Facultad de Odontología

Carrera de Odontología

“Onco-preventive management of oral leukoplakia lesions by topical 5-ALA-mediated photodynamic therapy: A systematic review of clinical trials”

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Resumen

La leucoplasia oral es el trastorno potencialmente maligno más prevalente de la mucosa oral a nivel mundial y su manejo sigue siendo un desafío. La terapia fotodinámica es un método alternativo mínimamente invasivo en el tratamiento de lesiones premalignas; y el uso del fotosensibilizador tópico 5-ALA más la irradiación con diodo emisor de luz (LED) o luz láser ha sido uno de los enfoques más recomendados para los tratamientos de la leucoplasia oral mediante terapia fotodinámica. El presente estudio se realizó para determinar su eficacia clínica como alternativa de quimioprevención en las diferentes formas clínicas de leucoplasia oral. Se realizó una búsqueda exhaustiva de artículos científicos publicados en los últimos 30 años en idioma inglés, utilizando palabras clave con la guía MeSH, sobre el uso de la terapia fotodinámica tópica mediada por 5-ALA como fotosensibilizador y bajo radiación láser de baja intensidad o luz LED como una fuente de iluminación, en diferentes bases digitales. La revisión sistemática bajo la guía PRISMA reconoció una eficacia del 88,6% para esta modalidad de fototerapia en el manejo de la leucoplasia oral, con un tamaño del efecto mayor en las formas clínicas homogéneas con cambios displásicos, independientemente del tipo de fuente de luz. Sin embargo, la evidencia utilizada en este análisis fue moderada. En base a los resultados del presente estudio, podemos concluir que la terapia fotodinámica mediada por 5-ALA tópico parece ser una alternativa de alto rendimiento en el manejo oncopreventivo de las lesiones de leucoplasia oral. Sin embargo, recomendamos realizar ensayos clínicos controlados y aleatorizados con metodologías homogéneas que nos permitan generar un metanálisis con un alto nivel de evidencia.

Palabras clave: Terapia Fotodinámica. Leucoplasia oral. Ensayos clínicos. Revisión sistemática

Abstract

Oral leukoplakia is the most prevalent potentially malignant disorder of the oral mucosa globally and its management remains a challenge. Photodynamic therapy is a minimally invasive alternative method in the treatment of premalignant lesions; and the use of the topical 5-ALA photosensitizer plus irradiation with light emitting diode (LED) or laser light has been one of the most recommended approaches for the treatments of oral leukoplakia by photodynamic therapy. The present study was carried out to determine its clinical efficacy as a chemoprevention alternative in the different clinical forms of oral leukoplakia. An exhaustive search of scientific articles published in the last 30 years in English was carried out, using keywords with the MeSH guideline, about the use of topical 5-ALA-mediated photodynamic therapy as a photosensitizer and under low intensity laser radiation or light LED as a source of illumination, in different digital bases. The systematic review under PRISMA guidance recognized an efficacy of 88.6% for this mode of phototherapy in the management of oral leukoplakia, with a greater effect size in the homogeneous clinical forms with dysplastic changes, regardless of the type of light source. However, the evidence used in this analysis was moderate. Based on the results of the present study, we can conclude that topical 5-ALA-mediated photodynamic therapy appears to be a high-performance alternative in the oncopreventive management of oral leukoplakia lesions. However, we recommend running controlled and randomized clinical trials with homogeneous methodologies that allow us to generate a met analysis with a high level of evidence.

Keywords: Photodynamic Therapy. Oral Leukoplakia. Clinical Trials. Systematic Review

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1. Introduction

Every year around 200,000 new cases of OSCC are diagnosed globally [1, 2] and, despite the progress in the therapeutics and molecular pathogenesis of oral cancer, the incidence of squamous cell carcinoma of the tongue has increased around the world in recent years [3-5]. Oral cancer is a long-term process, preceded in a high percentage due to precancerous lesions today called potentially malignant disorders of the oral mucosa [6]. Oral leukoplakia (OL) continues to be the most frequent potentially malignant disorder of the oral mucosa globally, so it is key to optimally apply minimally invasive prevention strategies, especially in the clinical forms of OL with a higher risk of transformation [6-10]. Topical photodynamic therapy (PDT) has been proposed as a chemoprevention strategy as well as other non-surgical alternatives such as chemoprevention with bleomycin, retinoic acid, adenovirus, and COX inhibitors [11].

