

Evaluation of Salivary IL-6, IFN- γ and RAGE Levels Before and After Topical Betamethasone Nanogel Therapy in Oral Lichen Planus Patients

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ABSTRACT

Background: Oral lichen planus (OLP) is a chronic immune-mediated inflammatory disorder associated with mucosal pain and functional discomfort. Salivary biomarkers such as IL-6, IFN- γ , and RAGE may reflect disease activity and treatment response. Betamethasone nanogel may improve topical corticosteroid delivery because of its mucoadhesive and sustained-release properties.

Aim: To evaluate salivary IL-6, IFN- γ , and RAGE levels before and after topical betamethasone nanogel therapy in patients with OLP and to assess associated clinical improvement using the Oral Disease Severity Score (ODSS).

Materials and Methods: This prospective pre–post interventional study included 10 patients with symptomatic OLP. All patients received topical betamethasone nanogel twice daily for 14 days. Clinical severity was assessed using ODSS at baseline and post-treatment. Unstimulated whole saliva samples were collected at both time points, and salivary IL-6, IFN- γ , and RAGE levels were estimated by ELISA.

Results: All patients completed the study and no adverse effects were observed. Mean ODSS decreased significantly from 6.40 ± 4.45 to 5.00 ± 2.98 ($p = 0.0313$). Salivary IL-6 decreased from 35.30 ± 0.43 pg/mL to 27.39 ± 0.74 pg/mL, IFN- γ from 56.89 ± 3.30 pg/mL to 35.27 ± 2.67 pg/mL, and RAGE from 357.56 ± 20.40 pg/mL to 274.26 ± 12.26 pg/mL. All biomarker reductions were highly significant ($p < 0.001$).

Conclusion: Topical betamethasone nanogel resulted in significant clinical and biochemical improvement in OLP. The reduction in ODSS and salivary IL-6, IFN- γ , and RAGE levels suggests that it may be an effective localized anti-inflammatory therapy, while salivary biomarkers may serve as useful adjuncts for monitoring treatment response.

Keywords: Oral lichen planus, betamethasone nanogel, salivary biomarkers, interleukin-6, interferon-gamma, receptor for advanced glycation end, oral disease severity score, topical corticosteroid therapy, disease, medicine, illness

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INTRODUCTION

Oral lichen planus (OLP) is a chronic immune-mediated inflammatory disorder affecting the oral mucosa and is considered one of the most frequently encountered oral potentially malignant disorders in clinical practice [1]. The disease is characterized by a persistent T-cell-mediated immune response directed against basal keratinocytes, resulting in epithelial degeneration and chronic mucosal inflammation [2]. Clinically, OLP presents in various forms including reticular, atrophic, and erosive patterns,

with symptomatic lesions commonly associated with burning sensation, pain, and difficulty in oral function, thereby significantly affecting patient quality of life [3].

Although the exact etiology remains unclear, current evidence suggests that OLP pathogenesis involves complex interactions between antigen-specific cellular immunity, cytokine imbalance, and oxidative stress pathways. Cytotoxic CD8⁺ T lymphocytes play a central role by inducing keratinocyte apoptosis through release of

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pro-inflammatory mediators and activation of immune signalling cascades [4]. Among these mediators, interleukin-6 (IL-6) has been identified as a key cytokine involved in sustaining chronic inflammation and promoting recruitment of inflammatory cells. Elevated salivary and serum IL-6 levels have been consistently reported in patients with active OLP and are associated with disease severity [5,6]. Similarly, interferon-gamma (IFN- γ), a Th1-associated cytokine, contributes to immune activation and epithelial injury by enhancing antigen presentation and cytotoxic T-cell responses [7]. Recent studies also highlight the role of the receptor for advanced glycation end products (RAGE), which amplifies inflammatory signalling through NF- κ B activation and oxidative stress mechanisms, contributing to persistence of chronic inflammation in oral mucosal disorders [8].

