DOI: 10.7860/JCDR/2025/74961.21928

Research Protocol

Dentistry Section

Comparative Efficacy of Topical Pomegranate Peel Extract and Topical Corticosteroid in Management of Oral Lichenoid Lesions: A Research Protocol

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ABSTRACT

Introduction: Oral Lichenoid Lesions (OLL) represent a group of oral lesions that share common clinical features and histological appearances but have different aetiologies. Lichenoid lesions may include oral lichen planus, lichenoid drug eruptions, lichenoid contact reactions, or lichenoid reactions of graft-versus-host disease. A number of treatment opportunities have been reported in the literature for the management of lichenoid lesions.

Need of the study: Among the various management options, corticosteroids are one of the drugs of choice. However, they are often known to cause various side-effects. Thus, it is reasonable to select a drug with minimal side-effect or the safest one. Pomegranate has been identified for its various health benefits and is expected to be helpful in the treatment of OLLs.

Aim: To evaluate the comparative efficacy of topical pomegranate peel extract and topical corticosteroids in the management of OLLs.

Materials and Methods: This randomised control trial double-blind study will be conducted in the Department of Oral Medicine and Radiology at Sharad Pawar Dental College and Hospital, DMIHER, Maharashtra, India, for a duration of six months from September 2025 to March 2026 (CTRI/2024/10/075071). The study will comprise 28 patients, who will be equally divided into two groups through simple randomisation. Group A will be treated with topical corticosteroids, while Group B will receive 10% pomegranate peel extract. Treatment response will be monitored after seven days, 15 days, and one month from the initial visit using two clinical parameters: 1) Visual Analog Scale (VAS) score and 2) Sign score. All observations will be recorded and subjected to appropriate statistical tests. Inter and intragroup comparisons will be made by comparing the observations of various parameters at the second and third recalls with the first recall in both groups. We will also compare the findings of both parameters at the first, second, and third recalls between the groups using the Wilcoxon Signed Rank test and Mann-Whitney U test, respectively. A p-value of <0.05 will be considered significant.

Keywords: Effectiveness, Health, Immunologic, Pain score, Sign score

INTRODUCTION

The OLL represents a group of oral lesions that share common clinical features and histological appearances but have different aetiologies [1]. OLL may include white keratotic lesions such as oral lichen planus, lichenoid drug eruptions, lichenoid contact reactions, or lichenoid reactions of graft-versus-host disease [1]. The common aetiological factors include systemic entities, autoimmune conditions, and local factors such as dental restorative materials, prosthetic materials, and flavoring agents [2]. The immune system plays an important role in most of these lesions, which may be drug-induced or contact reactions. The delayed hypersensitivity associated with an immunologic response may play a vital role, potentially resulting in the formation of white and red lesions in the oral cavity [1]. Clinically, white keratotic lesions are observed due to increased keratinisation of the affected mucosa, while in other cases, white lesions may be mixed with erythematous erosive lesions that can cause irritation and a burning sensation in the mucosa [3].

Corticosteroids are frequently used for the management of OLLs. In limited lesions, they are applied topically in gel or cream form, while their use as intralesional injections or systemic steroids is widely reported. Systemic administration may cause more adverse effects compared to local application [1,4]. Considering the potential adverse effects of steroids, various plant-based remedies have been researched over the past few years. Pomegranate is one such remedy that has garnered significant interest among researchers. Pomegranate (*Punica granatum L*) belongs to the family Punicaceae and is recognised for its various health benefits, including immunomodulatory activities, antioxidant properties, anticariogenic effects, as well as anti-inflammatory and antimicrobial properties [3].

Pomegranate contains polyphenols, anthocyanins, gallotannins, and other flavonoids that impart medicinal value to it [5]. This justifies its use in several pathological conditions such as metabolic syndrome, cancer, nephrolithiasis, urinary tract infections, and neurodegenerative diseases [6]. Similarly, pomegranate and its extracts whether peel extract or seed extract have been proposed to be helpful in the treatment of OLLs, mainly due to their immunomodulatory effects, although there is limited literature available on this topic [3]. Thus, the aim of this study is to evaluate the effectiveness of pomegranate peel extract in the management of OLLs by comparing it with one of the commonly used drugs, corticosteroids.

Primary objective: To evaluate the effectiveness of topical corticosteroids in the management of OLLs and the effectiveness of topical pomegranate peel extract in the management of OLLs.

