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-scappable 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 plaques 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 polyloid outgrowths, rounded red or white excrescences; verrucous: wrinkled or corrugated surface appearance. Proliferative verrucous leukoplakia (PVL) presents with multiple, simultaneous leukoplaikias 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 soluable 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 cancer prevention. 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**

<table>
<thead>
<tr>
<th>Author &amp; Year</th>
<th>No of patients &amp; Duration of study</th>
<th>Vitamin A form &amp; dosage</th>
<th>Adverse effects</th>
<th>Outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shah et al 1983</td>
<td>11</td>
<td>Topical Vitamin A 1–5mg</td>
<td>27% clinical resolution 18% recurrence. Malignant transformation not reported</td>
<td></td>
</tr>
<tr>
<td>Hong 1986</td>
<td>44</td>
<td>13-cis-retinoic acid 1 to 2 mg per kilogram</td>
<td>Two patients: Cheilitis, facial dryness and peeling of the skin, conjunctivitis and hypertriglyceridemia</td>
<td>Follow up for 9 months Clinical resolution 67% versus 10 % in placebo Reversal of dysplasia 54% versus 10% in placebo Relapse occurred in 9 of 16 patients in two to three months</td>
</tr>
<tr>
<td>Stich et al. 1988</td>
<td>30 : Vitamin A 35: Placebo 6 months</td>
<td>Systemic Vitamin A 200.000– Placebo capsules twice a day</td>
<td>No side effects</td>
<td>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</td>
</tr>
<tr>
<td>H. F. Stich et al 1988</td>
<td>Group 1 [beta carotene] Group 2: [carotene+vitaminA] Group 3: Placebo 6 months.</td>
<td>beta-carotene 180 mg/week + vitamin A 100.000 IU/week</td>
<td>Remission of OL in group 1 (14.8%) and group 2 (27.5%) differed significantly from that seen in group 3 (3%).</td>
<td></td>
</tr>
<tr>
<td>Garewal et al 1990</td>
<td>24 6months</td>
<td>Systemic Beta-carotene 30 mg/day</td>
<td>8% clinical resolution. 8% malignant transformation. Recurrence not reported</td>
<td></td>
</tr>
<tr>
<td>Toma et al 1992</td>
<td>23 7 months</td>
<td>Systemic Beta-carotene 90 mg/day</td>
<td>26% clinical resolution. 5% Recurrence. Malignant transformation not reported</td>
<td></td>
</tr>
<tr>
<td>S. Toma, P. E. et al 1992</td>
<td>16 6 months</td>
<td>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</td>
<td>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</td>
<td></td>
</tr>
</tbody>
</table>

*Retinoids, 13 cis-retinoic acid, Isotretinoin, betacarotene, 4 HPR*
<table>
<thead>
<tr>
<th>Study</th>
<th>Phase 1: Duration</th>
<th>Phase 2: Duration</th>
<th>Treatment Details</th>
<th>Response</th>
<th>Adverse Effects</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>S.M. Lippman 1993</td>
<td>6 months</td>
<td>9 months</td>
<td>isotretinoin (1.5 mg/kg/day)</td>
<td>20%</td>
<td>Headache, muscular pain</td>
<td>75% complete resolution</td>
</tr>
<tr>
<td>Tradati et al. 1994</td>
<td>4 months</td>
<td>2 months</td>
<td>isotretinoin (0.5 mg/kg/day)</td>
<td>92%</td>
<td>Headache, dry mouth</td>
<td>80% complete resolution</td>
</tr>
<tr>
<td>I. W. Dimery et al 1997</td>
<td>4 months</td>
<td>6 months</td>
<td>isotretinoin (0.5 mg/kg/day)</td>
<td>45%</td>
<td>Headache, dry mouth</td>
<td>80% complete resolution</td>
</tr>
<tr>
<td>Sankaranarayanan et al. 1997</td>
<td>1 year</td>
<td>1 year</td>
<td>Beta-carotene (150 mg/day)</td>
<td>50%</td>
<td>Headache, dry mouth</td>
<td>80% complete resolution</td>
</tr>
<tr>
<td>Liede et al 1998</td>
<td>6 months</td>
<td>6 months</td>
<td>Beta-carotene (20 mg/day)</td>
<td>70%</td>
<td>Headache, dry mouth</td>
<td>80% complete resolution</td>
</tr>
<tr>
<td>Garewal et al 1999</td>
<td>6 months</td>
<td>6 months</td>
<td>Beta-carotene (60 mg/day)</td>
<td>50%</td>
<td>Headache, dry mouth</td>
<td>80% complete resolution</td>
</tr>
</tbody>
</table>

**Response:**
- No-4
- Partial- 14
- Complete-3
- Recurrence :3

**Progression of lesion:**
- 2
### ROLE OF OTHER ANTIOXIDANTS IN TREATMENT OF ORAL LEUKOPLAKIA

Vitamin C (L- ascorbic acid), Vitamin E (alpha tocopherol) 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 appears to be a very promising antioxidant as a treatment modality in oral leukplakia 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.