Topical corticosteroids remain the gold standard for symptomatic management of OLP due to their potent anti-inflammatory and immunosuppressive effects. These agents reduce cytokine production, suppress immune activation, and promote clinical healing [9]. However, conventional topical formulations are limited by reduced mucosal retention time, dilution by saliva, and inconsistent drug delivery, which may reduce therapeutic effectiveness and contribute to recurrence [10]. Advances in drug-delivery systems have led to the development of nanogel formulations, which provide improved mucoadhesion, controlled drug release, and enhanced penetration into oral tissues. Such properties may enhance local bioavailability while minimizing systemic exposure, thereby improving therapeutic outcomes.

In addition to clinical evaluation, salivary biomarkers have gained increasing attention as non-invasive tools for assessing disease activity and monitoring treatment response. Saliva reflects local immune and inflammatory changes and allows repeated sampling without patient discomfort. Measurement of cytokines such as IL-6 and IFN- γ , along with oxidative stress mediators like RAGE, may provide objective insight into biochemical changes occurring during therapy.

Despite the widespread use of corticosteroids in OLP management, limited evidence exists regarding the biochemical impact of advanced delivery systems such as nanogel formulations on inflammatory biomarkers. Therefore, the present study aimed to evaluate the effect of topical betamethasone nanogel therapy on salivary IL-6, IFN- γ , and RAGE levels in patients with Oral Lichen Planus and to correlate biomarker changes with clinical improvement.

MATERIALS AND METHODS

Study Design

This prospective pre–post interventional clinical study was conducted to evaluate the effect of topical betamethasone nanogel therapy on clinical disease severity and salivary biomarker levels in patients with oral lichen planus (OLP). The study was carried out in the Department of Oral

Medicine and Radiology at Saveetha Dental College, Chennai.

Ethical approval

The study protocol was reviewed and approved by the Saveetha Dental College-Institutional Human Ethical Committee (SDC-IHEC) and the approval number for the same is IHEC/SDC/OMED-2304/26/TH-005. Written informed consent was obtained in English and Tamil languages from all participants prior to enrolment in the study.

Study Population

A total of 10 patients with symptomatic OLP were included in the study. The diagnosis of OLP was based on characteristic clinical findings, with histopathologic confirmation where indicated. Patients presenting with erosive, reticular, or plaque-like forms of OLP and associated symptoms such as burning sensation or pain were screened for eligibility.

Inclusion criteria

The inclusion criteria were as follows:

1. Patients clinically diagnosed with symptomatic OLP.
2. Presence of clinically visible oral lesions associated with pain or burning sensation.
3. Willingness to participate in the study and provide saliva samples before and after treatment.

Exclusion criteria

Patients were excluded if they had:

1. Received systemic corticosteroids or immunosuppressive therapy within the previous 3 months.
2. Presence of other autoimmune, vesiculobullous, or inflammatory oral mucosal diseases.
3. Systemic conditions known to alter salivary cytokine levels.
4. Tobacco or alcohol abuse that could influence inflammatory biomarker expression.
5. Pregnancy or lactation.

Intervention

All enrolled patients received topical betamethasone nanogel, which was applied directly over the lesional area twice daily for 14 days. Patients were instructed not to eat or drink for at least 30 minutes after application to ensure adequate mucosal contact and drug absorption. The nanogel formulation was selected for its presumed mucoadhesive and sustained-release properties, which may improve local corticosteroid bioavailability compared with conventional topical preparations.

Clinical assessment

Clinical disease severity was assessed using the Oral Disease Severity Score (ODSS) at two time points:

1. Baseline, before initiation of therapy

2. Post-treatment, after completion of 14 days of therapy

ODSS was used as the clinical outcome measure to quantify lesion extent, activity, and symptom burden.

Saliva collection

Unstimulated whole saliva was collected from each participant at baseline and after completion of treatment. Collection was performed between 9:00 AM and 11:00 AM to minimize circadian variation. Participants were instructed to refrain from eating, drinking, or performing oral hygiene procedures for at least 1 hour before sample collection. Saliva was obtained by the passive drooling method into sterile collection tubes. The samples were immediately placed on ice, centrifuged to remove cellular debris, and the supernatant was stored at -80°C until biochemical analysis.

