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Literature Review

Management of Oral Leukoplakia – A Systematic Umbrella Review of Global Evidence

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Abstract

Objective: To summarize the global evidence related to various interventions for treating Oral Leukoplakia.

Introduction: Oral leukoplakia is a common oral potentially malignant lesion that precedes the development of oral cancer. The main aim of any treatment is to prevent the malignant transformation. This umbrella review updates the global evidence of different medicinal treatment available for Oral Leukoplakia.

Methods: The databases searched were Cochrane database of systematic reviews, JBI Evidence Synthesis, MEDLINE, Web of Science, Scopus. The key terms used were leukoplakia, oral leukoplakias, Proliferative verrucous leukoplakia, interventions, management, chemoprevention, laser, photodynamic, topical agents. JBI Sumari software was used to screen and appraise the articles along with data extraction and data synthesis.

Results: A total of 670 citations were identified through the electronic search. Out of which 61 systematic reviews were recognized. Following removal of duplicates, 47 records were retrieved. The full texts of 13 papers were retrieved for further examination with 9 systematic reviews meeting the inclusion criteria and therefore included in this umbrella review. Study overlap calculation was conducted and pooled results showed that the treatments available for oral leukoplakia has little effect on clinical response and malignant transformation rate.

Conclusions: Currently we do not have evidence of a treatment that is preventing oral leukoplakia from converting to oral cancer. Treatments such as vitamin A and beta carotene may be effective in reducing clinical size of oral lesions. More long-term studies are required for surgical management, lasers and photodynamic therapy.

***Keywords:** Oral Leukoplakia; Oral cancer; Malignant transformation.*

Introduction

Oral leukoplakia (OL) is defined by the World Health Organization (WHO) as a white oral plaque with a risk of malignant transformation, after excluding other known lesions or disorders that carry no increased risk for cancer [1]. OL is the most common oral disorder with potential for malignant transformation. The overall global prevalence is about 4.11% [1,2].

The main etiological factor associated with OL is the use of tobacco in its various forms. The affected population is mostly men, older than 50 years old, although this predilection varies according to geographical parameters [2]. Malignant transformation of OL is associated with a variety of clinical and histological features, including: a previous history of cancer diagnosed in the head and neck region; advanced age; clinical appearance, size, anatomic site of the lesion; and, most importantly, the degree of epithelial dysplasia present [2,3]. Despite being the main histological marker, the degree of epithelial dysplasia remains a subjective criterion. Thus, predicting malignant transformation based on histopathological features. The malignant transformation potential ranges from 0.13% to 34% [3]. Despite appropriate management, the recurrence rates are still estimated to be around 30% Biopsy of the lesion is required to establish the correct diagnosis and the degree of epithelial dysplasia. Surgical excision is the most recommended management technique for case of lesions with moderate to severe dysplasia. Close surveillance and follow-up should be mandatory for lesions on other anatomic locations. [2,3] The aim of the present systematic review and meta-analysis was to evaluate the current literature regarding recurrence and malignant transformation rates following the treatment of OL by conventional scalpel or laser surgery.

Methods

The preferred reporting items for systematic reviews was used to report this review. Additionally, this review was conducted in an accordance with the JBI umbrella review methodology. The review protocol was in PROSPERO is under review.

Search Strategy

Search process was conducted in February and March 2022 to identify systematic reviews that reported on the Management of Oral Leukoplakia. Initial keywords, text words of title and abstract and index words were identified. Database was searched with specific search filters and cross references were searched. The databases searched were: Cochrane database of systematic reviews, JBI Evidence Synthesis, MEDLINE, Web of Science and Scopus. The key terms used were leukoplakia, oral leukoplakias, Proliferative verrucous leukoplakia, interventions, management, chemoprevention, laser, photodynamic, topical agents.

Inclusion criteria

- Systematic reviews and meta-analysis focusing on management of oral leukoplakia.

