

## THE EFFECTIVENESS OF PLACENTAL EXTRACT GEL IN THE TREATMENT OF RECURRENT APHTHOUS STOMATITIS: RANDOMIZED CLINICAL STUDY

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### ABSTRACT

**Background:** The most frequent oral ulcer that affects non keratinized oral mucosa is recurrent Aphthous stomatitis (RAS). The goal of the current investigation was to determine the effectiveness of the topical application of placental extract gel (PEG) in the treatment of RAS.

**Materials and methods:** 40 patients with RAS participated in this research. They were randomly allocated into two groups. Group I (control): include 20 patients treated with topical application of benzydamine hydrochloride gel and group II (test group) include 20 patients treated with topical application of placental extract gel. The effectiveness of the treatment modalities was assessed by measuring pain intensity, ulcer size at baseline, 3<sup>rd</sup> day and 7<sup>th</sup> day.

**Results:** both treated groups showed a statistically significant decrease ( $P \leq 0.001$ ) in pain intensity and ulcer size at days 3 and 7 compared to baseline data. However, the RAS treated with PEG showed statistical significant decrease ( $P \leq 0.001$ ) in pain intensity and ulcer size at days 3 and 7 compared to the control group.

**Conclusion:** Topical PEG is an effective topical agent in RAS treatment, which enhances the patient's normal activities and daily life events.

**KEYWORDS:** recurrent aphthous stomatitis, benzydamine hydrochloric, placental extract gel

### INTRODUCTION

Oral aphthous stomatitis typically presents as painful sharply circumscribed fibrin-covered mucosal defects surrounded by erythematous halo affecting non keratinized gingiva (Queiroz et al., 2018). It occurs in three forms: minor, major and

herpetiform aphthae, the most prevalent being the minor type that heal spontaneously without scarring in 7-10 days. RAS takes place in 5-25% of the population, with recurrence rates of 50% in 3 months, it affects both males and females and females being mostly affected (Tappuni et al., 2013, Liang et al., 2012, Tarakji et al., 2015).

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Even though RAS is a frequent oral lesion, its etiology is unknown. Some researches have indicated that it may be linked to genetic, psychological and socio-economic stress, inadequate nutrition, hormonal fluctuations and immunological deficiencies (Tarakji et al., 2015, Vaziri et al., 2016).

RAS treatments are predominantly symptomatic. Most preparations briefly alleviate pain (e.g. topical anesthesia) but do not promote healing. Other preparations used include antiseptics, anti-inflammatory, analgesics, antibiotics (doxycycline gel at low doses), topical or systemic corticosteroids, hyaluronic acid, natural substances (myrtle, quercetin, curcumin and alovera) and other treatment modality include Laser ( Sánchez et al., 2020, Irene et al., 2014). Despite the treatment of aphthous with both topical and systemic therapies diminishing the pain and the ulcer severity; it remains generally dissatisfying for the patient because neither therapy results in lifelong remission. There is a high demand for a quick-healing, well-tolerated drug to treat RAS. (Abd El-Meguid et al., 2010).

Placenta has been used for a long time as a pharmacological agent. A range of biologically and therapeutically active chemicals such as hormones, proteins, glycosaminoglycans, nucleic acids, and polydeoxyribonucleotides have been extracted from human placenta. The ingredient of the placental extract is determined by the method of processing. It, therefore, displays many therapeutic actions. In many countries, topical administration of the extract is a long-standing practice for burning lesions, chronic wounds and postsurgery. The placental extract is similar to human fibronectin type III glycoprotein, which is important for preserving the morphology and migration of the cells, homeostasis and also promote wound healing (Piyali et al., 2005, Shukla et al., 2015).

According to the author's information, no previous studies determine the effect of placental extract gel on recurrent aphthous ulcers.

Accordingly, the goal of the present study was to estimate the effectiveness of placental extract gel (PEG) in the treatment of RAS.

## MATERIALS AND METHODS

This research was performed in compliance with the ethics criteria of the World Medical Association (Declaration of Helsinki, 1978, as revised in 2008) for studies incorporating humans. The trial protocol was permitted by Research Ethics Committee of the Faculty of Dentistry, Suez Canal University, number 2021/408.

### Sample size calculation

To determine the minimal number of patients for this clinical trial, a power analysis was conducted. The convenient sample size was adjusted where the effect size was 0.5 using alpha ( $\alpha$ ) level of 0.05 and Beta ( $\beta$ ) level of 0.05 i.e power = 80%; the estimated sample size was 40 for both groups.

