MANAGEMENT OF ORAL LEUKOPLAKIA IN INDIAN SCENARIO - ANALYSIS OF THE LITERATURE

1) DR. RAJARSHI SAHA. B.D.S

JUNIOR RESIDENT DOCTOR - NORTH BENGAL DENTAL COLLEGE AND HOSPITAL, DEPARTMENT OF ORAL MEDICINE AND RADIOLOGY.

EX-JUNIOR RESIDENT DOCTOR- NORTH BENGAL MEDICAL COLLEGE AND HOSPITAL.

2) DR. RAKTIM BATMAN. B.D.S

JUNIOR RESIDENT DOCTOR - NORTH BENGAL DENTAL COLLEGE AND HOSPITAL, DEPARTMENT OF ORAL MEDICINE AND RADIOLOGY.

ABSTRACT

Oral leukoplakia is the most common potentially malignant disorder affecting oral cavity. Various surgicaland non-surgical treatments have been reported, but currently there is no universal consensus on the most appropriate one and on the duration or interval of follow-up of patients with this condition.The aim of this article is to present a review of the management of oral leukoplakia according to the literature until now. Management of oral leukoplakia should begin with elimination of risk factors (if any) such as tobacco abuse, betel chewing, alcohol abuse, superimposed candida infection over the lesion etc.Conservative 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, curcuma etc.

Surgical treatment includes conventional surgery,electrocoagulation, cryosurgery, and laser surgery (excisionor evaporation).

The main purpose of oral leukoplakia managementis to avoid malignant transformation of the lesion or if this happened to detect this in early stages.

Keywords: *Leukoplakia, management, surgical, non-surgical treatment.*

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INTRODUCTION

Leukoplakia is a potentially malignant disorder affecting oral cavity especially in males of middle aged.Establishing the clinical diagnosis of leukoplakia, followed by histopathologic analysis,leads to consideration of the appropriate clinical management which should be designed according to the anticipated clinical or biologic behavior. Balancing the lesional qualities with treatment modality and associated morbidity becomes the major clinical decision. With such considerations in mind, a wide choice of treatments has been used, ranging from those which are locally directed to others which are systemic[1] In the absence of histologically demonstrated dysplastic changes, careful and routine follow-up observations of leukoplakia may be appropriate in conjunction with elimination of any risk-associated behavior or habits. In order to conduct treatment for OL, the degree of epithelial dysplasia may be assessed. In the presence of moderate or severe epithelial dysplasia, surgical treatment is recommended. However, OL presenting low to moderate malignant risk may be either completely removed or not, and the decision should consider other factors such as location, size and, in the case of smokers, the patient's engagement in smoking cessation. This manuscript emphasizes on non-surgical management of oral leukoplakia in Indian scenario.

Purpose

The aim of this article is to present a review of the management of oral leukoplakia according to the contemporary standards.

Epidemiology

The prevalence of oral leukoplakia, worldwide, is approximately 1%-2% for all ages together. There are geographical differences with regard to gender distribution. Leukoplakias are usually diagnosed after the fourth decade of life and are six times more common among smokers than among non-smokers [2]. Alcohol may be an independent or synergistic risk factor. There may be a potentially important and causal association between human papilloma virus and oral potentially malignant disorders. Erythroplakia is much less common than leukoplakia. No reliable prevalence figures are available; estimated figures vary from 0.02% to 0.83%.The etiology is unknown, but tobacco and alcohol are probably predisposing factors [3].

Etiology

Etiology of OL is not clearly established yet. It is considered multifactorial origin of the lesion. Smoking, alcohol abuse, lasting mechanical injuries, Candida albicans infection and differences of local trauma or galvanic potentials are reported as the most important causative factors. Oral leukoplakia can accompany systemic disorders like hormonal disturbances, gastro-esophageal reflux, diminished saliva secretion or iron deficiency anemia. It is also stated that EBV, HPV (16 and 18 types), HSV and HIV viruses significantly influence OL development and carcinogenic transformation of this lesion.

