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(Randomized Clinical Trial)

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   Analysis and interpretation of study results.
   Revising the thesis.
2. **Professor Dr. Naguiba Mahmoud Elsayed**
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4. **Dr. Hagar Elkafrawy**
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ABSTRACT

Background: Oral leukoplakia (OL) is a prevalent, potentially malignant disorder of the oral mucosa, characterized by white patches that cannot be scraped off and are not attributable to any other definable disease. Affecting a significant portion of the adult population, OL carries a considerable risk of malignant transformation to oral squamous cell carcinoma (OSCC). Current management strategies for OL range from watchful waiting and surgical excision to various topical and systemic pharmacological interventions, all with varying degrees of success and potential side effects. Topical calcipotriol gel helps reverse dysplastic changes (OL) by promoting normal cell differentiation. Photo dynamic therapy using 5- aminolevulonic acid can selectively destroys abnormal cells. Treatment effectiveness can be monitored non-invasively through salivary levels of Matrix metallo proteinases-9 (MMP-9) and Tumor necrosis factor-alpha (TNF-α), biomarkers that reflect disease progression and treatment response.

Aim: Evaluate and compare the effectiveness of topical calcipotriol gel and photodynamic therapy using 5- aminolevulonic acid as a photosensitizer in the regression of OL which will be measured by a clinical score. The impact of these treatment modalities on levels of salivary MMP-9 and TNF-alpha will also be investigated.

Materials and Methods: A randomized clinical trial will be carried out on 30 patients diagnosed clinically with OL and histologically confirmed dysplasia. Group I (n=15 patients) will be treated using topical calcipotriol gel 0.005% twice daily for 4 weeks. Group II (n=15 patients) will be treated by photodynamic therapy using 635nm diode laser and 20% aminolevulonic acid gel. Each point will receive 3 minutes of irradiation at 500 mW/cm2 power density at a dosage of 150 J/cm2. Lesions will be evaluated clinically at baseline,,2,4,8 and 12 weeks using Femiano et al clinical scoring key. Salivary levels of MMP-9 and TNF-α will be evaluated at baseline, 4 and 12 weeks.

Analysis: The results will be tabulated and statistically analyzed.

Keywords: Oral leukoplakia, Oral potentially malignant lesions, Oral dysplasia, calcipotriol, Vitamin D3, Photodynamic therapy, 5- aminolevulonic acid, MMP-9, TNF-α.

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INTRODUCTION

Oral leukoplakia (OL) stands as the most common potentially malignant disorder of the oral cavity, representing a significant challenge in dental and medical practice due to its inherent risk of malignant transformation. It is defined by the World Health Organization (WHO) as "a white plaque of questionable risk having excluded (other) known diseases or disorders that carry no increased risk of cancer"(1). OL is a clinical diagnosis of exclusion. Its prevalence varies globally, with reported figures ranging from 1% to 5% in the general adult population, though this can be significantly higher in specific demographic groups, particularly those with a history of tobacco and alcohol use.(2)

Numerous risk factors contribute to the development of OL, with chronic irritation from tobacco smoking and chewing, alcohol consumption, and betel quid chewing being the most well-established risk factors. Other contributing factors can include candidal infections, human papillomavirus (HPV) infection, and even certain systemic conditions.(3)

The two primary clinical forms are homogeneous and non-homogeneous leukoplakia. Homogeneous leukoplakia typically manifests as a uniformly white, flat, and thin patch or plaque with well-defined margins and a smooth surface, though it may exhibit shallow cracks or fissures. These lesions are generally asymptomatic and are considered to have a lower malignant potential. In contrast, non-homogeneous leukoplakia presents with a more irregular and varied appearance, often characterized by a mixed white and red coloration (erythroleukoplakia or speckled leukoplakia), a nodular or exophytic (wart-like) surface, or an erosive quality. These non-homogeneous variants are associated with a significantly higher risk of malignant

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transformation into oral squamous cell carcinoma due to their increased likelihood of harboring epithelial dysplasia.(3)

Histologically, OL exhibits a spectrum of changes ranging from simple hyperkeratosis without dysplasia to varying degrees of epithelial dysplasia (mild, moderate), and eventually carcinoma in situ. The presence and severity of epithelial dysplasia are widely considered the most reliable indicators of malignant transformation risk. Current management strategies range from surgical excision and cryotherapy to laser ablation and various topical or systemic pharmacological agents. (4)

