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Chemoprevention Therapy for Oral Leukoplakia

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Abstract

Oral leukoplakia is the most frequent potentially malignant disorder of the oral mucosa. Nevertheless, currently, there is no consensus regarding the best therapeutic option for the oral leukoplakia. This study aims assess the chemopreventive treatments for oral leukoplakia. A search method used for this study is a PubMed database search through February 2018, using the following Medical Subject Headings (MeSH) terms was performed: "leukoplakia, oral", "leukoplakia, oral/therapy" and "precancerous conditions". The selection criteria in this study include the studies with findings on chemopreventive treatments of oral leukoplakia. There were no restrictions regarding language or date of publication. The obtained data were analyzed using statistical software RevMan 5.3 (The Cochrane Collaboration, Oxford, UK). For dichotomous outcomes, the estimates of effects of an intervention were expressed as risk ratio (RR) using Haenszel Mantel (HM) method with 95% confidence intervals. The results of17 studies on chemopreventive treatment for oral leukoplakia were included in this meta-analysis. Among the chemopreventive treatments, the most effective were retinoids (RR: 7.98) followed by carotenoids (RR: 7.17). Neither the treatments with non-steroidal anti-inflammatory drugs (NSAIDs) nor with herbal extracts showed significant therapeutic efficacy. Due to potentially malignant nature of oral leukoplakia, surgical treatment presently remains the treatment of choice. Chemopreventive therapies have a limited therapeutic efficacy and do not minimize the risk of malignancy of these lesions.

Key words: Drug therapy, Precancerous conditions, Oral leukoplakia.

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1. Introduction

Oral Leukoplakia (OL) is a potentially malignant disorder of the oral mucosa defined as "white plaques of questionable risk having excluded (other) known diseases or disorders that carry no increased risk for cancer" [1]. OL is the most common potentially malignant disorder of the oral mucosa with a global prevalence estimated at around 2.60% [2].

Oral leukoplakias can remain without apparent changes for a long time, can occur a spontaneous regression of the lesion or after smoking and/or alcohol cessation consumption or progress to an oral squamous cell carcinoma. At the present time, there is no consensus regarding the best therapeutic option for OL [3]. Surgery is still the first choice in the management of oral leukoplakia and various surgical techniques (scalpel, laser, and cryosurgery) have been suggested. However, there are no prospective studies that establish the efficacy and morbidity of these treatments, nor whether they reduce the recurrence rate or the risk of malignant transformation [4]. Alternatively, medical treatments based on chemoprevention such as vitamin A and retinoids, carotenoids, bleomycin, tea extract or ketorolac have also been proposed, although with inconclusive results [5].

In oral leukoplakias, chemoprevention concerns to the use of natural or synthetic agents to stop or reverse the possible malignant transformation of these lesions into oral cancer. The failure of conventional therapies for oral leukoplakia, mainly surgery, justifies the development of chemoprevention to prevent the recurrence of lesions and counteract "field cancerization" that facilitates the spread of genetically altered cells in oral cancer [6]. The aim of this study was to assess the effectiveness and safety of chemopreventive treatments of oral leukoplakia with the aim of preventing oral cancer.

2. Experimental

2.1. Materials and Methods

A PubMed database search of studies on chemoprevention and therapeutic options for oral leukoplakia to February 2018 was conducted. Search strategies included the combination of the following terms from the Medical Subjects Headings (MeSH): "leukoplakia, oral/therapy"[MeSH Terms] OR ("chemoprevention"[MeSH Terms]) AND "leukoplakia, oral" [MeSH Terms]).

The inclusion criteria were: a) Type of studies (clinical trials, clinical studies, comparative studies and multicenter studies). All the studies had to have an intervention group and a placebo group or two or more interventions to compare; b) Studies with full-text availability.

Exclusion criteria were studies with irrelevant or no usable data, lack of an adequate OL diagnosis and studies with important biases. After applying the inclusion and exclusion criteria remained seventeen studies that were included in this meta-analysis (Figure 1).

