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Comparing the Effectiveness and Salivary Levels of TNF-alpha in Patients with Oral Lichen Planus Treated with Topical Clobetasol Propionate and Fluocinolone Acetonide

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Abstract

Objectives: The purpose of this study was to compare the effectiveness and salivary levels of tumor necrosis factor-alpha (TNF-α) in patients with oral lichen planus (OLP) treated with topical clobetasol propionate (CP) and fluocinolone acetonide (FA).

Methods: A total of 26 patients diagnosed with erosive-atrophic OLP were randomly divided into 2 groups: the first group received CP 0.05%, and the other received FA 0.1%. Pain scores, clinical scores, and saliva samples from the patients were collected for analysis both prior to treatment initiation and after 4 weeks. Salivary TNF-α levels were evaluated using an immunology multiplex assay. The Wilcoxon signed-rank test and the Mann-Whitney U test were used for intra-group and inter-group comparisons, respectively.

Results: Both treatments showed significant reductions in pain scores, clinical scores, and salivary TNF-α levels compared with the pre-treatment values ($p<0.05$). After 4 weeks of treatment, CP 0.05% demonstrated a greater reduction in clinical score compared with FA 0.1% ($p<0.05$).

Conclusions: CP 0.05% and FA 0.1% effectively treat OLP. CP 0.05% demonstrated a quicker clinical score reduction than FA 0.1% over four weeks. Additionally, both steroids reduced salivary TNF-α levels, which could indicate the possibility of using disease-related biomarkers for monitoring.

Keywords: clobetasol propionate, fluocinolone acetonide, oral lichen planus, saliva, tumor necrosis factor-alpha

Introduction

Oral lichen planus (OLP) is a chronic inflammatory disease of oral mucosa. Patients typically experience a burning sensation, oral discomfort, and pain.[1-3] The exact etiology and pathogenesis of OLP have not been fully understood; however, several studies revealed an association with a T-cell-mediated immune disease in which cytotoxic CD8+ T cells trigger apoptosis of the oral epithelial basal cells.[1,4]

Topical steroids are commonly used for treating OLP due to their anti-inflammatory and immunosuppressive properties; they provide effective therapy that is cost effective and has minimal side effects.[5-8] Among these steroids, fluocinolone acetonide 0.1% (FA) is a potent medication listed in the Thailand National List of Essential Medicines and has been widely used for treating OLP in Thailand. Studies have shown that FA 0.1% completely heals OLP lesions in 50-73% of cases.[9,10] Recent research has highlighted the potential benefits of using ultrahigh-potency steroids such as clobetasol propionate 0.05% (CP) for OLP treatment; these investigations have demonstrated its success at reducing symptoms and clinical lesions.[8,11,12] CP 0.05% is not readily available in Thailand. Nevertheless, Chiang Mai University's Faculty of Pharmacy has the capability to manufacture it. Moreover, there have been only a limited number of studies directly comparing the effectiveness of FA and CP in treating OLP lesions.

Numerous studies have investigated biomarkers associated with the pathogenesis, progression, diagnosis, and prognosis of OLP, with a specific focus on cytokines as potential tools.[13] Among these cytokines, TNF-α has received considerable attention.[14] Several studies indicate that in patients with OLP, both salivary or serum TNF-α levels and the count of TNF-α-producing cells on tissue biopsy increase compared to healthy controls.[15] However, saliva-based tests can serve as a cost-effective and non-invasive method for measuring TNF-α levels in OLP patients.[13,16] According to Pezelj-Ribaric *et al.,*[17] concentrations of salivary TNF-α vary across different clinical types of OLP, with the heightened production of TNF-α in saliva evidently reflecting clinical changes and correlating with the severity of OLP. Moreover TNF-α levels have been observed decrease following glucocorticoid treatment. This fact suggests that salivary TNF-α levels might serve as a means of monitoring disease progression.[18] Thus, examining potential biomarkers to evaluate treatment responses with topical steroids presents an intriguing. This study sheds light on these critical aspects by comparing the efficacy of CP 0.05% and FA 0.1% in treating erosive-atrophic OLP at reducing pain levels, clinical scores, and TNF-α expression in the saliva for the treatment of OLP.

Materials and Methods

Study design

Patients were recruited from the Oral Medicine Clinic at the Faculty of Dentistry, Chiang Mai University, Thailand, between July 2022 and June 2023. A randomized, double-blind clinical trial was conducted, and the study protocol received approval from the Human Experimentation Committee of the Faculty of Dentistry at Chiang Mai University (No. 46/2021) and the Thai Clinical Trials Registry (TCTR20220705003). Before the study commenced, all patients were fully informed of the study's details and provided written consent to participate.