Biomarker estimation

Salivary concentrations of interleukin-6 (IL-6), interferon-gamma (IFN- γ), and receptor for advanced glycation end products (RAGE) were quantified using commercially available enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturer’s instructions. Optical density was measured using a microplate reader, and biomarker concentrations were calculated from standard calibration curves generated for each analyte. These biomarkers were selected because of their established or emerging roles in OLP-related inflammatory, immune, and oxidative signalling pathways.

Outcome measures

- The primary outcome measures were the changes in salivary levels of IL-6, IFN- γ and RAGE.

- The secondary outcome measure was change in ODSS following therapy.

Statistical Analysis

Data were expressed as mean \pm standard deviation (SD). Normality of data distribution was assessed before selecting the appropriate test. For normally distributed variables, pre- and post-treatment comparisons were performed using the paired t-test. For non-normally distributed variables, the Wilcoxon signed-rank test was used. A p value < 0.05 was considered statistically significant.

RESULTS

A total of 10 patients with oral lichen planus were included in the study. The age of the participants ranged from 18 to 85 years, with an equal sex distribution of 5 males and 5 females. The clinical forms included erosive, reticular, and plaque-like oral lichen planus. All enrolled patients completed the treatment protocol, and no adverse effects were observed during the study period.

Clinical improvement was assessed using the Oral Disease Severity Score (ODSS). The mean ODSS decreased from 6.40 ± 4.45 at the first visit to 5.00 ± 2.98 at the last visit, corresponding to a mean reduction of 1.40 and an overall percentage reduction of 21.88%. Since the ODSS difference scores were not normally distributed, the Wilcoxon signed-rank test was applied. The reduction in ODSS was found to be statistically significant ($p = 0.0313$), indicating an overall improvement in clinical disease severity following topical betamethasone nanogel therapy.

Table 1: Pre and post treatment comparison of salivary biomarkers

Biomarker	Before Treatment (Mean \pm Sd) Pg/MI	After Treatment (Mean \pm Sd) Pg/MI	Mean Reduction (Pg/MI)	% Reduction	P Value
IL-6	35.30 \pm 0.43	27.39 \pm 0.74	7.91	22.41	<0.001
IFN- γ	56.89 \pm 3.30	35.27 \pm 2.67	21.62	38.01	<0.001
RAGE	357.56 \pm 20.40	274.26 \pm 12.26	83.30	23.30	<0.001

Table 1 shows a significant reduction in all salivary biomarkers after topical betamethasone nanogel therapy. Mean salivary IL-6, IFN- γ , and RAGE levels decreased significantly after treatment, with percentage reductions of

22.41%, 38.01%, and 23.30%, respectively ($p < 0.001$ for all). Among the biomarkers evaluated, IFN- γ showed the greatest reduction.

Table 2: Pre and post treatment comparison of ODSS scores

Parameter	Before Treatment (Mean \pm Sd)	After Treatment (Mean \pm Sd)	Mean Reduction	% Reduction	Test Used	P Value
ODSS	6.40 \pm 4.45	5.00 \pm 2.98	1.40	21.88	Wilcoxon signed-rank test	0.0313

Table 2 shows the clinical response assessed using ODSS. The mean ODSS decreased from 6.40 ± 4.45 before treatment to 5.00 ± 2.98 after treatment, corresponding to a

21.88% reduction. This improvement was statistically significant on Wilcoxon signed-rank analysis ($p = 0.0313$).