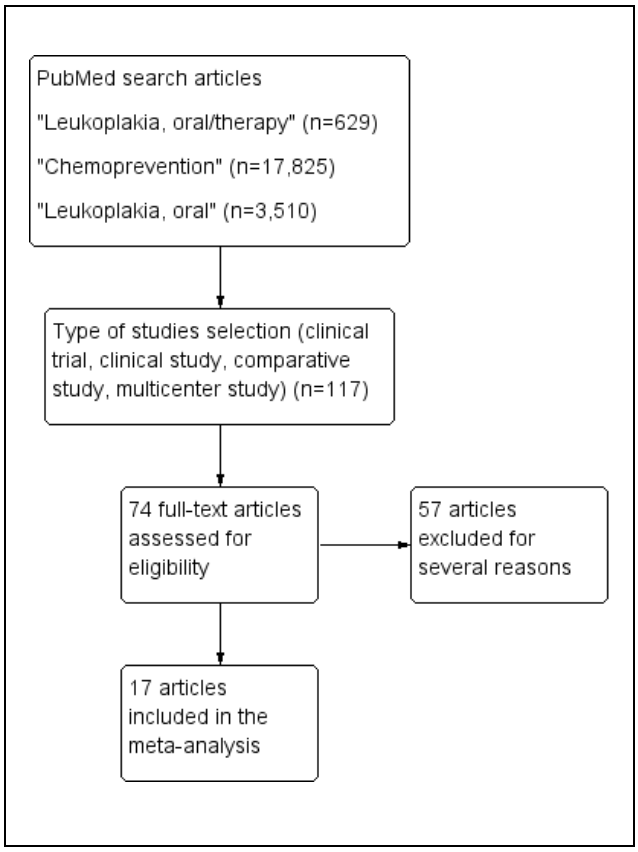


Figure 1. Study flow diagram.

2.2. Statistical Analysis

For the meta-analysis, the data were processed with the statistical software RevMan 5.3 (The Cochrane Collaboration, Oxford, UK). For the dichotomous variables, the Risk Ratio (RR) was used with the Haenszel-Mantel Chi-square formula (HM) with 95% Confidence Intervals (95% CI). Heterogeneity was determined according to the p-values and the Higgins statistic (I2). In cases of high heterogeneity, the random effects model was applied. The significance level was set at $p<0.05$.

3. Results

Table 1 presents the descriptive characteristics of the 17 studies of oral leukoplakia included in the meta-analysis. Six studies [7-12] and seven interventions analyzed the use of vitamin A or retinoids compared to a placebo for the complete resolution of oral leukoplakia (Figure 2). In general, the use of vitamin A or retinoids was 7.98 times more effective than placebo in the complete resolution of oral leukoplakia lesions (OL), with statistically significant differences (RR: 7.98, 95% CI: 3.73, 17.11, $p <0.001$).

Three studies [11, 13, 14] and four interventions considered the use of beta-carotene or carotenoids compared to a placebo for the complete resolution of OL (Figure 3a). The use of beta-carotene or carotenoids was 7.17 times more effective for the complete resolution of the lesions, with highly significant results observed in the statistical analysis (RR: 7.17, 95% CI: 2.79, 18.40, $p <0.001$). Two studies [15, 16] compared the use of beta-carotene and isotretinoin for the complete resolution of OL (Figure 3b). A greater effectiveness of isotretinoin for

the complete response of OL was observed, although no statistically significant association was found (RR: 0.18, 95% CI: 0.18, 1.18, p = 0.11).

Other two studies [17, 18] assessed the use of nonsteroidal anti-inflammatory drugs (NSAIDs) compared with a placebo for the complete resolution of OL (Figure 4). NSAIDs showed a greater efficacy for the complete resolution of the lesions. However, after statistical analysis, no significant differences were observed (RR: 2.28, 95% CI: 0.41, 12.82, p = 0.35).

Three studies [19-21] examined the use of herbal extracts in comparison with a placebo for the complete resolution of OL (Figure 5). Herbal extracts were more effective than placebo although also no statistically significant association was found (RR: 7.01, 95% CI: 0.22, 228.14, p = 0.27). Other proposed treatments for OL were Bowman-Birk inhibitor [22] or topical bleomycin [23], though they have not shown significant results measured in clinical efficacy.

