Faculty of Dentistry

Department of Oral Medicine, Periodontology, Oral Diagnosis and Oral Radiology

Research proposal plan to obtain a master's degree in oral medicine

Titled

EVALUATION OF DIODE LASER AND TOPICAL STEROID THERAPY IN THE TREATMENT OF EROSIVE ORAL LICHEN PLANUS.

(A RANDOMIZED CONTROLLED CLINICAL TRIAL)

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Name of Candidate: Reem Kamal Mohamed Abdelaziz

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Keywords: Oral lichen planus, diode laser, topical steroid therapy.

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- Helping in results interpretation and thesis revision.
- Follow up all results and verifying them.

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- Biochemical measurement and interpretation.
- Follow up all results and verifying them.

Dr. Yasmine Youssri Gaweesh

- Clinical work supervision.
- Helping in results interpretation and thesis revision.
- Responsible for patients' selection.

OUTLINE

ABSTRACT

Background: Oral lichen planus (OLP) is a chronic inflammatory mucocutaneous disease with uncertain etiology. It may appear as bilateral white striations, papules, plaques, erythema, erosions and blisters on the buccal mucosa, tongue and gingiva.

Conventionally, corticosteroid treatments are used as a treatment in Erosive OLP. As an alternative method to steroid therapies Diode lasers were introduced for the symptomatic relief of pain and burning sensation with no adverse effects.

Study objective: the objective of the study is to compare the effect of topical corticosteroid and 980nm Diode Laser in the treatment of erosive OLP.

Materials and Methods: This study will be conducted on 44 patients histologically diagnosed erosive OLP. Patients will be divided into two groups: Group I: 22 patients will be given conventional treatment (topical corticosteroid), Group II: 22 patients will be treated with 980nm Diode Laser. The pain score, clinical and biochemical evaluation will be done at the beginning of the treatment, 6 weeks and 12 weeks after treatment. The evaluation will be done using Visual Analogue Scale (VAS) for pain assessment, the criteria scale described and modified by Thongprasom et al 2003 for clinical assessment, and oxidative stress biomarker analysis for the biochemical evaluation.

Results: The data obtained will be collected and statistically analyzed.

Keywords: Oral lichen planus, 980 nm Diode Laser, topical steroid therapy.

Introduction

Oral lichen planus (OLP) is a chronic inflammatory mucocutaneous disease, which affects the skin, nails, hair and mucous membranes, recognized in 1866. [1] It affects 1%–2% of the population at middle age, with a female predominance. OLP etiology is unknown but evidence suggests that this disease is an immune-mediated process involving cytotoxic T cells as well as the release of a diverse array of proinflammatory cytokines that lead to the apoptosis of epithelial cells. [2]

Although the immunological system plays a substantial role in OLP, other factors may be also involved, such as psychological stress, drug intake, anxiety and some systemic diseases, including hepatitis C virus infection, hypertension, diabetes, and graft-vs-host disease. However, the precise role of most of these conditions in OLP remains unclear. [3]

Oxidative Stress (OS) may play a central role in the etiology of OLP as the sub epithelial infiltration of T lymphocytes in OLP contributes `to the local production of cytokines, which can stimulate production of ROS.[6]

OS affects the normal intracellular balance, producing excessive oxidant substances, i.e., reactive oxygen species (ROS) and reactive nitrogen species (RNS) resulting in a relative deficiency of enzymatic and non-enzymatic antioxidants as well as oxidation of unsaturated fatty acids in cell membranes or lipoproteins inducing lipid peroxidation.[7]

Research has demonstrated that increased lipid peroxidation in cell membrane can stimulate inflammatory and immune responses. Malondialdehyde (MDA) as the most important product of lipid peroxidation can be used as a marker for the measurement of oxidative stress. Higher levels of MDA were reported in saliva of patients affected by OLP. [8]

Oxidative stress can be evaluated by the measurement of total antioxidant capacity (TAC) in biological fluids. Since the body antioxidants are highly varied, use of an index that measures total capacity of antioxidants in biological fluids, such as TAC, could be a new and suitable method.[8]