Exclusion criteria

- Prevalence studies
- Primary data of Oral Cancer
- Systematic reviews of screening/diagnostic tests/ biomarkers

Systematic review selection

The duplicates were removed from all identified citations. The titles and abstract screening and full text screening were done in JBI SUMARI by 2 independent reviewers. Disagreements that arose between the reviewers were resolved through discussion.

Quality assessment

The quality of the selected articles were checked using JBI Critical Appraisal Checklist for Systematic Reviews and Research Syntheses. All studies regardless of their methodological quality were included in the review. Details of the quality assessment are shown in Table 1.

Data extraction

Data extraction of selected study was done in JBI Sumari software. Data extraction was undertaken independently by two authors and checked by third reviewer.

Data synthesis

The degree of overlap was calculated. Data synthesis was carried out in JBI Sumari.

Table 1. Quality Assessment.

Study	Review objectives	Descriptions of interventions/phenomena of interest	Descriptions of outcomes included in the review	Search details	Number of studies and participants included	Appraisal instruments used	Description of main results
Yuting Li 2019.	Photodynamic therapy (PDT) in the management of oral leukoplakia	Photodynamic therapy using photosensitizers used were aminolevulinic acid, Photofrin, methylene blue, and chlorine-e6	Complete response (CR), partial response (PR), and no response (NR)	Pubmed/Medline, EMBASE, ISI Web of Knowledge, OVID, CNKI, and WANFANG DATA were searched up to and including June 2018	352	Modified version of the Downs and Black checklist	11 patients showed no response to PDT, complete response were reported in 7.7%-90.9% of lesions, while 0-66.7% of lesions showed partial response to PDT. In the remaining fifteen studies, 0-59% showed no response to PDT. On the whole, the rates of complete and partial response were 32.9% and 43.2%, and the sum was 76.1%. Eleven studies reported the recurrence rate in oral leukoplakia patients treated with PDT ranging between 0 and 60%, and mostly below 20%.
Mogedas-Vegara 2016.	To evaluate treatment of oral leukoplakia with the carbon dioxide (CO2) laser	Carbon dioxide (CO2) laser	Recurrence rate and malignant transformation	A MEDLINE (pubmed) for studies published from 1981 to 2015	1159	Not mentioned	No consensus regarding the factors involved in higher recurrence and malignant transformation rates

Wesley M. Abadie 2015.	To characterize the risk factors, clinical course, and optimal treatment for PVL	Radiation laser therapy chemotherapy photodynamic therapy retinoids	Malignant transformation rate Recurrence rate	Pubmed, Cochrane Database, and gray literature was conducted of all PVL cases reported between 1985 and 2014	329	Not mentioned	71.2% of patients with PVL recurred and/or progressed to carcinoma despite interventions. 63.9% of patients with PVL progressed to invasive SCC.
Tianhui Xie Jinzhong Liu 2017.	To evaluate effectiveness of current chemopreventive agents in the treatment of oral leukoplakia lesions (opls) and prevention of their progression to oral cancer	Erlotinib, Freeze-dried black raspberry, Beta-carotene, Bowman-Birk inhibitor concentrate, zengshengping (a mixture of medicinal herbs), Green tea extract, Isotretinoin (13-cis retinoic acid), retinyl palmitate (RP), RP plus beta-carotene (BC), Cyclooxygenase-2 (COX-2) inhibitor ,	Oral cancer-free survival(CFS) Histologic grade, clinical size and loss of heterozygosity, Clinical response (CR+PR),), histologic response, Clinical response (CR+ PR), histologic response, cancer-free survival rates Clinical response (CR+ PR), adverse events	C pubmed database, Embase, Cochrane Library between 2008 and 2016.	689	Jadad scale	Significant differences found in clinical responses between chemopreventive agents with placebo in treatment of opls
Lucy Chau Justin T Jabara2017.	To evaluate the effectiveness of current chemopreventive agents in the treatment of oral leukoplakia lesions	Chemopreventive agents	Clinical response,change in lesion area and histological responses	Pubmed database, Embase and Cochrane Library between 2008 and 2016	689	Not mentioned	No significant differences in No comparing clinical responses between chemopreventive agents with placebo in treatment of oral leukoplakia
Giovanni Lodi. 2002.	To assess the evidence of efficacy for treatments for leukoplakia.	Vitamin A and retinoids	Potential malignant transformation rate , histological features, clinical resolution, and proportion of relapsing lesions	MEDLINE, EMBASE upto april 2002	365	Not mentioned	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