Participants

The inclusion criteria were as follows: (1) Patients were 18 years of age or older with a definitive diagnosis of OLP based on the 2003 modified WHO criteria,[19] (2) patients had not history of taking drugs that have been reported to cause lichenoid drug reactions, and the OLP lesion was not adjacent to or in contact with a dental restoration, (3) patients had neither other oral mucosal lesions nor a history of lichenoid-related systemic conditions.

The exclusion criteria were as follows: (1) Patients who had been given systemic or topical steroid treatments for oral lesions within the past three months, (2) patients who were pregnant or breast-feeding, (3) patients with a history of smoking or alcohol consumption, (4) patients who had used non-steroidal anti-inflammatory drugs within 14 days prior to the start of the study, (5) Patients who wore removable dentures but refused to remove them at all times during the study period.

The sample size of 12 patients in each group was statistically calculated as the minimum sample size, based on a previous study.[14] This calculation considered a power of 80% ($z\beta=0.84$) and a 95% confidence interval ($z\ \alpha/\ 2=1.96$). Therefore, 26 patients were included to account for any potential dropouts.

Interventions

The patients underwent screening, and their data were recorded. Subsequently, they were randomly assigned to one of two groups using stratified randomization based on sex and age. Each group received either clobetasol propionate gel 0.05% or fluocinolone acetonide in orabase 0.1% topically, four times daily for a duration of 4 weeks. The medications were provided in identical preparations and were placed in blinded containers by the Faculty of the Pharmacy Department at Chiang Mai University. Patients were instructed to apply the medication four times a day: three times after meals and once before bedtime. Additionally, patients were advised to abstain from eating or drinking for 30 minutes after applying the medication. The patients'-maintained diaries were utilized to monitor their treatment.

Assessment of treatment effectiveness

Evaluations were conducted both before and 4 weeks after the treatment. Each visit included a pain assessment, clinical evaluation, and collection of saliva samples. To determine the symptomatology score, a visual analogue scale (VAS) was used. The VAS consisted of a 10-point scale ranging from 0 (no pain) to 10 (most severe pain). During each visit, patients were instructed to indicate the number that corresponded to their pain level. The clinical response of the lesion was assessed using the Thongprasom criteria (TC).[10] The scoring ranged from 0 (no lesion, normal mucosa) to 5 (white striae with erosive area more than 1 cm^2), with various scores for different lesion characteristics. The scoring was performed by one specialist in oral medicine (Thai Board of Oral Diagnostic Sciences Certification) on the most severe site of the lesion throughout the study period. Following treatment completion, we assessed the disease remission (the difference between baseline and endpoint scores numerically indicates clinical and symptomatic improvement) based on the following criteria: (1) Complete remission (CR): no or very mild symptoms; disappearing lesions; or mild white striae, (2) Partial remission (PR): reduced symptoms, mild white striae, and mild erythematous area, (3) No response (NR): symptoms persisted with no improvement or worsening of the lesions.[10]

Saliva collection and cytokine assessment

Whole unstimulated saliva (WUS) was collected between 9:00 and 11:00 A.M. using established procedures.[20] Immediately after collection, the samples were stored at -80ºC until further analysis.[17,21] The tubes containing WUS were then centrifuged at 12,000 rpm for 20 minutes at 4ºC, and the resulting supernatants were utilized for the assays. TNF-α levels in saliva were measured using a Luminex 200 instrument and the MILLIPLEX MAP HCYTOMAG-60K-04 kit (Millipore, Billerica, MA, USA). The immunological multiplex test was conducted at the Merck Thailand Laboratories Service Center, adhering to the manufacturer's instructions, and utilizing MagPix software xPonent/Analyst. A standard curve was generated using the standard solution provided in the kit, and all procedures were performed in accordance with the manufacturer's guidelines. The test was conducted in duplicate, and the results were reported in picograms per milliliter (pg/ml).[22,23]

Statistical analysis

We used the median (first quartile, third quartile) for quantitative variables and presented the qualitative data as frequencies and percentages. VAS, clinical scores, and salivary TNF-α levels had a nonparametric distribution. The Mann-Whitney U-test assessed group differences, and the Wilcoxon signed rank test confirmed pre- and post-treatment significance. SPSS (version 26.0; IBM Corp., Armonk, NY, USA) conducted all statistical analyses. The significance level was $p<0.05$.