As a diagnostic fluid which may be easily collected, saliva is used for the measurement of markers of oxidative stress (OS) associated with local oral conditions.[6]

Clinically, OLP may affect several sites of the oral cavity and several clinical manifestations are reported, according to Andreasen classification system: reticular (Wickham's striae), papular, plaque-like "white form", atrophic (erythematous), erosive-ulcerous and bullous-erosive "red form"; however, the classic lesions are bilateral, symmetric and composed mainly of a reticular pattern. [4]

It is a challenge to diagnose OLP, particularly in the absence of the classic reticular pattern on oral mucosal surfaces. Therefore, an oral biopsy with histopathological examination is usually required to confirm the clinical diagnosis and exclude dysplasia and cancer. [3, 4, 5]

Symptoms associated with OLP are variable, ranging from no symptoms to severe pain. About two-thirds of the patients describe a burning sensation and pain in the area of the oral mucosa, which leads to difficulties and restrictions in eating, speaking and swallowing. [9]

The asymptomatic forms usually do not need management with drugs; they are periodically followed up by clinicians, while the clinical management and treatment in symptomatic patients is often required. However, the treatment of OLP is not curative, in fact its efficacy is related to the symptoms control and ulcers management (especially in erosive OLP). [9,10]

The conventional treatment of Symptomatic OLP is usually high potency topical corticosteroids, systemic prednisone or immunosuppressive agents like cyclosporine, tacrolimus and thalidomide. [10,11] However, long-term treatment with topical corticosteroids may cause obvious side effects, such as local pigmentation, oral candidiasis and dry mouth. Additionally, some studies reported persistent lesions with treatment resistance increasing the risk of cancer transformation. [11]

In this context, alternative therapies capable of relieving OLP symptoms with minimal or no side effects. Lasers emerge as an option for OLP treatment due to its known ability to reduce pain, resolve inflammation and promote tissue repair in different pathological conditions. [12]

Different types of lasers with different wavelengths have been utilized in the treatment of OLP. ND:YAG, CO2 laser and Low-intensity lasers (LLLT) had a remarkable effect on pain, size of lesions and also clinical response.[12]

Several LLLT have been used to treat oral lichen planus, but more recently, diode (a spectrum of red to infrared wave lengths, 600 to 1100 nm) lasers. These lasers have been used with different wave lengths, intensities, powers, durations, number of sessions, and therapeutic approaches. [13,14]

Patients with OLP who were treated by low level laser therapy (LLLT) with wavelength of 980 nm reported acceptable results in short follow-up studies, this may be due to the effect of LLLT on soft tissues. [15]

Physiologic effects of LLLT on tissues are primary and secondary. Primary effects consist of enhancement of blood flow, lymph drainage, cellular metabolism, neutrophil and fibroblast activation, and pain stimulation threshold. Secondary effects include aggregation of prostaglandins, immunoglobulins and

lymphokines, as well as beta-endorphin and encephalin in the tissue, decreasing the inflammation, immune response, and pain, respectively. [15]

However, the efficacy of laser in OLP treatment remains uncertain. Some studies have shown that conventional therapy with topical corticoids showed better control of OLP pain and size when compared to lasers. [14] On the other hand, other studies have demonstrated comparable outcomes for patients treated with both laser and corticoids. However, these studies used different laser parameters and no protocol for laser could be established. [15,16]

These different results of laser therapy may need further investigations to resolve the conflict and to assess the effectiveness of LLLT in treatment of OLP.

The purpose of this study is to evaluate the effectiveness of 980nm Diode Laser in the treatment of erosive OLP in relation to conventional corticosteroids.

The null hypothesis of this research is that there will be no statistically significant difference among the test group treated by 980nm Diode Laser and the control group treated by conventional therapy.

AIM OF THE STUDY

The aim of the study is to evaluate the effect of 980nm Diode Laser in the treatment of erosive OLP compared with conventional topical corticosteroid therapy.