Secondary objective: To compare the effectiveness of both treatments in the management of OLLs.

Null hypothesis: Topical pomegranate peel extract may not be effective in the management of OLLs when compared to topical corticosteroids.

Alternative hypothesis: Topical pomegranate peel extract may be effective in the management of OLLs when compared to topical corticosteroids.

REVIEW OF LITERATURE

The research question of the present study is to determine whether topical pomegranate peel extract is more effective than topical corticosteroids in the management of OLLs. Rotaru D et al., performed a review on the symptomatology and treatment strategies for OLL by analysing 58 studies. They mentioned that numerous treatment options are available, but none are curative. Therefore, selecting an appropriate drug poses a challenge. The management of OLL should focus on controlling the symptoms and improving the quality of life for the patient [4]. Binnie R et al., reported on the diversity of clinical presentations in OLL, highlighting the difficulty encountered in diagnosing the condition. They stated that differentiating between OLL and oral lichen planus can sometimes be challenging. Another concern is the potential malignant nature of OLL, which necessitates periodic monitoring by a dental practitioner [7].

Regarding the management of lichenoid lesions, Binnie R et al., extensively described primary care, secondary care, and the challenges and pitfalls encountered during the management of these lesions [7]. The present study will evaluate the efficacy of one natural product, pomegranate, in the management of OLLs [3]. Pomegranate, often regarded as a divine fruit, is considered one of the healthiest fruits in the world. Its extracts may boost human health and well-being to varying degrees if utilised extensively for the management of certain lesions and conditions. This study may demonstrate one of its benefits in treating symptoms of OLL with substantial results and no side-effect when compared with the commonly used drug, corticosteroids.

Zakaria M et al., conducted a study on the effectiveness of topical pomegranate in managing oral lichen planus [3]. They compared both pomegranate peel extract and pomegranate seed extract with corticosteroids. The Oral Health Impact Profile (OHIP-14) was assessed in each group before and after the management of the lesion, resulting in a significant decrease in pain scores and sign scores in both pomegranate groups. The present study will include patients with all types of OLLs, which is a novel aspect of this study.

Previous studies have also reported the efficiency of pomegranate in the treatment of aphthous ulcers [8,9]. Eltay EG et al., highlighted the promising role of pomegranate peel extract in managing chronic gingivitis [10]. Nevertheless, studies documenting the use of pomegranate in the management of OLLs remain scarce.

MATERIALS AND METHODS

This randomised control trial double-blind study will be conducted in the Department of Oral Medicine and Radiology at Sharad Pawar Dental College and Hospital, DMIHER, Maharashtra, India, for a duration of six months from September 2025 to March 2026. The Institutional Ethical Clearance (IEC) has been obtained for the study (IEC number is DMIMS (DU)/IEC/2022-23/1160). While the study is also registered in Control Trial Registry of India for which the registration number received is CTRI/2024/10/075071. The study will include 28 clinically diagnosed patients with OLLs. They will be randomly divided into two equal groups through simple randomisation: Group A (Control group) and Group B (Experimental group). Each patient will be included in the study after providing informed written consent.

Inclusion criteria: All patients with clinical presentations and signs of OLLs who have associated symptoms will be included in the study, irrespective of their age and gender. In cases with confusing or doubtful clinical presentations, a histopathological evaluation (incisional biopsy) will be performed to confirm the diagnosis.

Exclusion criteria: Patients who have received or are currently undergoing treatment for lichenoid lesions, those with associated malignant lesions, patients with a history of pomegranate allergy, and those suffering from any systemic disorder while receiving treatment for the same will be excluded from the study.

Sample size calculation: The sample size was calculated using the following formula [3]:

$$n_1 = \frac{(\sigma_1^2 + \sigma_2^2/K)\,(Z_{1-\alpha/2} + Z_{1-\beta})^2}{\Delta^2}$$

The notation for the formulae is:

n1= Sample size of Group-1

β= sample size of Group-2

σ1= standard deviation of Group-1

σ 2=standard deviation of Group-2

Δ =difference in group means

K=ratio = n2/n1.

Z1-α/2=two- sided Z value (e.g., Z=1.96 for 95% confidence interval).

