals. According to Liede et al., a diet rich in beta-carotene can prevent alterations in the oral mucosa, especially among the smokers, who have low serum levels of vitamin C and beta-carotene when compared to the non-smokers. It has also been demonstrated that beta-carotene has a better therapeutic clinic response in the prevention of OL lesions, and among the smoker patients than the non-smoker ones.[19,22]

2. Lycopene: Lycopene is a type of carotenoid without provitamin A action. Lycopene is considered to be one of most efficient biological agent having antioxidant property.[23] Lycopene consumption is associated with reduction in the risk of the development of degenerative diseases caused by free radicals, such as cancer and cardiovascular diseases.[24] Lycopene is supposed to modify intercellular exchange junctions, and hence, it becomes crucial in the management of potentially malignant disorders.[23]

B. Vitamins:

1. Retinoic acid (Vitamin A): Supplementation with retinoids for OL treatment started in 1960s; however, this treatment was not broadly accepted because of risk of hypervitaminosis, teratogenic effects, side effects and toxicity [19]. Retinoids interact with surface receptors and penetrate the cell. They are subsequently metabolized and transported to the nucleus through several proteins. Several processes are influenced by retinoids, such as production of keratin, the expression of growth factors and kinases, oncogenesis, apoptosis, production of collagen matrix, immune and inflammatory responses, cell differentiation, embryonic morphogenesis and carcinogenesis [19]. Studies aiming on topical vitamin A and their derivates in the treatment of patients with OL have been studied by Gorsky and Epstein. [18] They reported use of 0.05% tretinoin gel applied topically 4 times/day on non-malignant oral white lesions in 26 over a period of 3.5 years. After discontinuation of topical treatment, a complete clinical remission was seen in 27% of patients, a partial response was noted in 54% of patients, and clinical recurrence was experienced in about 50% of patients. Soreness on the site of application was reported by only 19% of the patients. [17] A recent study reported no difference in systemic and topical retinoids. Tretinoin or isotretinoin in gel form (0.05% to 0.1%) used topically for the treatment of proliferative verrucous leukoplakia, was generally similar to the systemic retinoid in terms of results obtained.[16]

2. β-Tocoferol (Vitamin E): β-Tocoferol (AT) is the most common and most active form of vitamin E. It is found in plant oil, margarine, and green leaves. β-Tocoferol is an effective antioxidant at elevated levels of oxygen, protecting cellular membranes from lipidic peroxidation. Supplementation with AT results in significant increase in the concentration of this antioxidant in the plasma.[22] A clinical response of 46% and histological response of 21% after administration of vitamin E twice daily for 24 weeks was reported by Benner et al. in his trial in 1993 that was conducted on 43 patients with oral leukoplakia. The treatment was well tolerated, without any side effect higher than grade 2 and with good compliance.[25] On the other hand, a meta-analysis of randomized controlled trials performed by Miller et al. assessing the dose-response relationship between vitamin E supplementation and total mortality found that high doses of vitamin E supplementation (>400 IU/day) may increase the risk of all-cause mortality and therefore should be avoided.[25]

3. L-Ascorbic Acid (L-AA)/ Vitamin C: L-AA has an antioxidizing property and reacts with superoxide produced as a result

of the cells' normal metabolic processes; this inactivation of superoxide inhibits the formation of nitrosamines during protein digestion and helps avoid damage to DNA and cellular proteins.[18] Citrus fruits such as kiwi, strawberries, papaya, mango etc are rich source of vitamin C. The current US recommended daily allowance for ascorbic acid ranges between 100–120 mg/per day for adults. It has been suggested that a daily intake of at-least 140 mg/day is recommended among smokers there is a risk of reduced levels of L-AA concentration in serum leukocytes.[18] Results from few randomized controlled trial conducted to assess effect of low dose of beta carotene and vitamin C supplements found out that Vitamin C in the study was neither effective for clinical remission, nor for protection against the development of cancer.[18,25]

4. Fenretinide: The compound N- (4-hydroxyphenyl) retinamide, also termed as fenretinide (4-HPR) was synthesized in the United States in 1960 and is used in the management of OL. This compound, that is similar to vitamin A, is employed as a chemo-preventive measure for various diseases, and several clinical trials have been conducted on the use of fenretinde for the treatment of OL.[26-28] A study conducted by Tradati et al., included eight OL cases that were treated with 4-HPR, by topical application twice a day for 30 days.[29] After one month of therapy, complete remission was observed in two patients, the others had a response higher than 75%, with no side effects or distant sites were reported.