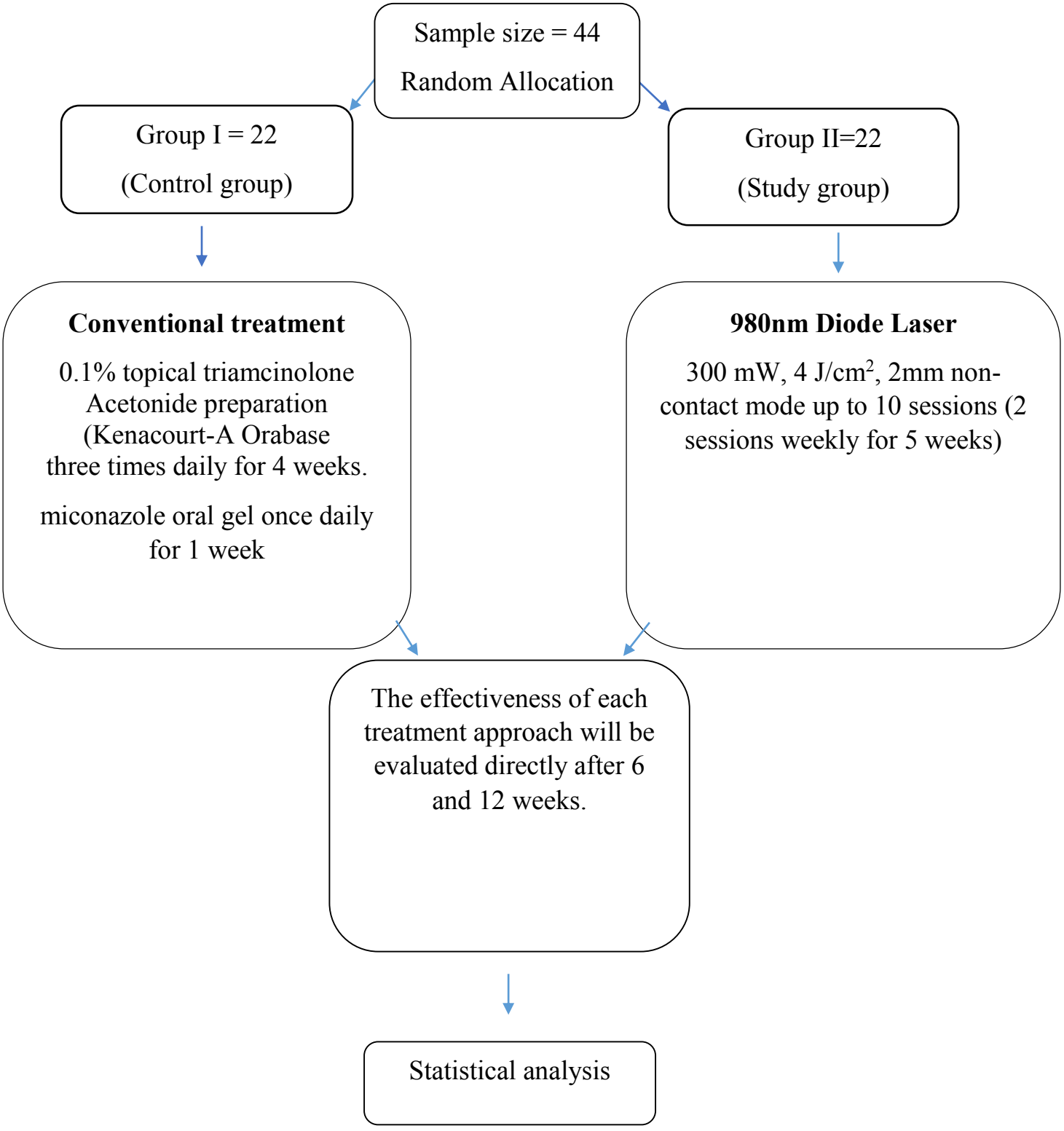
Primary Objective

To evaluate clinically on Visual Analogue Scale (VAS) the ability of 980nm Diode Laser to control pain compared with topical corticosteroid.

Secondary Objective

To test the clinical improvement of OLP according to Thongprasom et al 2003 scoring system and to evaluate the oxidative stress in saliva biochemically.

