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Review Article

Systematic Review on the Treatment Modalities in Management of Oral Leukoplakia

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Abstract

Background: Leukoplakia is potentially malignant disorder. Early management of leukoplakia can reduce the chances of oral cancer. Finding most effective treatment amongst the various treatment modalities is thus required.

Objectives: The purpose of study is to find most effective treatment in the management of oral leukoplakia.

Data Sources: An extensive systematic literature search was performed in PubMed, Google scholar, using combination of key words like leukoplakia, oral potentially malignant disorder, white patch, oral cancer, etc.

Study Eligibility Criteria: Inclusion criteria: Studies that provide information for treatment of oral leukoplakia from 2005 to 2015. Exclusion criteria: Review articles, letter to editor, case report.

Participants: Patient with oral leukoplakia.

Intervention: Various treatment modalities for leukoplakia.

Results: 82 Articles were screened on the basis of title to get 57 article. After removing duplicates 30 articles were obtained. Abstracts of all 30 article were screened to get 26 articles. Out of 26 article 13 were obtained as free full text. And thus 13 studies were finally used for this systematic review.

Limitations: Less number of studies were included due to inaccessibility to databases.

Conclusion: After studying all the article stating different treatment modalities of leukoplakia in depth we conclude that laser surgery is better treatment alternative for conventional surgery for instant clinical remission. Medical adjunctive therapy with chemopreventive agent like lycopene with vitamin E and selenium or rAd p53 intraepithelial injections or low dose fenretinide should be used to bring histological changes reducing the rate of malignant transformation.

Implication: Laser surgery is better treatment alternative for conventional surgery for instant clinical remission. Medical adjunctive therapy with lycopene with vitamin E and selenium or rAd p53 intraepithelial injections or low dose fenretinide should be used for chemoprevention.

Keywords: *Oral Leukoplakia; Laser surgery; Medical Adjunctive Therapy; Lycopene*

Introduction

Rationale

Oral Leukoplakia can be defined as "A predominantly white patch or plaque that cannot be characterized clinically or pathologically as any other disorder; oral leukoplakia carries an increased risk of cancer development either in or close to the area of the leukoplakia or elsewhere in the oral cavity or the head and-neck region" [1]. The prevalence of oral leukoplakia varies among scientific studies. A comprehensive global review points at a prevalence of 2.6%. Most oral leukoplakia's are seen in patients over the age of 50 and infrequently encountered below the age of 30 [2]. In population studies, leukoplakia are more common in men. 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" [3]. The rate of malignant transformation varies from almost 0 percent to about 20 percent in one to thirty years. 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 [4]. 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 [4]. Recently, measurement of DNA content (ploidy) has been proposed as a predictive factor of malignant change of leukoplakia with and without dysplasia. Although extremely promising, the results of these studies need further investigation before they can be clinically applicable on a routine basis [4].

Focused Question

Which is the most effective treatment modality for oral leukoplakia in different clinical situations?

Objectives

1. To assess the literature regarding the various treatment modality of leukoplakia.
2. To find out the most effective treatment modality in treatment of Oral Leukoplakia.

Methods

Eligibility Criteria

Inclusion criteria

1. Literature included clinical trial, case series mentioning the treatment modalities of leukoplakia.
2. Literature showing follow up results of the treatment modalities.
3. PubMed search which includes articles published from 1january 2005 up to 31st December 2015.
4. Literature written in English were accepted.

Exclusion criteria

1. Reviews, abstracts, editorials, letters, and historical reviews and in vitro studies were not included in the search.
2. Literature in any other language.

PIO from PICO

P – Participants: Patients with leukoplakia and/or dysplasia

I - Intervention: Various treatment modalities

O - Outcomes: Reduction in the size of lesion and severity of dysplasia and malignant transformation.

Information Sources

Internet source of evidence were used in the search of appropriate papers satisfying the study purpose: the National Library of Medicine (MEDLINE PubMed) and manual search using DPU college library resources. All cross reference lists of the selected studies were screened for additional papers that could meet the eligibility criteria of the study. The databases were Search up to and including December 2015 using the search strategy.

