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TREATMENT OF ORAL LEUKOPLAKIA WITH ANTIOXIDANTS – A SYSTEMATIC REVIEW

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ABSTRACT

Oral leukoplakia is one of the common potentially malignant disorder which is mostly associated with the use of tobacco either in the form of smoking or smokeless, though idiopathic leukoplakia in patients free from habits has also been reported. Diagnosis of the lesion in most of the cases is mainly based on history of use of tobacco and clinical finding such as raised elevated non-scrap able white patch seen in oral mucosa. Oral leukoplakia once diagnosed, the patient is advised to discontinue the habit after proper counselling of the risk of leukoplakia turning into malignancy and is supported with mainly antioxidants in mild cases. There are few clinical trials using other non surgical management like topical bleomycin, laser therapy, photodynamic therapy etc., but use of antioxidants is more common. This review article aims in evaluating all the clinical trials using antioxidants namely Vitamin A,E,C, and lycopene as they are the most commonly used antioxidants in treatment of oral leukoplakia to assess the outcome measures such as clinical resolution, adverse effects, recurrence and malignant transformation.

KEY WORDS: **Oral leukoplakia, antioxidants, beta-carotene, retinoids, lycopene, alpha tocoferol**

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INTRODUCTION

Leukoplakia should be used to recognise white plagues of questionable risk having excluded other known diseases or disorders that carry no risk for cancer. Leukoplakia is mainly classified clinically as homogenous and non homogenous based on surface colour and morphological (thickness) characteristics. Homogeneous lesions are uniformly flat, thin and exhibit shallow cracks of the surface keratin. The risk of malignant transformation is relatively low. Non-homogeneous lesions carry a much higher risk of malignant transformation and it includes speckled: mixed, white and red, but retaining predominantly white character; nodular: small polypoid outgrowths, rounded red or white excrescences; verrucous: wrinkled or corrugated surface appearance. Proliferative verrucous leukoplakia (PVL) presents with multiple, simultaneous leukoplakias as the disease is visibly multifocal and frequently covers a wide area[1].Oral leukoplakia located on the floor of the mouth, soft palate, and tongue are considered as high-risk lesions, while, in other areas, they may be considered as of low malignancy risk [2]. OL has an annual malignant transformation rate of 0.1% to 17% [3]. Recent report showed that proliferative verrucous leukoplakia has a malignant transformation rate as high as 70.3% (mean follow-up of 11.6 years) [4].

Role of Vitamin A in treatment of oral leukoplakia

Fat soluble Vitamin A is mainly obtained from animal foods like meat, milk, egg yolk etc., and the main function of vitamin A in retinal form is to maintain vision [5] and maintenance of epithelial integrity and is needed for proper haematological, immune and reproductive functions of the body. Deficiency of Vitamin A results in many signs and symptoms like, night blindness, xeropthalmia, bitot's spots in conjunctiva and main oral manifestations are hyperkeratinisation of buccal mucosa or tongue and enamel hypoplasia of teeth , as vitamin A is responsible for mineralisation of teeth along with vitamin D. Supplementation with retinoids for oral leukoplakia treatment began in the 1960s [6]. Vitamin A in the form of retinoids, isotretinoin, beta carotene, 13 cRA, 4 HPR are used in many clinical trials of oral leukoplakia and the use of topical and systemic retinoids is most commonly used antioxidant in treatment of oral potentially malignant disorders like leukoplakia, lichen planus an also in few cases for cancerprevention. 13-cRA though has been shown to be effective in resolving oral leukoplakia but high rate of recurrence after treatment and adverse effects are reported in some studies [7]. Beta carotene is the precursor of vitamin A and is commonly seen in the yellow colour fruits and vegetables like carrot, sweet potato, mango, papaya, oranges and is been reported to be most effective in leukoplakia associated with smokers and it's therapeutic effect is due to its linkage with oxygen which is an unstable reactive molecule, thus diminishing the damaging effects of free radicals [7]. Fenretinide ability to inhibit cell growth through the induction of apoptosis has proven to be less toxic than many other vitamin A analogues [8].

SEARCH STRATEGY

The search strategies used are the electronic data base pubmed [Mesh], Cochrane library, Science Direct and Hand searching. The key words used are leukoplakia and [antioxidants, retinoids, vitamins A, C, E and lycopene.]

