Systematic Review of Randomized Trials for the Treatment of Oral Leukoplakia

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Abstract: Oral leukoplakia is a relatively common oral lesion that, in a varying proportion of cases, undergoes malignant transformation. The aim of this review was to assess the effectiveness of treatments for leukoplakia. Randomized controlled trials (RCTs) enrolling patients with a diagnosis of oral leukoplakia were identified by searching biomedical databases, hand-searching relevant oral medicine journals, and contacting oral medicine experts through a European mailing list. The methodological quality of included studies was assessed on the basis of the method of allocation concealment, blindness of the study, and loss of participants. Data were analyzed by calculating relative risk. Malignant transformation of leukoplakia, demonstrated by histopathological examination, was the main outcome considered. Secondary outcomes included clinical resolution of the lesion and variation in dysplasia severity. Six RCTs were included in the review. Vitamin A and retinoids were tested in four RCTs; the other agents tested were bleomycin, mixed tea, and beta carotene. Malignant transformation was recorded in just two studies: none of the treatments tested showed a benefit when compared with placebo. Treatment with beta carotene and vitamin A or retinoids was associated with better rates of clinical remission, compared with placebo or absence of treatment. Whenever reported, a high rate of relapse was a common finding. Side effects of variable severity were often described; however, interventions were well accepted by patients since drop-out rates were similar between treatment and control groups. It is noteworthy that the possible effectiveness of surgical interventions, including laser therapy and cryotherapy, has apparently never been studied by means of an RCT. To date, in conclusion, there is no evidence of effective treatment in preventing malignant transformation of leukoplakia. Treatments may be effective in the resolution of lesion; however, relapses and adverse effects are common.

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"Oral leukoplakia is a predominantly white lesion of the oral mucosa that cannot be characterised as any other definable lesion."[1] Such a definition, also adopted by the World Health Organization, is the result of the effort of an international group of experts who met in Uppsala in 1994 to review leukoplakia definitions and classifications on the basis of previously published work[2,3] and new scientific acquisitions. Thus, leukoplakia is a clinical term used when any other white oral lesion has been excluded by means of clinical examination and histological assessment.

The frequency of leukoplakia is highly variable among geographical areas and demographic groups**.** The prevalence in the general population varies from less than 1 to more than 5 percent.[3-7] Leukoplakia is often associated with tobacco smoking, although idiopathic forms are not rare.[5] There are two clinical variants: 1) homogeneous leukoplakia, a lesion of uniform flat appearance that may exhibit superficial irregularities, but with consistent texture throughout; and 2) non-homogeneous leukoplakia, a predominantly white or white and red lesion (erythroleukoplakia) with an irregular texture that may present as a flat, nodular, or exophytic lesion. Histological features of both forms are quite variable and may include ortho- or para-keratosis of varying degree, mild chronic inflammation, and dysplastic changes of various degrees.

The major problem that the clinician has to face in the management of leukoplakia—a lesion mostly asymptomatic—is its tendency to change into squamous cell carcinoma. In fact**,** leukoplakia is a precancerous lesion, that is, "a morphologically altered tissue in which cancer is more likely to occur than in its apparently normal counterpart."[1] The rate of ma-

lignant transformation varies from almost 0 percent to about 20 percent in one to thirty years.[8-10]

Prevention of malignant transformation is particularly important in view of the poor prognosis associated with oral squamous cell carcinoma, a condition in which only 30-40 percent of patients are still alive five years after the diagnosis.[11] Every leukoplakia must be regarded as at risk of malignant transformation. Non-homogeneous clinical appearance and dysplasia are the more investigated prognostic factors for malignant change. However, at present, there is no definitive clinical or microscopic reliable method to identify which lesion will undergo malignant transformation and which will not.[12] Recently, measurement of DNA content (ploidy) has been proposed as a predictive factor of malignant change of leukoplakia with and without dysplasia.[13-14] Although extremely promising, the results of these studies need further investigation before they can be clinically applicable on a routine basis.

This systematic review is published in full in the Cochrane Library.[15] The aim was to assess the evidence of efficacy for treatments for leukoplakia.