So far, four systematic reviews related to the proposed topic have been published, the last one in 2019 [11-14], however, none of them bases their conclusions on a robust statistical analysis, and it has not yet been possible to reach a consensus on the impact of clinicopathological variables on the clinical response of OL lesions to PDT. Given this background, we proposed to carry out a systematic review of clinical trials published in the last 30 years on the efficacy of topical PDT mediated with 5-aminolevulinic acid (5-ALA) in the control of oral leukoplakia lesions, in order to provide head and neck clinicians with more decision criteria when choosing this therapy as a non-surgical treatment in the management of cancerous lesions such as OL.

2. Materials and methods

Based on the Preferred Reporting Items for Systematic Review and Meta-Analysis Guidelines [PRISMA] [15], an electronic search was performed in four digital databases, PubMed, Science Direct, Cochrane, EMBASE for the collection of scientific articles published during the period 1991 - 2021, for which MeSH terms [16] were used in all fields to maximize the search during the investigation. Only English-language publications were considered and duplicate articles in more than one database were considered only once.

2.1. Research question

"Is topical 5-ALA-mediated photodynamic therapy an effective chemopreventive alternative in the management of oral leukoplakia lesions, regardless of clinicopathological parameters (clinical type of leukoplakia and degree of dysplasia), and type of light source?"

2.1.1. PICO question

- P: patients with clinical and histopathological diagnosis of oral leukoplakia.
- I: topical 5-ALA-mediated photodynamic therapy.
- C: light source, clinical pattern, and degree of epithelial dysplasia.
- O: efficacy clinical rate and failure clinical rate.

2.2 Eligibility or inclusion criteria and data extraction

Clinical trials or intervention studies published in full text in the last 30 years (1991-2021) in English, obtained from the following databases: PubMed-Medline, Science Direct, Cochrane library and EMBASE. We included controlled or uncontrolled interventional studies with or without blinding method, which evaluated clinical efficacy of topical 5-ALA mediated photodynamic therapy as a photosensitizer and under low level laser therapy (LLLT) or LED light as a source of illumination.

2.2. Exclusion criteria

Case reports, letters to the editor, review articles, systematic reviews, literature reviews, analytical studies, experimental studies, articles that do not focus on the topic, and scientific articles in incomplete or inaccessible text.

2.3. Selection and evaluation of relevant studies

The keyword-directed search led to the selection of 17 studies published in the last thirty years, these were read in full text and independently evaluated in relation to the eligibility criteria. A consensus meeting was held to discuss differences between reviewers after evaluation. Based on this discussion, 11 articles were included for the qualitative analysis of this systematic review; between five to nine studies were used for quantitative analysis. (Fig. 1).

2.4. Data analysis

Two reviewers (CJ and AD) performed data extraction independently. The information obtained from the accepted studies was tabulated according to the demographic characteristics of the participants, clinical type and site of oral leukoplakia, follow-up period, main results, recurrence, quality of the studies and PDT parameters. All extracted data were cross-checked by the reviewers and the research director (RL). Discord was resolved through discussion until an agreement was reached.

2.6. Assessment of risk of bias

To assess the methodological quality and risk of bias, we used the Cochrane, Scottish Intercollegiate Guidelines Network (SIGN) [17, 18] and Grades of Recommendation, Assessment, Development, and Evaluation Work Group or GRADE guidelines [19].

