

EFFICACY AND SAFETY OF PLATELET LYSATE MUCO-ADHESIVE GEL IN TREATMENT OF PATIENTS SUFFERING FROM EROSIIVE FORM OF ORAL LICHEN PLANUS: A RANDOMIZED PLACEBO CONTROLLED CLINICAL TRIAL

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ABSTRACT

Trial design: The study is a randomized clinical placebo-controlled trial in parallel groups 1:1 allocation ratio.

Methods: 30 patients with erosive oral lichen planus were randomly assigned to receive either platelet lysate mucoadhesive gel or placebo vehicle gel 3 times per day for 4 weeks.

Outcomes: Assessment of outcomes included a visual analog scale (VAS) for pain as a primary outcome, and the secondary outcomes included improvement in the clinical picture according to Thongprasom sign score and any side effects of treatment.

Results: Results had shown a significant reduction of both pain and clinical scores in both groups at 2, 3, and 4 weeks and at 3 months of follow-up and a significant difference in pain and clinical scores between the intervention and control group at each visit as well as at 3 months follow up in which the intervention had greater pain reduction and clinical improvement.

Conclusion: Platelet lysate mucoadhesive gel is a promising material for managing erosive OLP and could be considered a suitable, safe, and easy alternative to other hemo-derived products. However, further larger randomized controlled trials are recommended.

KEYWORDS: Platelet lysate; Platelet-rich plasma; Platelet-derived growth factors; Oral lichen planus; Erosive oral lichen planus

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INTRODUCTION

Lichen planus is a common chronic T cell-mediated muco-cutaneous disease that affects both skin and oral mucosa in 50% of patients, while 25% of patients show only oral lesions. The prevalence of oral lichen planus (OLP) is roughly 1 percent of the general population. OLP mostly affects middle-aged women (Xue et al., 2005; Carrozzo, and Thorpe, 2009; Oliveira et al., 2010; Van der Waal, 2014).

OLP lesions are usually multiple and bilaterally symmetrical. Six clinical variants of OLP lesions are recognized namely; reticular (23%), papular, plaque-like, erosive (37%), atrophic (40%), and bullous forms. OLP lesions are characterized by being chronic, showing remission, and exacerbation; however, remission is rare. The reticular OLP is the most typical type because it is asymptomatic; it is typically accidentally discovered during routine tests. However, it may coexist with atrophic or erosive OLP, which can lead to pain, burning, and irritation (Payeras et al., 2013).

OLP features multifactorial pathogenesis that is not entirely understood. It has been postulated that it is caused by altered cell-mediated immunity, induced by endogenous or exogenous factors including specific and non-specific mechanisms. Consequently, there is an altered response to self-antigen that induces apoptosis of epithelial basal cells by cell-mediated cytotoxicity (Sugerman et al., 2002).

Unfortunately, the chronicity and persistence of OLP lesions and the unclear etiopathogenesis create challenges in the management of OLP, and hence, resistance to therapy. Therefore, the extent and severity of symptoms should be taken into consideration. Generally, treatment aims to relieve pain and symptoms of the disease (Sampaio and Rivitti, 2007; Bagan et al., 2012).

Currently, potent topical corticosteroids are considered the most effective treatment for mild and moderately symptomatic OLP lesions. Despite the overall safety of intraoral topical steroids, some ad-

verse effects may occur like oral candidiasis. Moreover, diffuse and multisite erosive OLP lesions usually do not respond well to topical steroids within which high doses of systemic steroids (1.5-2 mg/kg/daily) could be needed (Lodi et al., 2005; Lee et al., 2013; Petruzzi et al., 2013; Gujjar et al., 2015).

Recently, platelet-derived growth factors (PDGFs) have been proposed as a promising therapeutic option for the treatment of oral ulcers with the benefits of being an effective, safe, and economical treatment modality (Picardi et al., 2017).