Despite the availability of various treatment modalities for oral leukoplakia, a universally effective, safe, and recurrence-free therapy remains an unmet clinical need. Surgical excision is often curative for smaller lesions but can be disfiguring to larger ones, leading to functional impairment, and is associated with recurrence rates. Laser ablation and cryotherapy offer less invasive options but may also result in scarring and discomfort. Topical retinoids and other chemo preventive agents have shown variable efficacy and are often associated with systemic side effects, limiting their long-term use. Given the high recurrence rate and the potential for malignant transformation, there is a clear imperative to identify therapeutic strategies that not only achieve clinical remission but also reduce the long-term risk of progression to oral cancer.(1,3)

Calcipotriol, also known as calcipotriene, is a synthetic vitamin D3 analog that has primarily been established in the dermatological field for the treatment of psoriasis when used topically. Its therapeutic efficacy in conditions characterized by abnormal keratinocyte proliferation stems from its unique mechanism of action. Although calcipotriol exhibits a lower affinity for the vitamin D receptor (VDR) than calcitrol, the natural hormonal form, it shares the ability to regulate cell growth and differentiation. (6)

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VDR is a nuclear receptor expressed in a wide range of tissues, including keratinocytes, and plays a crucial role in cellular homeostasis. Upon binding to the VDR, calcipotriol forms a heterodimer with the retinoid X receptor (RXR), which then binds to specific DNA sequences known as vitamin D responsive elements (VDREs) in the promoter regions of target genes. This interaction modulates gene transcription, leading to a cascade of cellular events.(7)

In the context of hyperproliferative disorders like OL, the primary mechanism by which calcipotriol exerts its effect is through the inhibition of keratinocyte proliferation and the induction of their differentiation. Furthermore, calcipotriol has demonstrated immunomodulatory properties. It can suppress the proliferation of T lymphocytes and inhibit the production of various pro-inflammatory cytokines, which may contribute to the inflammatory component often observed in OL lesions. (6,8)

The topical use of calcipotriol for oral lesions is still relatively novel compared to its dermatological use. However, its established safety profile and targeted action on keratinocyte proliferation make it an attractive candidate for topical therapy in the management of OL, potentially offering a less invasive and well-tolerated alternative to more aggressive interventions.(9,10)

Photodynamic therapy (PDT) represents an innovative and minimally invasive therapeutic modality that has gained considerable traction in the treatment of various neoplastic and non-neoplastic conditions, including certain oral pathologies. PDT relies on the selective accumulation of a photosensitizing agent in target cells, followed by the activation of this agent by a specific wavelength of light. This light activation leads to the generation of highly reactive oxygen species (ROS), primarily singlet oxygen, which subsequently induce irreversible cellular damage and cell

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death. The three essential components of PDT are a photosensitizer, a light source of appropriate wavelength, and oxygen.(11,12)

Upon administration, the photosensitizer, 5-aminolevulinic acid (5-ALA), is preferentially taken up by rapidly proliferating or dysplastic cells. Inside the cells, 5-ALA is metabolized through the heme biosynthesis pathway to form protoporphyrin IX (PpIX), a potent endogenous photosensitizer(13). When the lesion is then illuminated with light of a specific wavelength (typically red light for PpIX, around 630 nm), the PpIX molecules become excited to a higher energy state. This excited PpIX can then transfer energy to molecular oxygen (O_2) present in the tissue, generating highly cytotoxic singlet oxygen ($^1O_2$)(11,13).

Singlet oxygen is extremely reactive and causes oxidative damage to various cellular components, including proteins, lipids, and nucleic acids, leading to irreparable damage to mitochondria, cell membranes, and DNA.This triggers a cascade of events leading to cell death primarily through apoptosis and, to a lesser extent, necrosis. Beyond direct cytotoxicity, PDT also induces vascular damage within the treated lesion, leading to microvascular occlusion and subsequent ischemic necrosis.(13)