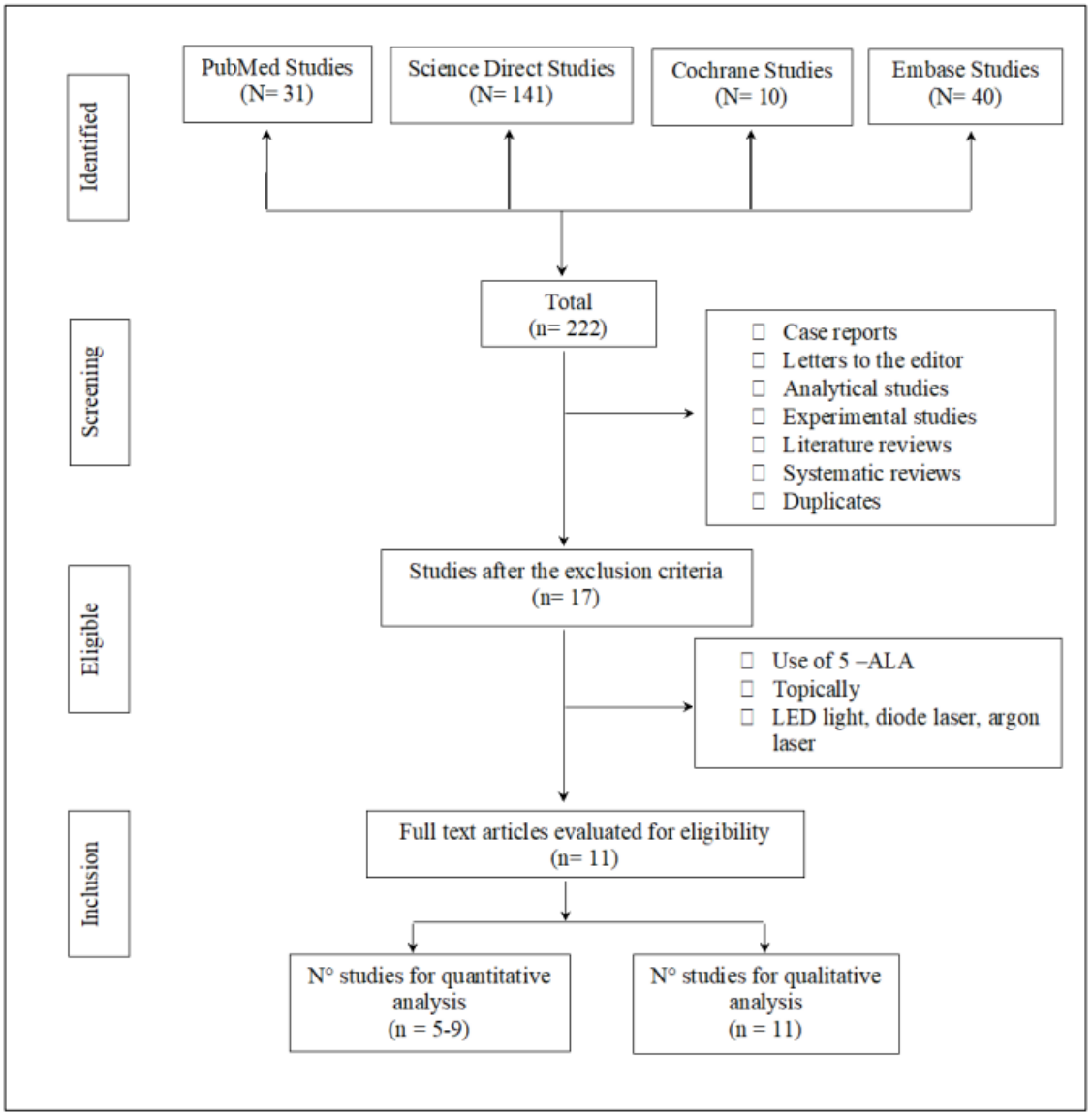


Figure 1 Search and selection of literature according to the PRISMA guidelines

2.7. Data collection and statistical analysis

The data were organized and processed in tables using Microsoft Excel 2010 software. The research was mainly aimed at summarizing the relevant information and, subsequently, determining by association analysis the impact of clinicopathological variables on the effect size generated by topical 5-ALA-mediated PDT in the management of oral leukoplakia lesions. To determine the consistency between selected studies, a comparison of means was made for the response variable "clinical

efficacy rate" based on an explanatory variable with two levels "light source"; after evaluating the assumption of normal distribution of the response variable and homoscedasticity with the Shapiro Wilks test plus Q-Q-plot, and F test for equality of variances, respectively. The null hypothesis of equality of population means was tested with a significance level of 0.05 and a confidence level of 95% using the Student´s t-test for two independent samples. To answer the question posed in the study, we used a statistical model for the comparison of means with a two tailed Student's t-test for two independent samples based on a categorical variable, after validating the assumptions of normality and homoscedasticity. The results of the t-test were validated by one factor ANOVA. Given the lack of homogeneity of variances, the comparison of means was carried out by non-parametric analysis with the Kruskal Wallis test. The relationship between two quantitative variables was determined by Pearson's correlation test, with a significance level of 0.05 and a confidence level of 95% [20]. The statistical analysis was carried out with the Info Stat software version 2020 of the National University of Córdoba.