Inclusion criteria

All human clinical trials related to leukoplakia with antioxidants

Exclusion criteria

Clinical trials related to leukoplakia with other medical or conservative therapy like [bleomycin, photodynamic therapy etc.,] or surgical treatment.
In vitro clinical trials of leukoplakia.
Animal clinical trials.

RESULTS

Table 1
Clinical trials: Oral leukoplakia with vitamin A
[Retinoids,13 cis-retinoic acid, Isotretinoin, betacarotene, 4 HPR]

Author &Year	No of patients & Duration of study	Vitamin A form & dosage	Adverse effects	Outcome measures
Shah et al 1983 [9].	11 11 mths	Topical Vitamin A 1–5mg		27% clinical resolution 18% recurrence. Malignant transformation not reported
Hong 1986 [10].	44 24 treatment 20 placebo 3 months	13-cis-retinoic acid 1 to 2 mg per kilogram of body weight per day	Two patients: Cheilitis, facial erythema, and dryness and peeling of the skin, conjunctivitis and hypertriglyceridemia	Follow up for 9 months Clinical resolution 67% versus 10 % in placebo Reversal of dysplasia 54% vesus 10% in placebo Relapse occurred in 9 of 16 patients in two to three months
Stich et al. 1988 [11].	30 : Vitamin A 35: Placebo 6 months	Systemic Vitamin A 200.000– Placebo capsules twice a day	No side effects	Complete remission was observed in 57% of patients that received vitamin A. In the placebo group, 7 patients (21%) formed new OL; whereas no new OL developed in the vitamin A group over the 6 months Malignant transformation, not reported
H. F. Stich et al 1988 [12].	Group 1 [beta carotene] Group 2: [carotene+vitaminA] Group 3: Placebo 6months.	beta-carotene 180 mg/week carotene 180 mg/week + vitamin A 100.000 IU/week Placebo		Remission of OL in group 1 (14.8%) and group 2 (27.5%) differed significantly from that seen in group 3 (3%).
Garewal et al 1990 [13].	24 6months	Systemic Beta-carotene 30 mg/day		8% clinical resolution. 8% malignant transformation. recurrence not reported
Toma et al 1992 [14].	23 7 months	Systemic Beta-carotene 90 mg/day		26% clinical resolution 5% Recurrence. Malignant transformation not reported
S. Toma, P. E. et al 1992 [15].	16 6 months	Oral 13-cis-retinoic acid The initial dose, given for 3 months, was 0.2 mg/kg/day, increasing by further 0.2 mg/kg/day in		Fourteen of the patients completed the trial and there was one complete response obtained at 0.4 mg/kg/day. After the retinoic acid treatment was

		successive 3 month cycles. The maximum dosage reached 1.0mg/kg/day		stopped, patients were followed-up for 12 months; 2 patients showed regression of the responses after 6 and 9 months
S.M. Lippman 1993 [16].	70 First phase :67 for three months Second phase: 59 maintenance therapy for nine months [patients, with responses or stable lesions, were randomly assigned]	Phase 1: 67 isotretinoin (1.5 mg/kg/day Phase 2: 59 n = 33 beta-carotene 30mg/day n = 26 isotretinoin (0.5 mg/kg/day		Twenty-two patients (92%) with isotretinoin and 13 patients (45%) with beta-carotene demonstrated a positive response .
Tradati et al. 1994 [17].	8 Duration not reported	Topical 4 HPR Dosage not reported		25%clinical resolution. Malignant transformation, recurrence not reported
I. W. Dimery et al 1997 [18].	7 4 months	13-cRA (10 mg/day) plus an escalating dose (beginning at 800 IU/day, until 2000 IU/day)		71% complete resolution
Sankaranarayanan et al. 1997 [19].	110 55-treatment 55-placebo 12 months	Systemic Beta-carotene 360 mg	headache, muscular pain	54% clinical resolution. 5% recurrence. Malignant transformation not reported
Sankaranarayanan et al. 1997 [19].	105 50 treatment 50 placebo 12 months	Systemic Isotretinoin 300.000 IU	headache, muscular pain, dry mouth	52 % clinical resolution. 67%recurrence. Malignant transformation not reported
Liede et al 1998 [20].	24 60-84 months	Systemic Beta-carotene 20 mg/day		clinical resolution, Malignant transformation, recurrence not reported
Garewal et al 1999 [21].	50 [21 males, 29 females] Phase 1: 6 months Phase 2: 6 months	Phase 1:Systemic Beta-carotene 60 mg/day Phase 2: beta carotene or placebo		Phase 1:52% Clinical resolution Phase 2: Recurrence rate 18% of beta carotene & 17% of placebo. 38% Malignant transformation
Joel B. Epstein & Meir Gorsky 1999 [22].	26 (17 men and 9 women) The mean duration of the application of vitamin A acid gel was 3.5 years in the patients with clinical improvement and 1.5 years in those with no such improvement	Topical 0.05% Vitamin A (tretinoin) acid gel 4 times a day	Lichenoid reaction: 35% Sensitivity :19%	**Response:** No-4 Partial- 14 Complete-3 **Recurrence** :3 **Negative outcome:** Progression of lesion: 2