Platelets can release a large array of growth factors (GFs) from their alpha granules upon activation. These growth factors have an important function in the initiation and modulation of tissue repair and regeneration mechanisms, including cell migration, proliferation, differentiation, angiogenesis, chemotaxis, extracellular matrix deposition, and removal of tissue debris (Pietrzak and Eppley, 2005).

Accordingly, the wound healing potential of PL and its superiority over PRP as a non-invasive growth-promoting agent gained our interest. In addition, PL is an autologous material with no tendency to elicit any reaction. This encouraged us to analyze the efficacy of PDGF-rich PL preparation in the management of chronic and resistant erosive OLP lesions. Also, it is prepared in a muco-adhesive vehicle to prolong contact time and mask the unpleasant taste of plasma.

Thus, we employed this randomized placebo-controlled trial to judge the level of efficacy and safety of platelet lysate mucoadhesive gel in the treatment of patients suffering from erosive OLP versus placebo gel.

- Eligibility criteria:

1. Inclusion criteria:

(1) Patients who show clinical presentation that indicates the diagnosis of erosive OLP and histological picture that verifies the diagnosis of

erosive OLP (**Rad et al., 2009**); (2) middle-aged patients, 30-50 years old (to avoid major difference in healing potential), of both sexes.

Exclusion criteria:

(1) Patients who had dysplastic lesion/lesions (2) Patients who received topical treatment for OLP within the last 2 weeks or systemic treatment for OLP within the past 3 months; (3) Platelet count $< 150,000/\text{mm}^3$; Hgb $< 11 \text{ g/dl}$ (**Andrade et al., 2008**); (4) any systemic disease; (5) pregnant or lactating females; (6) tobacco chewers, smokers or alcoholics; (7) those receiving any medication for a medical condition or oral ulcers for the last 2 months of the study; (8) those with prosthetic or orthodontic appliances; (9) subjects with active periodontitis or other oral lesions.

-Intervention:

Participants who joined the trial were arbitrarily allocated into one of the two trial groups; either group (A) (Intervention) who received platelet lysate gel or group (B) (Control) who received topical placebo gel.

-Outcome measures:

Primary outcome

Patients performed self-assessment for pain intensity employing the visual analog scale (VAS) of 0–10, where “0” represents no pain, and “10” is the worst possible pain (**Semyour, 1982**).

Secondary outcomes:

1- We assessed the Clinical picture using Thongprasom sign scoring (Thongprasom et al., 1992), and recorded it with a calibrated squared grid as follows:

Score 0= no lesions, normal mucosa; Score 1= mild white striae, no erythematous area; Score 2= White striae with the atrophic area about 1 cm^2 Score; 3= White striae with an atrophic area over 1 cm^2 Score; 4= White striae with the erosive area but 1 cm^2 Score; 5= White striae with an erosive area over 1 cm^2

2-Any adverse effects

-Study setting and recruitment:

Eligible subjects were selected after the database from the department of oral medicine, diagnosis and Periodontology, Faculty of Dentistry, Fayoum University was filtered. They were contacted to get their agreement to be enrolled in the trial. Those who agreed to enroll in the study were asked to sign informed enrollment consent after explanation of the entire procedure. Histopathology for lesional biopsy was done to substantiate the diagnosis of erosive OLP.

After that, those who met the inclusion criteria were allocated randomly to either study groups (intervention or control) in line with the generated sequence.

In this study, 40 patients were selected from the outpatient clinic. Seven patients did not meet the inclusion criteria, and three patients refused to participate and were excluded. One patient from the intervention group was not involved in the final analysis because of a lack of adherence to the treatment protocol (**Figure 1**).