3. Results

3.1. General characteristics of the included studies

A total of 17 citations were obtained after searching with the keywords and filtering by exclusion criteria as well as duplicates; of which, 11 articles went to the stage of complete reading and data extraction, after fulfilling the eligibility criteria proposed in this research (Fig. 1). The risk of bias in the chosen studies was evaluated under the Cochrane guidelines, obtaining 100% of studies with a high risk of bias. The overall quality of the evidence, according to GRADE standardized criteria, turned out to be moderate due to the absence of inter-study heterogeneity regarding the main outcome (T: 0.34/p = 0.7382), and an important effect size with a rate mean response estimated

at 55% (95% CI 23- 83%) for photodynamic therapy with topical 5-ALA. All investigations were clinical studies with no comparison of PDT with other treatment modalities, except for three studies that used a non-randomized controlled design, with one of them comparing the efficacy of topical 5-ALAmediated PDT versus cryotherapy, the second comparing the efficacy of PDT with LED light versus laser light and the third comparing topical 5-ALA-mediated PDT in a once a week versus twice a week application schedule. No randomized controlled clinical trial has been reported so far on the issue raised in this research.

3.2. Patient characteristics and clinicopathological attributes of oral leukoplakia lesions

A total of 427 patients between 18 and 89 years of age received topical 5-ALA-mediated PDT and laser radiation or LED light, of which 64% were men, with an average age between 50 and 52 years for the total of the cohort addressed with the treatment approach under study (Table 1).

Table 1 General characteristics of the studies included.

Authors and year of publication	Patients	Age range	Gender (Male)	Follow up	Study outcome	Recurrence (%)
A. Kúbler, 1998	12	No reported	11	6 – 16 months	**CR:** 5 **PR:** 4 **NR:** 3	0%
Aleksander Sleron, 2003	12	32-72	No reported	4-34 months	**CR:** 10 **PR:** 0 **NR:** 2	8.33%

Aleksandra Kawczyk, 2012	48	32-75	20	4-34 months	**CR:** 35 **PR:** 7 **NR:** 6	27.08
Hung Pin Lin, 2010	80	34-89	3	6-37 months	**CR:** 78 **PR:** 2 **NR:** 0	10%
Chuan-Hang Yu, 2009	46	34-89	44	16-76 months	**CR:** 42 **PR:** 4 **NR:** 0	22%
Kotya Naik Maloth,2016	12	39-53	No reported	No reported	**CR:** 2 **PR:** 8 **NR:** 2	0%
Ying Han , Si Xu, 2019	29	18-80	11	3 months	**CR:** 16 **PR:** 9 **NR:** 4	12%
Hsin-Ming Chen, 2005	32	30-73	30	3-12 months	**CR:** 16 **PR:** 16 **NR:** 0	12.50%
Hsin-Ming Chen 2007	127	26-79	120	3 - 42 months	**CR:** 44 **PR:** 56 **NR:** 27	2,27%

Niranzena Panneer Selvam, 2021	5	35-49	5	24 months	**CR:** 2 **PR:** 2 **NR:** 1	0%
Gal Shafirstein, 2011	24	37-79	14	30-90 days	**CR:** 9 **PR:** 11 **NR:** 4	11.11%

Note: CR: complete response; PR: partial response; NR: null response.

In all studies, oral leukoplakia lesions were confirmed by clinical and histopathological diagnosis. Of the 11 studies analyzed, 7 provided information on the clinical pattern of the leukoplakia lesion, registering a total of 189 non-homogeneous leukoplakia [Verrucous leukoplakia (HVO) and Erythroleukoplakia] and 142 homogeneous leukoplakia, topographically compromising sites of the lining buccal mucosa, keratinized mucosa, and specialized tongue mucosa; of which 163 presented histological evidence of dysplastic changes, which were mild to moderate in 83.9% of the foci. The response of the oral leukoplakia lesion to treatment was the main variable in all studies.

3.3. Parameters linked to PDT of the included studies

Of the 11 intervention studies evaluated, 63.6% used laser radiation as a light source with different active ingredients (argon, diode, xenon, helium / neon) and with wavelengths between 420 and 635 nm, with the third quartile ubicated in 635 nm. Regarding the radiation dose used, 75% of the studies applied a power density equal to or less than 150 mw / cm2, with fluences that ranged from 8 to 180 J / cm2. However, 72.7% of the studies used a fluence equivalent to 100 J / cm2 (Table 2).