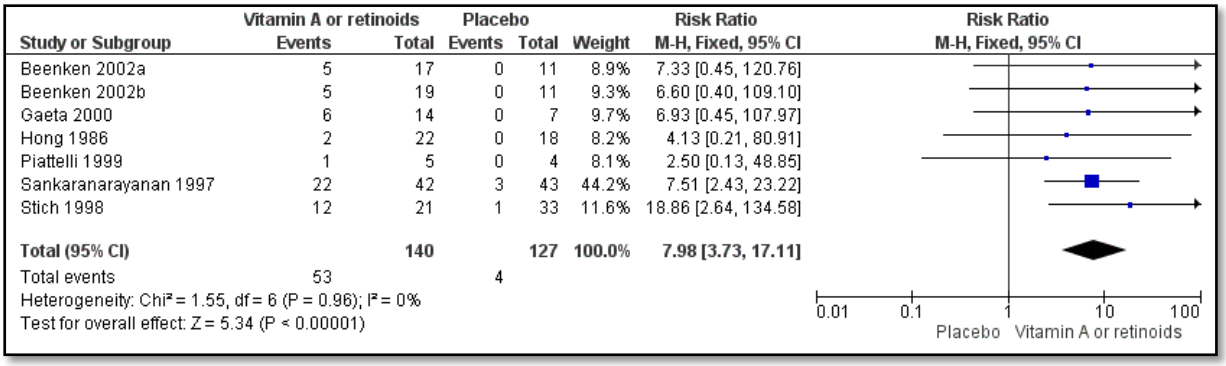
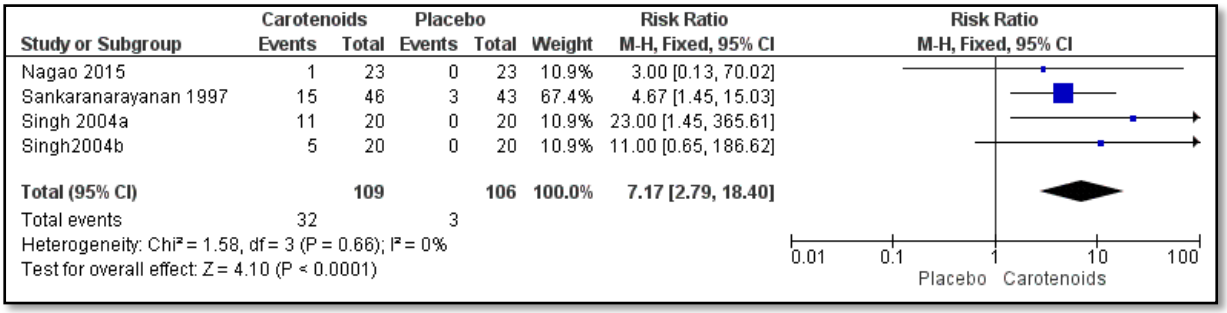
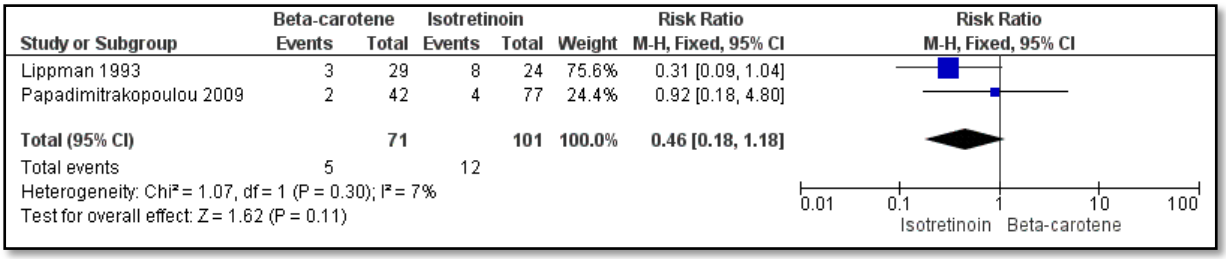


Figure 2. Study data and forest plot graph for complete resolution of oral leukoplakia (OL) using vitamin A or retinoids compared to a placebo.