Results

Twenty-six patients were screened and analyzed in this study (Figure 1). The majority were women (20 out of 26 patients), The age of the cohort ranged from 21 to 84 years. The most commonly reported symptoms included a burning sensation (69.20%), pain (15.40%), and discomfort (15.40%). The observed OLP lesions were predominantly atrophic (76.90%) and erosive (23.10%). The median VAS was 5.65 (5.00-7.07), the median clinical score was 3.00 (3.00-3.25), and the median salivary level of TNF-α was 37.76 (16.22-48.52) pg/ml. Table 1 lists baseline characteristics for both treatment groups, indicating no significant initial differences ($p>0.05$).

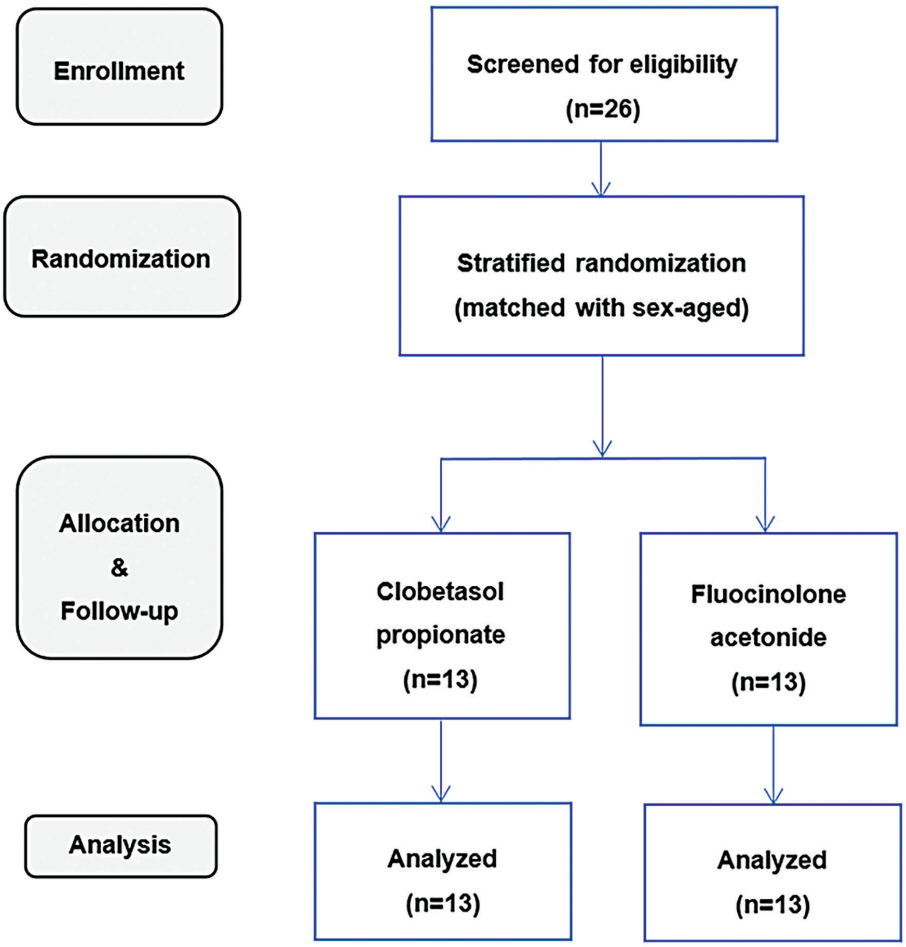

Figure 1: The flow diagram of patients' recruitment and the progress through stages of the study

Table 1: Baseline characteristics for both treatment groups

	Clobetasol propionate (n=13)	Fluocinolone acetonide (n=13)	*p*-value
Age, years[a]	55.00 (46.00-63.50)	57.00 (41.50-68.00)	0.880[c]
Sex[b]			
Female	10 (38.46)	10 (38.46)	1.000[d]
Male	3 (11.54)	3 (11.54)	
Type[b]			
Atrophic	9 (34.62)	11 (42.31)	0.652[d]
Erosive	4 (15.38)	2 (7.69)	
Chief complaint[b]			
Burning	10 (38.46)	8 (30.77)	0.667[d]
Pain/Discomfort	3 (11.54)	5 (19.23)	
Symptoms, VAS[a]	6.60 (5.35-7.45)	5.30 (4.20-6.60)	0.081[c]
Clinical score, TC[a]	3.00 (3.00-4.00)	3.00 (3.00-3.00)	0.418[c]
Salivary TNF-α, pg/ml[a]	29.38 (15.87-44.39)	39.72 (33.26-50.32)	0.235[c]

VAS=Visual analog score
TC=Thongprasom criteria
[a]*Data are presented as median (Q1-Q3)*
[b]*Data are presented as frequency (percentage)*
[c]*Mann-Whitney U Test*
[d]*Fisher's Exact Test*

CP 0.05% and FA 0.1% reduced signs and symptoms of OLP.