Classification/clinical aspects

Considering the macroscopic appearance, oral leukoplakia is broadly classified into homogeneous and non-homogeneous subtypes. The distinction between this two types is purely clinical, based on surface color and morphological (thickness) characteristics, and do have some bearing on the outcome or prognosis. Homogeneous plaques are predominantly white, uniform flat, thin appearance with shallow cracks of surface keratin, and have a smooth, wrinkled, or corrugated surface with a consistent texture throughout. Despite the fact that the risk of malignant transformation is relatively low - about 5%, these lesions seem to warrant careful follow-up as well [4].

Non-homogeneous plaques varieties include:
• speckled: mixed, white and red
(erythroleukoplakia), but retaining predominantly white character;
• nodular: small polypoid outgrowths, rounded red or white excrescences;
• verrucous: wrinkled or corrugated surface appearance.[5]
• proliferative verrucous leukoplakia (PVL)- Proliferative verrucous oral leukoplakia is a subtype of verrucous leukoplakia according to some authors[3,6]. It involves multiple mucosal areas with confuent, exophytic and proliferative features. The PVL is characterised by an aggressive evolution, resistance to treatment, and high rate of malignant transformation.
Non-homogeneous lesions carry a higher risk of malignant transformation.

Additional clinical descriptions that may assist the characterization of oral leukoplakia are [6]:
· Etiological description: clearly associated with tobacco or areca nut use; idiopathic[6].
· Site description giving anatomical sub-site in the mouth or oropharynx.
· Size or extent of the lesion(s).

Leukoplakia is a clinical term and the lesion has no specific histology. [6] Pathohystological examination of leukoplakia can show hyperkeratosis, atrophy, acanthosis and may or may not demonstrate different degrees of epithelial dysplasia.Dysplasia reflects histological changes which are followed by the loss of uniformity of the architecture of the epithelial cells[7]. According to these findings, oral leukoplakia can be distinguished as dysplastic and non dysplastic lesions. Based on histological examination the presence of dysplasia has been associated with a risk of malignant transformation to oral cancer. At the last world seminar of Oral Medicine about potentially malignant lesions, London 2010, it has been recommended a binary classification of histological changes[8]. Lesions are graded as low risk (mild and moderate dysplasia) and high risk (severe dysplasia and carcinoma insitu) depending on the architecture and cytological changes. This aims to reduce subjectivity in grading dysplasia, thus increasing the possibility of conformity between histological interpretations of different pathologists.
Epithelial dysplasia has been regarded as one of the most important indicators of future malignant potential. Dysplastic oral leukoplakia has a 5 times higher risk of malignant transformation than non-dysplastic. A study showed that for a period of 5 years follow-up dysplastic lesions had a incidence of malignant transformation of 41% and non dysplastic lesions 9.5%[9].

DIAGNOSIS

Histopathology examination is at present still the gold standard for diagnostic purposes. DNA ploidy measurements may be helpful in identifying lesions that carry a high risk of malignant transformation.
The biopsy should be taken at the most clinically suspicious area, if any, such as redness, an area of surface thickening or a symptomatic area. In patients with multifocal or widespread leukoplakia multiple biopsies (‘field mapping’) should be considered. Particularly in the case of a non- homogeneous leukoplakia an incisional biopsy may not be representative. In small leukoplakias, e.g. < 2 - 3 cm, an excisional biopsy may be considered. The value of oral brush cytology is a subject of controversy, as is the use of toluidineblue.[10]
Malignancies may develop at the site of treated or untreated leukoplakia, but may also occur elsewhere in the oral cavity or upper aerodigestive tract. The commonly recognized factors that statistically carry an increased risk of malignant transformation into a squamous cell carcinoma are listed below. Of these risk factors, the presence of epithelial dysplasia – often correlating with a clinically non- homogeneous, erythroleukoplakic subtype – is in general regarded the most important indicator of malignant potential[11]
Nevertheless, it should be recognized that some dysplastic lesions may remain unchanged or may even show complete regression.
Furthermore, carcinomatous transformation may also take place in non-dysplastic leukoplakia.
In several studies from the Western world, the borders of the tongue and the floor of the mouth have been mentioned as high-risk sites, while in a study from Denmark also size was shown to be of importance, particularly when exceeding 200 mm.
In spite of tremendous progress in the field of molecular biology, there is as yet no single marker or set of markers that reliably enables to predict malignant transformation of leukoplakia in an individual patient with leukoplakia, perhaps with the exception of DNA ploidy measurements. The use of non-invasive genetic tests, using exfoliated or brushed cells of lesional tissue or molecular markers from saliva may prove to be a step forward in the search for relevant prognostic markers[12].
Most erythroplakias will probably undergo malignant transformation. There are not enough documented series that would allow to calculate a reliable annual malignant transformation rate.Reported risk factors of statistical

