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Protocol

Efficacy of 5% methylene blue photodynamic therapy in the treatment of potentially malignant oral disorders: a randomized, double-blind, controlled trial

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ABSTRACT

Background: Potentially malignant oral disorders (PMOD) play a vital role in the secondary prevention of oral cancer, especially considering the difficulty in identifying specific risk factors. Oral leukoplakia (OL), the most common PMOD, has a variable malignant transformation rate. Photodynamic therapy (PDT) emerges as a promising alternative in treating these conditions. This approach is particularly valuable for extensive lesions or patients with contraindications to conventional treatments. Despite promising results, the choice of photosensitizer agent still lacks consensus. The aim of this study is to evaluate the efficacy of PDT with 5% methylene blue compared to 20% aminolevulinic acid (ALA) in the treatment of OL.
Methods: This is a randomized, controlled, double-blind clinical trial with a non-inferiority testing approach. Patients will be allocated into two groups: leukoplakia experimental group (PDT with methylene blue) and leukoplakia control group (PDT with ALA). The analysis of results will be based on primary outcomes (clinical remission) and secondary outcomes (histological/cytological worsening, lesion appearance, symptoms, function, psychological impact, economic impact, treatment adherence, and adverse effects). Allocation will be performed in a randomized and stratified manner, ensuring equivalence between groups. Cost-effectiveness analysis will consider the direct costs of treatment from both professional and patient perspectives.
Conclusions: This study aims to contribute to the establishment of an effective, safe, and accessible treatment protocol for the most prevalent PMOD, filling an important gap in the scientific literature and providing guidelines for future clinical practices.

Keywords: PDT, Methylene blue, Treatment, Effectiveness, PMOD

INTRODUCTION

Oral cancer poses a considerable challenge to global public health, with over 350,000 new cases reported annually and a significant record of 177,757 deaths in 2020, according to the latest data from the global cancer observatory.[1] The high morbidity rate and low survival rate emphasize the importance of prevention as a fundamental strategy to the reduce these statistics.[2]

The recognition and treatment of PMOD are essential for the secondary prevention of oral cancer, as many malignant lesions in the oral cavity originate from these disorders. Moreover, it is not always possible to identify and prevent specific risk factors for oral cancer in its carriers[3], highlighting the importance of identifying and treating lesions that may precede oral cancer.

OL is the most common PMOD, characterized by white plaque of varying risk, after the exclusion of other lesions and conditions that do not pose an increased risk for the development of oral cancer.[4] Its prevalence varies between 1.49% and 4.27%, with a malignant transformation rate ranging from 1.1% to 40.8%.[5] Approaches to the treatment of OL range from simple clinical observation ("watch-and-wait") to surgical removal of lesions. However, surgical removal is not always a viable option, especially in extensive lesions, as it may result in scarring and consequent functional loss to the patient, besides not completely eliminating the risk of malignant transformation.[6] Additionally, the lack of well-defined risk criteria for the malignant transformation of PMOD makes the choice and management of treatment complex, which can hinder strategies for the secondary prevention of oral cancer.

PDT has emerged as a promising alternative for managing these conditions, with an approximate complete remission rate of 52%.[7,8] In addition to promising results, PDT offers the advantage of lower morbidity, being less invasive and more selective regarding the affected tissue, with potential cumulative antiproliferative effects.[9] Another advantage of PDT is the possibility of managing multifocal lesions or treating patients with contraindications to surgical treatment, such as patients with heart disease or bleeding disorders.[10] PDT is based on the activation of a photosensitizer agent through exposure to visible light. This process triggers a photochemical reaction in the presence of molecular oxygen, resulting in the production of singlet oxygen. This singlet oxygen is responsible for cell destruction, causing cell membrane lysis or protein inactivation. When it comes to dysplastic cells, photosensitizing agents seem to induce apoptosis by releasing reactive oxygen species. This effect is selective for dysplastic cells, making the PDT promising for the PMOD management.[11,12]

There is evidence supporting the efficacy of PDT with ALA in the treatment of OL.[13-15] However, this substance entails high costs, low availability in the market, is associated with some adverse events in treated patients, and has a long pre-irradiation incubation time. A significant portion of published studies has shown that methylene blue can be incubated for significantly shorter times, being much more opportune. Additionally, it is a better tolerated substance by oral tissues, of lower cost, and more readily available in the market, which could favor its use in the public and the private healthcare systems.