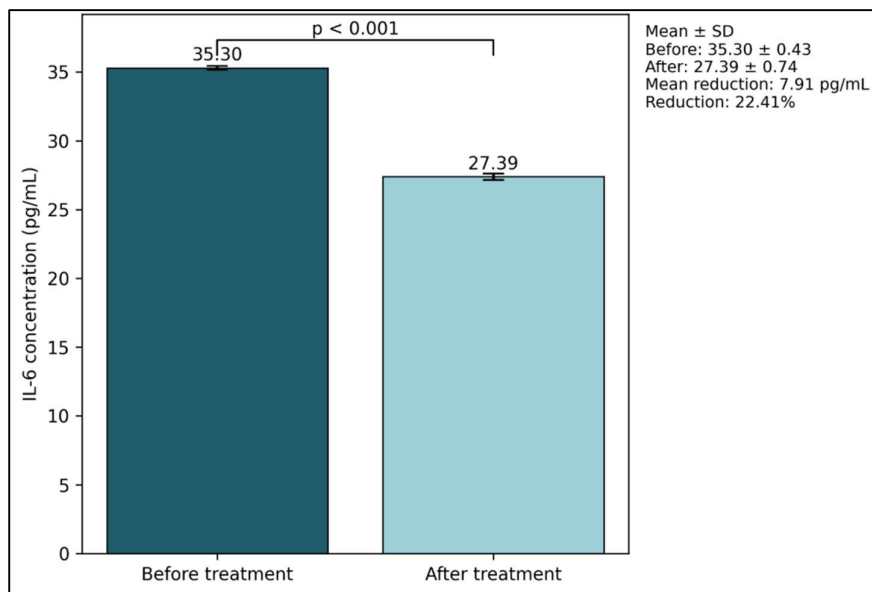


Figure 1: Salivary IL-6 levels before and after treatment

Figure 1 showed that IL-6 levels had a significant reduction following therapy, the mean IL-6 concentration decreased from 35.30 ± 0.43 pg/mL before treatment to 27.39 ± 0.74 pg/mL after treatment. This represented a mean reduction of 7.91 pg/mL with an overall percentage reduction of 22.41%. Statistical analysis demonstrated that the decrease in IL-6 levels was highly significant ($p < 0.001$).

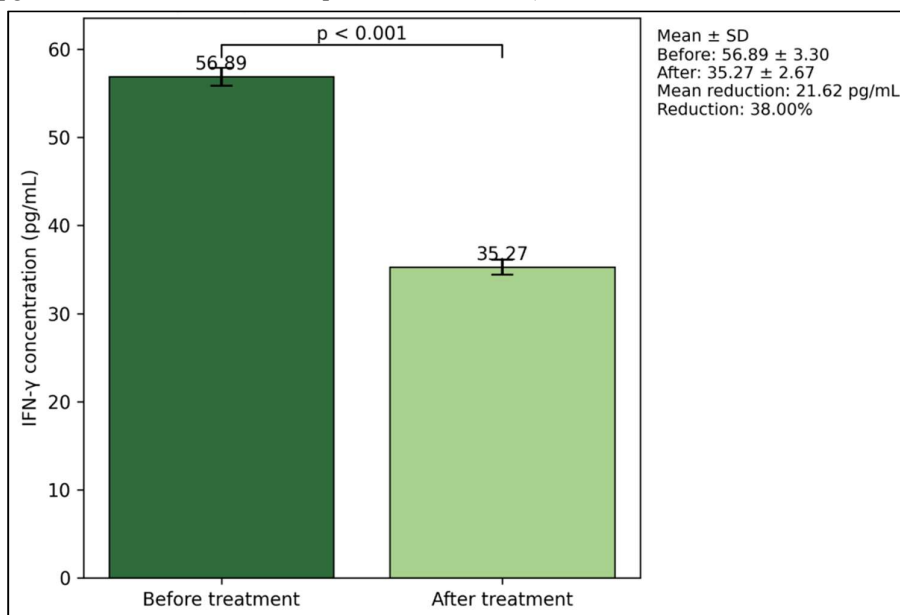


Figure 2: Salivary IFN- γ levels before and after treatment

IFN- γ levels also demonstrated a marked reduction following therapy as seen in figure 2, the mean IFN- γ concentration decreased from 56.89 ± 3.30 pg/mL before treatment to 35.27 ± 2.67 pg/mL after treatment. This corresponded to a mean reduction of 21.62 pg/mL, with an overall percentage reduction of 38.01%. The reduction was found to be highly significant on paired analysis ($p < 0.001$).