significance for malignant transformation of leukoplakia, listed in an at random order (not reliable for use in the individual patient)
· Female gender
· Long duration of leukoplakia
· Leukoplakia in non-smokers(idiopathic leukoplakia)
· Location on the tongue and/or floor of the mouth
· Size >200 mm2
· Non-homogeneous type
· Presence o C. albicans
· Presence of epithelial dysplasia
· DNA aneuploidy
· History of previous head-and-neck carcinoma

Even though numerous manuscripts have dealt with management of oral leukoplakia, still there is lack of a proper protocol and no universal consensus on its management.The standard treatments for OL range from careful consideration to complete excision in histological clearmargins.Even despite treatment the disease can recur, undergo
malignant transformation, or new lesions can develop in patients treated previously.
Various non-surgical and surgical treatments havebeen reported, but currently there is no consensus on which is best. The main aim of oral leukoplakia management is to avoid malignant transformation.Proper clinical examination should be done on the day of reporting of the lesion; type, size and location of lesion should be carefully recorded.
A consideration of their risk potential i.e. low risk leukoplakia and high risk leukoplakia should be done.

(A)Low risk leukoplakia-
Leukoplakias having no dysplastic features or having mild dysplasia
associated with following features is considered as low risk leukoplakias.

a. Site not in high risk area
b. Size less than 200mm
c. Homogenous clinical form

Their treatment protocol requires regular follow up along with usage of topical or oral medications like Beta carotene, Lycopene and others. If no benefit is attained then non surgical ablasive therapies like Cryotherapy or CO2 laser are used[13]. If the resolution of the lesion has occurred then only regular follow up is required. While if the lesion does not resolve then the
treatment is repeated, but on repetition of negative response surgical decortications is advised. The histological analysis of the specimen is done if the specimen show areas of squamous cell carcinoma then radical excision are planned with or without radiotherapy or chemotherapy. While if the areas of squamous cell carcinoma are absent then only regular follow up is done every 3 months for the first year and subsequent follow up is done within 6-12 months.

(B)High risk leukoplakia-
A leukoplakia is considered to be a high risk if it shows mild dysplasia associated with following features:
a. Site in high risk area
b. Size greater than 200mm
c. Non homogenous clinical form Or it displays moderate to severe dysplasia. In such cases surgical decortications is advised followed by histopathological analysis of the specimen. If the specimen show areas of squamous cell carcinoma then radical excision are planned with or without radiotherapy or chemotherapy. While if the areas of squamous cell carcinoma are absent then only regular follow up is done every 3 months for the first year and subsequent follow up is done within 6-12 months.

Treatment modalities

(1) ELIMINATION OF RISK FACTORS:

Such as tobacco abuse, superimposed candida infection over the lesion especially in cases of nonhomogenous leukoplakia.

Habit counseling: Counseling alone or counseling with medication that is being used for tobacco cessation should be started on day of reporting of the lesion. Significantly high continuous abstinence rates are seen with the medications as compared to the counsellingalone,that is why pharmacotherapy should be initiated at earliest in cases of tobacco cessation.Pharmacotherapy has to be initiated at least a week before the quit date for better results.