The VAS for pain and the clinical score significantly decreased in both groups when comparing values before and after treatment (Figure 2). Moreover, there was no significant difference in the reduction of VAS for pain between CP 0.05% and FA 0.1% groups (Figure 3). However, at the 4-week mark of treatment, CP 0.05% exhibited a significant decrease in the clinical score compared to FA 0.1% (Figure 3). Regarding disease remission, the two study groups exhibited 34.62% (9 out of 26) complete remission, 65.38% (17 out of 26) partial remission, and 0% (0 out of 26) no response to treatment. There was no significant difference in disease remission (p>0.05) between the CP 0.05% and FA 0.1% groups (Table 2). These results highlight that CP 0.05% and FA 0.1% have comparable clinical effects; however, CP 0.05% decreases clinical scores more rapidly than FA 0.1%. Figure 4 shows a patient's bilateral atrophic OLP lesions before CP 0.05% treatment (top panels) and 4 weeks after treatment (bottom panels). The clinical improvement is evident: the lesion is almost completely healed after 4 weeks of treatment. There were no clinical signs of oral candidiasis, atrophy, abnormalities in the taste sense, or allergic reactions detected in the treatment groups after the to the end of the trial.

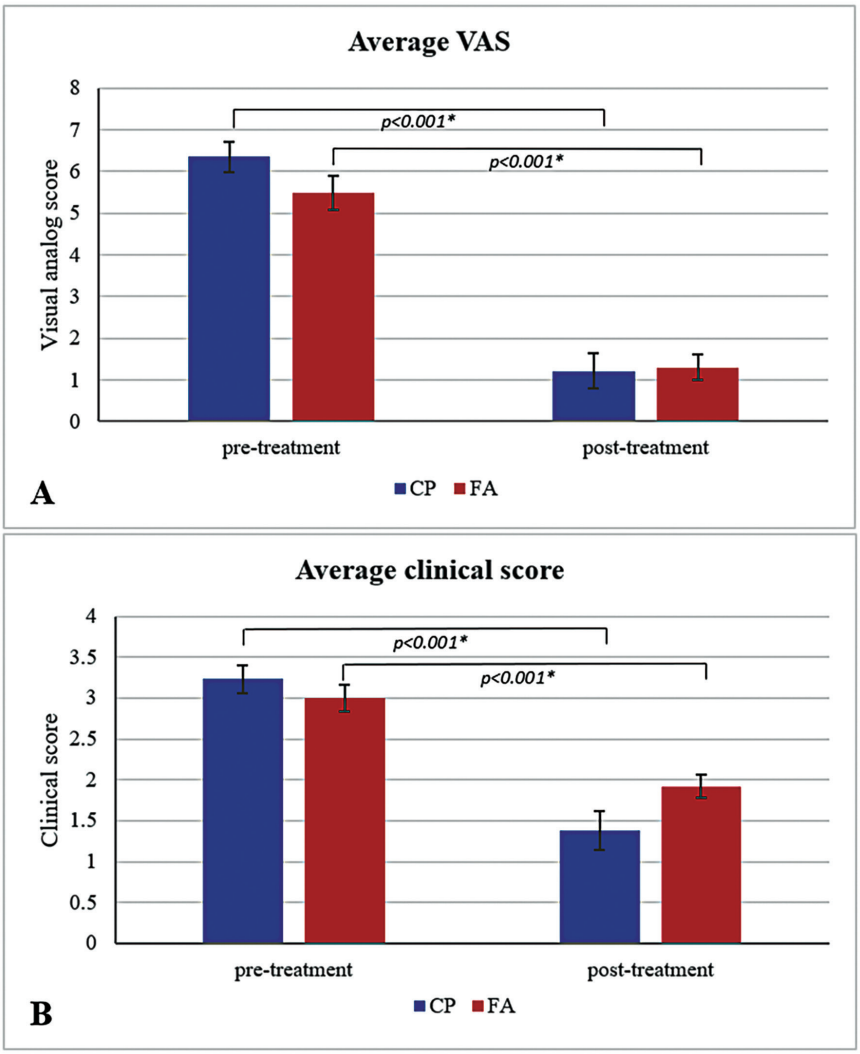

Figure 2: Comparison of clinical parameters pre-treatment and post-treatment. (A) After 4 weeks of treatment, the average pain scores (VAS) for the CP 0.05% and FA 0.1% groups decreased to 1.22±0.42 and 1.30±0.31, respectively. (B) The average clinical scores (Thongprasom scale) for the same groups also diminished to 1.38±0.24 and 1.92±0.14, respectively