Prasana et al reported a relevant response rate of OLs to PDT with 5% methylene blue, although their study consisted only of describing a series of 10 cases.[16] In recent systematic reviews, the scarcity of controlled randomized clinical trials on PDT in OLs was evident, and even scarcer were the trials that investigated methylene blue compared to ALA as a photosensitizer agent in these disorders.[13-15] An additional highlight is the lack of well-established diagnostic criteria for OL in previously published studies, as well as the absence of microscopic parameters to assess cytological remission of these lesions under the influence of PDT.[17]

Further studies are needed to evaluate the efficacy of PDT in treating the most prevalent PMOD, as well as the efficacy of this therapy associated with methylene blue compared to ALA, thereby contributing to the establishment of an effective, safe, and accessible treatment protocol.

Aim

The aim of this protocol is to evaluate the efficacy of PDT using 5% methylene blue compared to 20% ALA as an agent in the treatment of patients with OL.

Hypotheses

The 5% methylene blue demonstrates clinical efficacy not inferior to 20% ALA as a photosensitizer agent in PDT for the treatment of the most prevalent PMOD. This agent will provide greater tissue tolerance and patient acceptability, along with a lower cost.

Rationale

Despite promising results, there is still no consensus on the most suitable photosensitizer agent for PMOD. Some studies have used ALA in OLs, while others have explored a variety of other photosensitizer agents, including 5% methylene blue.[18] Methylene blue has already been shown to selectively induce cell death in malignant neoplastic cells, making it a promising antineoplastic agent.[19] Although porphyrin precursors like ALA have been more commonly used in the treatment of PMOD and superficial malignant lesions, methylene blue offers several potential advantages, including its non-toxicity, affordable cost, and widespread availability.[20] Additionally, PDT with methylene blue has been shown to be effective in treating PMOD, with a significant remission rate and symptom control, without the disadvantages usually associated with ALA, such as photo-allergy and pain.[13,21]

METHODS

This protocol was developed in accordance with SPIRIT guidelines (Standard protocol items: recommendations for interventional trials) and will be registered on the ClinicalTrials.gov platform.

Study design

This is a randomized, parallel, controlled, double-blind clinical trial with a non-inferiority test approach involving clinically diagnosed OL patients. The aim of this study is to compare the efficacy of PDT with 5% methylene blue to 20% ALA (active control) in treating patients with the mentioned PMOD. For its execution, the recruited individuals will be allocated into two distinct groups as follows: OL experimental group (OLEG): Participants with OL treated by PDT with 5% methylene blue, and OL control group (OLCG): Participants with OL treated by PDT with 20% ALA.

Study location and aspects

All stages of this study will be conducted at federal university of Goiás (UFG) in the postgraduate outpatient clinic. After approval by the research ethics committee, patients over 18 years of age, of both genders, diagnosed with OL, attending the oral diagnosis teaching, research, and extension center of our university, which provides clinical care for patients with oral lesions, will be recruited. Participant consent will be obtained through the signature of the informed consent form in duplicate. The study is scheduled to take place between August 2024 and July 2026. To ensure transparency in the planned procedures for conducting this study, this research protocol will be registered on the clinicaltrials.gov platform.

Participant selection

The study population consists of adults of both genders, aged 18 and older, with suspected OL in the form of a single lesion or multiple lesions larger than 40 mm^2, or smaller lesions with imprecise borders, or in anatomical locations that contraindicate surgical removal.

Inclusion criteria

Patients with a history of chronic (>6 months in duration) and persistent (without remission episodes) lesions, whose primary clinical diagnosis hypothesis is OL; presence of a predominantly white spot or plaque that cannot be removed by scraping; absence of chronic traumatic irritation in the affected area (e.g., a sharp tooth traumatizing the tongue, a white spot on the alveolar ridge or retromolar region due to masticatory friction, a white spot on the gums due to overly vigorous tooth brushing); not reversible with the elimination of apparent traumatic causes, i.e., demonstrates a persistence characteristic; does not disappear when stretching (retracting) the tissue; by clinical exclusion and/or histological exclusion of other white or white/red lesions such as: white spongy nevus, frictional keratosis, lip or buccal mucosa biting, chemical injury, oral lichen planus, pseudomembranous candidiasis, hyperplastic candidiasis, leukoedema, oral hairy leukoplakia, nicotine stomatitis, and uremic stomatitis were included in study.