Table 2 Parameters of photodynamic therapy in the included studies

Authors	Concentration Photosensitizer ALA 5	Light Source	Wavelength (nm)	Power density (mW/cm2)	Energy fluence (J/cm2)	Duration of irradiation (second)	Frequency
A. Kúbler, 1998	20%	LED red light/Argón laser	630	100	100	3600	No reported
Aleksander Sleron, 2003	10%	Argón laser	635	150	100	900	6-8 sessions
Aleksandra Kawczyk, 2012	Group 1 (20%) Group 2 (10%)	Group 1 (Diomed Laser) Group 2 (Argon-pumped dye laser)	Group 1 (630) Group 2 (635)	No reported	100	900	6-8 sessions
Hung-Pin Lin, 2010	20%	Laser light	635	100	100	1000	6 sessions
Chuan-Hang Yu, 2009	20%	LED red light/Laser light	635	100	100	1000	5 sessions

Kotya Naik Maloth, 2016	98%	LED blue light	420	500	No reported	600	3 sessions
Ying Han, 2019	20%	HE-NE laser	632	500	90-180	180	No reported
Hsin-Ming Chen, 2005	20%	LED red light / Laser light	635	100	100	1000	6 sessions
Hsin-Ming Chen, 2007	20%	LED red light	635	100	100	1000	6 sessions
Niranzena Panneer Selvam, 2021	10%	Xenon laser	630	100	100	1000	6-8 sessions
Gal Shafirstein, 2011	20%	Single laser pulse	585	No reported	No reported	No reported	No reported

3.4. Clinical response obtained in the included studies

The results in all studies were categorized as complete response (CR), partial response (PR), and no response (NR). Of the total number of patients treated with topical 5-ALA mediated PDT, 60.7% demonstrated a complete response to treatment (absence of signs compatible with leukoplakia evidenced by clinical examination),

27.9% responded partially, with a reduction in the maximum diameter of the lesion greater than 20%. The absence of response was observed in 11.4% of the intervened patients, and disease progression was not reported in any study.

Of the 11 clinical trials evaluated, only three did not present cases of recurrent disease and the average recurrence rate calculated for all the studies was less than 10%.

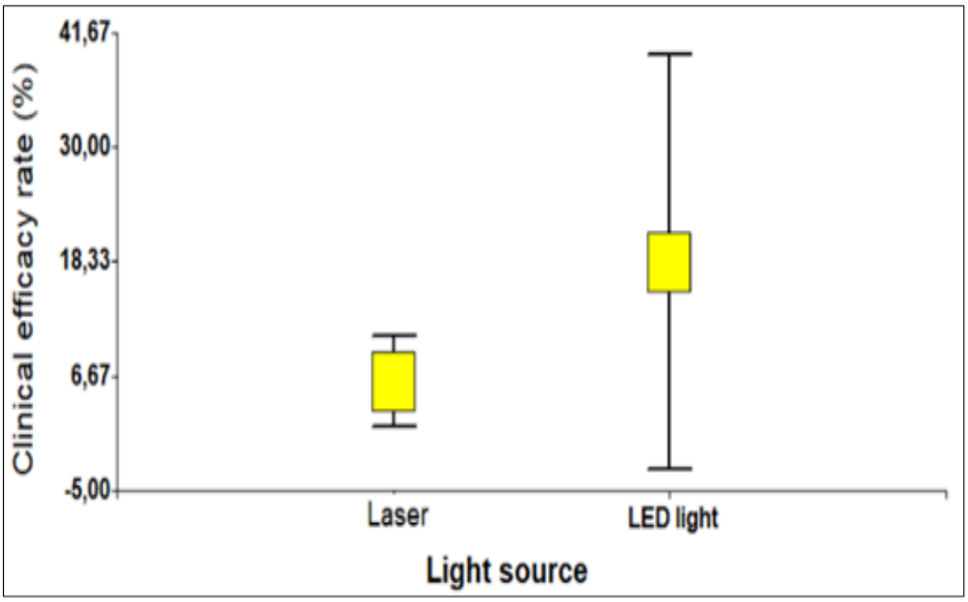
Given these encouraging data, we wonder if the clinical response of oral leukoplakia lesions to topical 5-ALA mediated PDT is dependent on physical parameters such as the light source, and clinical-pathological aspects of leukoplakia (semiological pattern and epithelial dysplasia).

The impact of the light source (laser or LED light) on the clinical oral leukoplakia response was evaluated by non-parametric ANOVA (Kruskal Wallis test) for two independent samples. Although the size of the p-value did not allow rejecting the null hypothesis of equality of population means ($p = 0.4643$), meaning that both treatments have the same clinical impact; however, the variability in the “LED Light” group was very wide. Similar results were obtained when performing the analysis with the “clinical failure rate” variable (Figs. 2, 3).

The relationship between the effect (clinical efficacy) and the rate of epithelial dysplasia was evaluated by Pearson's correlation test, obtaining a coefficient of 0.73 and a p-value of 0.0248, so that null hypothesis was rejected for lack of existence in the linear relationship between variables. The value obtained for the Pearson coefficient shows a positive and linear relationship between both variables, indicating that only 27% of the variability in the clinical efficacy rate cannot be explained by the epithelial dysplasia rate (Fig. 4).