CP = Clobetasol propionate, FA = Fluocinolone acetonide

* Statistically significant p<0.05 (Wilcoxon signed rank test)

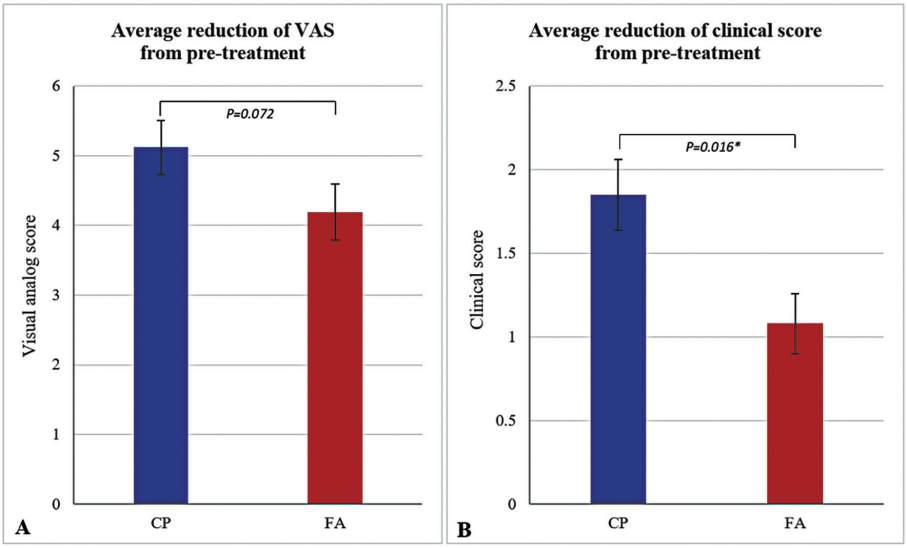

Figure 3: Comparison of the reduction of VAS and clinical scores in the two groups of treatment. (A) After 4 weeks of treatment, the average reduction in VAS for the CP 0.05% and FA 0.1% groups was 5.12 ± 0.40 and 4.19 ± 0.41, respectively. Additionally, (B) the average reduction in clinical scores for the same groups was 1.85±0.22 and 1.08±0.18, respectively

CP = Clobetasol propionate, FA = Fluocinolone acetonide

* Statistically significant $p<0.05$ (Mann–Whitney U test)