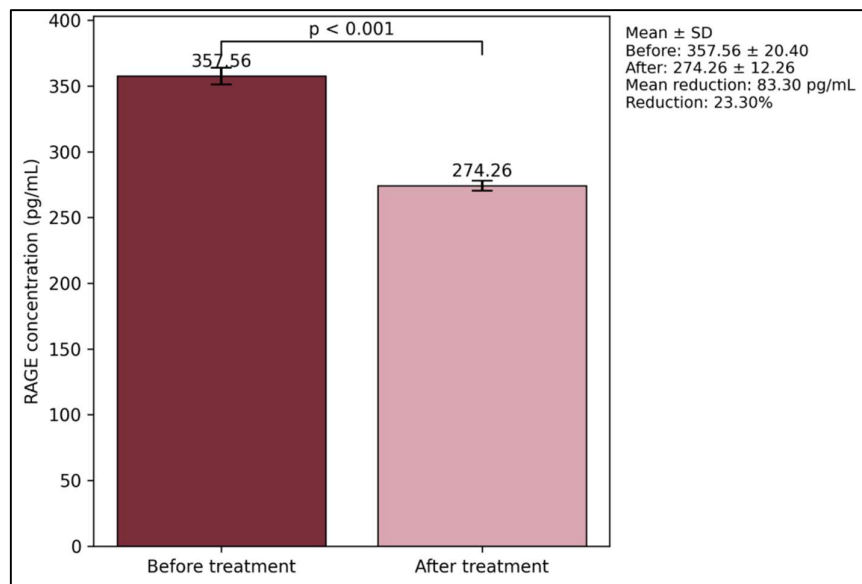


Figure 3: Salivary RAGE levels before and after treatment

Similarly, figure 3 showed salivary RAGE levels that had a significant reduction following therapy, the mean RAGE concentration decreased from 357.56 ± 20.40 pg/mL before treatment to 274.26 ± 12.26 pg/mL after treatment. This corresponded to a mean reduction of 83.30 pg/mL, with an overall percentage reduction of 23.30%. This change was also highly significant ($p < 0.001$).

Overall, both the clinical and salivary biomarker findings demonstrated improvement following topical betamethasone nanogel therapy.

DISCUSSION

Oral lichen planus is a chronic immune-mediated inflammatory disorder in which persistent epithelial injury, cytokine dysregulation, and oxidative-inflammatory pathways contribute to lesion persistence and symptom severity [11]. In the present study, topical betamethasone nanogel therapy produced significant improvement at both the clinical and biochemical levels. ODSS decreased significantly from 6.40 ± 4.45 to 5.00 ± 2.98 , while salivary IL-6, IFN- γ , and RAGE also showed significant post-treatment reduction. These findings suggest that betamethasone nanogel exerts a meaningful local anti-inflammatory and immunomodulatory effect in OLP.

Clinical improvement in our study was assessed using ODSS, which showed a significant decline after treatment. Although the absolute reduction was modest, this should be interpreted in light of the relatively lower baseline disease severity and shorter treatment period in our cohort. A useful comparison can be made with the randomized clinical trial by Vinay et al., [12] in which ODSS was used as the primary response measure in symptomatic OLP. They reported that 88% of patients receiving oral acitretin plus topical triamcinolone achieved ODSS-75 at 28 weeks compared with 47% receiving topical triamcinolone alone, and this difference persisted at 36 weeks (84% vs 41%).

Their study confirms that ODSS is a meaningful clinical endpoint in OLP trials. Compared with that trial, our study involved a shorter treatment period, a smaller sample, and a lower baseline ODSS, yet still demonstrated significant clinical improvement with topical betamethasone nanogel alone.

Salivary IL-6 showed a significant reduction in the present study, from 35.30 ± 0.43 pg/mL before treatment to 27.39 ± 0.74 pg/mL after treatment. This finding agrees with the study by Rhodus et al., [13] who demonstrated that salivary IL-6 decreased significantly after 0.1% dexamethasone mouthwash therapy in erosive OLP, along with symptomatic improvement. Their study supports the concept that topical corticosteroid therapy can suppress salivary inflammatory cytokines in OLP [14]. Our findings are also supported by the meta-analysis by Mozaffari et al., which showed that both salivary and serum IL-6 levels are significantly higher in OLP patients than in healthy controls, with salivary IL-6 showing particular relevance for diagnostic and therapeutic monitoring [10,15]. Thus, the reduction in IL-6 seen in our study strengthens the evidence that IL-6 is both a disease-associated and treatment-responsive biomarker in OLP.