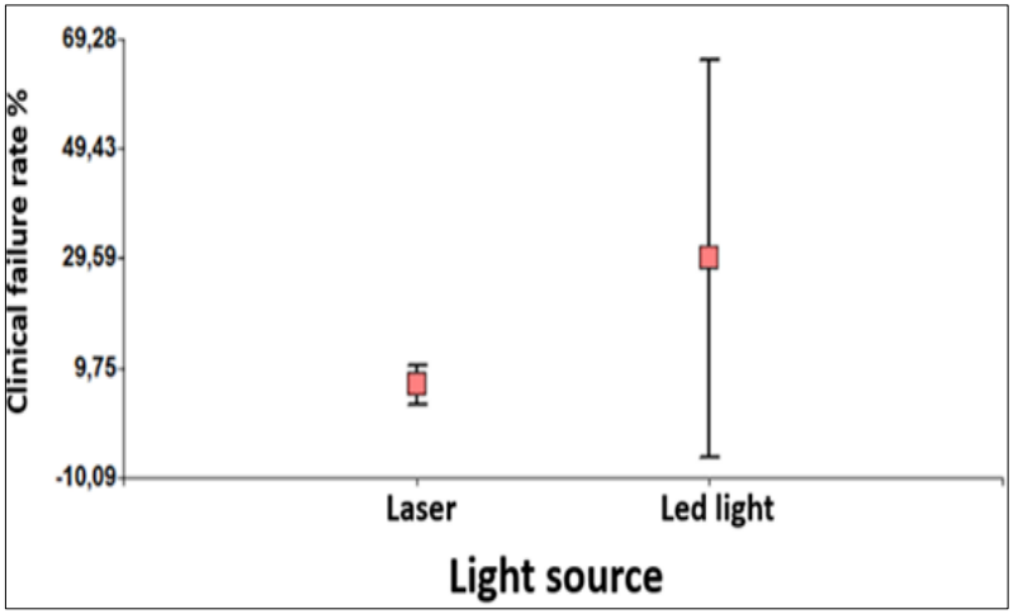
The relationship between the effect (clinical efficacy) and the clinical pattern of oral leukoplakia was initially evaluated by profile graph to determine the trend of the data, obtaining a difference in the mean of the evaluated groups (Fig. 5).

To confirm that such a difference is not due to chance, we tested our hypothesis (the impact of topical 5-ALA mediated PDT on oral leukoplakia lesions varies according to the clinical type) by two-tailed Student's t-test for two independent samples, subsequently validated with one factor ANOVA under the means comparison model; obtaining in both tests a statistically significant difference with a confidence level of 95%.



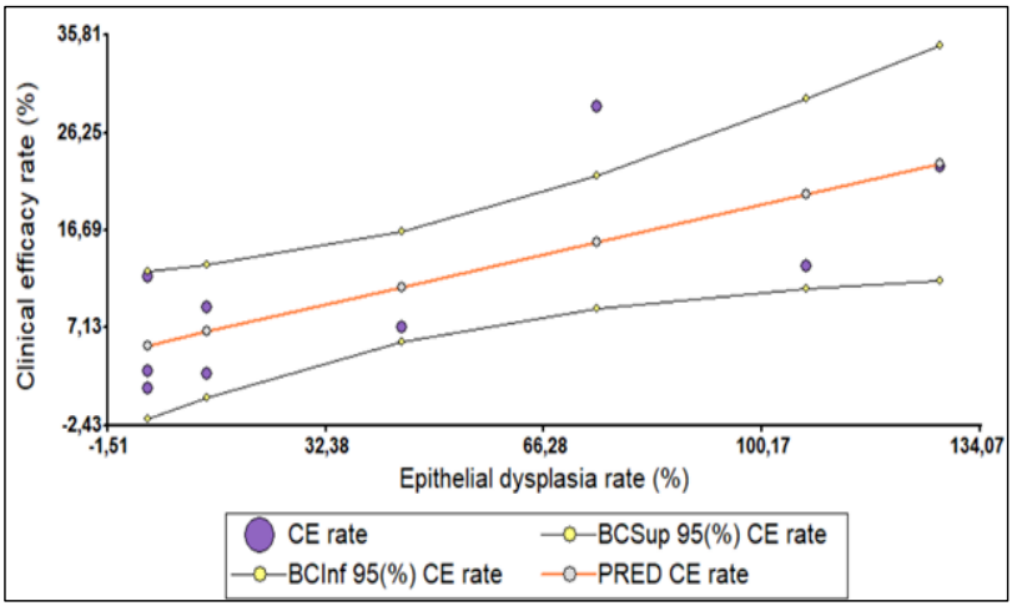
Note: The statistical analysis by comparison of means (non-parametric, one factor ANOVA) generated a value of the statistic H = 0.69 with a value of p = 0.4643, so that, it's not possible to reject null hypothesis (H0) for equality of means; however, the variation is less in the group treated with laser. The data were obtained from 8 studies, using a confidence level of 95% and an alpha error of 5%.