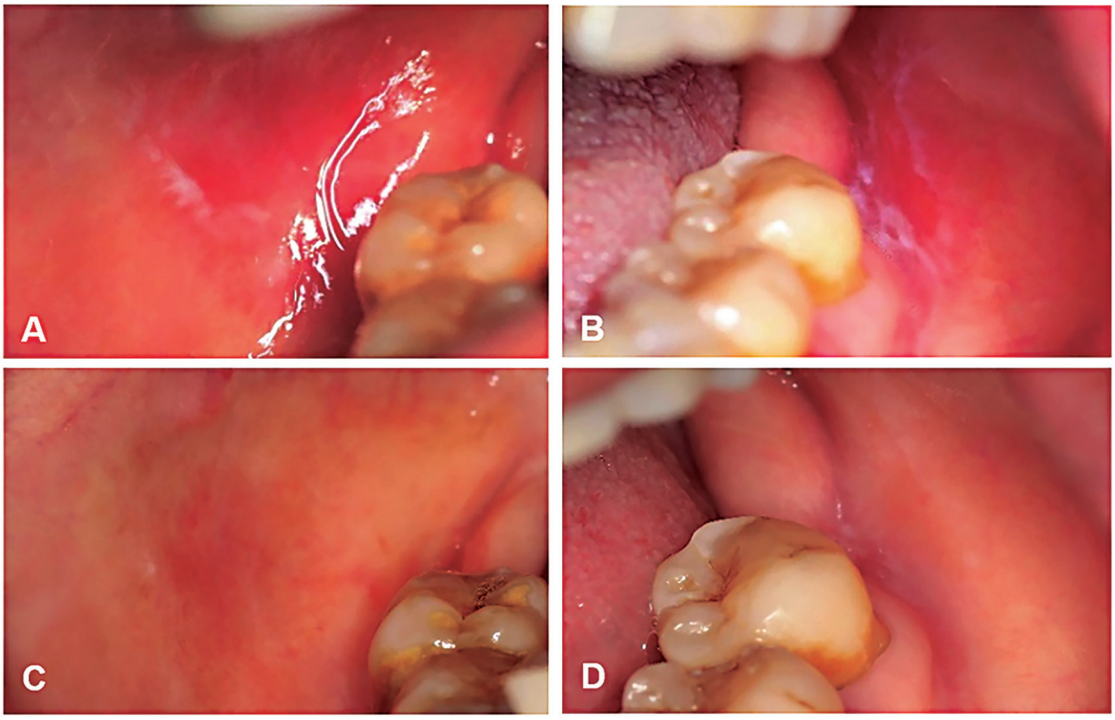

Figure 4: Clinical response of OLP to treatment. (A,B) Bilateral atrophic lesions of the buccal mucosa; following CP 0.05% treatment, clinical improvement was observed. (C,D) Almost complete healing was observed following 4 weeks of treatment

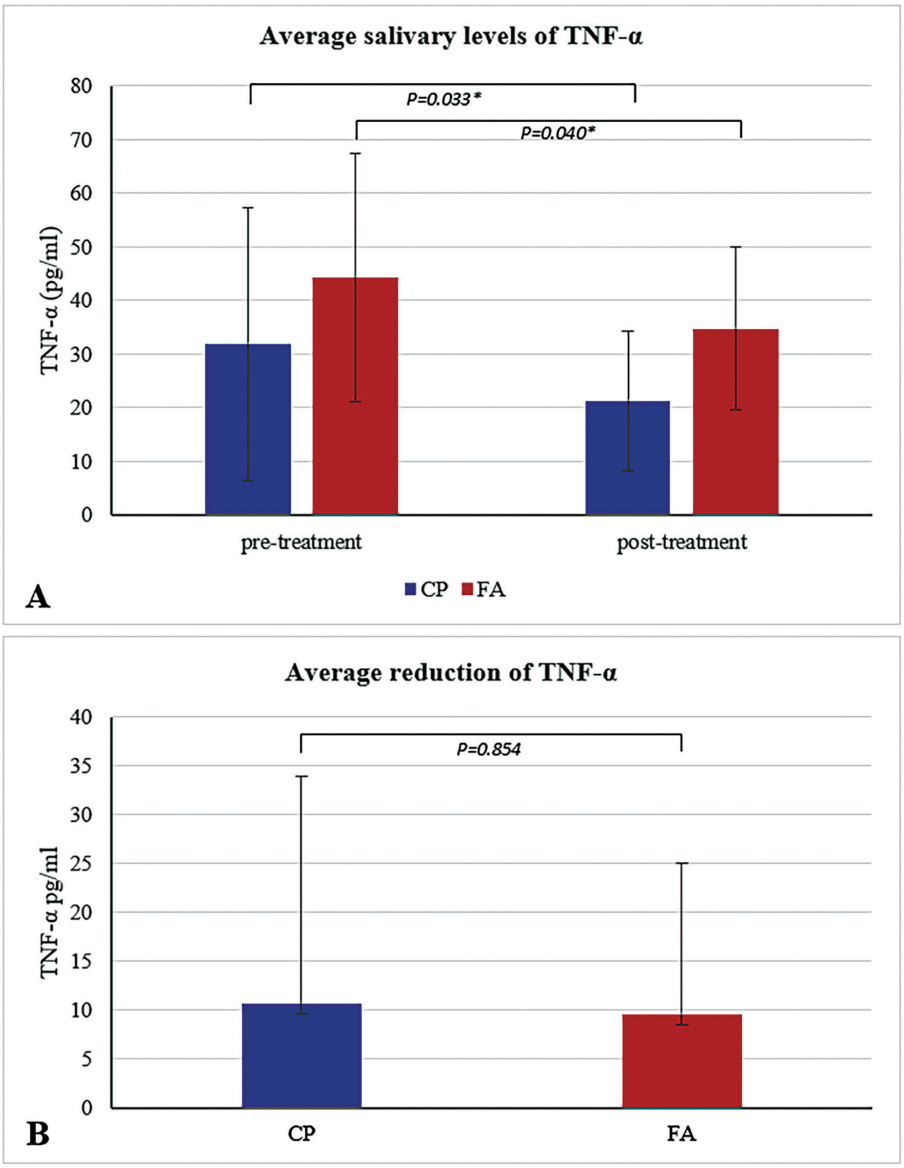

Figure 5: TNF-α in saliva.Following treatment, (A) the average salivary levels of TNF-α in the CP 0.05% and FA 0.1% groups decreased to 21.25±3.78 and 34.71±4.56, respectively. (*Statistically significant $p<0.05$ (Wilcoxon signed rank test)) (B) The average reduction of TNF-α from baseline for these groups was 10.63±23.34 and 9.56±15.47, respectively (No statistically significant $p>0.05$ (Mann-Whitney U test)) CP = Clobetasol propionate, FA = Fluocinolone acetonide

Table 2: Comparison of disease remission between two treatment groups after treatment.