C. Anti-neoplastic agent:

1. Bleomycin: Bleomycin with iontophoresis has been evaluated in the treatment of leukoplakia and papillomas of the head and neck region.[30] This method of application was not effective against malignant lesions, but was effective in minimizing leukoplakia lesion in the oral mucosa. Complete resolution of hyperkeratotic leukoplakia with atypia was observed in a single case after the administration of local injections of 5 mg of bleomycin weekly in eight treatments.[31] Six patients with OL were treated with a daily topical application of bleomycin in dimethylsulphoxide (DMSO) with 12 to 15 application. Repeat biopsies from 10 to 84 days after therapy demonstrated reduction in keratinization and dysplasia.[32] The authors assumed total absorption of all topically applied bleomycin, yielding a maximum 15-mg systemic dose which is well below the dose used in the usual systemic therapy.

D. Polyphenols:

1. Curcumin: Curcumin has been used since ages in traditional Indian medicine. Curcumin possesses several pharmacological properties, including anti-inflammatory, antibacterial, antiviral, antifungal, antioxidant, chemo-sensitizing, radio-sensitizing, and wound healing properties. It is known to inhibit tumor initiation, promotion and metastasis in experimental models, and it can also act as an anti-proliferative agent by interrupting the cell cycle, disrupting mitotic spindle structures, and inducing cell death and micronucleation.[33] A study conducted in 2010 reported increase in salivary and serum vitamin C and E levels and decrease in oxidative stress markers among patients of leukoplakia after administration of curcumin to the patients.[34] Some authors observed reduction in the size of the lesions in 10 of the 62 patients receiving topical turmeric/curcumin preparation for oral cancer and leukoplakia; however the report was lacking the control group and standard method of curcumin preparation.[35]

2. Green Tea Polyphenols: Epigallocatechin gallate (EGCG), a major polyphenol found in green tea possesses antioxidant and chemo-preventive properties. Epigallocatechin gallate (EGCG) has shown promising results.[25] A study reported decrease in oral lesion size by almost 40% after 6 months among leukoplakia patients that were randomized to receive mixed tea extract orally as well as a topical tea extract.[25]

E. Other agents:

1. Spirulina: The blue green microalgae Spirulina, used in daily diets by natives of Africa and America, have been found to be a rich natural source of proteins, carotenoids, and other micronutrients. Experimental studies in animal models have shown an inhibitory effect of Spirulina algae on oral carcinogenesis. Mathew et al. in 1995 evaluated the effect of *Spirulina Fusiformis* (1g/day for 12 months) among pan tobacco chewers in Kerala suffering from OL. They reported regression of lesion among 45% of the subjects supplemented with *S. Fusiformis* as compared to 3% subjects in placebo group.[22]

2. Acitretin: Acitretin is a synthetic aromatic retinoid that is considered as a possibility in the treatment of severe keratinisation disorders. Acitretin is a free acid of etretinate and its main metabolite, therapeutic activity and side effects, including teratogenecity, are identical to those of etretinate. These side effects make a topical form of actitretin with no reduced systemic adverse effects desirable. Gaeta et al., in their study reported that that 71% of patient showed clinical remission or

marked improvement. The muco-adhesive tablet of topical acitretin are efficacious in the treatment of OL without systemic side effects.[36]

F. Photodynamic therapy: Photodynamic therapy (PDT) is a non-invasive therapy for the treatment of potential malignant lesions and cancers of the head and neck region.[37,38] The principle of PDT occurs through photochemical reactions associated with photosensitizing drugs which are photosensitizers, oxygen and visible light. After a period, photosensitizer that accumulates in target tissue is activated by exposure to low energy visible light with a specific wavelength for the drug. Mainly, the light source consists of a portable diode laser and the light is transmitted via laser fibers to or into the tumor. This treatment through the application of the laser wavelength promotes activation of cell destruction by a radical oxidation process. Thus, PDT is a photochemical reaction, and photosensitizing agents are inherent, low systemic toxicity, the repair is especially true for regeneration instead of healing, important structures are maintained and preserved with good functional and aesthetic results. [39,40] Several photosensitizers have been developed: 1) photofrin has been approved in many countries for the treatment of esophageal cancer and lung cancer; 2) 5-Aminolevulinic Acid (ALA) has also been approved in several countries for the treatment of skin cancer; 3) Verteporfin for the treatment of macular degeneration 4) Foscan photosensitizer is the only one approved for the treatment of squamous cell carcinoma of the head and neck in Europe in 2001.[40]