Methods

Inclusion Criteria and Search Strategy

We included studies of patients with a diagnosis of oral leukoplakia as defined, at the time of the studies, by the consensus conferences held in 1978, 1983, and 1994.[1-3] The study designs considered in the present review were randomized controlled trial and quasi-randomized controlled trial, comparing active intervention with placebo or non-intervention. No active intervention was excluded. Studies in all languages were considered for translation.

The full search strategy is described elsewhere.[15] The search included MEDLINE, EMBASE, CancerLit, Biological Abstracts, the Cochrane Library, and hand-searching of main oral medicine journals. In addition, we scanned the reference lists of relevant articles and contacted experts active in the area for further relevant studies.

The title and abstract of each article resulting from the different search strategies were examined separately by two reviewers. When at least one reviewer considered the article relevant, it progressed in the review process, full text version was obtained, and it was included in a digital archive prepared using a dedicated software.

Outcomes

The main outcome considered was malignant transformation of leukoplakia (as demonstrated by histopathological examination). Secondary outcomes included variation in histological features, clinical resolution, and proportion of relapsing lesions. We also considered incidence of adverse effects and proportion of patients dropping out as indicators of safety and acceptability.

Critical Appraisal of Studies

Validity of every randomized or quasi-randomized clinical trial identified was assessed[16,17] on the basis of

- method of allocation concealment,
- protection against performance bias (blindness of the study), and
- loss of participants.

Each of these criteria was rated as "met," "partially met," "unmet," or "unclear." The global validity of the study was assessed using three categories:

1. Low risk of bias: all of the criteria met.
2. Moderate risk of bias: one or more criteria partially met.
3. High risk of bias: one or more criteria unmet.

Statistical Analyses

When valid and relevant data were collected, a meta-analysis of the data was undertaken. For each intervention, statistical analysis evaluated the available data on differences among effects in terms of morbidity (that is, malignant changes), relapse (for interventions directed toward elimination of the lesion), adverse effects, and patients dropping out.

For each intervention, data on the number of patients in the intervention and control group who experienced the event (outcome) and the total number of patients were sought and summarized. Dichotomous data were analyzed by calculating relative risk. As we pooled together data from studies in which true treatment effects are likely to differ, a random effect model was used in the statistical analyses.

Subgroup analysis was undertaken for class of drug (vitamin A and retinoids). A sensitivity analysis was undertaken to exclude studies of lower methodological quality (i.e., studies at high risk of bias).

Review manager 4.1 and Metaview 4.1 statistical softwares were used for the calculation and generation of graphs.

Results

Included Studies

Fourteen potentially eligible RCTs were identified, but only six were included in the review. Two were excluded because of the study design,[18,19] three for diagnostic problems (absence of histological diagnosis and inclusion of traumatic lesions),[20-22] and three were ongoing studies.[23-25] Of the six studies included in the review, two tested a topical treatment,[26,27] three a systemic treatment,[28-30] and one RCT assessed the association of topical and systemic treatments.[31] Vitamin A and retinoids were tested by four RCTs.[27-30] The other agents tested were bleomycin,[26] mixed tea,[31] and beta carotene.[29] One of the studies was a three-arm trial, that is, a study comparing the effects of three treatments, usually two active treatments and one placebo.[29] The total number of patients in the included studies was 365. We found no RCTs that evaluated surgical interventions or interventions directed against risk factors.

The reported proportion of smoking and alcohol-user patients (the two main risk factors for oral cancer) varied from 30 to 71.9 percent and from 18 to 70 percent, respectively. In two studies,[29,30] all of the subjects recruited were tobacco-containing betel quid chewers (another well-known risk factor for oral cancer) from one Indian village (Trivandrum, Kerala).

The follow-up period reported in the four RCTs[26,28,29] varied from six to fifteen months.