Exclusion criteria

Patients with oral malignant neoplasms, or with a previous diagnosis of this condition; immunosuppressed patients; recurrent lesions; lesions with a history of previous surgical treatment; lesions diagnosed as proliferative verrucous leukoplakia were excluded.

Sample size calculation

For sample size calculation, an approach based on a statistical power of 80% and a significance level of alpha of 5% will be adopted. Data dispersion will be estimated based on the results of the study by Jin et al.[7] The primary outcome used as a parameter for sample size calculation will be clinical remission. The clinically significant outcome size considered will be 20%. Based on this calculation, 21 participants per group were estimated, totaling 42 research volunteers.

Participant allocation to study groups and randomization

As recommended by the world health organization (WHO), for the exclusion of other diagnostic possibilities, and to assess the risk of malignant transformation, the incisional biopsy procedure may be indicated. Subsequently, the specimen obtained by biopsy will be sent for histopathological examination. The histopathological examination will be performed by two experienced pathologists, who will consensually classify the specimens according to the degree of dysplasia. The histological grading system mentioned here involves the classification of OL samples as: without dysplasia, mild dysplasia, moderate dysplasia or severe (intense) dysplasia, according to criteria adopted by WHO.[22]

To ensure balance in the distribution of cases of OL categorized into various degrees of dysplasia (without dysplasia, mild, moderate, and severe/intense), which can significantly influence clinical outcomes due to the greater intrinsic risk of worsening and persistence in cases of moderate and intense dysplasia, this study will adopt a stratified block randomization strategy. For this purpose, the cases will be subdivided into two groups according to the risk of malignant transformation, with the first group comprising participants classified as without dysplasia or with mild dysplasia, and the second group containing participants with cases classified as moderate and severe dysplasia (Figure 1).

Participant distribution will be performed randomly with an allocation rate of 1:1 for the experimental and active control groups. To ensure an equal chance of participation in both groups, i.e., random allocation, an online random number generator will be used through the sealedenvelope.com application.

Regarding allocation concealment, the allocation sequence will be hidden in opaque, sealed envelopes,

which will be opened consecutively in the previously established sequence to inform the operator, minutes before the clinical session, of the type of treatment that will be instituted for each patient.

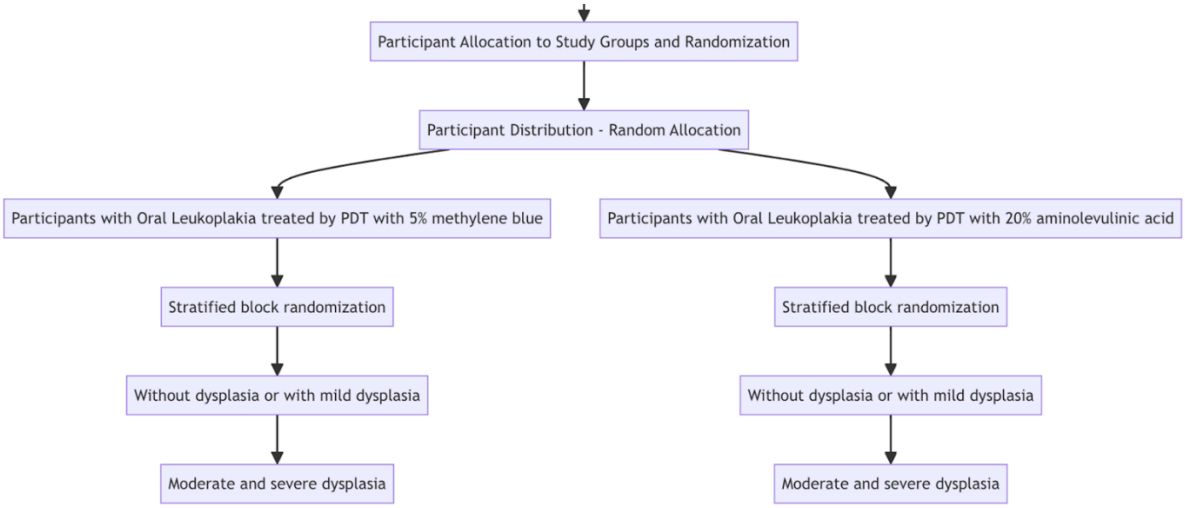

Figure 1: Allocation flow diagram illustrating the distribution of participants between the intervention and comparison groups.