Piattelli et al 1999 [23].	10 5 treatment 5 placebo 48 months	Topical Isotretinoin 1%	No adverse effects	10% clinical resolution Malignant transformation, recurrence not reported
J. Jack Lee et al 2000 [24].	70 Phase 1: 3 months Phase 2: 9 months	phase1:isotretinoin (1.5 mg/kg phase 2: low dose isotretinoin (0.5 mg/kg/day) or β-carotene (30 mg/day		9/26 (34.6%), 11 /33 (33.3%), and 2/11 (18.2%) developed cancer in 3 groups with low dose isotretinoin, β-carotene, and induction.
Gaeta et al 2000 [25].	21 14-treatment 7-placebo	topical acitretin (with and without lactose) versus placebo	No adverse effects	
Beenken 2000 [26].	30 3 months	oral fenretinide daily (except days 1 to 3 each month)		
F. Femiano et al 2001 [27].	40 5 weeks	20 : treated with calcipotriol (50mg/g), 20 : tretinoin cream (0.05%).	No topical & systemic adverse effects reported in 4 months follow up	16 patients in both group had Complete resolution:
Fausto Chiesa et al 2005 [28].	170 [surgically operated cases with histologically proved non carcinoma cases] [121 males,49 females] 84-treated 86-control 12 months	4-HPR 200 mg/day [100 mg twice a day]	9 out of 43 had mild adverse effects 14 with major effects: hematologic toxicity in 7, cutaneous toxicity in 6 and gastric toxicity in one.	43 completed treatment at full dosage with 90% compliance. 15 recurrence and 10 new lesions in control and 15 recurrence and 4 new lesions in 4-HPR treated cases. Malignant transformation was reported in both groups.
Lippman et al. 2006 [29].	35 9 months	Systemic 4 HPR 200mg/day		0% clinical resolution. 23% malignant transformation. Recurrence not reported
G. A. Scardina et al 2006 [30].	3 months	topical use of isotretinoin at 0.18%, as compared with 0.05%. twice a day	No adverse topical and systemic reactions in 10 years follow up.	Clinical resolution was 85% in the 0.18% group

ROLE OF OTHER ANTIOXIDANTS IN TREATMENT OF ORAL LEUKOPLAKIA

Vitamin C [L- ascorbic acid],Vitamin E [alpha tocoferol] and lycopene are the other oxidants tried in few clinical trials when compared to vitamin A. Lycopene is the natural pigment synthesised by plants and microorganism and is present in tomatoes, water melon, guavas, grapefruits, red chillies etc., Lycopene [31]. appears to be a very promising antioxidant as a treatment modality in oral leukoplakia and can protect cells against cell damage and play a protective role against progression of dysplasia by inhibiting tumour cell proliferation and the first report of efficacy of lycopene against human oral cancer cell was published describing the significant therapeutic effect

Table 2

Clinical trials: Oral leukoplakia with other antioxidants
Vitamin E [Alpha Tocoferol], Vitamin C [L –AA], Lycopene