Furthermore, PDT can elicit an immune response, with the release of damage-associated molecular patterns (DAMPs) and subsequent activation of immune cells, contributing to the long-term eradication of the lesion and providing an anti-tumor immune surveillance effect. The inherent selectivity of PDT, based on the preferential accumulation of photosensitizer in dysplastic cells and the localized application of light, allows for targeted destruction of the abnormal tissue while largely sparing surrounding healthy tissue, making it a promising option for the treatment of OL with reduced side effects compared to conventional destructive methods.(12,14)

The use of saliva as a diagnostic medium for both oral and systemic

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diseases is a rapidly growing research field because saliva offers multiple advantages over blood and other bodily fluids. It is easy to collect, non-invasive, inexpensive, and can be easily stored. Recent studies have identified a number of salivary biomarkers with diagnostic and prognostic potential for OL and OSCC , with tumor necrosis factor-alpha (TNF-α) and matrix metalloproteinase 9 (MMP-9) emerging as promising candidates. [(15,16)

TNF-alpha strongly links chronic inflammation to carcinogenesis, which is a major pathway in OL progression. MMP-9 is a zinc-dependent endopeptidase that plays a critical role in extracellular matrix (ECM) degradation and tissue remodeling. While essential for normal physiological processes, its overexpression is a hallmark of many cancers.(17,18)

Combining TNF-α and MMP-9 offers a more comprehensive assessment, where TNF-α provides insights into the inflammatory microenvironment and overall proliferative activity, and MMP-9 offers a direct measure of the invasive potential and ECM degradation. Evaluating both could provide a more robust picture of the lesion's biological activity, treatment response, and long-term prognostic outlook.(18,19)

To the best of our knowledge, two clinical trials investigated the efficacy of topical calcipotriol for OL, and a few studies evaluated the efficacy of 5 ALA-PDT. The impact of these two treatment modalities on salivary biomarkers has not been studied yet. Thus, the purpose of this study is to evaluate and compare the effect of topical calcipotriol gel and 5 ALA-PDT on clinical regression of OL and on the levels of salivary biomarkers TNF-alpha and MMP-9.

The null hypothesis of this research is that there will be no statistically significant difference between the group treated by topical calcipotriol gel and the group treated by 5 ALA-PDT in clinical regression and salivary biomarkers.

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AIM OF THE STUDY

General aim

The present study aims to evaluate and compare the effectiveness of topical calcipotriol gel and 5-aminolevulonic acid mediated photodynamic therapy in treatment of oral leukoplakia with dysplastic changes.

Specific aims

1- To evaluate clinical response of oral leukoplakia in response to the two studied treatment modalities over a period of 3 months.
2- To investigate the impact of the 2 treatment modalities on salivary levels of TNF- alpha and MMP-9.
3- To establish correlation between the levels of the investigated salivary biomarkers and clinical outcomes.

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Materials and methods

Study design

A randomized, single-blinded single center clinical trial with 2 parallel groups will be carried out. The study will fulfill the CONSORT guidelines (20). The PICOT question will be: Will patients diagnosed with OL (Population; P) when treated by topical calcipotriol gel (Intervention; I) in comparison with 5 ALA- PDT (Comparison; C) show more regression in size, clinical and biochemical features (Outcome; O) when followed up at 0, 2,4and 12 weeks(Time; T)?

Study setting

The study will be conducted at Oral medicine, Periodontology, Diagnosis and Radiology Department, Faculty of Dentistry, Alexandria University, Egypt. Biochemical analysis of salivary biomarkers will be conducted at Department of Medical Biochemistry, Faculty of Medicine, Alexandria University.

Participants

The study will be conducted on 30 patients diagnosed with OL.

Study sample and Sample size estimation

Sample size was based on 95% confidence level to detect a difference in oral leukoplakia resolution between topical calcipotriol and photodynamic therapy (PDT). According to Ghalwash et al., (10) complete resolution occurred in 25% of lesions treated with calcipotriol, while Di Stasio et al. (21) reported a 40% resolution rate following PDT, indicating a 15% absolute difference (95% CI: –17.7% to 45.1%). Based on these parameters and assuming 80% power, the minimum required sample size was estimated at 14 patients per

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group, which was increased to 15 to account for loss to follow-up. The total required sample size= number of groups × number per group= 2 × 15= 30 patients. (22)

Software

Sample size was based on MedCalc Statistical Software version 19.0.5 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2019)

Eligibility criteria

Inclusion Criteria (9,10,14)

1.Patients, both males and females, 25 to 55years old will be included in this clinical trial.(9)
2. Patients with oral leukoplakia with histologically confirmed mild and moderate epithelial dysplasia.(9,10)
3. Patients willing and able to return for multiple follow up visits.