Figure 2 Mean and standard deviation for the variable “clinical efficacy rate” as a function of the light source used



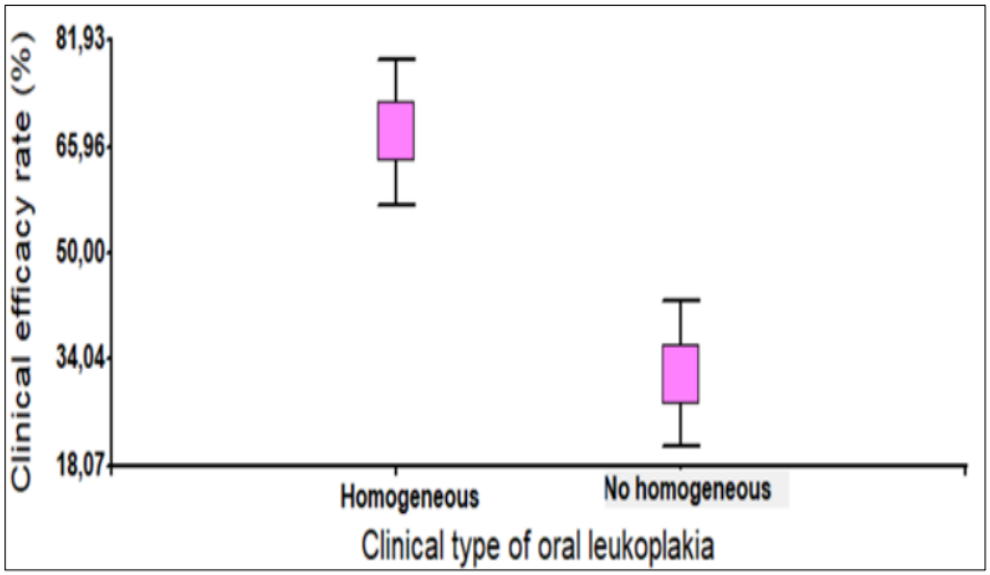
Note: The non-parametric statistical analysis by comparison of means with the Kruskal Wallis test generated a value of the H statistic = 0.25, therefore, the H0 of equality of means cannot be rejected; however, the variation is less in the group treated with laser. The data were obtained from 8 studies, using a confidence level of 95% and an alpha error of 5%.

Figure 3 Mean and standard deviation of the variable “clinical failure rate” as a function of the light source used



Note: The data shown comes from 9 clinical trials, using a 95% confidence level and a significance level of 0.05. CE (clinical efficacy); BC (upper and lower confidence band for clinical efficacy rate); PRED (predicted value for variable CE)

Figure 4 Linear and positive correlation between the variables "clinical efficacy rate" and "epithelial dysplasia rate" graphically evidenced by a scatter diagram



Note: The dot plot clearly demonstrates the difference between the group means, with similar variances and no outliers. Both the Student's t-test (T: 5.28) and one factor ANOVA (F: 27.90) generated a p-value of 0.0007, therefore, H0 for equality of means was rejected. The data come from the processing of 5 clinical trials, using a confidence level of 95% and a significance level of 0.05

Figure 5 Mean and standard deviation for the response variable “clinical efficacy rate” as a function of the explanatory variable “clinical type of oral leukoplakia”

4. Discussion

Photodynamic therapy or PDT is a minimally invasive alternative approach, which has shown high selectivity and repeatability in the treatment of potentially malignant lesions such as OL [14].

In the present study, we review the relevant literature on the efficacy of PDT in the treatment of OL. The sum of the complete response rate and the partial response rate was 88.6%. Yuting Li et al, in his analysis, obtained a success rate of 76.1%, demonstrating a high effective rate in general [12]. However, Fahim Vohra obtained a complete response in 27-100% of premalignant lesions, mentioning that complete resolution occurred only in specific types of lesions [21].