### Study design

This research is a double-blinded, randomized clinical trial. The participants in the research were chosen from the outpatient clinic of the Department of Oral Medicine and Periodontology, Faculty of Dentistry, Suez Canal University. A code number was provided for each patient during the registration appointment and a computer-generated table with 40 random numbers was allocated in two blocks to the control group and test group using a 1:1 allocation ratio.

Another practitioner had the key blinded the treatment protocol in sequentially numbered sealed envelopes, blinding both the principle investigator and the participants. The treatment methods that were included were in measured tubes with a total of 20 for each in order to correctly evaluate their effectiveness: benzydamine hydrochloride gel (Tantum® oral gel, Egyptian International Pharmaceutical Industries Company (EPICO), And

placental extract gel (PEG) (PLACENTREX<sup>®</sup>, Manufactured by ALBERT DAVID LIMITED 5/11, D. Gupta lane, Kolkata-700050, INDIA). (Fig. 1)



Fig. (1): Show placental extract gel used in this study

This results in a total of 40 treatment tubes. All of the gel used in this study was packaged in the same way, was computer tagged, and was assigned by the second doctor (MN) who had the key to the treatment options. After the principal investigator (SH) measured the baseline parameters, the subjects were randomly assigned to the coded tubes using a computer program that divided the individuals into two groups without discriminating on the basis of age or gender by another clinician who was blind to the selected parameters. To guarantee a thorough double-blind study procedure, the tubes were not decoded until all follow-up assessments and final statistical analysis were completed.

The participants were evaluated for eligibility based on the inclusion and exclusion criteria, and those who signed informed consent forms and followed the timetable of visits were considered.

#### The inclusion criteria

18–35 years old, males and females aged and individuals presenting with RAS with the following criteria: ulcer appear less than 48 hours duration before enrolment, with a history of recurrence at least 2 years, size not exceeding 10 mm in diameter

and for ease of management, each ulcer should be in the near reachable region.

#### Exclusion criteria

Known history of immunological or systemic disease with RAS as one of its clinical manifestations, pregnancy, smoking, treatment with a systemic steroid or other immunomodulatory drugs within 1 month before the enrollment in the study; use of nonsteroidal anti-inflammatory drugs or oral antihistamines within 1 month before the study; treatment of the ulcer with any medication or preparation within 72 hours before the study and systemic antibiotic treatment within 2 weeks before the study.

#### Treatment groups

The participants in the current investigation were evenly divided into two parallel equal groups.

Group I (control n = 20) the ulcers treated with benzydamine hydrochloride gel.

Group II (test n=20) the ulcers treated with placental extract gel.

Patients in both groups were prescribed to apply the oral gel to the ulcers 3 times a day (after each meal and before bedtime) for 7 days using an applicator. They have been urged not to consume fluids for 1 hour after the application of the oral gel. Patients in all groups have been requested daily therapy till complete treatment has taken place and have been informed not to use any other topical or systemic medication (e.g steroidal or non steroidal medication or antihistaminic) from the beginning of the study (day zero) till the end of the study (day 7) to avoid conflicting results.

#### Clinical evaluation

Patients in both groups were evaluated based on a reduction in pain and ulcer size. The collection of data was done every morning at baseline, day 3, and day 7 in the clinic of the Department of Oral

Medicine and Periodontology, Faculty of Dentistry, Suez Canal University. In addition, during the examination periods, all patients have been requested to register any discomfort.

Pain assessment was performed with visual analogue scale (VAS) of 10 cm (horizontal line) between poles denoting no pain to intolerable pain was employed to test the non-contact pain (spontaneous pain without ulcer stimulation). The participants were advised to make a mark on the line with the vertical line at the place where the existing ulcer pain level was best reflected (Wewers et al., 1990).

The size of the ulcer was evaluated with Baker® SND-10 digital caliper (maximum margin of mistake of 0.005 mm) utilizing the maximum and minimum diameters of the ulcer. The ulcer's cross-sectional area was calculated by multiplying the two dimensions. (Ángela et al., 2015).

The changes in the VAS between the studied group throughout the follow-up period were considered as a primary outcome. Secondary outcomes were the changes in the ulcer sizes between the test and control groups throughout the follow-up intervals.