Exclusion criteria (10,23)

1. Presence of any visible oral lesions other than leukoplakia. (9,10)
2. Periodontitis patients: since chronic periodontitis may affect salivary TNF-alpha and MMP-9 level.(9,10)
3. Contraindications for the use of calcipotriol or amino levulonic acid as allergy.(10)
4. History of topical and/or systemic therapy for 2 months before the start of study. (23)
5. Patients with conditions that could affect saliva collection as xerostomia.(23)

Randomization and Allocation Concealment

Participants will be randomly allocated into the two test groups using computer generated random list. (24) The participant allocation lists will be kept in opaque, sealed envelopes and arranged sequentially by a dental assistant who will not be involved in the study. Each envelope will be opened at the time of intervention. (25)

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Blinding:

A single blinded clinical trial; the outcome assessor will be blinded to the treatment of each patient.

Training and Callibration:

The main researcher will be trained and calibrated for assessment of the study clinical outcome.

Intra-examiner reliability:

Intra-examiner reliability will be tested by examining 5 patients twice with 4 days interval between the first and second time. These patients will be excluded from the study sample. Intra-examiner reliability will be assessed using Cohen's Kappa (K). Obtaining Kappa score ≥ 0.8 is considered good.

Intervention

Group I (n= 15) patients of this group will be prescribed topical 0.005% calcipotriol gel applied twice daily for 4 weeks. (9,10) The gel will be prepared by a specialist at Faculty of Pharmacy, Alexandria University.

Preparation of Calcipotriol gel:

The gel will be prepared as reported by Ghalwash *et al.*(10), with modifications to accommodate calcipotriol incorporation and enhance mucosal penetration. Calcipotriol 0.005% oral gel will be prepared using Carbopol 940 as the gelling agent. Initially, calcipotriol is dissolved in propylene glycol under continuous stirring at room temperature. Separately, methyl paraben (0.1% w/w) and menthol (0.05% w/w) are dissolved in polyethylene glycol 400 (5% w/w). Carbopol 940 (1.5 % w/w) was

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dispersed in distilled water and allowed to hydrate for 2 hours at ambient temperature. Once fully swollen, the calcipotriol-propylene glycol solution and the PEG 400 solution containing methyl paraben and menthol are added to the hydrated Carbopol dispersion with gentle mixing to ensure uniform distribution. Triethanolamine is then added dropwise to neutralize the gel and adjust the pH to 6.5–7.0, forming a clear and homogenous gel. The formulation is inspected for clarity, uniformity, and pH, then transferred into sterile, airtight plastic containers protected from light and stored at 4–8 °C until further evaluation.

Group II (n=15) patients of this group will receive 4 sessions of photodynamic therapy (once per week) using 635nm diode laser.(14) Lesions will be covered with 20% aminolevulonic acid gel, properly isolated from saliva, then it will be divided so that every cm will be considered as one point for irradiation. Each point will receive 3 minutes of irradiation using 635nm at 500 mW/cm^2 power density at a dosage of 150 J/cm^2 .(11,12,14) The 5 ALA gel will be prepared by a specialist at Faculty of Pharmacy, Alexandria University.

Preparation of 5-ALA gel:

The 5-aminolevulinic acid (ALA) gel will be prepared according to the method of Chen *et al.* (26), with modifications. ALA will be incorporated at a concentration of 20% w/w into a suitable gel matrix composed of Carbopol 940 (1.5% w/w).