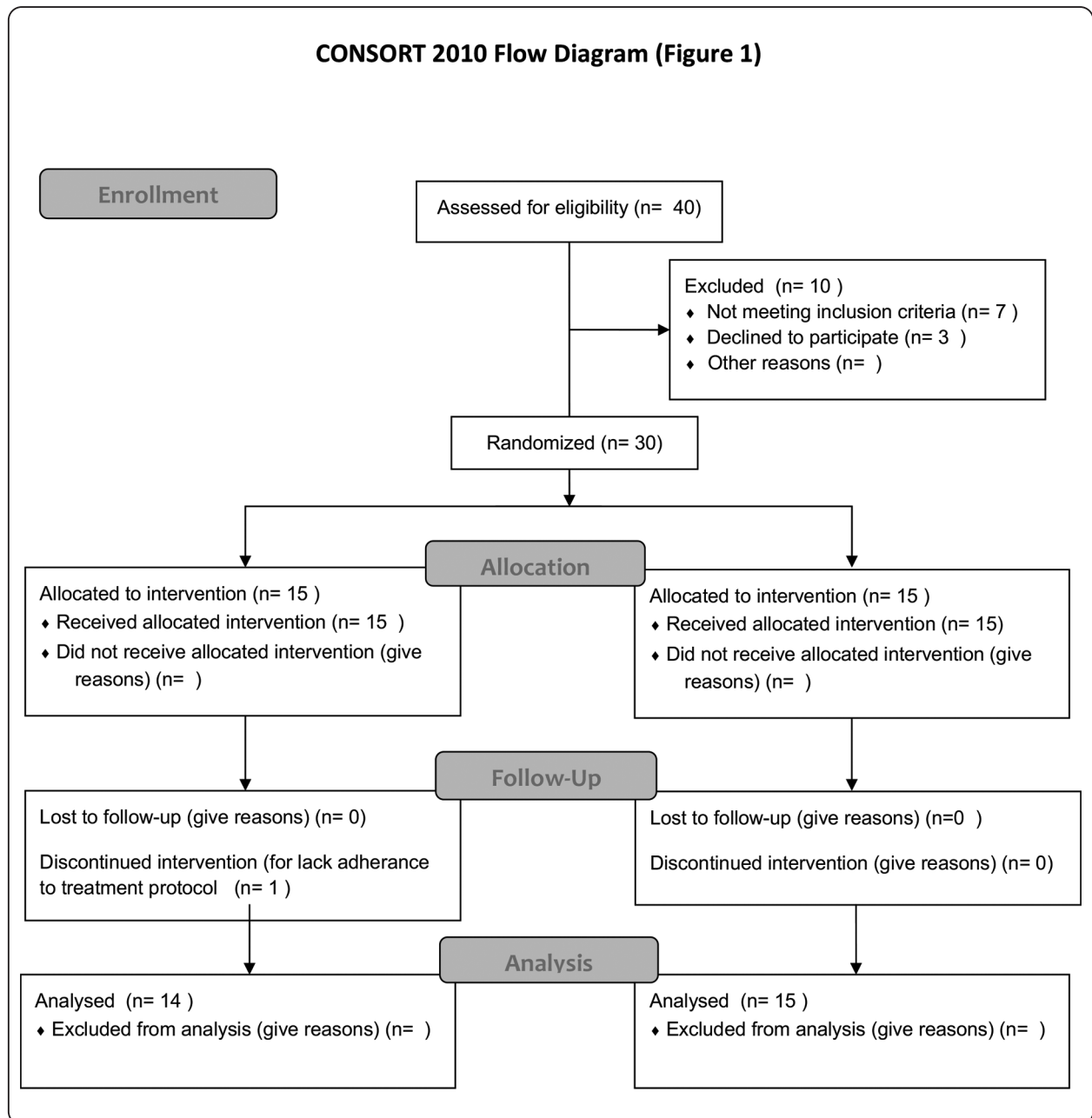
-Sample size calculation

Based on a previous study by **Hijazi et al. (2022)**, we calculated the sample size for the probability of type I error (α) = 0.05 and power ($1-\beta$) of 0.9 for the first outcome (VAS pain score). Sample size estimation revealed 36 participants (18 in each group) using a two-tailed t-test with a 0.05 significance level of the difference in VAS means between the two groups.