Keywords

Leukoplakia	White patch, white lesion, oral potential malignant disorder, precancerous lesion, white plaque
Oral	Mouth, mucosa, face
Treatment	Management, modality, therapy

Search Strategy for PubMed

1. Oral and Leukoplakia and Treatment.
2. Oral and leukoplakia and Therapy.
3. Oral and leukoplakia and Modality.
4. Oral and leukoplakia and Management.
5. Oral and Potentially premalignant disorder and Therapy.

Study Selection

Preliminary screening consisted total of 82 articles out of which 13articles were finally included in the study. The papers were screened independently by 4 reviewers. At first the papers were screened by title. Out of four reviewer, reviewer which selected maximum number of article were taken in consideration. The selected articles were 57 in number. Duplicates from 57 screened articles were then removed to get 30 articles and abstract of same was made ready. As a second step, 30 abstracts were again screened to remove 04 article to get 26 articles. Free full text 13 papers were then obtained out of 26 abstracts.
And thus 13 paper were finally selected for the study.

Data Collection Process

A standard pilot form in excel sheet was initially used and then all those headings not applicable for review were removed. Data extraction was done for one article and this form was reviewed by an expert and finalized. This was followed by data extraction for all the articles.

	Search strategy	Number of articles	Number of selected articles (Screening titles)
Search 1	Oral and Leukoplakia and Treatment	35	27
Search 2	Oral and leukoplakia and Therapy	34	22
Search 3	Oral and leukoplakia and Modality	02	0
Search 4	Oral and leukoplakia and Management.	05	04
Search 5	Oral and Potentially premalignant disorder and Therapy	03	02
Other sources		03	02
Total		82	57

Data Items

The data items included were

1. Author – The name of the author
2. Location – The country in which the study took place
3. Year of publication – The year in which the study was published
4. Study design – If the study was a control or a clinical trial.
5. Sample size – No. of participants included in the study
6. Setting – Place where the study was conducted
7. Participant description- Patient with leukoplakia.
8. Study end point – Objectives of the study
9. Intervention – various treatment modalities for leukoplakia
10. Time –Time of intervention and follow up
11. Outcome – Result of the study
12. Conclusion