For Carbopol-based gels, Carbopol 940 (1.5 % w/w) will be dispersed in distilled water and allowed to hydrate at room temperature for 2 hours. Once fully hydrated, ALA (200 mg) will be added to 800 mg of the Carbopol dispersion and mixed thoroughly. The dispersion will then be neutralized by the dropwise addition of triethanolamine to adjust the pH to 6.5–7.0 and induce gel formation. The prepared gels will be filled into sterile, light-protected, needleless 1 cc plastic syringes and stored at 4–8 °C. Due to the

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aqueous instability of ALA, the formulation is to be used within 3 hours of preparation to preserve drug integrity and ensure effective protoporphyrin IX production during photodynamic therapy.(26)

Patient Preparation and Saliva Sampling:

- Comprehensive oral diagnosis will be carried out using the department's oral diagnosis chart.
- Phase I therapy (good oral hygiene instructions, scaling, and root planing will be performed to all patients(27) then biopsy will be carried out to confirm the presence of dysplasia histologically.
- Removal of etiological factors (trauma or smoking) should be achieved before initiation of treatment. The patient will be strictly advised to stop smoking.
- After histological confirmation of diagnosis, tissue re-evaluation and preoperative photos will be recorded. Patients who need another session of scaling will do it at least one day prior to saliva collection to avoid contamination of saliva with blood.(27)
- Whole unstimulated saliva will be collected from all participants enrolled in this clinical trial at baseline, 4 weeks and 12 weeks.
- Salivary samples will be collected between 9 and 11 a.m. where participants will be asked to refrain from eating, drinking, and brushing their teeth at least 2 hours before saliva collection.
- All study participants will be asked to rinse their mouth with distilled water before saliva collection. (28)
- Study subjects of all groups will expectorate 5 ml of saliva into a clean dry glass beaker for 5 min. (28)
- Saliva samples will be transferred to clean dry centrifuge tubes and centrifuged at 2500 xg for 10 min to remove cellular debris and bacteria. (28,29)

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- The supernatant will then be divided into small aliquots in Eppendorf. Saliva samples will be given the sequential number of the corresponding patient. All salivary samples will be stored at −80°C till the time of analysis.(29)

Outcome Measures

1- Clinical outcome

Lesions will be evaluated, recorded photographically and measured using endodontic ruler or periodontal probe at baseline, with regular clinical assessments at 2 and 4,8 and 12 weeks for groups 1 and 2 as follows: Clinical scores for roughness & intensity of whiteness was estimated visually according to Femiano et al.(9) to which the following values were given: 0: Total resolution of lesions. 1: Moderate resolution=reduction of consistence with leveling of the lesion. 2: Minimal change=reduction of consistence without leveling of the lesion. 3: No visible change.

2-Detection of salivary TNF -alpha and MMP-9 using enzyme-linked immunosorbent assay (ELISA) technique (10)