Methodological Quality of Included Studies

On the basis of the criteria used in the critical appraisal of the studies, two studies had a low risk of bias.[26,28] In both studies, the methods of allocation concealment were adequate and reported in detail, and more than 80 percent of the patients who entered the study were included in the final analysis. Three RCTs were judged at moderate risk of bias[27,29,31] because the methods of allocation concealment were not described. The remaining study[30] was considered at high risk of bias because of the unclear method of allocation concealment and the absence of protection against performance bias (blindness of the study).

Outcomes

Only two studies[26,29] reported useful data on cancer development (227 patients). In Epstein's trial, only part of the placebo group was taken into account, because seven out of twelve patients of this group received the active treatment at the end of the study period, and thus were excluded from the placebo group for this outcome. Three agents were evaluated in these studies: topical bleomycin,[26] systemic vitamin A,[29] and systemic beta carotene.[29] None of the treatments in these studies showed a benefit when compared with the placebo (Figure 1).

All the included studies reported clinical changes in the leukoplakias. Data on complete resolution of the oral lesions were available from all six studies included in the review (365 patients). Two treatments (bleomycin, tea) were only assessed in single studies, and these treatments showed no ben-

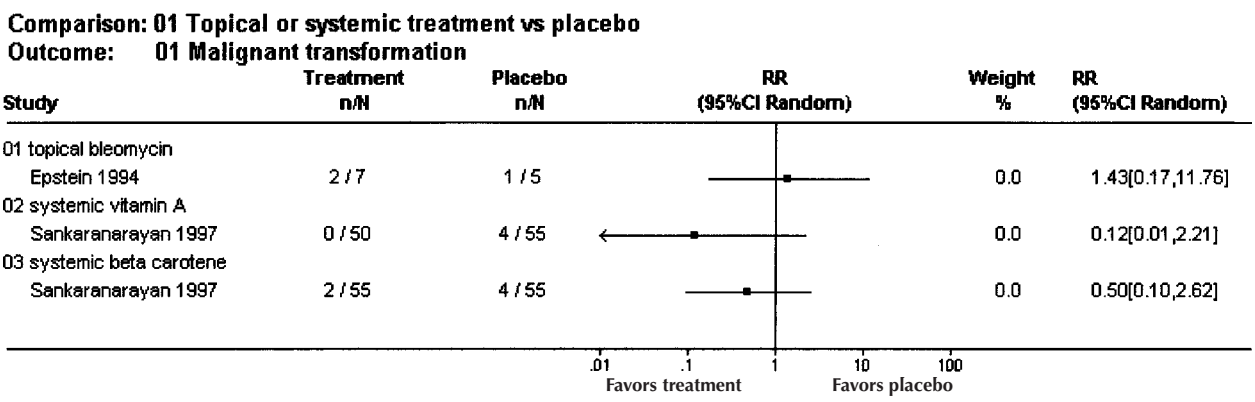

Figure 1. Effect of active treatment and placebo in preventing malignant transformation of oral leukoplakia

efit when compared to the placebo/control group. A single study[29] showed a significant benefit for the systemic treatment with beta carotene when compared to the control (RR=0.77, 95%CI = 0.65, 0.92). Four studies investigated the effectiveness of vitamin A or retinoids[27-30] and found a small but not significant benefit (RR=0.72, 95% CI, 0.50 to 1.05) (Figure 2).

Among patients treated with topical bleomycin,[26] two out of four patients with a complete response, for whom follow-up information was available, relapsed; the same happened for one out of two patients with a partial response and for whom follow-up data was also available. Sankaranarayanan's study reported that fourteen out of twenty-two (64 percent) complete responders of the first arm[29] and eight out of fifteen (54 percent) complete responders of the second arm developed recurrent lesions (no information was available regarding the three complete responders of the placebo group). Relapses were also reported by Hong and colleagues: nine out of sixteen (56 percent) patients responding to treatment (partially or completely) relapsed (no information was available regarding the two partial responders of the placebo group).[28] In Piattelli's study, one out of five (20 percent) patients responding to the experimental treatment and one out of four (25 percent) patients responding to placebo relapsed.[27] No data on relapses were available for the other studies.