Study procedures

The professionals responsible for administering PDT and monitoring clinical outcomes related to the use of 5% methylene blue or ALA will be kept unaware of the information regarding histological classification and other details of the disease history that may influence their assessment of the case severity and the impact of PDT on OLs. Complete masking regarding the procedure to be performed, according to the random allocation sequence, may not be entirely feasible. However, those responsible for verifying clinical outcomes and analyzing results will remain unaware. Participants in both groups will be instructed not to use concomitant treatments for their lesions or other oral conditions without proper dental or medical guidance. If any participant chooses to use medication during the clinical trial, their continuation in the study will be evaluated, considering the drug used and the administration period.

Experimental group

Participants in these two groups will be treated with PDT using 5% methylene blue gel formulation, which will be applied with gauze for 10 minutes on the lesion(s) present before the light application procedure. For satisfactory impregnation of the solution with the lesion, corresponding to the pre-irradiation procedure, and prevention of its solubilization by saliva soaking, relative isolation will be performed using cotton rolls, which will be placed in the upper and lower posterior vestibule and in the sublingual and parotid papilla regions. Additionally, a piece of PVC plastic film will be applied over the gauze after the application of the 5% methylene blue solution. After the pre-irradiation period, the red laser will be applied using the therapy EC equipment (DMC, Ribeirão Preto, Brazil), at a wavelength of 660 nm, continuous mode, with the following parameters: spot size of 0.028 cm^2, average output power of 100 mW, energy per point of 3J, energy density of 107 J/cm^2, and 30 seconds of irradiation time per point.[16] Overlapping of 3 to 5 mm per application point will be adopted, with 2 applications per week for 4 weeks proposed, this period being established as the average time for PDT treatments for erythroleukoplakias.[23] The number of points will vary according to the size of the lesion.

Control groups

Participants in these two groups will be treated with PDT using a 20% ALA gel formulation, which will be applied for 90 minutes on the lesion(s) present before the light application procedure.[23] Like the treated group, the photosensitizer solution will be applied over the lesion(s) with gauze, and the region will be covered with PVC plastic film to prevent soaking of the photosensitizer solution by saliva. After the pre-irradiation period, the red laser will be applied using the therapy EC equipment (DMC), at a wavelength of 660 nm, continuous mode, with the following parameters: spot size of 0.028 cm^2, average output power of 100 mW, energy per point of 3 J, energy density of 107 J/cm^2, and 30 seconds of irradiation time per point.[23,24] Overlapping of 3 to 5 mm per application point will be adopted, with 2 applications per week for 4 weeks.[23] The number of points will vary according to the size of the lesion.

Clinical follow-up

Participants in both groups will be followed up after the end of treatment at intervals of 1 week, 3, 6, 12, and 24 months. During these consultations, objective and

subjective parameters regarding the clinical response to treatment will be evaluated, as well as the worsening of histological or cytological condition of the lesion. Among the evaluated parameters are:

Objective evaluation: The criteria adopted for objective clinical evaluation are based on the protocol proposed by Chen et al:[23] 1) complete remission of the lesion clinically evaluated; 2) partial reduction of at least 20% in the total diameter of the lesion; 3) reduction of the lesion by less than 20% in diameter; 4) alteration in the clinical pattern of the lesion (homogeneous and non-homogeneous). All responses to lesions will be evaluated at the end of each initial eight treatment sessions. If the lesion shows initial complete remission in fewer than eight PDT sessions, PDT will be terminated, and the patient will be scheduled for follow-up appointments (1 week (T1), 3 months (T2), 6 months (T3), 12 months (T4), and 24 months (T5)). If the lesion shows only partial reduction or alteration in clinical pattern after eight PDT sessions, patients may choose a plan for total excision of the residual lesion or clinical follow-up. Lesions will be photographed in a standardized manner during each PDT session and stored in .jpeg files for measurement of their largest diameter, using the freely distributed software Image J (National institute of health, Bethesda, Maryland, USA). Images will also be acquired during the follow-up period until 24 months. Leukoplakia lesions will be clinically classified as homogeneous or non-homogeneous, according to the criterion adopted by Speight et al.[25]

Subjective evaluation: The visual analog scale (VAS) will be used as a score for assessing the intensity of pain reported by the patient. It is a validated subjective scale for the assessment of acute and chronic pain, where 0 (zero) represents total absence of pain and 10 denotes the maximum level tolerable by the patient. After each PDT application session, participants will be asked to mark a point along the line representing the perceived intensity of the sensation, ranging from 0 for total absence to 10 for maximum intensity. The measurement is then made in centimeters from the initial end to the marked point, providing a quantitative value for the intensity of the sensation.[26]