Result

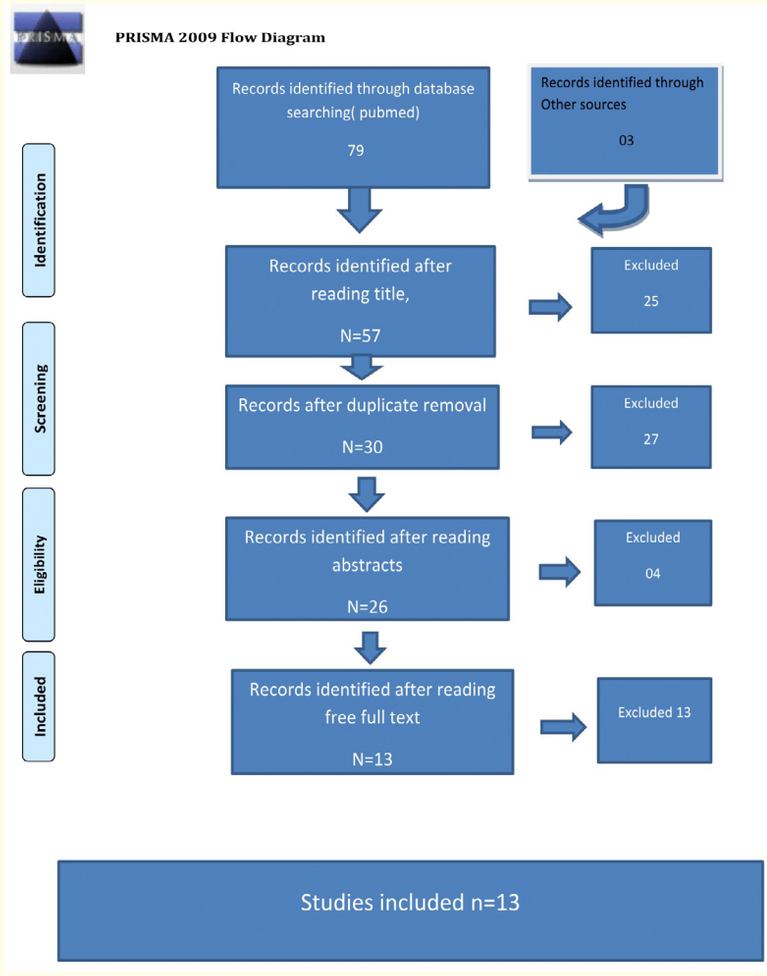

Figure: *PRISMA 2009 Flow Diagram.*

Discussion

Oral Cancer is a disease with high morbidity and mortality. Oral cancer is 6th most common cancer in World. Oral cancer has increasing incidence in developing countries and mostly develops from the site of leukoplakia. Among the different precancerous conditions leukoplakia shows highest rate of malignant transformation (2.7% - 9%). Leukoplakia though a chronic painless disease for the patient should be always considered as serious health problem by health care takers.

Despite of tremendous progress in the field of cancer there is no medical treatment proven to be effective and reliable at every clinical situation of cancer. Quality of life of those taking available surgical, radiological and medical treatment for cancer is poor. Recently more stress is given on chemoprevention rather than the definitive treatment after cancer diagnosis. Oral leukoplakia shows the preliminary sign were chemopreventive actions should be started.

True as that for the oral cancer, definitive treatment for leukoplakia is yet not formulated, so the management focuses toward clinical remission, histological reduction in degree of dysplasia and decrease in the rate of malignant transformation.

If leukoplakia, oral potentially premalignant disorder as recently categorized by WHO is treated can bring about substantial decrease in the rate of oral squamous cell cancer development.

As oral physician identifying the lesion as leukoplakia and formulating the appropriate treatment plan is of utmost importance.

Recently substantial research is taking place in the field of management of leukoplakia, various treatment are tried, different claims are made depending upon the researchers experience which creates confusion in the minds of general health care taker. With help of present systematic review we aim to provide a line of treatment in the management of leukoplakia and decrease the treatment dilemma amongst the general healthcare taker.

Following the PRISMA guidelines, 13 studies stating the treatment modalities were selected for this systematic review. Surgical and nonsurgical both treatment modalities were included in the study. Nonsurgical treatment headed towards histological changes and reducing malignant transformation more than only clinical remission. Nonsurgical or medicinal treatment were longer duration and slow in action but proved to bring about histological changes with clinical regression. Surgical treatment aimed mostly towards clinical remission. Surgical treatment are short duration and showed instant clinical changes. This is motivating to both healthcare provider and patient, though the histological usefulness was unknown.

Nagao T., *et al.* [3] studied low dose beta carotene (10 mg/day) and vitamin C supplement given for one year to 46 leukoplakia patient found it as ineffective for clinical remission and reduction in malignant transformation over follow up period of 5 years.

Saba N., *et al*. [5] conducted a study for chemoprevention of head and neck cancer with Celecoxib and Erlotinib. 7 patient with varying degree of dysplasia were histologically evaluated after 400 mg celecoxib and 50 - 100 mg erlotinib was administered for 6 month showed 43% complete remission and 14% showed partial remission. Major pitfall was small sample size. Erlotinib induced skin rash was another concern. The toxicity concern clearly open the door to explore better tolerated agents such as natural compounds as future chemopreventive agents.

A study on aminolevulinic (ALA) acid as photosensitizer and photodynamic therapy (PDT) on oral leukoplakia of 11 subjects by Wong S., *et al*. [6] resulted in no clinical responses though there was no significant toxicity from ALA PDT.