A study conducted by Zakrzewska et al. reported better prognosis among leukoplakia patients treated with carbon dioxide laser PDT as compared to other forms of treatments.[41] In a study of Kübler et al., 20 OL treated with PDT using ALA topical 20%, followed by application of light, after 3 months showed that five patients responded completely to treatment (there were no clinical signs of OL), four partially responded (the injury was reduced), three did not respond (no clinical change) and 1 had a partial response being subjected to a further treatment, which resulted in the disappearance of the lesion. No recurrence was observed in nine months after this treatment.[42] Similar results were reported in a study conducted by Sieron et al. in 2003.[43] Chen et al. treated 24 patients with OL using 20% ALA-PDT, once a week; another 24 patients used 20% ALA-PDT twice a week. In the latter group, 8 patients completely responded to the treatment, 16 partially responded, and 9 did not. The response was better among those

treated twice a week as compared to those treated once a week.[44]

G. Cryotherapy: Cryotherapy involves local destruction of lesional tissue by freezing in situ.[43] It has several benefits that consist of bloodless treatment, a relative lack of scarring and pain and a very low incidence of secondary infections.[42-44] It can be carried out with either a closed or an open system. Closed-system cryotherapy has been employed in the treatment of OL lesions with promising clinical outcomes. Sako et al. reported complete regression among OL lesions in 60 patients treated using a special cryosurgical unit, after one to five treatments.[45] Simlarly, Chapin and Burkes reported use of cryotherapy with a gold cryoprobe to treat four patients with dysplastic and non-dysplastic OL lesions and observed complete regression of all the lesions after one or two treatments.[46] Leopard used closed-system cryotherapy with two consecutive freeze thaw cycles of up to 1.5 minutes to treat over 40 OL lesions in a 3-year period; only two extensive and long-term OL lesions failed to respond.[47] Open-system cryotherapy for OL is carried out by the direct application of either carbon dioxide snow or liquid nitrogen to OL lesions by the cotton swab or open spray.[43,44,48]

CONCLUSION:

The evaluation of degree of epithelial dysplasia is necessary for the proper choice of the treatment. Presence of epithelial dysplasia calls for surgical intervention. In case of absence of dysplasia where lesion is either completely or partially removed, choice of treatment should take into account the clinical factors such as location & size of the lesion and patient factors such as smoking or tobacco consumption status & patient compliance. All the individuals suffering from leukoplakia, and those who have undergone the treatment for leukoplakia, should be followed-up regularly, irrespective of their response to topical or systemic treatment, including clinical resolution.

REFERENCES:

1. Kramer IR, Lucas RB, Pindborg JJ, et al. Definition of leukoplakia and related lesions: an aid to studies on oral precancer. Oral Surg Oral Med Oral Pathol. 1978 Oct;46(4):518-39.
2. Axell T, Holmstrup P, Kramer IRH, et al. International seminar on oral leukoplakia and associated lesions related to tobacco habits. Community Dent Oral Epidemiol. 1984 Jun;12(3):145-54.