-Randomization:

Sequence generation:

Allocation sequence was generated through computer-generated randomization (www.rand.org) at a ratio of 1:1, performed by the first investigator (S.R.) after patients' consent of enrollment.



- Allocation and Implementation

There was no concealment during this trial because the intervention cannot be blinded from the patients or the investigator (as the plasma was drawn from the intervention group only which makes the intervention clear to know). All participants of the intervention group provided a recent complete blood picture to verify that their platelet count is

$\geq 150,000/\mu\text{L}$ (i.e. minimum accepted normal PLT value). After that, the pre-treatment records for the lesions were obtained.

Then, a 40 mL of autologous anti-coagulated (ACD-A) peripheral blood sample was taken from OLP patients of the intervention group. The randomization table was sent to the Faculty of Pharmacy, MTI University where containers coded as A

(Intervention) and B (placebo) were prepared by the third investigator (T.D.) The primary investigator (S.R.) was responsible for the sequence generation, allocation and enrollment of the participants.

-Blinding

The second investigator (H.S.) who was responsible for assessment of outcome was blinded as she did not participate in any step during patients' allocation or treatment delivery.

Platelet lysate gel preparation

The Platelet Lysate gel was prepared consistent with the method done by **Del Fante et al. (2011)**. The (ACD-A) peripheral blood sample underwent centrifugation at 900 rpm for 10 min and therefore the platelet-rich plasma (PRP) was collected and frozen at -80°C (thermal shock), and subsequently unfrozen at 37°C causing the lysis and release of PDGFs. Blood sample products were diluted with saline at a final concentration of 1:1 (one volume of PL and one volume of saline solution). All steps were done under sterile conditions.

Polymer

Carbopol 974P-NF (polyacrylic acid, PAA) (viscosity 29400–34900 cP) was used. This can be the grade with less content of solvents. Particularly, no benzene (EP class I solvent) and cyclohexane (EP class II solvent) residues were present. This grade is polymerized in ester (EP class III solvent) less critical. Carbopol 974P NF encompasses a medium crosslinking and medium-high viscosity, and it is recommended for prime viscosity gels.

Preparation of Formulation

Gel vehicle (GV) was prepared during a isosmotic solution (0.9% w/v NaCl) using 5% w/w PAA, 0.2% w/w Sodium saccharine and 0.2% w/w flavors were added. After the whole dispersion of PAA, the vehicle was buffered at pH 7.0 using 4 N of NaOH solution. GV was sterilized using steam sterilization at 121°C for 15 min under a nitrogen

atmosphere. The final platelet lysate gel vehicle (PLGV) for clinical use was prepared by mixing a 1:1 (w/w) vehicle with PL. PLGV contained a final concentration of PAA capable 2.5% w/w. Finally, PLGV was aliquoted into sterile disposables of 4 mL volume each. Disposables were maintained at 4°C for a maximum of 14 days.

Quality Controls

A sample from PLGV (immediately after preparation and after 14 days of storage at 4°C) was obtained to detect potential contaminations due to manipulation. 8 mL of every sample was inoculated within the substance and incubated for 10 days at 37°C .

-Gel application

Patients were trained to perform the application procedure using a cotton-tipped applicator to involve the entire ulcerative area with a sufficient amount of gel 3 times per day for 4 weeks. Patients were instructed to avoid the consumption of any type of food or liquid for half an hour after applying the gel and not to use any other topical or systemic treatment during the trial period. Patients also received instructions on the maintenance and storage of the gel.

-Data collection methods

Baseline characteristics were recorded by the first investigator (S.R.), while the assessor (H.S.) (who was blinded before the treatment) recorded data each visit during the trial and after the three months follow-up using the previous scale and scores. Patients were seen at 2, 3, and 4 weeks during the trial and 3 months follow-up. VAS scores and clinical scores were recorded for each treatment and at the follow-up visits.