Cytological/histological evaluation: During clinical follow-up, lesions will undergo the procedure of exfoliative cytology to monitor cellular improvement or worsening in cases treated with PDT. If the cytological exam results suggest malignancy, the patient will undergo biopsy. The collection and analysis will follow the "Papanicolaou" protocol adapted for the oral cavity, using a metal spatula for obtaining the cell smear. The method will allow for morphological cellular evaluation: nuclear/cytoplasmic ratio and morphology, typically used for identifying epithelial lesions and the presence of inflammatory components. Participants will be instructed not to use mouthwashes before collection. Each sample will be individually identified with specific coding for subsequent cytological processing.

Cytological analysis will be performed using a light optical microscope at 4× magnification. The specimen will be observed to check fixation and staining quality. Quantitative assessment will be conducted, examining the quantity of cells present, cell composition/type, and cellular distribution. A sample will be considered satisfactory/adequate for use if it presents 8,000-12,000 epithelial cells evenly distributed, fixed, and stained. Only slides meeting these criteria will be considered for diagnostic purposes. Otherwise, a new collection will be necessary. Subsequently, analysis will be conducted under 10× and 40× objective lenses for visualizing cellular characteristics and classification according to Papanicolaou and Traut in 1941: a) Class I: Normal cells; b) Class II: Presence of benign alterations related to inflammation; c) Class III: Suggestive, but inconclusive for malignancy; d) Class IV: Findings strongly suggestive of malignancy; e) Class V: Conclusive findings of malignancy.

Outcomes

Primary outcome-Clinical remission of the lesion. Secondary outcomes-Prevention of epithelial dysplasia recurrence or worsening of histological classification of epithelial dysplasia; lesion appearance (red and/or white and ulceration); severity (extent); symptoms (pain, burning, and sensitivity); function (impact on speech, eating, and brushing); psychological impact (anxiety and depression); economic impact (cost); treatment adherence and tolerability; patient satisfaction; adverse effects (local or systemic); timeline (time to onset of effect and duration of effect). The secondary outcomes considered here were adapted from the standardized outcomes of the VIII world workshop on oral medicine consensus.[27] Researchers in this study will be trained and calibrated for the analysis of the planned outcomes, including both objective and subjective analyses.

The psychological impact of PDT treatment on participants with OL will be examined through the Brazilian version of the short form oral health impact profile (OHIP14). The OHIP14 is a standardized instrument used to comprehensively assess oral health-related quality of life (OHRQoL). OHRQoL and patient expectations will be evaluated through questionnaires filled out at three time points: an initial assessment (T0), conducted before PDT initiation, and two follow-up assessments, 1 week (T1), 3 months (T2), and 6 months (T3) after PDT treatment completion. The questionnaire will address the following questions: Did you have trouble speaking any word? Did you feel that the taste of food worsened? Did you feel pain in your mouth or teeth? Did you feel uncomfortable eating any type of food? Were you worried? Did you feel stressed? Was your eating affected? Did you have to stop your meals? Did you find it difficult to relax? Did you feel embarrassed?

Were you irritated with other people? Did you have difficulty performing your daily activities? Did you feel that life, in general, worsened? Were you totally unable to do your daily activities? Responses will be given according to the following sequence: never (0), rarely (1), sometimes (2), repeatedly (3), and always.

Cost analysis of PDT treatment will be conducted from the perspective of the service provider professional, considering direct costs with professional fees of a private practice dentist in a Brazilian capital city, the number of necessary appointments for treatment, and the time spent in each session. The clinical time of each PDT treatment session will be recorded in the patient's medical record, as well as the number of sessions required for treatment. Consumable materials used for clinical care (surgical mask, procedural gloves, gauze, etc.), photosensitizer agents, and the equivalent annual cost of laser equipment will be included in the cost analysis, with variable costs for consumables and fixed costs for equipment. A specific researcher will be responsible for monitoring participant appointments to measure and record in real-time the quantity of each consumable used for clinical care, with this information recorded in the patient's medical record. For laser equipment, a discount rate of 5% and a 5-year usage period will be considered. The CHEERS (Consolidated Health Economic Evaluation Reporting Standards) checklist will be used for planning and reporting the economic analysis of this study, available on the EQUATOR initiative website (https://www.equator-network.org/).