### Statistical Analysis

The following statistical tests were used to analyze and tabulate all collected data, a normality test (Kolmogorov-Smirnov) was applied to check the normal distribution of the samples. Descriptive statistics were calculated in the form of Mean  $\pm$  Standard deviation (SD). One-way ANOVA was applied to compare between groups for each variable and to compare between each two groups, an independent sample t-test was used. P-value  $\leq 0.05$  is considered to be statistically significant. All Statistical analyses were carried out using the computer program SPSS software for windows version 26.0 (Statistical Package for Social Science,

Armonk, NY: IBM Corp) at significant levels 0.05 (P- Value $<0.05$ )

### RESULTS

This research was carried out on 40 patients with minor RAS. The gender was 17 male and 23 female, with age range between 18 to 35 years (mean age: 23.07  $\pm$ 4.62 years) (Table 1). The investigation was carried out without any withdrawal by all research subjects. Patients of the test group did not register any adverse responses or hypersensitivity reactions and did not complain from the applied gel as it has an acceptable taste. Also, patients in the control group did not exhibit adverse drug reactions and patients in both groups accept the medication used in this research.

Concerning the baseline data of age and gender, no statistical difference (P $>0.05$ ) was found between the control group and PEG group (Table 1). In addition, pain and ulcer size between the two groups displayed no significant differences (P $>0.05$ ) Table 2 & 3).

Concerning pain score (VAS), a statistically significant decrease (p $<0.001$ ) was found in both the control group and PEG group at day 3 and day 7 when compared to baseline. Comparison between the two study groups, PEG showed more improvement with a statistically significant decrease (P $<0.001$ ) in VAS at 3 days and 7 days compared to the control group (Table 2).

Concerning the size of the ulcer, both the control group and the PEG group represent a statistically significant decrease (p $<0.001$ ) in the mean of ulcer size at day 3 and day 7. In comparison between the two study groups, PEG showed more improvement with a statistically significant decrease (P $<0.001$ ) in the mean of ulcer size at day 3 and day 7 compared to the control group (Table 3, Fig. 2).

TABLE (1): Demographic records of the study participants.

	Control n=20	PEG n=20	Test	95% confidence interval		P value<0.05	Effect size d
				lower	Upper		
Age	22.70±4.49	23.45±4.84	<b>0.51</b>	<b>-3.73</b>	<b>2.24</b>	<b>0.61</b>	<b>0.044</b>
<b>Gender</b>							
Male	8 (40%)	9(45%)	<b>0.102</b>	-	-	<b>0.75</b>	
Female	12(60%)	11(55%)		-	-		

Age data are reported as mean and standard deviations, Statistical significance at  $P < 0.05$ .

TABLE (2): Comparison of pain score (the primary outcome) recorded at different intervals within and between groups

	VAS 0	VAS 3	VAS 7	F test	P value
Control	5.75±1.25 <sup>a</sup>	3.45±0.76 <sup>b</sup>	1.45±0.51 <sup>c</sup>	115.62	<b>&lt;0.001**</b>
PEG	5.60±1.14 <sup>a</sup>	2.15±0.67 <sup>b</sup>	0.70±0.47 <sup>c</sup>	192.35	<b>&lt;0.001**</b>
<i>Indep.T-test</i>	<b>0.39</b>	<b>5.74</b>	<b>4.83</b>		
<i>P value</i>	<b>0.69</b>	<b>&lt;0.001**</b>	<b>0.01**</b>		
95% confidence interval	lower	<b>5.41</b>	<b>2.53</b>	<b>0.81</b>	
	upper	<b>5.94</b>	<b>3.10</b>	<b>1.34</b>	
<i>Effect size d</i>	0.12	1.81	1.52		

Different letters at the same row means significant difference at  $P < 0.05$

TABLE (3): Comparison of ulcer size (the secondary outcomes) recorded at different intervals within and between the groups

	Size 0	Size 3	Size 7	F test	P value
Control	7.82±1.13 <sup>a</sup>	4.92±1.04 <sup>b</sup>	1.67±0.70 <sup>c</sup>	199.59	<b>&lt;0.001**</b>
PEG	8.00±0.95 <sup>a</sup>	2.88±0.64 <sup>b</sup>	0.98±0.70 <sup>c</sup>	441.78	<b>&lt;0.001**</b>
<i>Indep.T-test</i>	<b>0.43</b>	<b>7.52</b>	<b>3.06</b>		
<i>P value</i>	<b>0.57</b>	<b>&lt;0.001**</b>	<b>0.01**</b>		
95%confidence interval	lower	<b>7.635</b>	<b>1.49</b>	<b>0.23</b>	
	upper	<b>8.18</b>	<b>2.56</b>	<b>1.13</b>	
<i>Effect size d</i>	0.17	2.36	0.98		