- Data management:

Each participant had two separate files, one with the investigator S.R. and the other with the assessor of outcomes (H.S.).

STATISTICAL METHODS

Normality testing of all quantitative variables was done using Kolmogorov-Smirnova and Shapiro-Wilk tests to select the proper parametric and non-parametric tests. The mean and variance values were calculated for every group in each test. Paired sample t-test and Wilcoxon Signed Ranks tests were used for testing the pre-post measurements within each group, while independent sample t-test and Mann and Whitney U test were used for comparing the mean changes between the two groups. The z statistics were used for hypothesis testing of two proportions. Significance level is taken into account at $P < 0.05$; while $P < 0.01$ is considered highly significant.

RESULT

The intervention group consisted of 15 patients with erosive OLP; 7 (46.7%) males and 8(53.3%) females. Their age ranged from 35 to 52 with a mean age of 43.2 ± 10.1 . The control group consisted of 14 patients with erosive OLP; 4 (28.6%) males and 10 (71.4%) females. Their age ranged from 38 to 54 with a mean age of 46.05 ± 8 .

At baseline, there was no statistically significant difference in VAS pain scores between the 2 study groups ($P=0.108$). In the final analysis, pre-post treatment values within each group of the 2 study groups there were reduction in pain scores with a statistically significant difference between baseline

and 2, 3, and 4 weeks post-treatment and at 3 months follow-up as shown in (Table 1), with mean values shown in Figure (2).

By comparing the post-treatment values of VAS pain scores of the two study groups at 2, 3, and 4 weeks post-treatment and 3 months follow-up, there was a higher statistically significant difference between the intervention than the control group (P value= $0.01, 0.006, 0.036$ and 0.021 respectively) as represented in (Table 3 and Figure 4).

Regarding clinical scores, there was no statistically significant difference at baseline between the 2 study groups ($P=0.595$). The comparison of pre-post treatment measurements within each group revealed a reduction in clinical scores with a statistically significant difference between baseline and 2, 3, and 4 weeks post-treatment and at 3 months follow-up within the two study groups, as shown in (Table 2), with mean values shown in Figure (3).

While by comparing clinical scores of the two study groups at 2, 3, and 4 weeks post-treatment and 3 months follow-up, there was a higher statistically significant difference between the intervention than the control group ($0.06, 0.002, 0.001, \text{ and } 0.00$ respectively) as represented in (Table 3 and Figure 5). There were no adverse effects reported apart from complaining about bad taste from only three patients in the intervention group.

TABLE (1): VAS pain scores before and after treatment.

	Control				Intervention			
	VAS-2w - VAS-base line	VAS-3w - VAS-base line	VAS-4w - VAS-base line	VAS-3m - VAS-base line	VAS-2w - VAS-base line	VAS-3w - VAS-base line	VAS-4w - VAS-base line	VAS-3m - VAS-base line
Z	-2.640(a)	-3.337(a)	-3.429(a)	-3.311(a)	-2.889(a)	-3.401(a)	-3.321(a)	-3.191(a)
p value	0.008	0.001	0.001	0.001	0.004	0.001	0.001	0.001

Based on positive ranks.

(a) Wilcoxon Signed Ranks Test

TABLE (2): Clinical scores before and after

	Control				Intervention			
	Clinical-2w - Clinical- base line	Clinical-3w - Clinical- base line	Clinical-4w - Clinical- base line	Clinical-3m - Clinical- base line	Clinical-2w - Clinical- base line	Clinical-3w - Clinical- base line	Clinical-4w - Clinical- base line	Clinical-3m - Clinical- base line
Z	-2.236(a)	-3.606(a)	-3.473(a)	-3.376(a)	-3.357(a)	-3.442(a)	-3.373(a)	-3.372(a)
p value	0.025	0.000	0.001	0.001	0.001	0.001	0.001	0.001

Based on positive ranks.