3a. Beta-carotene or carotenoids *vs.* Placebo.



3b. Beta-carotene *vs.* Isotretinoin.

Figure 3. Study data and forest plot graph for the complete resolution of oral leukoplakia (OL) using beta-carotene or carotenoids compared to a placebo or isotretinoin.

Table 1. Descriptive characteristics of studies of oral leukoplakia (OL).

First Author	Year	Country	Study population (n*, mean age, male/female, % tobacco users[&])	Interventiongroups (n)	Follow-up
Beenken [7]	2002	USA	47, 69.4 yr, 17/30, NR[#]	High-dose 13-cis retinoic acid (17) Low-dose 13-cis retinoic acid (19) Placebo (11)	6 months
Gaeta [8]	2000	Italy	21, 52.2 yr, 16/5, NR	Acitretin (14) Placebo (7)	4 weeks
Hong [9]	1986	USA	44, 64.3 yr, 31/13, 45.0%	13-cis retinoic acid (24) Placebo (20)	6 months
Piattelli [10]	1999	Italy	9, 63.3 yr, 5/4, 44.4%	Isotretinoin (5) Placebo (4)	4 months
Sankaranarayanan [11]	1997	India	131, 51.1 yr, 84/47, 31.2%	Vitamin A (42) Beta-carotene (46) Placebo (43)	1 year
Stich [12]	1988	India	54, NR, NR, 37%	Vitamin A (21) Placebo (33)	6 months
Nagao [13]	2015	Japan	46, 65.3 yr, 25/21, 33.0%	Beta-carotene (23) Placebo (23)	1 year
Singh [14]	2004	India	60, NR, 44/16, NR	High-dose lycopene (20) Low-dose lycopene (20) Placebo (20)	5 months
Lippman [15]	1993	USA	59, 60.5 yr, 27/32, 55.9%	Isotretinoin (26) Beta-carotene (33)	9 months
Papadimitrakopoulou [16]	2009	USA	109, 56.0 yr, 65/54, 67.2%	13-cis retinoic acid (77) Beta-carotene (42)	5 years
Mulshine [17]	2004	USA	57, NR, 38/19, 84.2%	Ketorolac (38) Placebo (19)	90 days
Papadimitrakopoulou [18]	2008	USA	50, 61.3 yr, 26/24, 62.0%	Celecoxib (32) Placebo (18)	12 weeks
Li [19]	1999	China	59, 54.5 yr, 35/24, 77.9%	Mixed tea (29) Placebo (30)	6 months
Mallery [20]	2014	USA	40, 39.8 yr, 16/24, 40.0%	Black raspberriesextract (22) Placebo (18)	3 months
Tsao [21]	2009	USA	39, 56.0 yr, 18/21, 61.5%	Green tea extract (28) Placebo (11)	12 weeks
Armstrong [22]	2013	USA	89, 60.7 yr, 57/32, 21.0%	Bowman Birk Inhibitor Concentrate (43) Placebo (46)	6 months
Epstein [23]	1994	Canada	22, 56.6 yr, 10/12, 63.7%	Bleomycin (10) Placebo (12)	6 months