At baseline, 4 and 12 weeks

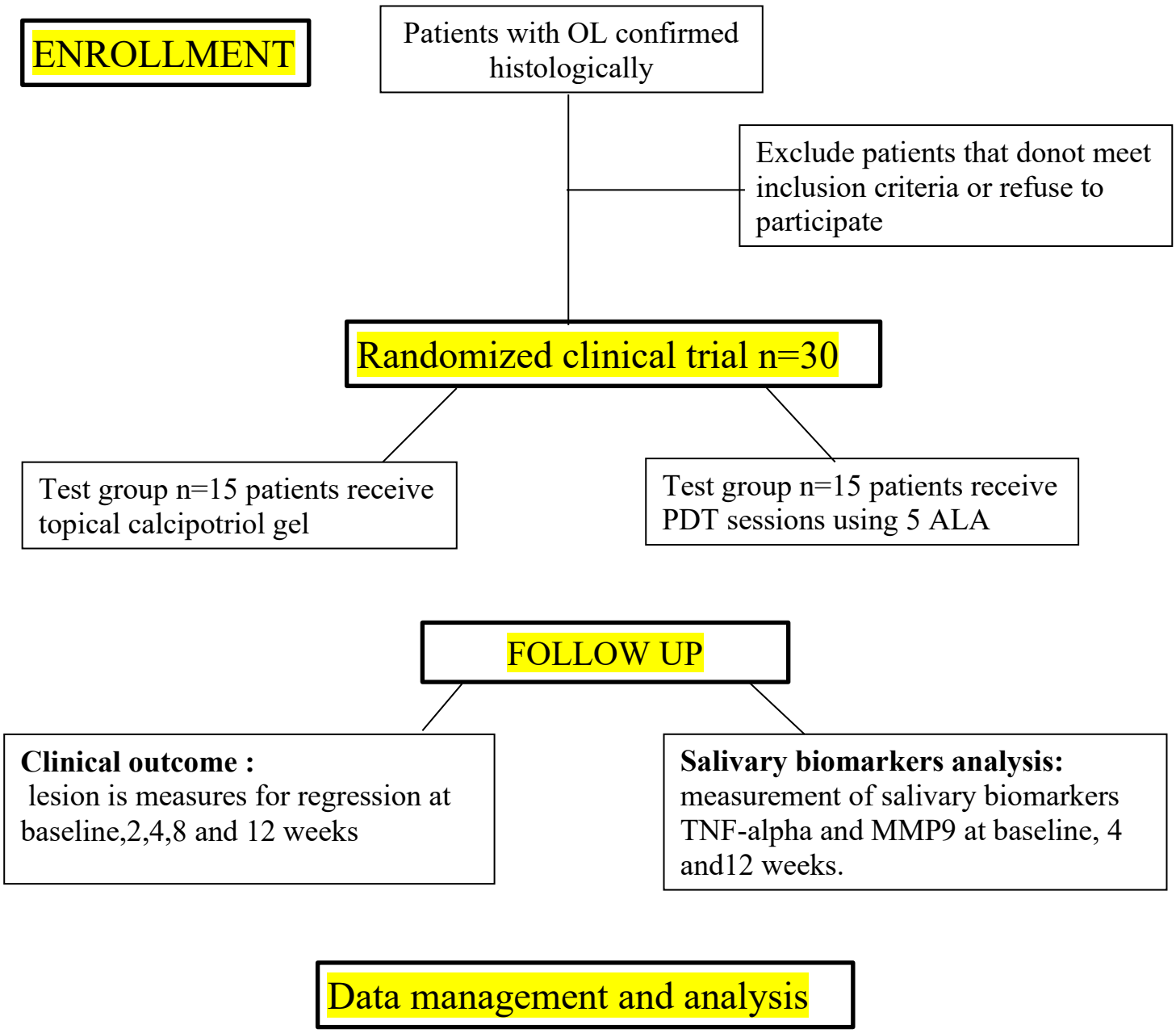
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DATA MANAGEMENT AND STATISTICAL ANALYSIS

The data will be collected, tabulated, processed, and statistically analyzed using appropriate statistical tests to fulfill the aim of work. Statistical significance will be set at $p \leq 0.05$. Statistical analysis will be conducted using the statistical Package for the Social Sciences (SPSS). The statistician will be blinded to the treatment modality received by each group.

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Flow chart


ENROLLMENT
Patients with OL confirmed histologically
Exclude patients that donot meet inclusion criteria or refuse to participate
Randomized clinical trial n=30
Test group n=15 patients receive topical calcipotriol gel
Test group n=15 patients receive PDT sessions using 5 ALA
FOLLOW UP
Clinical outcome :
lesion is measures for regression at baseline,2,4,8 and 12 weeks
Salivary biomarkers analysis:
measurement of salivary biomarkers TNF-alpha and MMP9 at baseline, 4 and12 weeks.
Data management and analysis

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ETHICAL CONSIDERATIONS

1-The research protocol will be approved by the Research Ethics Committee of Alexandria University Faculty of Dentistry (IRB No. 001056 – IORG 0008839) prior to any research-related activities.

2. The two treatment modalities that will be used in this clinical study will abide the principles of the modified Declaration of Helsinki for conducting human clinical studies (2013) * and other ethical guidelines adopted by the Research Ethics Committee of Alexandria University Faculty of Dentistry.

3. The benefits to the participant and/or the community:

- Offering two novel treatment modalities for one of the most common precancerous lesions
- These two modalities are totally non-invasive
- Both treatment modalities are considered cost and time effective.
- The patients will not be subjected to hazards associating invasive surgical treatments.
- Offering treatment to OL will sequentially reduce the prevalence of OSCC.
- The patients will not be exposed to any harm or risk during the study procedures because the studied treatment modalities have already been used and tested for safety, biocompatibility and toxicity [12, 17].

4. The risks to the participant and/or the community:

- Complications during biopsy procedures and wound healing. However, routine laboratoey investigations including complete blood count, coagulation profile and fasting blood sugar level will be carried out to confirm the patient is fit for the biopsy procedure.

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• Heat generation during PDT can lead to discomfort or burns. However, unnecessary heat generation will be avoided using proper device settings.