3. Axell T, Pindborg JJ, Smith CJ, et al. Oral white lesions with special reference to precancerous and tobacco-related lesions: conclusions of an international symposium held in Uppsala, Sweden, May 18-21 1994. International Collaborative Group on Oral White Lesions. J Oral Pathol Med. 1996 Feb;25(2):49-54.
4. Warnakulasuriya S, Johnson NW, van der Waal I. Nomenclature and classification of potentially malignant disorders of the oral mucosa. J Oral Pathol Med. 2007 Nov;36(10):575-80.
5. Axéll T, Pindborg JJ, Smith CJ, van der Waal I. Oral white lesions with special reference to precancerous and tobacco-related lesions: conclusions of an international symposium held in Uppsala, Sweden May18–21 1994. An International Collaborative Group on Oral White Lesions. J Oral Pathol Med 1996;25:49–54.
6. van der Waal I. Potentially malignant disorders of the oral and oropharyngeal mucosa: present concepts of management. Oral Oncol 2010;46:423–5.
7. van der Waal I, Axéll T. Oral leukoplakia: a proposal for uniform reporting. Oral Oncol 2002;38:521–6.
8. Oral leukoplakia. BMJ Best Practice. [Internet]. Available from: https://bestpractice.bmj.com/topics/en-us/621.
9. Liu W, Wang YF, Zhou HW et al. Malignant transformation of oral leukoplakia: a retrospective cohort study of 218 Chinese patients. BMC Cancer. 2010;10:685.
10. Amagasa T, Yamashiro M, Ishikawa H. Oral Leukoplakia Related to Malignant Transformation. Oral Science International. 2006; 3(2):45-55.
11. Liu W, Shi LJ, Wu L, et al. Oral cancer development in patients with leukoplakia—clinicopathological factors affecting outcome. PLoS ONE 2012;7:e34773.
12. Girod SC, Pfahl M. Retinoid actions and implications for prevention and therapy of oral cancer. Int J Oral Maxillofac Surg. 1996; 25: 69-73.
13. Schepman KP, van Der Meij EH, Smeele LE, Van Der Waal I. Malignant transformation of oral leukoplakia: a follow-up study of a hospital-based population of 166 patients with oral leukoplakia from the Netherlands. Oral Oncol. 1998; 34: 270-275.
14. Ishii J, Fujita K, Munemoto S, Komori T. Management of oral leukoplakia by laser surgery: relation between recurrence and malignant transformation and clinicopathological features. J Clin Laser Med Surg 2004;22:27–33.
15. Gorsky M, Epstein JB. The effect of retinoids on premalignant oral lesions: focus on topical therapy. Cancer 2002;95:1258–64.
16. Ioanina P, Serban T, Lelia M. Treatment approach of oral leukoplakia. Review of literature. Med Con. 2013;8;3:39-43.
17. Tanwar R, Dave A, Kalra M, Saluja P. Non-surgical management of oral leukoplakia in Indian scenario. University J Dent Scie. 2015; 1(2):49-54.
18. Singh SK, Gupta A, Sahu R. Non-Surgical. Management of Oral Leukoplakia. Journal of Dentofacial Sciences. 2013; 2(2):39-47.
19. Arruda JAA, Álvares PR, Sobral APV, Mesquita RA. A Review of the Surgical and Nonsurgical Treatment of Oral Leukoplakia. J Dent & Oral Disord. 2016; 2(2):1009.
20. Starzynska A, Pawlowska A, Renkielska D, Michajlowski I, Sobjanek M, Blazewicz I, et al. Estimation of oral leukoplakia treatment records in the research of the Department of