Five-aminolevulinic acid or 5-ALA, is a second-generation photosensitizer with a low molecular weight, a short period of photo toxicity (24 to 48 h) and good tissue penetration. It is the most widely used photosensitizer for the treatment of OL by PDT, given its versatility, since it can be administered intravenously or topically [14].

In this study we obtained a linear and positive relationship between the clinical efficacy rate and the epithelial dysplasia rate (Fig. 4). This suggests that the leukoplakia's that most benefit from topical 5-ALA mediated PDT are dysplastic OL. This result is consistent with the observations of Hun Pin Lin et al., and Chuan Hang Yu et al [22, 23]. According to these authors, dysplastic epithelium can retain more 5-ALA than hyperplastic epithelium, and the thinner keratin layer of dysplastic OL may have only a minimal effect in reducing light intensity [22, 23]. However, Yin Han's group did not obtain a significant association between the degree of epithelial dysplasia and the overall clinical efficacy of topical 5- ALA mediated PDT, but paradoxically, they observed that OL with moderate and severe dysplasia require less irradiation time to achieve a complete clinical response with respect to OL with or without mild dysplasia [24].

Regarding the relationship between the effect (clinical efficacy) and the clinical pattern of OL, we obtained a significantly higher clinical efficacy rate for homogeneous OL compared to non-homogeneous ones (Fig. 5). This result is consistent with the findings

of Yin Han et al. (2019), who also observed a greater benefit of this therapy for homogeneous OL [24].

Treatments based on phototherapy can be carried out with LED light or laser radiation, both LEDs and lasers emit photons to produce light. The light from LED is more dispersed and multidirectional, while the laser light is highly focused and monochromatic, characteristics that give the latter system greater efficiency when converting electrical energy to light, since the emissions of these photons are stimulated thanks to a mirrored surface only present in laser system. This laser system reflects photons towards the electric field to generate a new cycle or loop of excited electrons that release extra energy, which is converted, again, into a photon. Once enough photons are released, a light escape cavity allows a narrow, bright, and focused beam of laser light to be emitted.

The choice of a light source depends on several factors such as type of lesion (tissue characteristics, size, location, and accessibility), type of PDT (absorption and administration spectrum), cost and availability of the light systems [25, 26].

The impact of the light source (laser or LED light) on the oral leukoplakia response was evaluated by non-parametric ANOVA (Kruskal Wallis test) for two independent samples, obtaining an average clinical efficacy rate and average clinical failure rate similar between both systems (Figs. 2, 3), which is consistent with the systematic review by Figueira et al [27]. However, the variability in the “LED Light” group was very wide for both analyzes (Figs. 2, 3). This result suggests that a PDT performed with laser light would generate more homogeneous and predictable clinical responses among OL patients. This is the first study to report this difference in clinical impact between LED and laser light with topical 5-ALA mediated PDT.

The weaknesses of our study are restricted to the small sample size, since the investigations related to the proposed topic are scarce. We need more clinical trials with homogeneous methodologies and a low risk of bias, which allow for more robust secondary investigations that will lead us to the generation of a meta-analysis.

5. Conclusion

Topical 5-ALA mediated PDT appears to be a high-performance alternative in the onco-preventive management of oral leukoplakia lesions, however, there is no evidence to ensure that the clinical efficacy of this therapy depends on the type of light source (laser or LED light); nevertheless, treatment with LED light shows wide variability in the observations, therefore, we recommend the development of randomized clinical trials with more homogeneous methodologies, which allow us to confirm the absence of true differences. In contrast, this research obtained evidence to suggest that the clinical response of oral leukoplakia to treatment with topical 5-ALA mediated PDT differs significantly between clinical forms of oral leukoplakia and grade of epithelial dysplasia.

Contribution roles

RL: conceptualization, methodology, data validation, formal analysis, preparation, and writing, editing and supervision. AD: bibliographic search, writing of methods and results, edition. CJ: bibliographic search, method writing, results and discussion.

Compliance with ethical standards

Acknowledgments

We express our gratitude to our patients for his collaboration and trust.

Disclosure of conflict of interest

The authors completed the ICMJE conflict of interest declaration and stated that they did not receive funds for the completion of this article. They do not have financial

relationships with organizations that may have an interest in the article published in the last three years and they do not have other relationships or activities that may influence the publication of the article. The forms can be requested by contacting the responsible author or the Editorial Committee of the Journal.

Statement of ethical approval

The present study did not require an evaluation by an ethics committee, since as it is a systematic review, it uses secondary data sources.

Financing

The authors declare that they did not have external sources of financing to carry out this study.

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