Group	Complete remission	Partial remission
CP	6 (46.15)	7 (53.85)
FA	3 (23.07)	10 (76.93)
p-value	0.411[a]	

CP=Clobetasol propionate 0.05%, FA=Fluocinolone acetonide 0.1%

Data are presented as frequency (percentage)

[a]*Fisher's Exact Test*

The effects of CP 0.05% and FA 0.1% on inflammation were comparable.

TNF-α was detected in all saliva samples obtained from patients with OLP. After 4 weeks of treatment, salivary TNF-α levels in both groups were statistically significantly lower than pre-treatment ($p<0.05$). However, there was no statistically significant difference in the reduction of salivary levels of TNF-α between the CP 0.05% and FA 0.1% treatments (Figure 5). Therefore, this finding suggested that the effects of CP 0.05% and FA 0.1% on inflammation exhibited similarities.

Discussion

OLP is a chronic condition characterized by recurrent flare-ups and symptom-free intervals; achieving remission is challenging.[1,5] The treatment objectives include alleviating painful symptoms, promoting the healing of ulcerative lesions, reducing the risk of malignant transformation, extending symptom-free intervals, maintaining excellent oral hygiene and dental health, and ultimately improving the patient's quality of life.[1,4] Despite numerous guidelines and studies of symptomatic OLP treatment, topical corticosteroids remain the most widely used and effective approach.[6,24] Ultrapotent halogenated corticosteroids such as clobetasol and potent fluorinated corticosteroids like fluocinolone acetonide and fluocinonide have demonstrated success rates ranging from 30-100%.[1,11,24]

This randomized, controlled, double-blind study found that topically applied corticosteroids significantly improved the condition of patients with atrophic-erosive OLP. Both CP 0.05% and FA 0.1% exhibited favorable outcomes; both drugs reduced pain and clinical scores significantly. The effectiveness of CP 0.05% was comparable to that of previous findings.[11,12,25] The efficacy of FA 0.1% was consistent with the findings of Thongprasom *et al.,*[10] and Buajeeb *et al.,*[9] both of whom reported that topical steroids yielded good therapeutic effects and that the drugs were safe and free of serious side effects. After 4 weeks of treatment, we found that CP 0.05% was more effective at reducing the clinical severity of OLP than FA 0.1%. However, the difference between symptom reduction and disease remission was small and did not reach statistical significance, which is consistent with a comparative study of CP 0.05% and FA 0.1% effectiveness on 26 OLP patients in Thailand. The study showed that both medications effectively reduced pain scores, clinical score, and disease remission over a four-week period, with no statistically significant differences observed.[26] In addition, two studies have compared clobetasol with fluocinonide, a potent fluorinated corticosteroid, as well as FA 0.1%. Carbone *et al.,*[27] found that clobetasol was more effective at reducing lesion size and clinical severity than fluocinonide 0.05% after 2 months of treatment, which was consistent with the findings of our study. On the other hand, Lozada-Nur *et al.,*[28] found no difference between the two medications in terms of reducing clinical severity and lesion size. However, those authors found that clobetasol was more effective at reducing pain than fluocinonide. Consistent with previous research, we found that an ultrapotent topical steroid, specifically clobetasol, exhibited superior therapeutic efficacy against OLP compared with a high potent topical steroid (i.e., fluocinolone acetonide). This discrepancy in efficacy can be attributed to the divergent potency profiles of the two medications. Based on our findings and those of other studies, using a super-potent topical steroid like clobetasol to treat oral lichen planus was more effective than using a high-potency topical steroid like fluocinolone acetonide. However, the efficacy gap between the two medications may narrow as treatment progresses. As a result, we recommend that clinicians initiate treatment of an erosive OLP (painful lesion) with a full dose of an ultrapotent corticosteroid, closely monitor a patient's signs and symptoms until noticeable improvement occurs, and then gradually taper the dosage of the drug by reducing the frequency of application. Managing OLP serves as challenges because of its chronic characteristics. It is essential to focus on treating the symptoms. Evidently, the cost of treatment with CP 0.05% is higher compared to FA 0.1%.[29] Although our study couldn't find any adverse effects, candidiasis is commonly associated with the application of topical steroids.[5,10] Therefore, in addition to considering the drug's effectiveness, it is important to take consideration of these factors when tailoring treatment for each patient. Salivary biomarkers are used for diagnosing and monitoring various oral diseases, including OLP. Several studies have revealed abnormal expression patterns of inflammation-related cytokines in saliva, such as interleukins (ILs), transforming growth factor-beta (TGF-β), interferon-gamma (IFN-γ), and TNF-α.[13,18] Specifically, patients with OLP exhibit significantly elevated levels of TNF-α compared with healthy individuals.[16] Ribaric