Maxillofacial and Oral Surgery, Medical University of Gdansk. Postepy Dermatol Alergol. 2015;32(2):114–122.
21. Kumar A, Cascarini L, McCaul JA, Kerawala CJ, Coombes D, Godden D, et al. How should we manage oral leukoplakia? Br J Oral Maxillofac Surg. 2013 Jul;51(5):377-83.
22. Manigandan T, Hemlatha VT. Insight of Various Medical Management of Oral Leukoplakia. Biomedical and Pharmacology Journal. 2015;8(Spl.Edn):393-401.
23. Rao AV, Agarwal S. Role of antioxidant lycopene in cancer and heart disease, Journal of the American College of Nutrition. 2000;19(5):563–569.
24. Riccioni G, Mancini B, Di Ilio E, Bucciarelli T, D'Orazio N. Protective effect of lycopene in cardiovascular disease, European Review for Medical and Pharmacological Sciences. 2008;12(3):183–190.
25. Behura SS, Singh DK, Masthan KMK, Babu NA, Sah S. Chemoprevention of oral cancer: a promising venture. IJOCR. 2015 Apr-Jun;3(2):80- 87.
26. Chiesa F, Tradati N, Grigolato R, Boracchi P, Biganzoli E, Crose N, et al. Randomized trial of fenretinide (4-HPR) to prevent recurrences, new localizations and carcinomas in patients operated on for oral leukoplakia: long-term results. Int J Cancer. 2005; 115: 625-629.
27. Torrisi R, Decensi A. Fenretinide and cancer prevention. Curr Oncol Rep. 2000; 2: 263-270.
28. Chiesa F, Tradati N, Marazza M, Rossi N, Boracchi P, Mariani L, et al. Fenretinide (4-HPR) in chemoprevention of oral leukoplakia. J Cell Biochem Suppl. 1993; 17F: 255-261.
29. Tradati N, Chiesa F, Rossi N, Grigolato R, Formelli F, Costa A, et al. Successful topical treatment of oral lichen planus and leukoplakias with fenretinide (4-HPR). Cancer Lett. 1994; 76: 109-111.
30. Hayasaki K, Kitamura T, Kaneko T ef al. Application of BLMiontophoresis for the tumour therapy of the head and neck area. J Jpn Soc Cancer Therapy 1977; 12:522-527.
31. Hisano Y, Satoh T, Suzuki M, Kanai Y. An effective case of local injection therapy of oral leukoplakia with bleomycin. Shigaku 1978; 66.
32. Hammersley N, Ferguson MM, Rennie JS. Topical bleomycin in the treatment of oral leukoplakia: A pilot study. Brit J Oral Maxillofac Surg 1985; 23:251-258.
33. Vijayalaxmi N, Reddy RS, Ramesh T, Saimadhavi N, Reddy RL, Swapna LA. Efficacy of curcumin in treating palatal changes associated with reverse smoking. Arch Oral Res. 2012 Jan-Apr;8(1):47-34.
34. Michalak M, Paulo M, Pudo K. Therapeutic significance of curcumin and its role in cancer treatment. J PreClin Clin Res. 2012, 6(2):73-76.
35. Basnet P, Skalko-Basnet N. Curcumin: An Anti-Inflammatory Molecule from a Curry Spice on the Path to Cancer Treatment. Molecules. 2011 Jun 3;16(6):4567-4598.
36. Gaeta GM, Gombos F, Femiano F, Battista C, Minghetti P, Montanari L, et al. Journal of the European Academy of Dermatology and Venereology. 2000;14:473-478.
37. Sieron A, Namyslowski G, Misiolek M, Adamek M, Kawczyk-Krupka A. Photodynamic therapy of premalignant lesions and local recurrence of laryngeal and hypopharyngeal cancers. Eur Arch Otorhinolaryngol. 2001; 258: 349-352.
38. Kubler AC. Photodynamic therapy. Medical Laser Application. 2005; 20: 37-45.

39. Konopka K, Goslinski T. Photodynamic therapy in dentistry. J Dent Res. 2007; 86: 694-707.
40. Kelty CJ, Brown NJ, Reed MW, Ackroyd R. The use of 5-aminolaevulinic acid as a photosensitiser in photodynamic therapy and photodiagnosis. Photochem Photobiol Sci. 2002; 1: 158-168.
41. Zakrzewska JM, Lopes V, Speight P, Hopper C. Proliferative verrucous leukoplakia: a report of ten cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1996; 82: 396-401.
42. Kübler A, Haase T, Rheinwald M, Barth T, Mühling J. Treatment of oral leukoplakia by topical application of 5-aminolevulinic acid. Int J Oral Maxillofac Surg. 1998; 27: 466-469.
43. SieroÅ A, Adamek M, Kawczyk-Krupka A, Mazur S, Ilewicz L. Photodynamic therapy (PDT) using topically applied delta-aminolevulinic acid (ALA) for the treatment of oral leukoplakia. J Oral Pathol Med. 2003; 32: 330-336.
44. Chen HM, Yu CH, Tu PC, Yeh CY, Tsai T, Chiang CP. Successful treatment of oral verrucous hyperplasia and oral leukoplakia with topical 5-aminolevulinic acid-mediated photodynamic therapy. Lasers Surg Med. 2005; 37: 114-122.
45. Sako K, Marchetta FC, Hayes RL. Cryotherapy of intraoral leukoplakia. Am J Surg. 1972; 124: 482-484.
46. Chapin ME, Burkes EJ Jr. Cryosurgery of oral white lesions. J Oral Surg. 1973; 31: 584-591.
47. Leopard PJ. Cryosurgery, and its application to oral surgery. Br J Oral Surg. 1975; 13: 128-152.
48. Gongloff RK, Samit AM, Greene GW Jr, Inneo GF, Gage AA. Cryosurgical management of benign and dysplastic intraoral lesions. J Oral Surg. 1980; 38: 671-676.