Mariana de Pauli 2020.	To evaluate the current literature regarding recurrence and malignant transformation rates following the treatment of OL by conventional scalpel or laser surgery	Laser excision	Recurrence or malignant transformation rate of OL treated	MEDLINE/ pubmed, and Embase upto September 10th, 2019	3718	Not mentioned	Surgical laser excision of OL may decrease recurrence rates but have no effect on the malignant transformation of OL when compared with conventional treatments.
Lodi G Franchini R 2016.	To assess the effectiveness, safety and acceptability of treatments for leukoplakia in preventing oral cancer	Surgical and medicinal interventions for leukoplakia	Healing of lesions relapse adverse effects	Cochrane Oral Health's Trials Register,the Cochrane Central Register of Controlled Trials MEDLINE Ovid, Embase Ovid and clinicaltriaand the World Health Organization (WHO)	909	We assessed risk of bias in studies by using the Cochrane tool. The overall quality of the evidence by using standardised criteria (Grades of Recommendation, Assessment, Development and Evaluation Working Group (GRADE))	Treatments such as vitamin A and beta carotene may be effective in healing oral lesions, but relapses and adverse effects are common.
Yunmei Dong.2018	To evaluate the series of studies are dedicated to research the clinical outcomes of OLK treated with CO2 laser	Carbon dioxide laser (CO2 laser)	Recurrence and malignant transformation	Cochrane Library, EMBASE, Pubmed, Web of Science, and SCOPUS	24	Der-Simonian Liard method	Result revealed that it was the male,homogeneous type, no tobacco consumption, and without alcohol-use who had a higher tendency of malignancy after laser surgery

Results

Study characteristics

A total of 670 citations were identified through the electronic search. Out of which 61 systematic reviews were recognized. Following removal of duplicates, 47 records were retrieved. Out of these articles, only systematic reviews and meta-analysis of leukoplakia management articles were identified. Total 26 articles underwent screening of the title and abstracts. Fourteen papers were excluded as they did not meet the inclusion criteria. The full texts of 13 papers were retrieved for further examination with 9 systematic reviews meeting the inclusion criteria and therefore included in this umbrella review.

Four systematic reviews were excluded as they provided only malignant transformation rate and there was no mention of treatment. The 9 included systematic reviews included a total of 120 primary studies from worldwide. Various treatment modalities were used to manage leukoplakia (Table 1).

Study overlap

Study overlap was calculated. As the interventions were different the studies were further divided into 3 groups: 1. Medicinal treatment 2. Laser Treatment and 3. Others. In others only 2 articles were present, one about photodynamic therapy and other one was treatment of PVL, the degree of overlap ranged from 0.3 to 0.57% presents the degree of overlap between the studies.