- Side effects from topical application of calcipotriol gel. However, the safety profile of the topical use of this gel has been studied and proved in dermatological use.

5. Measures taken to ensure the privacy and confidentiality of the participants, their specimen, and/or their private information:

• Participants will be ensured of the data confidentiality and will be informed of the right to retract their approval at any time.

• A signed informed consent will be obtained from the respective patients before proceeding with the study.

• Participants metadata will be accessible to the principal investigator.

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BUDGET ESTIMATE

No.	Items	Total price (L.E.)
1	Calcipotriol powder	24,000
2	5-aminolevulonic acid powder	14,000
3	ELISA kits for salivary biomarkers	20,000
4	Tools and materials for gel preparation	10000
5	Statistical analysis	5000
6	Thesis printing and plagiarism checking cost	6000
7	Publication cost	10000
Total		**89,000LE**

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DURATION OF STUDY

Estimated time: 12 Months

			By Months									
Tasks	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Patient rectuitment and material preparation and purchase	**X**	**X**	**X**									
Clinical procedure				**X**	**X**							
Follow up, clinical and biochemical analysis.						**X**	**X**	**X**				
Data management and statistical analysis									**X**			
Writing Thesis/manuscript										**X**	**X**	
Thesis submission												**X**

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ANTICIPATED PROBLEMS

1. Recruiting patients with OL who fulfill the eligibility criteria over a long period of time .

2. Retaining patients to fulfill the whole duration of the clinical trial.

3. Material availability in Egypt and lack of price stability.

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PUBLICATION POLICY

Findings will be disseminated through peer-reviewed publication.

The order of names will be:

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2. Prof. Dr. Naguiba Mahmoud Elsayed
3. Associate Prof. Dr. Asmaa Mohamed Ashour
4. Dr. Hagar Elkafrawy
5. Dr. Nancy Shaaban
6. Prof. Dr. Eglal Mohamed Moussa

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REFERENCES

1. Maloney DB, Galvin DrS, Healy PC. Oral leukoplakia: an update for dental practitioners. J Ir Dent Assoc.2024 Feb 9
2. Zhang C, Li B, Zeng X, Hu XS, Hua H. The global prevalence of oral leukoplakia: a systematic review and meta-analysis from 1996 to 2022. BMC Oral Health 2023 Dec 1
3. What is Leukoplakia? Causes, Symptoms, Prevention & Treatment | Jefferson Dental & Orthodontics
4. A digital manual for the early diagnosis of oral neoplasia
5. Gisondi P, Gracia-Cazaña T, Kurzen H, Galván J. Calcipotriol/Betamethasone Dipropionate for the Treatment of Psoriasis: Mechanism of Action and Evidence of Efficacy and Safety versus Topical Corticosteroids. Journal of Clinical Medicine 2024, Vol 13, Page 4484 2024 Jul 31
6. What is the mechanism of Calcipotriene?
7. Trémezaygues L, Reichrath J. Vitamin D analogs in the treatment of psoriasis: Where are we standing and where will we be going? Dermatoendocrinol. 2011,3(3):180.
8. Femiano F, Gombos F, Scully C, Battista C, Belnome G, Esposito V. Oral leukoplakia: Open trial of topical therapy with calcipotriol compared with tretinoin. Int J Oral Maxillofac Surg 2001;30(5):402–6.
9. Ghalwash D, Mahmoud E, Shaker O. Evaluation Of The Therapeutic Effect Of Topical Calcipotriol Versus Topical Tretinoin In Treatment Of Oral Leukoplakia And Their Effect On Clinical Improvement And Salivary Level Of Mmp-9, Il-6 And Tgf- B: A Randomized Clinical Trial. Dentistry. 2017 Jan 1
10. Zhang R, Gao T, Wang D. Photodynamic therapy (PDT) for oral leukoplakia: a systematic review and meta-analysis of single-arm studies examining efficacy and subgroup analyses. BMC Oral Health. 2023 Dec 1;23(1).
11. Ou J, Gao Y, Li H, Ling T, Xie X. Application of 5-aminolevulinic acid-mediated Waterlase-assisted photodynamic therapy in the treatment of oral leukoplakia. Sci Rep. 2022 Dec 1 [cited 2025 Jul 1];12(1):9391
12. Mahmoudi K, Garvey KL, Bouras A, Cramer G, Stepp H, Jesu Raj JG, et al. 5-Aminolevulinic Acid Photodynamic Therapy for the Treatment of High-Grade Gliomas. J Neurooncol . 2019 Feb 15 ;141(3):595.
13. Han Y, Xu S, Jin J, Wang X, Liu X, Hua H, et al. Primary clinical evaluation of photodynamic therapy with oral leukoplakia in Chinese patients. Front Physiol. 2019 ;10(JAN). Available from: https://pubmed.ncbi.nlm.nih.gov/30723421/
14. Kim J, Kim JH. Salivary protein biomarkers for the early detection of oral cancers. International Journal of Oral Biology. 2025 Mar 30 ;50(1):1–7.