(2) COUNSELLING DELIVERED BY PHYSICIANS AND OTHER PROFESSIONALS:

Significantly increases quit rates over self-initiated strategies.Even a brief (3-minute) period of counseling to urge smoker to quit results in smoking cessation rates of 5-10%.National cancer Institute, USA has formulated brief strategies to help the patients willing to quit and this includes a "5A"(ask, advise, assess, assist and arrange) UniversityJDentScie2015;[14] based intervention in a primary care set up-

{i} "ASK" the patients about tobacco use and identified at each visit. Tobacco use status is queried and documented, and general and vital informations are obtained.

{ii} "ADVICE" to the patient should be clear, strong and personalized according to the patient's current health/illness, motivation level or impact on children in the household.

{iii} "ASSESS" the willingness of the patient to quit. Provide motivational assistance to those unwilling to quit and provide additional information in special situations such as adolescence and pregnancy.

{iv} "ASSIST" the patient with a quit plan. Set a quit date within the next two weeks. Patient is advised to tell friends, family and co-workers about quitting and request understanding and support. Anticipate challenges to quit attempt and educate about nicotine withdrawal symptoms. Remove all tobacco products from environment and avoid places associated with smoking. Provide practical counselling(problem solving and skill training). Total abstinence is essential. If the patient had past quit experiences, identify what helped and what hurt.Anticipate triggers or challenges in upcoming attempts. Alcohol use to be minimized and tell the patient about risk of relapse if he/she continues to drink. Encourage housemates to quit smoking or not smoke in subject's presence. Provide intra treatment social support and help to provide extra treatment social support. Recommend intensive treatment in the form of pharmacotherapy for those willing to quit.Provide supplementary materials, which is culturally, racially educationally and age appropriate for the patient.

{v} "ARRANGE" for follow up contact. Timing of the first contact should be soon after the quit date and the second follow up depends on physician preference preferably within the first month of quit date. Congratulate those who have succeeded to quit smoking. If failed, identify the cause and be supportive. Identify problems and anticipate future challenges. Consider referral to more intensive treatment.

(3)NON-SURGICAL TREATMENT OF ORAL LEUKOPLAKIA:

(A) Carotenoids-

Carotenoids belong to a group of highly hydrophobic molecules with little or no solubility in water.

1. ***Beta-Carotene:***
   Beta-carotene is a vitamin A precursor.[2, 4] This carotenoid is commonly found in dark green, orange or yellowish vegetables, such as spinach, carrots, sweet potato,mango, papaya, and oranges.The use of beta-carotene has been recommended for the prevention of potential malignant lesions, such as OL and cancer, possibly oral cancer. [15]The potential benefits and protective effects against cancer are possibly related to its antioxidant action. This function is accomplished through a ligation between beta-carotene and oxygen, which is an unstable reactive molecule, thus diminishing the damaging effects of free radicals.
   It has been shown that beta-carotene has a better therapeutic clinical response in preventing oral leukoplakia lesions in smokers than in nonsmokers. A known side effect of excessive beta-carotene

consumption is a change in skin color, which becomes very yellowish, called carotenoderma, which disappears in a few weeks after the reduction of consumption.Some studies report that clinical resolution of oral leukoplakia ranges from 4% to 54%, with dosages regimes from 20 to 90mg/day of beta-carotene in time periods from 3 to 12 months.[16]