The costs of photosensitizer formulation and consumable materials will be obtained through a range of cost per unit, calculated by consulting different compounding pharmacies and dental/hospital material sales companies. The cost per unit of photosensitizer gel used per consultation, and for the entire treatment, will be obtained by recording the quantity of this material used using a polypropylene measuring spoon, with a capacity of 1.25 mL, and recorded in the patient's medical record. The laser equipment cost will be calculated considering the average market price. Procedure costs will be calculated for both groups, using 5% methylene blue gel and 20% ALA gel. The timeline (time to onset of effect and duration of effect) and treatment impact on symptoms (pain, burning, and sensitivity) and function (impact on speech, eating, and brushing) will be used as parameters for cost-effectiveness analysis between the two treatments. All costs will be estimated in Brazilian currency (Real, BRL) and later converted into international dollars, the latter being a hypothetical currency that allows cost comparison between different countries using the US dollar as a reference.

Analysis of results

Initially, descriptive statistics will be applied to analyze qualitative and quantitative variables and describe sample characteristics, using measures such as frequency, mean, median, standard deviation, and interquartile range. The Kolmogorov-Smirnov test will be used to verify if the data distribution follows a normal distribution. Subsequently, multiple regression analysis will be performed to investigate the relationship between independent variables (secondary outcomes) and dependent variables (clinical remission and worsening in histological/cytological condition). The Kaplan-Meier test will be used to examine the lesion-free or non-worsening survival time over time. To evaluate the direct costs of treatments concerning clinical outcomes, cost-effectiveness analysis will be performed through Markov modeling, a technique that will allow simulation of scenarios and evaluation of the economic impact of treatments over time. These steps will provide information on treatment efficacy and its cost-effectiveness, contributing to the development of more efficient and accessible clinical protocols. Values of $p<0.05$ will be considered significant, and a confidence interval of 95%.

DISCUSSION

The study protocol outlined here proposes a randomized controlled trial comparing the efficacy of PDT using 5% methylene blue versus 20% ALA in the treatment of OLP. This protocol addresses an important gap in current knowledge regarding the optimal photosensitizer agent for PDT in treating PMOD.

One notable aspect of this protocol is its rigorous methodology, including the use of randomization, blinding, and stratified allocation based on the risk of malignant transformation. These methodological considerations enhance the validity of the study findings and minimize bias, thus increasing the reliability of the results.

The inclusion criteria for participants are clearly defined, ensuring that the study population represents individuals with clinically diagnosed OLP. Additionally, the protocol outlines detailed procedures for treatment administration, follow-up assessments, and outcome evaluation, demonstrating careful planning and execution of the study protocol.

Furthermore, the protocol incorporates both clinical and cytological/histological evaluations to assess treatment outcomes comprehensively. By including measures such as remission rates, recurrence prevention, lesion appearance, symptoms, function, psychological impact, and economic factors, the study aims to provide a comprehensive understanding of the Efficacy and impact of PDT in OLP treatment.

In addition to evaluating treatment efficacy, the cost analysis component of this study protocol is essential for assessing the economic implications of different PDT agents in the management of OL. By considering direct costs such as professional fees, consumables, and

equipment, as well as indirect costs associated with treatment delivery, this analysis provides valuable insights into the economic feasibility and sustainability of implementing PDT in clinical practice. Moreover, by utilizing a standardized approach for economic evaluation and reporting, such as the CHEERS framework, the study ensures transparency and comparability of cost data, facilitating interpretation and generalization of findings. Ultimately, the cost analysis component of this study not only enhances our understanding of the economic burden of OL management but also informs resource allocation decisions and healthcare policy development aimed at improving access to affordable and effective treatments for potentially PMOD.

CONCLUSION

This study aims to establish an effective treatment for OLP, which is an important step in preventing its progression to oral cancer. Furthermore, comparing different photosensitizer agents in PDT may provide valuable insights for clinical practice and the development of treatment protocols that are not only effective but also safe. This study will enable the widespread dissemination of evidence highlighting 5% Methylene blue gel as a cost-effective and biologically effective alternative for OLP treatment. It is worth noting that this topic is of utmost importance, considered a priority on the research agenda of the WHO, and as a result, it has attracted attention and interest both nationally and internationally.

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