#### Summary of Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Distribution</th>
<th>Treatment Details</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piattelli et al 1999</td>
<td>10</td>
<td>Topical isotretinoin 1%</td>
<td>No adverse effects</td>
</tr>
<tr>
<td>J. Jack Lee et al 2000</td>
<td>70</td>
<td>Phase 1: isotretinoin (1.5 mg/kg)</td>
<td>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.</td>
</tr>
<tr>
<td>Gaeta et al 2000</td>
<td>21</td>
<td>Topical acitretin</td>
<td>No adverse effects</td>
</tr>
<tr>
<td>Beenken 2000</td>
<td>30</td>
<td>Oral ferretinide daily</td>
<td>14/26 (34.6%), 11/33 (33.3%), and 2/11 (18.2%) developed cancer in 3 groups with low dose isotretinoin, β-carotene, and induction.</td>
</tr>
<tr>
<td>F. Femiano et al 2001</td>
<td>40</td>
<td>Topical treatment</td>
<td>No topical &amp; systemic adverse effects reported in 4 months follow up</td>
</tr>
<tr>
<td>Fausto Chiesa et al 2005</td>
<td>170</td>
<td>4-HPR 200 mg/day</td>
<td>0% clinical resolution. 23% malignant transformation. Recurrence not reported</td>
</tr>
<tr>
<td>Lippman et al. 2006</td>
<td>35</td>
<td>Systemic 4 HPR 200mg/day</td>
<td>0% clinical resolution. 23% malignant transformation. Recurrence not reported</td>
</tr>
<tr>
<td>G. A. Scardina et al 2006</td>
<td>3 months</td>
<td>Topical use of</td>
<td>No adverse topical and systemic reactions in 10 years follow up</td>
</tr>
</tbody>
</table>

**References:**

1. Piattelli et al 1999
2. J. Jack Lee et al 2000
4. F. Femiano et al 2001
5. Fausto Chiesa et al 2005
6. Lippman et al. 2006
7. G. A. Scardina et al 2006
Table 2  
Clinical trials: Oral leukoplakia with other antioxidants
Vitamin E [Alpha Tocoferol], Vitamin C [L –AA], Lycopene

<table>
<thead>
<tr>
<th>Author &amp; Year</th>
<th>No of patients &amp; Duration of study</th>
<th>Antioxidants &amp; dosage</th>
<th>Outcome Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benner et al. 1993 32.</td>
<td>43 &amp; 24 months</td>
<td>Systemic</td>
<td>Alpha Tocoferol 400 IU</td>
</tr>
<tr>
<td>G. E. Kaugars et al 1994 33.</td>
<td>79 &amp; 9 months</td>
<td>30 mg of beta-carotene, 1000 mg of L-AA [L-ascorbic acid] and 800 IU of AT [alpha tocopherol] per day.</td>
<td>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%)</td>
</tr>
<tr>
<td>T. J. Barth et al 1997 34.</td>
<td>24</td>
<td>Beta-carotene, vitamin E, and L-AA</td>
<td>In 97.5% of patients, dysplasias were diminished by use of antioxidant combinations and is more evident in patients with cessation of habit.</td>
</tr>
<tr>
<td>Singh et al. 2004 36.</td>
<td>58 Group 1: 20 Group 2: 20 Group 3: 18 3 months</td>
<td>Systemic Lycopene Group 1: 4mg Group 2: 8 mg Group 3: Placebo</td>
<td>80%, 66.25% and 12.5% clinical resolution in 3 groups respectively, Recurrence &amp; Malignant transformation not reported</td>
</tr>
<tr>
<td>Win Pa Pa Aung et al 2013 37.</td>
<td>5/72 oral potentially malignant diseases 3 months</td>
<td>10 mg along with 500 mg lycopene twice a day</td>
<td>Mild improvement in thin leukoplakia cases when used with topical corticosteroids</td>
</tr>
</tbody>
</table>

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-tocopherol 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.

**REFERENCES**