2. ***Lycopene***:
Lycopene is a fat-soluble red pigment found in some fruit and vegetables.The greatest known source oflycopene is tomatoes.There is a positive relationship between lycopene consumption and a reduction in the risk of the development of degenerative diseases caused by free radicals, such as cancer and cardio-vascular diseases. Lycopene appears to be a very promising antioxidant as a treatment modality in oral leukoplakia and can protect cells against damage.In addition to its antioxidizing property, lycopene also has the capacity to modify intercellular exchange junctions, and this is considered to play a protective role against progression of dysplasia by inhibiting tumor cell proliferation. Lycopene brings about histological changes of a significant degree in patients with oral leukoplakia.In vitro experiments have shown the inhibition of the process of human neoplastic cellular growth by lycopene, since this protein interferes in growth factor receptor signaling and, thus, in cellular cycle progression.[17] Lycopene is hypothesized to suppress carcinogen-induced phosphorylation of regulatory proteins such as p53and Rb anti oncogenes and stop cell division at the Go-G1 cell cycle phase. Some authors tried to estimate the relation between nutrient intake and prevalence of oral leukoplakia. They observed that tomato consumption, the main source of lycopene, has the most protective effect on oral leukoplakia among all dietary factors. Lycopene is
better absorbed in oil resin capsules and in tomato juice than in the form of raw tomatoes.

(B) Vitamins-

1. Retinoids (Vitamin A/ Retinol):

The current definition of retinoid includes all the
natural and synthetic compounds with an activity similar to that of Vitamin A.The most biologically, naturally occurring retinoidis vitamin-A. Vitamin A, also known as retinol, is an alcohol that can be converted into an aldehyde (retinal) or retinoic acid[18]Retinoids interact with surface receptors and penetrate the cell. They are subsequently metabolized and transported to the nucleus through several proteins.Vitamin A is required in the normal pathway of epithelial cell differentiation and production of keratin.An
association between vitamin A deficiency and the enhanced susceptibility to carcinogenesis was reported with an increased risk for developing different epithelial carcinomas.Several other processes are influenced by retinoids, such as the expression of growth factors and kinases, on-cogenesis, apoptosis, production of collagen matrix, immune and inflammatory responses, cell differentiation, embryonic morphogenesis and carcinogenesis.Supplementation with retinoids for oral leukoplakiatreatment begin in the 1960s, however, this treatment was not widely accepted due to its side effects-hypervitaminosis, teratogenic effects, toxicity, and alterations in various organic systems[19].Topic retinoid were initially tested against diseases related to keratinization.

2. Vitamin E:

Vitamin-E is the collective term for a family of chemical substances that are structurally related to alpha-tocopherol. Alpha-tocopherol, the major constituent of Vitamin E has anti-tumor proliferation capacity as well as functionas a free radical scavenger to prevent lipid peroxidation of polyunsaturated fatty acids.
It is found in plant oil, margarine, and green leaves.Benner et al., in his trial in 1993 showed that among 43 patients with oral leukoplakia who took vitamin E twice daily for 24 weeks had clinical response of 46% and histological response of 21%. The treatment was well tolerated,without any toxicity higher than grade 2 and with good compliance.On the other hand, Miller et al., performed a meta analysis of the dose-response relationship between vitamin E supplementation and total mortality by using data from randomized controlled trials. It was found that high dosesof vitamin E supplementation (> 400 IU/d) may increase all cause mortality and should be avoided[20].

3. L-Ascorbic Acid (L-AA)/ Vitamin C:

L-AA has antioxidizing properties 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 andhelps avoid damage to DNA and cellular proteins.Vitamin C can be found in citrus fruits such as kiwi, strawberries, papaya, mango etc.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 required for smokers because they usually present a reduction of the L-AA concentration in serumleukocytes. L-AA toxicity does not occur, since vitamin is water-soluble.The ability of L-AA to maintain oral mucosa integrity is very little documented.There are no studies regarding the efficacy of the useof L-AA alone for OL treatment.Some studies conducted a randomized controlled trialon treatment of oral leukoplakia with low dose of beta caroltene and vitamin C supplements. Vitamin C in the study was neither effective for clinical remission, nor for protection against the development of cancer.