Clinical response

Data were inputted into the software and transformed using the Freeman-Tukey double arcsine transformation to calculate a summary. Pooled estimates for the systematic reviews were not calculated due to overlap of primary studies. Clinical response of oral leukoplakia for topical or systemic treatment shown (Fig. 1) and Malignant transformation rate of oral leukoplakia for topical or systemic treatment shown (Fig. 2)

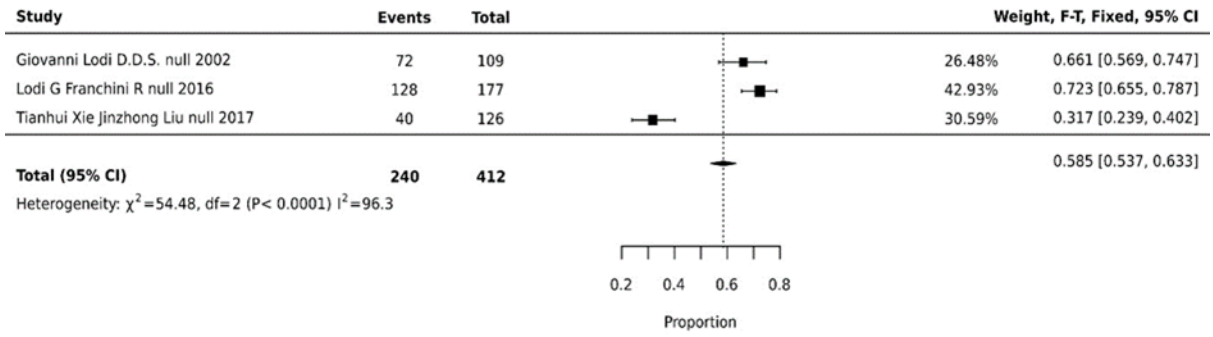

Fig. 1 *Clinical response of oral leukoplakia for topical or systemic treatment.*

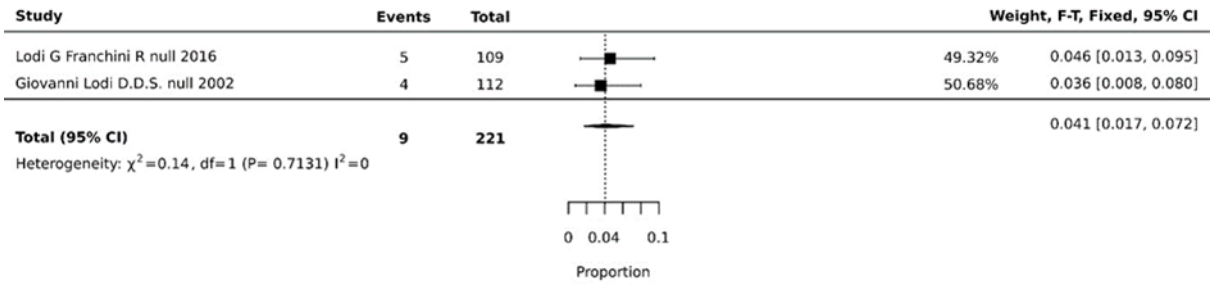

Fig 2. *Malignant transformation rate of oral leukoplakia for topical or Systemic treatment.*