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15. Liew YX, Kadir K, Phan CW, Leong KH, Kallarakkal TG, Tilakaratne WM. Salivary biomarkers: Effective diagnostic tool for oral leukoplakia and oral squamous cell carcinoma. Oral Dis. 2024 Sep 1
16. Deepthi G, Nandan SRK, Kulkarni PG. Salivary tumour necrosis factor-α as a biomarker in oral leukoplakia and oral squamous cell carcinoma. Asian Pacific Journal of Cancer Prevention . 2019
17. Pazhani J, Chanthu K, Jayaraman S, Varun BR. Evaluation of salivary MMP-9 in oral squamous cell carcinoma and oral leukoplakia using ELISA. Journal of Oral and Maxillofacial Pathology. 2023 Oct 1
18. Krishnan R, Thayalan DK, Padmanaban R, Ramadas R, Annasamy RK, Anandan N. Association of serum and salivary tumor necrosis factor-α with histological grading in oral cancer and its role in differentiating premalignant and malignant oral disease. Asian Pacific Journal of Cancer Prevention. 2014
19. Turner L, Shamseer L, Altman DG, Weeks L, Peters J, Kober T, et al. Consolidated standards of reporting trials (CONSORT) and the completeness of reporting of randomised controlled trials (RCTs) published in medical journals. Cochrane Database of Systematic Reviews. 2012 Nov 14
20. Di Stasio D, Romano A, Russo D, Fiori F, Laino L, Caponio VCA, et al. Photodynamic therapy using topical toluidine blue for the treatment of oral leukoplakia: A prospective case series. Photodiagnosis Photodyn Ther .2020 Sep 1
21. Petrie, A., Sabine C. Chapter 39: Assessing agreement. Medical Statistics at a Glance. Third Edit. 2009
22. Zhang CZ, Cheng XQ, Li JY, Zhang P, Yi P, Xu X, et al. Saliva in the diagnosis of diseases. Int J Oral Sci .2016 Sep 29
23. Saghaei M. Random allocation software for parallel group randomized trials. BMC Med Res Methodol . 2004 Nov 9
24. Sil A, Kumar P, Kumar R, Das NK. Selection of control, randomization, blinding, and allocation concealment. Indian Dermatol Online J . 2019 Sep 1
25. Chen HM, Chen CT, Yang H, Kuo MYP, Kuo YS, Lan WH, et al. Successful treatment of oral verrucous hyperplasia with topical 5-aminolevulinic acid-mediated photodynamic therapy. Oral Oncol . 2004 Jul 1
26. Önder C, Kurgan Ş, Altıngöz SM, Bağış N, Uyanık M, Serdar MA, et al. Impact of non-surgical periodontal therapy on saliva and serum levels of markers of oxidative stress. Clin Oral Investig .2017 Jul 1
27. De Vicente JC, Rodrigo JP, Rodriguez-Santamarta T, Lequerica-Fernández P, Allonca E, García-Pedrero JM. Podoplanin expression in oral leukoplakia: Tumorigenic role. Oral Oncol. 2013

.

28. Tvarijonaviciute A, Aznar-Cayuela C, Rubio CP, Tecles F, Ceron JJ, López-Jornet P. Salivary Antioxidant Status in Patients with Oral Lichen Planus: Correlation with Clinical Signs and Evolution during Treatment with Chamaemelum nobile. Biomed Res Int . 2018

* World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013 27; 310(20):2191-4. doi: 10.10001/jama.

.