Assessment of the histological modifications following treatment was reported by two RCTs that tested topical bleomycin[26] and systemic 13-cis-retinoic acid.[28] In both studies, the histological aspect of oral lesions got worse more frequently with placebo than with active treatment, but the difference was only significant in Hong's study, where the overall relative risk of histological deterioration was in favor of active treatment (RR = 0.51, 95%CI = 0.32, 0.81). One RCT investigated some biomarkers of DNA damage and cell proliferation,[31] but the results of this study were not included as it was not comparable with the two studies just mentioned. A further study reported histological changes in the treatment group only.[30]

Safety and Acceptability

Frequency of adverse effects varied widely among studies. Topical 13-cis-retinoic acid, 200,000 IU per week of vitamin A, and mixed tea did not cause any adverse effects. Topical bleomycin, systemic 13-cis-retinoic acid (1 to 2 mg/kg/day), vitamin A (300,000 IU per week), and beta carotene (360 mg/week) caused adverse effects of various severity in 100 percent, 79 percent, 26 percent, and 9 percent of patients, respectively (Table 1). Adverse effects included erythema and erosion of oral mucosa (topical belomycin), cheilitis, facial erythema, dryness and peeling of skin, conjunctivitis, hypertrigliceridemia (systemic 13-cis-retinoic acid), headache, muscolar pain, dry mouth (vitamin A), headache, and muscolar pain (beta carotene). Whenever reported, they were always more common in the study group than in the control group. Adverse effects caused patients to withdraw in one study only, when systemic 13-cis-retinoic acid induced severe conjunctivitis and hypertrigliceridemia. Information on the reasons for patient withdrawal were missing in five out of six studies that reported at least one missing patient.

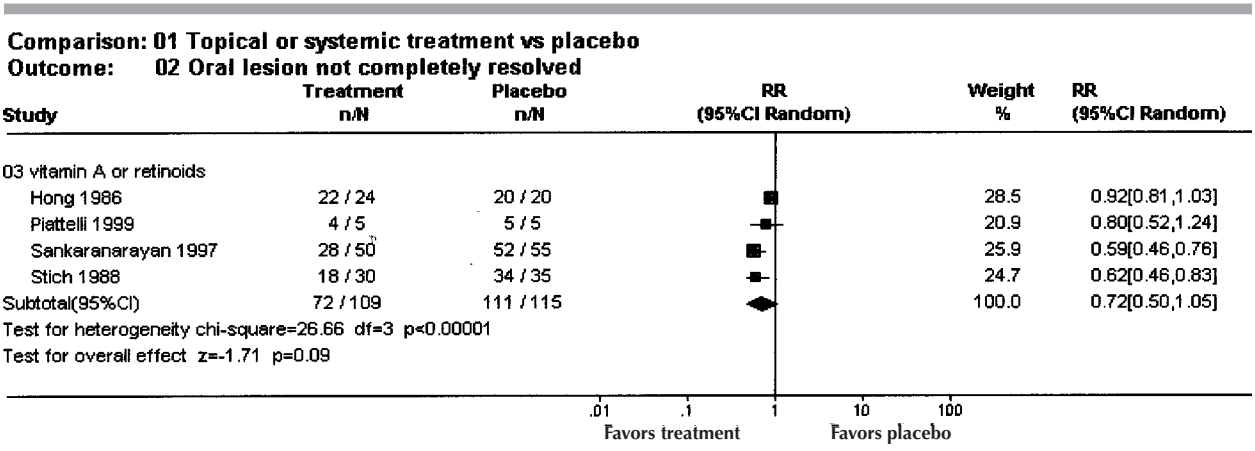

Figure 2. Effect of vitamin A or retinoids and placebo on clinical resolution of oral leukoplakia