et al.,[17] noted that symptomatic erosive OLP patients had notably higher salivary TNF-α levels than patients with asymptomatic reticular OLP. These findings suggest that salivary TNF-α has the potential to serve as a biomarker for assessing the severity of OLP.[30]

Our study found that all of the saliva samples collected from patients with OLP contained TNF-α (median value: 37.76 (16.22-48.52) pg/mL). This finding aligns with the results of previous studies.[20,21] After 4 weeks of treatment with CP 0.05% and FA 0.1%, we found a significant decrease in salivary TNF-α levels. However, there was no statistically significant difference in the reduction of TNF-α levels between the CP 0.05% and FA 0.1% treatments; both effectively lowered salivary TNF-α levels. These results are also consistent with our clinical observations-the treatment demonstrated effectiveness at reducing pain and diminishing the severity of the lesions after 4 weeks of administration. Our findings are consistent with the results of several studies that investigated TNF-α levels in OLP patients undergoing corticosteroid treatment. Thongprasom *et al.,*[31] reported a significant reduction in the number of TNF-α-positive mononuclear cells in patients with erosive or atrophic OLP after one month of treatment with FA 0.1%. Rhodus *et al.,*[30] found a statistically significant decrease in salivary levels of proinflammatory cytokines, including TNF-α, IL-1, IL-6, and IL-8, in individuals with erosive OLP who were treated with dexamethasone mouthwash for six weeks. Ghallab *et al.,*[21] demonstrated that systemic prednisone significantly reduced salivary TNF-α levels. Additionally, Othman *et al.,*[14] compared the efficacy of triamcinolone acetonide and laser treatments in OLP and found that triamcinolone acetonide was more effective at reducing TNF-α levels. It is worth noting that TNF-α levels decreased after the application of topical steroids, which can be attributed to the anti-inflammatory and immunosuppressive properties of glucocorticoids. These glucocorticoids are believed to inhibit the expression of cytokine genes, such as TNF-α, IL-1, IL-2, IL-3, IL-6, IL-11, and chemokines[7] by suppressing the transcription factors that control cytokine expression within the cell nuclei.[32] Although our findings support the association between TNF-α and OLP lesions, the use of TNF-α inhibitors like infliximab, etanercept, and adalimumab for the treatment of OLP lesions requires careful consideration: anti-TNF-α therapy has been linked to potential risks, including serious infections, congestive heart failure, malignancy, and autoimmune diseases, when used for treating rheumatoid arthritis.[33] Additionally, paradoxical complications have been observed in three female patients with inflammatory bowel disease who developed OLP-like lesions while receiving TNF-α inhibitors.[34] Therefore, further studies on this topic are necessary; it is crucial that clinicians possess a comprehensive understanding of the physiological effects of cytokines involved in the immunopathogenesis of OLP.

The results of this study add to the body of evidence that suggests using saliva testing for TNF-α to gauge treatment response and track the progression of OLP. TNF-α production in saliva mirrors clinical changes and is closely linked to the severity of OLP.[17,35] If high TNF-α levels persist in saliva over time, they could potentially promote the malignant transformation of OLP lesions.[36] Given the detection of TNF-α in whole saliva, we consider saliva analysis to be a valuable, non-invasive, and worthwhile method for screening, diagnosing, and monitoring OLP.[13,16] However, this study has its limitations, such as a small sample size and a relatively short study duration. Also, because TNFα has some controversial biological effects in the etiopathogenesis of OLP, it's important for future research to focus on looking at and comparing the levels of this cytokine at different stages of the disease and with different treatment plans.

Conclusions

Our study suggests that both CP 0.05% and FA 0.1% had comparable effectiveness in curing OLP. However, CP 0.05% reduced the clinical score more than FA 0.1% over a 4-week timeframe. Furthermore, treatment with these medications resulted in a substantial decrease in salivary TNF-α levels, implying that TNF-α in whole saliva may serve as a useful biomarker of OLP disease monitoring.

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Conflicts of interest

The authors declare no conflicts of interest.

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