FLOW CHART STUDY DESIGN



PLAN OF THE STUDY

Material and Methods

I. Material

i. Study design and setting:

This randomized, controlled, clinical trial will be conducted on 44 patients of both sexes who complain from erosive OLP. They will be selected from the outpatient clinic of Department of oral medicine, Faculty of dentistry.

Patients will be given a detailed explanation of the study and will sign an informed consent form according to the guidelines of the Ethical Committee of the Faculty of Dentistry, Alexandria University. They will be treated according to the principles of the modified Helsinki's code for human clinical studies (2013). [17]

Inclusion Criteria

1. Patient histologically diagnosed with erosive OLP based on WHO modified criteria 2003. [18]
2. Patients 30-70 years of age.
3. Presence of painful erosive OLP lesions diagnosed by biopsy. [18]

Exclusion Criteria

1. Pregnant or breast-feeding women. [18]
2. Patients currently treated for cancer with Chemotherapy or Radiotherapy. [15]
3. Patient currently on Corticosteroid therapy or had been on treatment on the past 3 months. [18]

4. Those who had used Anti-inflammatory drugs topical or systemic in the last month. [2]
5. Those who reported use of drugs related to Oral Lichenoid Lesions. [2]
6. Presence of Amalgam restorations near the OLP lesions. [20]
7. Those with description of dysplasia in histopathological examination. [20]
8. Patients suffering from any uncontrolled systemic diseases (such as diabetes, cardiovascular, liver disorder, renal dysfunction) [20]
9. Patients with findings of any physical or mental abnormality which would interfere with or be affected by the study procedure. [2]
10. Patients with skin lesion.

ii. Sample size calculation:

Sample size will be estimated assuming confidence level = 95% and study power = 80%. The mean (SD) reported pain scores measured by the Visual Analogue Scale after 3 months for the laser group was 0.79 (1.23) and for the steroid group was 2.81 (2.84). The minimum sample size was calculated to be 20 patients, increased to 22 patients per group to make up for possible loss to follow up.

The total sample size = number of groups × number per group= 2 X 22= 44 patients.

Sample size was based on Rosner's method calculated by G power 3.0.10. [21, 22, 26]

II. Methods

Randomized Controlled Clinical Study

The purpose and nature of the study will be explained for the selected 44 patients and an informed consent will be obtained from patients who agree to participate in this study prior to any procedure.

An incisional biopsy will be performed under local anesthesia from the lesion to exclude dysplasia and cancer.

Grouping and Randomization

The selected patients will be randomly assigned to the following groups:

Group I (Control group)

22 patients will be given topical corticosteroid 0.1% topical triamcinolone acetonide preparation (0.1% triamcinolone acetonide orabase, Kenacort-A Orabase Pomad, DEVA HOLDING A.Ş, Istanbul, Turkey) three times daily for 4 weeks.

The application should be in one direction with no food or fluid after administration for a minimum of 1 hour post application. Also, patient will be applying miconazol oral gel once daily to avoid superimposed fungal infection. [20]

Group II (Study group)

22 patients will be subjected to laser therapy by the 980 nm diode laser (MEDENCY ,PRIMO – Vicenza Italy) for photobiomodulation (PBM) and the treatment will be continued up to 10 sessions (2 sessions per week).

A Fiber Tip with a diameter of 400µm will be used. The output power will be 300 mW and the average power density about 1 W/cm^2. A "spot" technique will be used, with a slight overlapping in order to evenly distribute energy covering all the mucosal lesions and also the peri-lesional tissues up to 0.5 cm.

Each session will be performed delivering a fluence of 4 J/cm2 per lesion, and the probe will be held perpendicularly at a distance of about 2 mm. The time of delivery per point of application is approximately 4 Sec in continuous wave with 2 sessions weekly. After each laser session, a cold diet will be recommended. [20,22]

Allocation concealment

Allocation of cases will be via block randomization method using a computer generated random sequence into 2 groups of equal numbers (N=22 patient/ group).[27]

Allocation will be informed by a trial independent individual. The participant allocation will be kept in opaque, sealed envelopes and arranged sequentially by a dental assistant, who will not be involved in the study.

Each envelop will be opened after completing the oral examination and right before the application of the intervention.