(a) Wilcoxon Signed Ranks Test

TABLE (3): Comparing intervention and control

	Clinical- base line	Clinical-2w	Clinical-3w	Clinical-4w	Clinical-3m	VAS-base line	VAS-2w	VAS-3w	VAS-4w
Mann-Whitney U	94.500	65.500	39.000	33.500	8.500	69.000	48.000	44.000	60.000
Wilcoxon W	214.500	170.500	144.000	138.500	113.500	174.000	153.000	149.000	165.000
Z	-0.532	-1.878	-3.162	-3.269	-4.386	-1.605	-2.581	-2.742	-2.099
p value	0.595	0.060	0.002	0.001	0.000	0.108	0.010	0.006	0.036

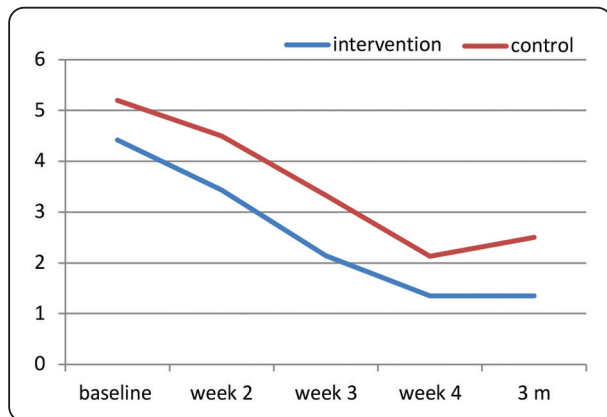


Fig. (2): Line graph shows mean pain scores in both groups during the study period.

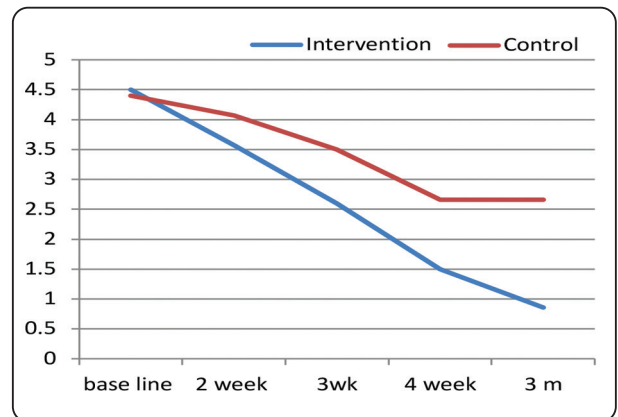


Fig. (3): Line graph shows mean clinical scores in both groups during the study period