Different letters at the same row means significant difference at  $P < 0.05$

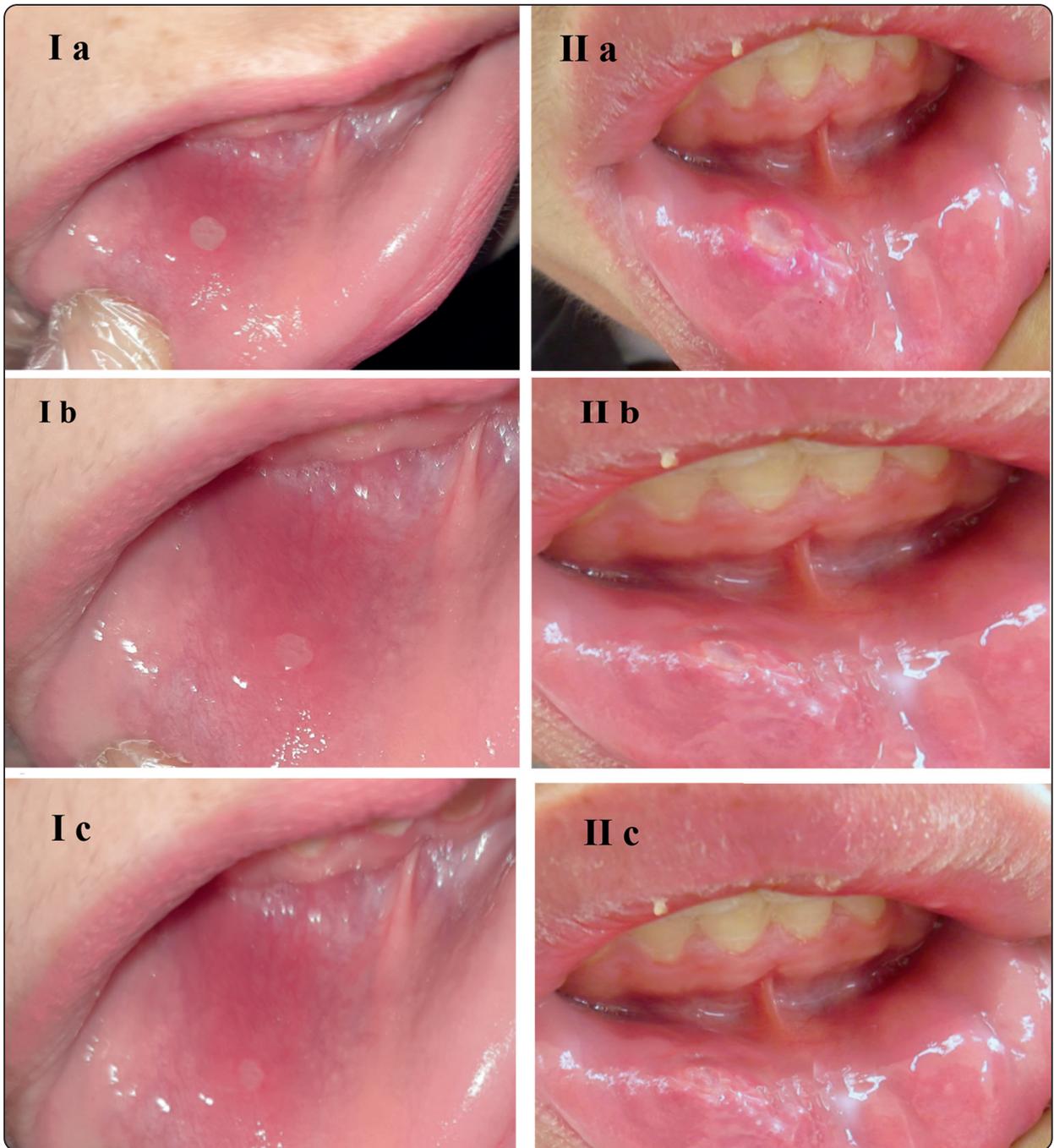


Fig. (2): photograph I show ulcer treated with benzydamine hydrochloride: I a ulcer at baseline, I b ulcer at 3rd and I c ulcer at 7th days. Photograph II show ulcer treated with placental extract gel: II a ulcer at baseline, II b ulcer at the 3rd day and IIc ulcer at 7th day.