A) After biopsy and before treatment:

1. Detailed medical and dental history will be obtained from the selected patients.
2. Thorough intraoral examination will be performed to determine the need for scaling and treatment of any source of irritation.
3. Oral hygiene instructions will be carried out to all patients.
4. Adequate hydration will be advised.
5. Every group of patients will be given their treatment protocol.

B) During and after treatment:

Clinical Evaluation:

All patients will be clinically and biochemically evaluated before treatment, after 6 and 12 weeks with following criteria:

1- Subjective assessment

Discomfort and pain severity will be reported by each patient using Visual Analogue Scale (VAS). The VAS consisted of a 10-cm horizontal line marked 0 (=

no pain) to 10 (= most severe pain ever experienced). Patients will be requested to mark the scale at each visit, before and after treatment for each group . Complete resolution of the symptoms (no symptoms) will be defined as the absence of any discomfort, corresponding to a zero VAS score.

The stability of the results in the follow-up period will be also described. [20, 22]

2- Objective assessment

- The size of the lesion and the healing pattern will be monitored. The clinical data will be scored according Thongprasom et al 2003 scoring system. Score 5: white striae with erosive area >1 cm2, Score 4: white striae with erosive area <1 cm2, Score 3: white striae with erythematous area >1 cm2, Score 2: white striae with erythematous area <1 cm2, Score 1: mild white striae only, Score 0: no lesions, normal mucosa. [2,24]
- Measurement of Total Oxidative Stress in saliva including Total antioxidant capacity (TAC) and malondialdehyde (MDA). Saliva will be collected before treatment and after 6 and 12 weeks. Saliva will be collected, centrifuged at 30 g for 10 min to evacuate cellular debris and microscopic organisms. The filtered saliva will be stored at −80°C until the time of the biochemical investigation (Tvarijonaviciute, Aznar-Cayuela, Rubio, Ceron, & López-Jornet, 2017). The determination will be measured using the established colorimetric method (Koracevic, Koracevic, Djordjevic, Andrejevic, & Cosic, 2001). Biochemical analysis will be conducted at the Department of Biochemistry, Faculty of Medicine, Alexandria University.[25]

3- Photographs:

Photographs will be taken at baseline and at the end of the study.

STATISTICAL ANALYSIS

The data will be processed and analysed using Statistical Package for Social Sciences program SPSS software*.

* Armonk, NY: IBM Corp, USA.

ETHICAL CONSIDERATIONS

The clinical part of the study will be performed after the approval of the Research Ethics Committee, Faculty of Dentistry, Alexandria University.

The volunteers will provide written informed consent and the study will be conducted in accordance with the modified Helsinki Declaration of 2013.[14]

The patients will receive written consent about the study protocol before agreeing to participate in the study. The patients will have the right to withdraw at any time during the study.

Clinical trials need written informed consent in order to clarify objectives, risks and benefits of the study.

Medical therapy for potential risks will be provided (cortico steroids will be administered in case of severe pain after laser treatment).

DURATION OF THE STUDY

Estimated time: Twelve Months.

Months / **Study activities**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Purchase of materials	✓	✓										
Patient selection and Clinical study			✓	✓	✓	✓	✓	✓				
Data management and statistical analysis									✓			
Writing thesis									✓	✓		
Thesis submission											✓	✓

ESTIMATED BUDGET

Item	Cost in LE
Laser equipments	10000
Medications	2000
Statistical analysis	3000
Thesis printing and Binding	5000
Publication cost	2000
Total	22,000

PROBLEMS ANTICIPATED

- Availability of patients with satisfactory oral hygiene and not medically compromised.
- Difficulty in convincing the patients to participate in the study.
- Cooperation of the patients and compliance to treatment .
- High cost of the proposed interventions .

PUBLICATION POLICY

This study will be sent for either national or international Journal for publication, in the following order:

- Reem kamal Mohamed Abd elaziz
- Prof. Dr. Naguiba Mahmoud Elsayed.
- Prof. Dr. Sabah Abdelhady Mahmoud .
- Dr Yasmine Yousri Gawish .

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