***n:** number of subjects; [&]**% tobacco users:** percentage of tobacco users; [#]**NR:** Not reported.

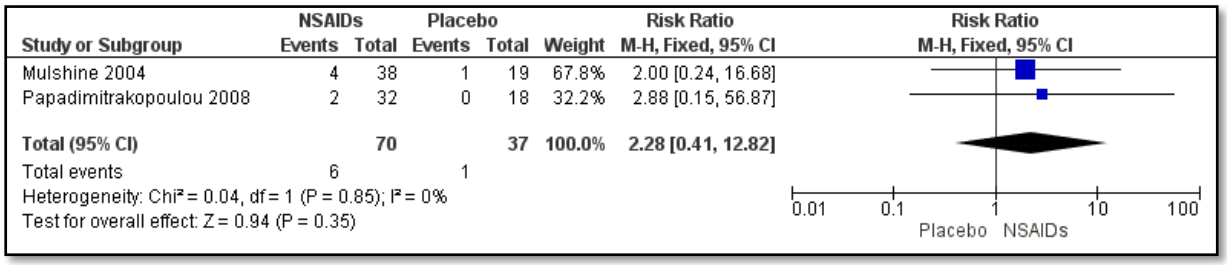


Figure 4. Study data and forest plot graph for the complete resolution of oral leukoplakia (OL) using nonsteroidal anti-inflammatory drugs (NSAIDs) compared to a placebo.

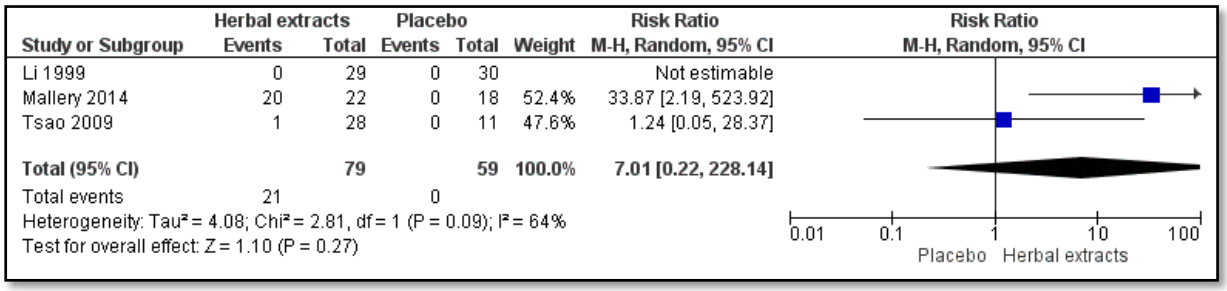


Figure 5. Study data and forest plot graph for the complete resolution of oral leukoplakia (OL) using of herbal extracts compared to a placebo.

4. Discussion

In the present meta-analysis on different medical treatments for oral leukoplakia (OL), data from 17 studies have been included. In this study, OL treatment with vitamin A or retinoids supposed 7.98 times more benefit for complete resolution of the lesion compared to a placebo with statistically significant differences ($p < 0.001$). Our findings agreed with those published in 6 studies concerning these drugs [7-12], although in 4 of them [7-10], the results were not statistically significant. Probably this lack of association is related to the small sample sizes of these studies, the several clinical types of OL, the different criteria used to establish the complete resolution of OL or the differences in doses and/or route of drug administration. Even one study [7] was performed with only dysplastic oral leukoplakias that have a worse biological behavior and are more resistant to medical treatment. On the contrary, the two studies [11, 12] which did observe statistical significance, used larger population samples, with more uniform clinical OL types and longer periods of drug administration and follow-up. These facts allowed a better evaluation of the efficacy of these treatments.

Regarding adverse effects due to the use of retinoids in the OL treatment, oral dryness (4.8% [11] - 25% [9]) or elevation of serum triglyceride levels (14.3% [11] - 70.8% [9]) were the most common adverse effects observed. Although retinoids have a great therapeutic efficacy, they present important adverse effects derived from prolonged use. Main adverse effects related to chronic use are bone pain, cutaneous desquamation, alopecia, hepato-splenomegaly, hemorrhagic phenomena or intracranial hypertension. Its use is totally contraindicated in pregnant women due to the risk of malformations and neural, cranial-facial or cardiovascular defects [24].