4. Fenretinide:

The compound N- (4-hydroxyphenyl) retinamide,also known as fenretinide (4-HPR) was synthesized in theUnited States in 1960 and is used for treating OL.It has proven to be less toxic than many other vitamin A analogues. 4-HPR is well tolerated, and no local ordistant side effects are observed.A characteristic feature of 4-HPR is its ability to inhibit cell growth through the induction of apoptosis with mechanisms that may be both receptor-dependent and receptor-independent.

This compound is used for the chemo-preventivetreatment of various diseases, and has been studied and tested in clinical trials for the treatment of OL.Eight patients with diffuse (non operable) oral lichen or OL were treated with 4-HPR applied topically twice daily. After one month of therapy, two patients had com-
plete remission and the other six had a greater than 75% response. A phase II trial of 4-HPR (200 mg/day) was carried out for 3 months in OL patients who had not responded("de novo" resistance) or who had responded and then relapsed (acquired resistance) to the previous treatment with natural retinoids. Of 35 patients with retinoid-resistant OL,no patient had complete responses and 12 (34.3%) had partial responses to 4-HPR.[21]Nine patients had clinical responses within 9 months of stopping 4- HPR. Systemic use of 4-HPR with 200 mg/day for 3 months in 35 patients demonstrated partial clinical resolution of OL of leukoplakia.

(C) Anti-neoplastic agents:

Bleomycin:

Bleomycin is a cytotoxic antibiotic which was first used for the treatment of neoplasms. It can be used as an alternative for treatment of oral leukoplakia. It is not very often used in practice for its adverse effects.The most commonly adverse effects are muco-cutaneous reactions, which include stomatitis, alopecia, pruritic erythema, and vesiculation of the skin.Topical bleomycin in treatment of OL was used in dosages of 0.5%/day for 12 to 15 days or 1%/day for 14 days.Topical administration of bleomycin usually reduces lesion size and has little toxic side effects. It is beneficial to use bleomycin adjuvant with the surgical procedure for extensive leukoplakia to decrease the size of lesion before surgery. This helps to avoid grafting after removal of the lesion and prevent the dysplastic change of benign form of lesion.In a study, eight patients with OL were treated by the daily application of a 0.5% solution of bleomycin sulphate in dimethyl sulphoxide (DMSO). After 12 to 15 applications, the white patch peeled off and the resultant raw
suface was epithelialized over the following 14 days. Reeated biopsies showed a significant reduction of dysplasia and keratinisation. The use of topical 1% bleomycin in DMSO was evaluated for the treatment of dysplastic OL.

(D) Polyphenols as chemo-preventive agents:

1. Curcumin:

Curcumin has been used for thousands of years in traditional Indian medicine.

Curcumin reportedly possesses several pharmacological properties, including anti-inflammatory, antimicrobial, antiviral, antifungal, antioxidant, chemo-sensitizing,radio-sensitizing, and wound healing activities. It is known to suppress tumor initiation, promotion and metastasis in experimental models, and it can also act as an anti-proliferative agent by interrupting the cell cycle, disrupting mi-totic spindle structures, and inducing apoptosis and micronucleation.Small doses of curcumin are taken daily as a spice by the population in many Asian countries. In one epidemiologic survey, in terms of its dietary use in Nepal,curcumin consumption was found to be approx. 50 mg/day.In India, where the average intake of curcumin can be as high as 100 mg per day, no