Z1-β= power

Mean Sign Score in group C = 2

Mean Sign Score in group P = 1.64

σ1= SD of Sign Score in group C=0.39

σ2= SD of Sign Score in group P=0.50

For detecting mean difference of 0.36 i.e., Δ =2-1.64=0.36

K =1

N = (0.39*0.39 + 0.50*0.50) (1.96+0.84)2

0.36*0.36

=24.32 = 25 patients needed in each group (25*2=50)

Power of the test: 80%

Level of significance: 5% (95% confidence interval)

Patients will be divided into two equal groups: Group A (Control group) and Group B (Experimental group). The efficacy of the treatments will be monitored after 7 days, 15 days, and 30 days from the initial visit using two clinical parameters:

1. **VAS score:** This will be used to evaluate pain levels before and after treatment, assessed using a VAS involving a straight 10-cm line, with 0 indicating no pain and 10 representing intolerable pain [11].
2. **Sign scoring scale:** This will be done before and after treatment using the parameters described by Thongprasom K et al., 1992, as follows [12]:

Depending on the clinical presentation and size of the lesion, score varies from 0 to 5.

5 = (white striae with an erosive area >1 cm^2)

4= (white striae with an erosive area <1 cm^2)

3= (white striae with an atrophic area >1 cm^2)

2= (white striae with an atrophic area <1 cm^2)

1= (mild white striae only)

0= (no lesions, normal mucosa).

Study Procedure

The patient demographic details (age, gender, education, occupation, family income), presenting complaints, history of present illness, history of systemic illness, and history of adverse habits will be recorded. Patients with OLLs will be identified.

Patients in Group A will be advised to apply a topical corticosteroid (0.1% triamcinolone acetonide, Tess oral paste, Troikaa Pharmaceuticals Ltd., Ahmedabad-380 054, Gujarat, India) on the affected area three times daily. Group B will receive a 10% pomegranate peel extract gel to apply topically on the affected area three times daily. Drug application will be performed at 6:00 AM, 2:00 PM, and 10:00 PM.

Method of preparation of pomegranate peel extract: Pomegranate peels will be procured from the botanical garden of Mahatma Gandhi Ayurvedic College and Research Centre at Wardha. The peels will be finely minced using a blender. Subsequently, the minced peels will be placed in a Soxhlet extractor, where they will be subjected to continuous extraction with ethanol (80%) at 50-60°C for one hour. Following the extraction process, the ethanol will be allowed to evaporate, resulting in the acquisition of the pomegranate peel alcoholic extract (80%). To prepare the gel base, 1.8 g of Carbopol will be dispersed in 200 mL of distilled water. The pomegranate peel alcoholic extract (80%) will then be incorporated into the Carbopol gel base, along with the addition of 100 mL of glycerin to enhance its humectant properties. Finally, Triethanolamine will be added dropwise to the mixture to act as a thickening agent and preservative [13]. The final pomegranate peel extract will be dispensed in a dropper bottle, ready for topical application. The preparation of the drug and the investigation for the cytotoxicity of the pomegranate peel extract will be conducted in the Pharmacology department at Mahatma Gandhi Ayurvedic College and Research Centre at Wardha, Maharashtra, India.

Each patient in the experimental group will be assessed after seven days, 15 days, and 30 days. Both groups will be observed for the efficacy of the drugs over a one-month duration. At each visit, patients will be evaluated for both the Sign score and the VAS score.

Outcomes

Primary outcome: Both topical corticosteroids and topical pomegranate peel extract might be effective for the management of OLLs.

Secondary outcome: Topical pomegranate peel extract might be more effective compared to topical corticosteroids in the management of OLLs.

STATISTICAL ANALYSIS

All observations will be recorded in a Microsoft Excel sheet and then subjected to appropriate statistical tests to determine significance. Comparison of the observations of various parameters at the 2nd and 3rd recall with the 1st recall will be conducted for both groups. Additionally, the comparison of findings from both parameters at the 1st, 2nd, and 3rd recalls will be performed between both groups using the Wilcoxon Signed Rank Test and the Mann-Whitney U Test, respectively. A p-value of <0.05 will be considered significant.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Aug 20, 2024
- Manual Googling: Mar 12, 2025
- iThenticate Software: Mar 19, 2025 (10%)

ETYMOLOGY: Author Origin

EMENDATIONS: 8

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Aug 17, 2024**
Date of Peer Review: **Nov 05, 2024**
Date of Acceptance: **Mar 23, 2025**
Date of Publishing: **Oct 01, 2025**