Table 1. Patients reporting adverse effects and leaving the studies

Study	Interventions	Patients Reporting Adverse Effects		Patients Leaving the Studies	
		Active Treatment	Placebo	Active Treatment	Placebo
Epstein 1994[26]	Topical bleomycin vs placebo	10/10	0/12	0/10	1/12
Hong 1986[28]	Systemic 13-cis-retinoic acid (from 1 to 2 mg/kg per day) vs placebo	19/24	4/20	2/24	2/2
Li 1999[31]	Systemic and topical tea vs placebo	0/32	0/32	3/32	2/32
Piattelli 1999[27]	Topical 13-cis-retinoic acid vs placebo	0/5	0/5	0/5	1/5
Sankaranarayanan 1997[29]	Vitamin A (300,000 IU per week) vs placebo	13/50	1/55	8/50	15/55
Sankaranarayanan 1997[29]	Beta carotene (360 mg per week) vs placebo	5/55	1/55	9/55	12/55
Stich 1988[30]	Vitamin A (200,000 IU per week) vs placebo	0/30	0/35	9/30	2/35

In spite of adverse effects, treatment acceptability was good, as drop-out rates between treatments and placebo were similar in all but one study (Table 1).

Discussion

Oral cancer is a disease with high morbility and mortality, and one that is showing an increasing incidence and, in many cases, developing at the site of a leukoplakia.[32] Hence, leukoplakia should be considered a serious health problem. Nevertheless, only six studies were eligible for the present systematic review. From the results of these studies, no treatment in the prevention of malignant transformation can be considered as effective. There is some evidence that vitamin A and beta carotene may clinically resolve the oral lesions, and that retinoic acid may prevent histological deterioration, but this was only based on a small number of patients.[28-30]

One weakness of the studies considered was the length of follow-up, which never exceeded fifteen months. This limitation can lead to an underestimation of malignant transformation, since less than half (33-42 percent) of leukoplakias undergo malignant change within two years of diagnosis[8,9] and the incidence of malignant transformation increases with the duration of follow-up.[33] Therefore, in order to properly assess modifications in the rates of leukoplakia malignant transformation, it would be necessary to plan studies with large groups of patients and a longer follow-up; that means multicenter RCTs.

Oral leukoplakias with epithelial dysplasia are much more likely to undergo malignant transformation, and many studies have suggested that the risk of cancer incidence may increase with the severity of dysplastic changes.[10,34] Unfortunately, available data did not allow us to perform a sub-group analysis of lesions with and without dysplasia. Thus, it is not possible to establish if any particular treatment may be more effective for dysplasia of varying severity.

Some researchers used outcomes other than cancer development, for example, various cytological and/or histological markers. Although easier to perform, studies using such outcomes pose a double problem: first, there is little evidence of the predictive value of many of those outcomes; second, they are hardly comparable and, therefore, do not allow a proper comparison or a pooling of the results. In addition, widespread outcomes, such as dysplasia grade, may be affected by high observer variation.[35,36]

Regarding the external validity of the studies, the applicability of the results of two of the studies included[29,30] should be considered very carefully; in fact, patients included in those studies were all betel chewers, a risk factor that is not common in individuals from geographical areas outside the Indian subcontinent.

Because leukoplakias are not morbid or lethal by themselves and have a relatively low risk of transformation, many subjects receiving treatments have lesions that will never progress to cancer. For this reason, proposed treatments should have minimal adverse effects in terms of incidence and severity. This is not the case for some of the interventions evaluated. In particular, high doses of retinoids may cause toxic effects severe enough to cause patients to stop treatment. However, in all but one trial, the number of patients leaving the study group was not much bigger than the number of those leaving the placebo group (see Table 1).

Noteworthy is the absence of RCTs evaluating the effects of surgical excision, the first choice in leukoplakia management for many clinicians.[37] The

only data available are from follow-up studies that compare rates of malignant transformation in patients who did and did not undergo surgical treatment of oral leukoplakias. Although results from such studies are hardly comparable because of differences in diagnostic and inclusion criteria, follow-up interval, patient characteristics, and surgical techniques employed (scalpel, laser, cryotherapy), they show highly variable results and, sometimes, conflicting conclusions.[10,38] Trials evaluating interventions directed against risk factors such as smoking are also missing.

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 and malignant change. For this reason, oral leukoplakias need to be regularly followed up by the clinician, regardless of their response to topical or systemic treatment, including clinical resolution.

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