toxicities or adverse effects have been reported or studied at the population level.However the doses administered in clinical trials are expected to be rather higher than those normally consumed in the diet.In spite of reported minor adverse effects, large
doses of up to 12,000 mg per day of curcumin were found to be well tolerated in humans. Therefore, based on the safety and toxicity profile, in several clinical trials the targeted doses for curcumin can be recommended in between 4,000–8,000 mg to obtain the maximum therapeutic effects.
In 2010, some clinicians conducted a study on patients aged 17-50 years, divided into three groups with 25 patients in each. The first group consisted of patients suffering from leukoplakia, while patients suffering from oralsubmucous fibrosis or lichen planus, and those in full health constituted the second and the third groups, respectively. Evaluation of markers of oxidative stress in saliva,serum in salivary glands (malondialdehyde (MDA), 8-hy-droxy-22 -deoxyguanosine (8-OHd), and the level of vitamin C and E was made before administering curcumin to the patients, a week later, and after recovery.[22]
It was noted that the markers in saliva, serum and vitamin level increased, whereas MDA and 8-OHd levels decreased simultaneously in patients suffering from leukoplakia, oral submucous fibrosis and lichen planus. Considering the results of the Rai et al. study, it can be assumed that curcumin demonstrates anticancer properties by increasing the levels of vitamins C and E, suppressing the peroxidation of lipids, and preventing DNA damage.Some authors observed the reduced size of the lesions in 10 of the 62 patients receiving topical turmeric/curcumin in oral cancers and leukoplakia, however the report is lacking the control group and standard method of
curcumin preparation.

2. Green Tea Polyphenols:

Epigallocatechin gallate (EGCG), a major polyphenol found in green tea possesses antioxidant and chemo-preventive properties. Epigallocatechin gallate (EGCG) shows very promising results[23].
According to one study, 29 out of 59 patients with oral leukoplakia were randomized to use a mixed tea extract orally as well as a topical tea extract. After the 6-month trial,the oral lesions had decreased in size in almost 40% of the patients treated, which was associated with a decrease in proliferation in the treatment group on histopathologic examination.

(E) Photodynamic Therapy (PDT):

Photodynamic therapy is a non-invasive method of treatment for head and neck tumors and premalignant lesions .It is based on photo-chemical reaction, initiated by light activation of a photosensitizing drug causing tumor cell death. It requires the simultaneous presence of a pho-
tosensitizing drug (photosensitizer), oxygen, and visible light and it is a non-thermal reaction.
The photosensitizer is administered systemically by intravenous injection or can be topically applied.After a period to allow the photosensitizer to collect in the target tissue, the photosensitiser is activated by exposure to low-power visible light of a drug specific wave-length.Mainly, the light source consists of a portable diode laser and the light is transmitted via laser fibers to or into the tumor Intracellular activation of the photosensitizer drug results either in the production of radicals (type I mechanism) or the formation of intracellular singlet oxygen (typeII mechanism), which causes cell death by vascular shut down mechanisms and intracellular oxygenation.

The main advantages of PDT are:
• Photodynamic therapy is a localized therapy and it has only localized effects as the photosensitizer is selectively absorbed by the target tissues.
• Photosensitizing agents have low systemic toxicity.
• Photodynamic therapy is more economical than radiation therapy and surgical therapy for cancer patients.
• PDT is less invasive, has no long-term side effects and can be repeated many times at the same site, if needed.
• Photodynamic therapy has excellent cosmetic results and the healing process results in little or no scarring.

There are several photosensitizers which have been developed and approved in time: (1) Photofrin;

(2) 5-Aminolaevulinic acid (ALA);

(3) Verteporfin ;

(4) Foscan.

(5)-Aminolevulinic acid (ALA)- mediated photodynamic therapy (PDT) is a new therapy for the treatment of oral leukoplakia.

(4)SURGICAL TREATMENT OF ORAL LEUKOPLAKIA:

(A) Conventional surgery-excision:

Conventional surgery refers to scalpel excision of the lesion.This is followed by a primary closure or secondary healing in case of reduced mucosal defects or with a transposition of local mucosal faps or even skin graft in caseof large defects.Conventional surgery may not feasible for extensive lesions or those in certain anatomical locations. The associated morbidity of surgery also makes it less appealing for extensive lesions.The use of a scalpel may induce wide areas of denudated mucosa with unfavorable b scarring changes and secondary functional alterations as surgical sequelae.It should be noted however that curative surgical resection has the potential to be effective as a prophylactic treatment of lesions on the tongue having a tendency todevelop cancer.