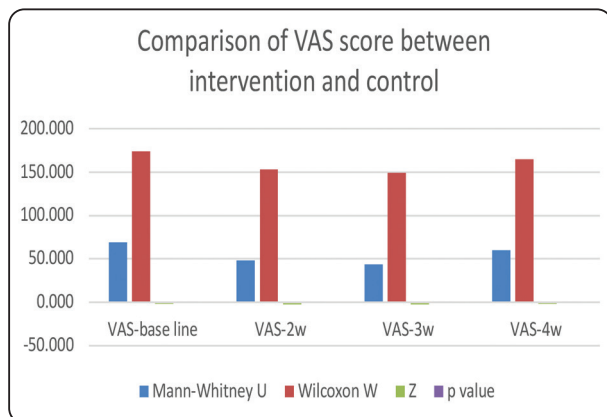


Fig. (4): Comparison of VAS scores between intervention and control

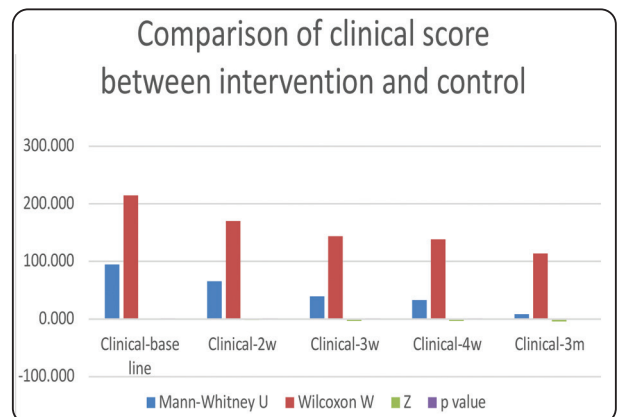


Fig. (5): Comparison of clinical scores between intervention and control

DISCUSSION

Several treatment alternatives have been used for the management of symptomatic OLP. However, no single agent has proved effective for all OLP cases. The main challenge in the management of OLP is its chronicity, in which a complete cure is difficult to achieve (**Thongprasom et al., 2013**).

Corticosteroids are the most widely accepted treatment modality for the management of erosive OLP owing to their anti-inflammatory and immunosuppressive properties. Nevertheless, their prolonged use has been associated with several adverse effects (**Lee et al., 2013**).

To date, all available treatment alternatives are associated with various side effects and the most efficient curative treatment has not yet been established. This rationalizes the need for more effective treatment for erosive OLP with fewer or no adverse effects.

Recently, PDGFs have gained interest and were extensively studied for their healing and repair potential. However, it has been postulated that the repair mechanism is a more complex process that requires the interplay of several factors rather than the effect of a single agent. Therefore, to better investigate the therapeutic potential of PDGFs, they were employed in hemo-derived platelet-rich preparations in which they could release all their biologically active factors to allow the required regeneration process (**Anitua et al., 2006**).

Hemo-derived products are autologous materials obtained from a patient's whole blood, this includes; human serum, PRP, platelet-rich fibrin (PRF), and PL. These products have a high concentration of GF with high regenerative potential as they can promote cell proliferation, differentiation, angiogenesis, osteogenesis, and cell regeneration (**Pietrzak and Eppley, 2005; Acebes-Huerta., 2020**).

Furthermore, these GFs have proved to play a crucial role in reducing inflammatory reactions including pain, swelling, and oral ulcers. This

role is attributed to their anti-inflammatory and immunomodulatory action in which they can induce a significant change in the level of pro-inflammatory mediators and inhibition of cytokine production, thus, reducing the inflammatory process and promoting tissue healing (**El-Sharkawy et al., 2007**).

Elkomy et al. (2015) investigated the effectiveness of PRP injections in chronic resistant oral ulcers of pemphigus Vulgaris (PV). They reported pain reduction and rapid healing of oral ulcers with PRP injections without the development of new lesions or any side effects during the study period other than pain during injection.

Picardi et al. (2017) evaluated platelet concentrates (PC) gel in patients with oral ulcers that occurred after bone marrow allogeneic transplants causing graft-versus-host disease (GVHD). They found that PC gel reduced pain and accelerated wound healing. In another study, the use of PRF after excision of oral lichen planus improved tissue healing (**Pathak et al., 2015**).

Huber et al. (2021) demonstrated a significant decrease in frequency and time of healing of oral ulcers associated with Behcet's disease that were resistant to other therapies with PRP injections. They reported no side effects other than pain at the site of application.

More recently, researchers' attention has been directed toward the use of intralesional PRP injection in the management of symptomatic lesions of OLP (**Ahuja et al., 2020; Sobhy et al., 2020; Bennardo et al., 2021; Hijazi et al., 2022**).

Interestingly, PL is considered a novel and promising agent containing relatively more growth factors than PRP. PL has gained more interest from researchers as an alternative to PRP as it is more cost-effective; preparation is relatively easier and contains a higher concentration of GF that is less temperature sensitive than those prepared in PRP (**Del Fante et al., 2011; Rauch et al., 2011**).