Search for non-toxic agent with cancer preventive activity led author Armstrong W., *et al*. [7] evaluate bowman birk inhibitor. In 89 subjects he yielded statistically significant decrease in size of lesion by 20.6% but it was not statistically significant in comparison with placebo.

In the study of William W., *et al*. [8] with high dose fenretinide (900 mg) for oral leukoplakia. He found it as well tolerated but elicited objective response only in 3/15 patient which made him terminate the trial at first stage.

Cheista F., *et al*. [9] did a study using fenretinide 200 mg daily for 0ne year in 170 patients operated for leukoplakia and found fenretinide as tolerable and effective at preventing relapses and new leukoplakia's but it was inconclusive regarding protective effect against oral cancer.

Lipmann S., *et al*. [10] evaluated 35 patient with retinoid resistant leukoplakia with low dose 200 mg fenretinide for 3 months and follow up of 9 month, he found 34.3% partial responses and increase in level of apoptosis.

Patel J., *et al*. [11] evaluated efficacy of oral lycopene with vitamin E and selenium in oral leukoplakia proving it as effective and safe chemopreventive agent with 85% mean improvement in clinical and histological features.

ZSP is herbal mixture of 6 herbs used as chemopreventive agent by Sun Z., *et al*. [12] on oral leukoplakia reduces size of lesion in 67.8% patient.

Li Y., *et al*. [13] he gave intra epithelial injection of recombinant human adenovirus P53 (rAd p53) in 22 patient with dysplastic oral leukoplakia after 2 years of follow up 72.7% mean regression was observed. Also it was safe, feasible and biologically active in patient with leukoplakia.

Kharadi U., *et al*. [14] used 940 nm diode laser on 10 patient of oral leukoplakia for complete excision. after 6 month 80% patient showed complete clinical disappearance and none patient showed malignant transformation. Author quotes association between location of lesion and its recurrences after surgery.

Montebugnoli L., *et al*. [15] studied the new epithelium after excision of oral leukoplakia by ND:YAG laser up-to 62 months and found 11/13 patient (84.6%) showing normal mucosa but altered cell turnover can persist in about 20% of cases. Also Ki67 as a marker of proliferative status can be of prognostic value.

Jornet P and Alonso F [16] used CO_2 laser and cold knife for excision of leukoplakia. There was no any malignant transformation during the follow up period but there is no evidence that surgical treatment is protective against cancer development.

Out of 13 studies and 15 interventions, 3 studies were based on the use of fenretinide which is a synthetic retinoid, each study had used different dose of fenretinide. Low dosage were found to be more effective than the high dose.

In surgical therapies study all the types of laser like CO_2, diode and Nd: YAG were used also cold knife excision was compared with ND:YAG laser. Laser were found to be more effective as compared with cold knife surgery in relation to post-operative pain and swelling though healing was delayed. Also excision by laser do not make tissue available for histological examination. None of the article have mentioned about the histological changes except for the one which used Nd: YAG laser. And its results were also positive.

One article had mentioned role of herbal medicine mixture which is approved by government of china as a chemopreventive agent, in protection from cancer development from oral leukoplakia. Results found were promising but the use and availability of same product should be further evaluated.

Beta carotene and vitamin C was not found useful but lycopene with vitamin E and selenium showed positive results. Aminolevulinic acid photodynamic therapy was also not positive in management of leukoplakia. Celecoxib and Erlotinib showed positive results but toxicity was a concern factor. Bowman birk inhibitor should negative results.

Limitations of this review was unavailability of full text article and inability to take literature from another databases.

Conclusion

After studying all the article stating different treatment modalities of leukoplakia in depth we conclude that laser surgery is better treatment alternative for conventional surgery for instant clinical remission. Medical adjunctive therapy with chemopreventive agent like lycopene with vitamin E and selenium or rAd p53 intraepithelial injections or low dose fenretinide should be used to bring histological changes reducing the rate of malignant transformation.

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