In the present study, the use of beta-carotene or carotenoids increased 7.17-fold the probability of complete resolution of OL lesions in contrast to placebo with a highly significant statistical association ($p < 0.001$). All the

studies analyzed [11, 13-14] coincided with our results, one of them [13] with statistically significant results, another not [11]. Another study [14] considered two interventions, one with significant results and the other not. These apparent discrepancies could be due to the different sample sizes, the diverse OL clinical types, doses and/or drug administration patterns. The concentration of the drug seems to be a quite influential factor in its therapeutic action. Thus, when lycopene was compared at different doses with a placebo, at a dose of 8 mg/day, the results had a significant clinical relevance, whereas when it was reduced to 4 mg/day, they were not significant. A daily dose of 8 mg of lycopene achieved a 55% of OL with a complete response, meanwhile, a daily dose of 4 mg, only achieved a 25% of the complete response. The different characteristics (age and sex) of each treatment group and the concentration of the drug probably influenced the results [14].

Precursors of vitamin A such as beta-carotene and other carotenoids are natural compounds present in vegetables, fruits, algae and in a great variety of fungi, bacteria and animals. They are considered cytoprotective substances related to the decrease in the cancer incidencedue to their antioxidant capacity. The main advantage of these substances is that they are quite safe with little noticeable adverse effects (mucocutaneous dryness) [25].

Two studies [15-16] also compared the therapeutic efficacy of the use of carotenoids (beta-carotene) versus retinoids (isotretinoin) in the chemopreventive treatment of OL. A better clinical response was observed with the retinoids although the results were not statistically significant. However, the therapeutic efficacy of retinoids is hindered by its potential undesirable effects. Lippman *et al* [15] reduced the usual dose of isotretinoin, trying to minimize the risk of adverse effects at the expense of a lower therapeutic effectiveness. On the other hand, Papadimitrakopoulou *et al* [16] included in their study a significant number of erythroleukoplakia, a non-homogenous clinical form of OL which exhibit a more aggressive biological behavior, a higher risk of malignant transformation and a worse response to medical treatment.

In the present meta-analysis, the therapeutic action on OL lesions of widely used drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs) was also evaluated, finding a slightly higher efficacy of NSAIDs compared to placebo, without statistical significance. According to our findings, two clinical trials [17, 18] analyzed the use of selective cyclooxygenase inhibitors (ketorolac and celecoxib) in the medical treatment of OL with s discrete clinical response and no statistically significant results. The route of topical administration of the drug as a mouthwash [17] or the histological type of OL with dysplastic lesions [18] may have influenced these results. However, new clinical trials with a greater number of cases are required in order to determine the real therapeutic efficacy of NSAIDs on OL chemopreventive treatment.

Other medical treatments proposed for OL are based on the use of herbal extracts and natural fruits. In the present study, a better clinical response was found with herbal extracts compared with placebo, although they were not statistically significant either. Two studies [20-21] corroborated these results, although a third one [19] that used a tea-based mouth wash did not have any clinical effect on OL. One study [20] used a bioadhesive gel with blackberry extracts versus a placebo, obtaining a complete resolution in 90.1% of OL treated with extracts. However, these results should be analyzed with caution since this study only considered a limited sample (22 cases) with small and non-dysplastic oral leukoplakias. Moreover, complete resolution was recorded only as a

reduction of the lesion size, not as its complete disappearance. Another study [21], used green tea capsules with little encouraging results and a very poor therapeutic response. The use of natural, complementary or alternative therapies for OL treatment might not be justified for the limited therapeutic response of these agents and the potential risk of malignancy of oral leukoplakias.

All findings of this meta-analysis must be interpreted with caution due to the high heterogeneity of some studies considered and the presence of different bias. The differences among studies could be conditioned by the study design, the methods used to collect data, the type of analysis used, the characteristics of the study populations and samples or the follow-up of the studies.

5. Conclusions

Considering the potentially malignant nature of OL, surgical treatment should be the first therapeutic option since the lesion is removed and the risk of transformation into oral cancer is minimized. Among the chemopreventive treatments, the most effective were retinoids (RR: 7.98) followed by carotenoids (RR: 7.17). Neither the treatments with NSAIDs nor with herbal extracts showed significant therapeutic efficacy.

6. Conflicts of Interest

The author(s) report(s) no conflict(s) of interest(s). The author along are responsible for content and writing of the paper.

7. Acknowledgment

NA

8. References

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