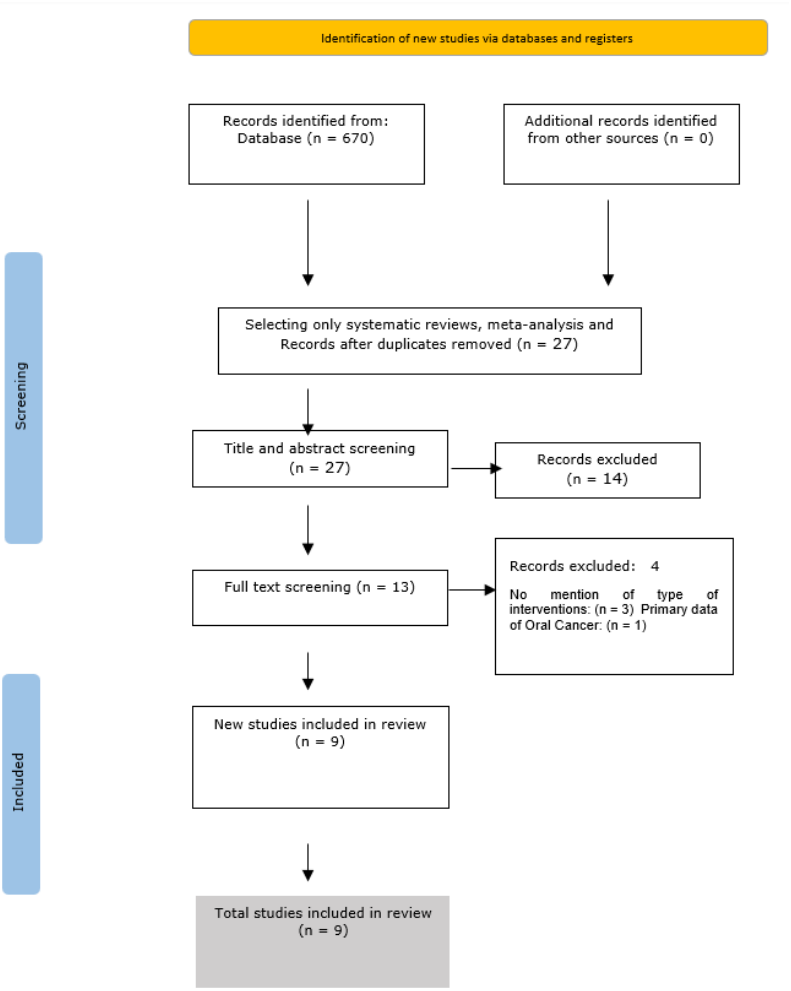

Fig 3. *PRISMA flow diagram of search and study selection process.*

Discussion

Oral leukoplakia is the most common premalignant lesion in oral cavity and is associated with the development of oral cancer. [4] Many therapeutic agents and surgical techniques are used to defeat the lesion from getting converted into malignancy. Oral cancer can be originated longstanding oral leukoplakia if they are left untreated. [5]

This Umbrella review conducted to pool the global data of various interventions of Oral Leukoplakia. [6] Every case of leukoplakia must be regarded as at risk of developing to OSCC. Non-homogenous leukoplakia and PVL has increased risk of developing into OSCC. There is no evidence that treatment of leukoplakia prevents from malignant transformation. [5,6]

Beta Carotene or carotenoids, topical or systemic Vitamin A or Retinoids, topical bleomycin (0.5% bleomycin topical application or a 1.0% bleomycin application) had no superior effect in clinical resolution or malignant transformation rate. [7] With use of Laser (laser techniques include CO2, Nd:YAG, Er:YAG, diode, and KTP lasers, with CO2 the most widely used), there is decrease in the recurrence rate but there is no effect on malignant transformation rate. [8] There is limited data is available an oncolytic adenovirus and use of topical application of COX inhibitors. [9] Photodynamic therapy seems to be less effective in leukoplakia to reduce malignant transformation rates.[10] It is helpful in reducing the size of the lesions. PDT included aminolevulinic acid, Photofrin, methylene blue, and chlorine-e6. For PVL surgical treatment is considered better. [10] Use of lycopene has some improvement in terms of histological features. [11] There is limited data regarding efficacy of Freeze-dried black raspberry (BRB), erlotinib, Bowman-Birk inhibitor concentrate, ZengShengPing (a mixture of medicinal herbs) and green tea extract. [12,13,14,15]

Conclusion

The available evidence on interventions for treating people with oral leukoplakia is inadequate. We do not currently have evidence of any treatment for preventing the development of oral cancer for different clinical forms of oral leukoplakia. Larger trials of longer follow-up are required to properly evaluate the treatment effects of leukoplakia treatments on the risk of developing oral cancer. More studies are required to evaluate effect of surgical treatment on malignant transformation.

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None

Conflict of Interest Statement

None

Authors' Contribution

The manuscript has been read and approved by all the authors, that the requirements for authorship as stated earlier in this document have been met, and that each author believes that the manuscript represents honest work.

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