Author &Year	No of patients & Duration of study	Antioxidants & dosage	Outcome Measures
Benner et al. 1993 [32].	43 24 months	Systemic Alpha Tocoferol 400 IU	20% clinical resolution Recurrence & Malignant transformation Not reported
G. E. Kaugars et al 1994 [33].	79 9months	30 mg of beta-carotene, 1000 mg of L-AA [L-ascorbic acid] and 800 IU of AT [alpha tocoferol] per day.	55.7% showed reduction in the size. Clinical improvement was observed in 90% of the patients who had reduced risk factors, compared with 48.8% of improvement in those who did not. Squamous cell carcinoma developed in seven patients (8.9%)
T. J. Barth et al 1997 [34].	24	Beta-carotene, vitamin E, and L-AA	In 97.5% of patients, dysplasias were diminished by use of antioxidant combinations and is more evident in patients with cessation of habit.
Singh et al. 2004 [36].	58 Group 1: 20 Group 2: 20 Group 3: 18 3 months	Systemic Lycopene Group 1:4mg Group 2: 8 mg Group 3: Placebo	80%, 66.25% and 12.5% clinical resolution in 3 groups respectively. Recurrence & Malignant transformation not reported
Win Pa Pa Aung et al 2013 [37].	5/72 oral potentially malignant diseases 3 months	10 mg along with 500 mg lycopene twice a day	Mild improvement in thin leukoplakia cases when used with topical corticosteroids

DISCUSSION

Retinoids are promising chemopreventive agents. They exert a beneficial effect on epithelial differentiation and can inhibit malignant transformation and suppress tumor promotion; hence more clinical trials are tried with vitamin A and its analogues than other antioxidants like lycopene, alpha-tocoferol and ascorbic acid. Antioxidant combinations [Vitamin A, E, C] had proved to be most effective with maximum clinical resolution [90%] recorded [33] and regression of dysplasia recorded as 97.5% [34]. Topical isotretinoin (0.18%) with 85% clinical resolution and 4 mg systemic lycopene with 80% clinical resolution had proved to produce higher clinical resolution comparatively. In 21 clinical trials of leukoplakia with vitamin A analogues only 7 trials have used topical preparations [tretinoin, isotretinoin, acitretin, 4HPR] while in 5 clinical trials with other antioxidants, systemic preparations only are used. Topical applications of antioxidants proved to produce slightly better results than systemic antioxidants. Adverse effects are very low with both systemic and topical vitamin A analogues. Lichenoid and sensitivity reaction are reported in one study where tretinoin cream [22] is used while with other topical preparations, no adverse effects are reported. Clinical trials with systemic 13- cis- retinoic acid [10], systemic beta carotene and isotretinoin[19] had produced mild side effects in very few patients and systemic 4HPR had produced major side effects like haematological, gastric and cutaneous toxicity [28].Recurrence is common after discontinuation of antioxidants and 7 trials with vitamin A analogues have recorded the recurrence rate ranging from 5%-67% while recurrence have not been reported in most of the studies. Malignant transformation in follow up studies is reported in 4 trials with vitamin A analogues and the maximum rate recorded is (34.6%) [24] while only in one trial with antioxidant combination, minimum rate of malignant transformation is recorded as [8.9%] [33].

CONCLUSION

Reactive oxygen species like malondialdehyde (MDA), nitroxide (NO), lipid peroxidation, and decreased activities of antioxidants including glutathione (GSH), ascorbic acid (AA), glutathione peroxidise (GPx), glutathione reductase (GR), superoxide

dismutase (SOD), and catalase associated with tobacco users and potentially malignant disorders, produce both phenotypic and genotypic alterations which may progress to cancer. Thus the use of antioxidants at early stages becomes utmost essential for prevention of malignant transformation. Review had proved the significance of retinoids versus placebo in leukoplakia in most of the trials with successful outcome measures.

AUTHOR'S SUGGESTIONS

This review proves that there is a demand for future clinical trials in larger samples with proper follow up to evaluate the efficiency of topical lycopene, as among the other antioxidants, research studies on lycopene has proved that it is an effective natural antioxidant. Future research can concentrate in a topical preparation with combination of all antioxidants and can be tried in leukoplakia and in other potentially malignant disorders and the efficiency of the drug can be compared with vitamin A. Randomised double blinded clinical trials comparing both topical retinoids with topical lycopene in all potentially malignant disorders like leukoplakia, erosive lichen planus, oral submucous fibrosis can also be helpful to devise the best treatment protocol for all potentially malignant disorders based on the outcome measures such as clinical resolution, recurrence, adverse effects and malignant transformation.

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