(B) Electrocoagulation:

Electrocoagulation can be used alone or as an adjuvant to scalpel surgery. Electrocoagulation produces thermal damage in the underlying and surrounding tissue, which causes postoperative pain and oedema, and leads to considerable tissue scarring. Postoperative pain and oedema are also severe after cryosurgery.

(C) Cryosurgery:

Cryosurgery is a method of treatment which involves controlled tissue damage caused by low temperatures. This method locally destroys lesional tissue by freezing in situ by liquid nitrogen (N) or dinitrogen dioxide (N_2O_2).Arnott, a British physician, was the first person to use cryosurgery in the year 1851. Initially, its use was limited to the treatment of cancer of the lip and oral cavity. At present, cryosurgery has an extensive application in the treatment of both benign and malignant lesions in the head and neck region.It has several advantages including bloodless treatment, a very low incidence of secondary infections, and a relative lack of scarring and pain. Furthermore, newly rebuilt epithelium is less likely to become corneous again. It can also be used for high-risk group patients like those with a pacemaker, the elderly, and those with coagulopathies. In addition, it would be the first choice in the case of multiple and extensive lesions, areas of difficult surgical access, and areas where esthetics is important.
Cryosurgical effectiveness is high and ranges from 80% to 100%. The effectiveness depends on adequate freezing time and proper freezing depth.The choice of cryosurgical methods in the treatment of oral leukoplakia depends on the depth, area, and shape of the pathological lesion, as well as on access to cryosurgical equipment and operator's experience. Available cryosurgery apparatus are classified into open and closed systems. Closed-system cryotherapy offers a greater degree of temperature control but requires complex, delicate, and expensive equipment. It is performed by direct contact of the cryoprobe onto the lesional surface. Because of the small and flat contact area of the cryoprobe end, closed-system cryotherapy is usually suitable for treatment of uniform, smooth-surfaced oral lesions less than 1 cm in diameter.Open-system cryotherapy involves directly applying the cryogen to the lesion with a cotton swab or a portable spray apparatus. It is more difficult to maintain a constant lower temperature in the lesional tissues during the whole treatment period. However, it does not need expensive equipment. Open-system cryotherapy with the spray apparatus is suitable for treatment of medium and large oral lesions with either a smooth or a rough surface.During cryotherapy the ice crystals are formed in both extracellular and intracellular fluid leading to the cellular dehydration, toxic intracellular electrolyte concentration, inhibition of enzymes, protein damage. These mechanisms associated with the thermal shock induce the vacuolization of cells, their expansion and finally their rupture.Also the vascular changes are followed by ischemic necrosis of the treated tissue and immunological responses which will produce the damage of tissue by cytotoxic immune mechanism.

(D) Laser surgery (excision or evaporation):

The laser surgery has been reported as most appreciated in the last 30 years.Carbon dioxide, neodymium: yttrium-aluminium garnet (Nd:YAG), argon, and potassium-titanyl-phosphate(KTP) lasers are used in the

management - vaporization or excision- of oral leukoplakia. Their precision allows a conservative and site-specific, minimally invasive surgery with sterilization of the surgical area and minimal intraoperative hemorrhage. These lasers also permit a better postoperative period, with lessswelling and pain and healing with minimal scarring.This can be performed even for extensive lesions.Wound healing is excellent because of limited contraction; it produces satisfactory mobility of the oral mucosa and minimum oral dysfunction.

CONCLUSION

Several clinical trials have investigated the treatment of OL with use of supplements. Although the administration of retinoic acid and beta-carotene has some efficacy to resolve OL, the studies were based on small samples and short periods of follow-up. Given the side effects and counter-indications of antioxidizing agents, with the exception of lycopene, the use of agents requires careful control.It can be concluded that, although some treatments may be effective in healing oral leukoplakia they do not seem to be able to prevent relapses andmalignant change. For this reason, oralleukoplakiasneed to be regularly followed up by the clinician, regardless of their response to topical or systemic treatment,
including clinical resolution.

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