## DISCUSSION

RAS occurs due to cellular immune responses that lead to epithelial destruction. Immune response imbalances in Th1-T2 can contribute to a loss of oral mucosal immunological tolerance, Promoting inflammatory responses, including RAS (Dalghous et al., 2006). Therefore, suppression of inflammatory effects involved in RAS development might play an important therapeutic role. Placental extract is a commonly utilized therapeutic substance for the promotion of wound healing by several medical properties. The placental extract possesses anti-inflammatory, antioxidative, and antiplatelet effects. It also enhances the impact of cell-mediated and humoral-mediated immunity (Cianfarani et al., 2006, Raj et al., 2014, Shing et al., 2017). In this context, the present research was designed to evaluate the effectiveness of placental extract gel in the treatment of minor recurrent aphthous ulcers.

In the present study benzydamine hydrochloride gel was used as a control because patients with aphthous ulcers are prefer to treat their ulcers with over-the-counter products primarily. The assessment of pain using (VAS) and evaluation of ulcer size were used for evaluation of both control and test group.

Placental extract gel used in this study are HIV Antibody free, HCV antibody free and Hepatitis B- Surface Antigen free according to the product manufacturer description so it can be used safely in human. In the present study both PEG and benzydamine hydrochloride significantly decrease pain intensity compared to baseline and both decrease pain intensity at days 3 and 7. This was in accordance with Scully et al., 2008 who documented that benzydamine hydrochloride merely offers pain relief without speeding up the healing of ulcer.

The reduction of pain intensity was significantly decreased in PEG compared to the control group this may be explained by its anti-inflammatory effect, this was obvious since the erythematous halo of the

ulcers in the majority of patients who participated in this study was fully resolved by the third day. The extract is likely to exert an anti-inflammatory effect via mediating the release of glucocorticoids, and ability to inhibit or activate the chemical mediators or by direct modulation of prostaglandin synthesis through cyclooxygenase (COX) inhibition (Biswas et al., 2001).

In the current study, ulcer size was significantly decreased in PEG treated group compared to the baseline and control group. According to the best of the author's knowledge, no previous studies evaluated the effect of placental extract gel in the treatment of RAS. On the other hand, the study of Gagan et al., 2015 estimated the influence of placental extract on wound healing, the opening of the mouth and postoperative pain in patients treated with oral submucous fibrotomy (OSMF) and coronoidectomy. The findings of placental extract were shown to provide better outcomes in fibrotomy wound healing with acceptable mouth opening in the postoperative fibrotomy wound in OSMF patients compared to the control group in which placental extract was not employed. Also, it was concluded in the vitro study of Akagi et al., 2016 that human placental extract promotes the production of collagen type-1 from the primary human gingival fibroblasts which may suggest its regenerative effect in the periodontal tissue.

The human placental extract is a biosynthesis activator that promotes anabolic phases and the repair of tissue. It has been demonstrated to enhance the proliferation of epidermal keratinocytes, Placental extracts contain a substantial amount of growth factors including granulocyte-colony stimulating factor, granulocyte-macrophage colony-stimulating factor, epidermal growth factor, fibroblast growth factor, hepatocyte growth factor, insulin-like growth factor, platelet-derived growth factor, transforming growth factor, and Vascular endothelial growth factor showing a range of physiological actions

including immunomodulation, anti-inflammatory effect, healing of the wound, cell proliferation and regeneration (Cukrová et al., 1987, Uzunaki et al., 1989, Horibe et al., 1990, Choi et al., 2016, Shing et al., 2017).

## CONCLUSION

The present study concluded that placental extract gel could be considered as an alternative treatment option for the treatment of RAS that may be attributed to its biologically active component that has anti-inflammatory effects and accelerates wound healing.

## Limitation

Some limitations, such as the frequency of recurrence and sample size, should be noted when analyzing the results gained from this study. To confirm the findings presented here, additional randomized controlled clinical trials with a longer duration and a larger sample size are needed to determine the benefits and drawbacks of employing human placental extracts in the treatment of RAS. Additional studies also are required to further elucidate the histopathologic examination on its effect on ulcer healing.

## CONFLICT OF INTERESTS:

There are no conflicts of interest declared by the authors in this publication.

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