In several studies, PL has been used successfully in the management of skin ulcers and wound healing. It was observed that PL had a dermis-like tissue formation with evidence of wound closure, re-epithelialization, and proliferation of fibroblast-like cells at the wound site. PL has proved to be beneficial in clinical procedures such as; socket preservation, implant surgery, and sinus and ridge augmentation (Torres et al., 2009; Nagaveni et al., 2010; Gonzosteonecrosisález- Sánchezand Jiménez-Barragán, 2011; Marukawa, et al., 2011; Del Corso et al., 2012; Gupta et al., 2013; Eskan et al., 2014; Ramanathan and Cariappa, 2014; Meshram et al., 2015; Panda et al., 2016; Al-Hamed et al., 2017; Castro et al., 2017; Annunziata et al., 2018; Mauceri et al., 2018; Stähli et al., 2018).

However, the dynamic nature of the oral environment and the atrophic mucosa, which is exposed to the washing effect of oral fluids and continuous tongue movement, represents a particular challenge for the use of PDGFs topical formulation that differs from those used with skin wounds (Del Fante et al., 2011).

In addition, the unpleasant taste of plasma might limit the patient's compliance with treatment. This necessitates the employment of a mucoadhesive vehicle in the application of PDGFs rich PL to prolong contact time and mask the unpleasant taste of plasma (Del Fante et al., 2011).

To our knowledge, our clinical trial is the first to investigate the topical application of PL mucoadhesive gel in the treatment of erosive OLP. In the current study, we used Carbopol, which is a mucoadhesive polymer that can bond with the oral mucosal layer efficiently through hydrogen forming groups, chain interpenetration, or electrostatic interaction. Moreover, Carbopol is a biologically compatible material with good mechanical strength that ensures longevity, efficacy, and stability of formulation (Del Fante et al., 2011).

In addition, Del Fante et al. (2011) assessed the feasibility, safety, and efficacy of mucoadhesive vehicles using the mucoadhesive polymer, Carbopol, to produce gel mixed with platelet lysate in vitro and in vivo. Their results revealed good consistency, mucoadhesion, in vitro proliferation, and wound healing properties of the mucoadhesive formulation.

Moreover, oral application of PL gel was safe and effective in the management of GVHD patients with oral mucositis. Our results could even be reinforced by the findings of some studies which demonstrated a significant reduction in pain scores and improved healing of oral ulcers in erosive OLP with intralesional PRP injection (Ahuja et al., 2020; Sobhy et al., 2020; Bennardo et al., 2021 and Hijazi et al., 2022).

In these studies, despite the difference in preparations and treatment protocol, results suggest the efficacy of topical application of PDGF preparations for promoting the healing of oral ulcers occurring with erosive OLP. The overall evidence suggests the safety of PL same as other hemo-derived products like PRP. Our results support this suggestion, since no adverse effects were noted aside from the bad taste reported by barely three patients.

The limitation of this work is the short duration and that the primary outcome was primary outcome was reporting the extent of pain reduction because it is the main objective in the treatment of erosive OLP bearing the inherent weakness of the subjective evaluation of pain reported by the patient, which could be affected by several factors including the psychological factor. However, the measurement of clinical improvement using clinical scores enhanced the credibility of results obtained within the primary outcome.

Of note, PL comprises other growth factors such as; TGF-B and thrombospondin which can suppress cell growth (Ito et al., 2013 Chen et al., 2018). Therefore, the effect obtained from PL relies on the

amount of those growth factors, and their balance as well as the centrifugation protocol used (**Dohan et al., 2018**). Accordingly, the lack of standardization of preparation and treatment protocols could lead to different and conflicting results.

CONCLUSION

It may well be concluded that PL is a promising material for managing erosive OLP. Additionally, it might be considered an appropriate, safe and easy alternative to other hemo-derived products including PRP and PRF; however, due to limited studies, further larger randomized controlled trials are recommended.

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CONFLICT OF INTEREST:

The authors declare no conflict of interest.

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