Among the biomarkers assessed, IFN- γ showed the greatest percentage reduction, decreasing from 56.89 ± 3.30 pg/mL to 35.27 ± 2.67 pg/mL after therapy. This finding is important because IFN- γ reflects T-cell-mediated immune activation, which plays a central role in OLP pathogenesis. Tao et al. reported that salivary IFN- γ was significantly elevated in erythematous/ulcerative OLP and correlated with tissue levels, suggesting that salivary IFN- γ reflects the local lesional immune environment [16,17]. Similarly, Malekzadeh et al. found elevated salivary IFN- γ in OLP patients and reported an increased IFN- γ /IL-4 ratio, supporting a relative Th1 predominance

in OLP [5,18]. While these studies were not treatment-response studies, they support the biological relevance of IFN- γ in active disease. Therefore, the significant post-treatment reduction in IFN- γ observed in our cohort suggests that betamethasone nanogel was able to attenuate the immune activation underlying lesion persistence.

The evaluation of salivary RAGE is one of the novel aspects of the present study. RAGE decreased significantly from 357.56 ± 20.40 pg/mL before treatment to 274.26 ± 12.26 pg/mL after treatment. Direct salivary RAGE studies in OLP are scarce, so this result is best interpreted in the context of its established inflammatory role. The review by Radziszewski et al. highlights that RAGE amplifies chronic inflammation through pathways such as NF- κ B, MAPK/ERK, PI3K/Akt, and JAK/STAT, and also summarizes human studies showing increased RAGE and HMGB1 expression in lichen planus tissues [8,18]. Thus, the reduction in salivary RAGE in our study is biologically plausible and suggests that betamethasone nanogel may influence not only classical cytokine pathways but also inflammation-associated oxidative signalling. Since comparable salivary outcome studies are limited, this finding should be presented as preliminary but promising evidence.

An important strength of the present study is that the salivary biomarkers and clinical score improved in the same direction. The reduction in ODSS, together with the fall in IL-6, IFN- γ , and RAGE, suggests that the biochemical changes were accompanied by real clinical benefit. This supports the view that salivary biomarkers may complement clinical scoring in OLP follow-up, particularly because saliva collection is non-invasive and repeatable.

The favourable response observed in our study may also be related to the nanogel delivery system. Conventional topical corticosteroids are often limited by rapid salivary washout and short mucosal contact time. A nanogel-based formulation may improve local retention and prolong drug contact with the lesion [19,20]. Although our study did not include a direct comparison with a conventional steroid preparation, the significant clinical and biomarker improvement observed suggests that localized nanogel delivery of betamethasone may be therapeutically advantageous.

LIMITATIONS

The present study has certain limitations. First, the sample size was small, which limits the generalizability of the findings. Second, the follow-up period was short, and therefore long-term clinical response, recurrence, and sustained biomarker changes could not be assessed. Third, the study did not include a comparator arm, which restricts direct comparison of betamethasone nanogel with conventional topical steroid preparations. In addition, while IL-6 and IFN- γ are supported by existing OLP literature, comparable salivary treatment-response data for RAGE remain limited, and this finding should therefore be interpreted with caution. Despite these limitations, the

study provides preliminary evidence that topical betamethasone nanogel can improve both clinical severity and salivary inflammatory markers in OLP.

CONCLUSION

Within the limitations of the present study, topical betamethasone nanogel demonstrated significant therapeutic benefit in patients with oral lichen planus. Treatment was associated with a significant reduction in ODSS, along with decreased salivary IL-6, IFN- γ , and RAGE levels, indicating improvement at both the clinical and molecular levels. These findings suggest that betamethasone nanogel may be an effective localized anti-inflammatory therapy in OLP and that salivary biomarkers may serve as useful adjuncts for monitoring treatment response. Further randomized controlled studies with larger sample sizes and longer follow-up are required to confirm these findings and define the long-term clinical value of this formulation.

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