

## Topical Platelet Lysate Hydrogel in Patients With Anal Fissure

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**Background:** Anal fissure is a painful tear or crack in the distal part of anal canal. It usually involves the epithelium, but in the long term it may extend to the whole anal mucosa. Platelet Lysate (PL) hydrogel is a hemoderivative pharmaceutical formulation that contains plenty of growth factors. These growth factors can induce tissue regeneration and revascularization as well as fibroblast proliferation.

**Objectives:** This study aimed to evaluate the effectiveness of PL hydrogel in the treatment of the anal fissure or retardation of its development.

**Patients and Methods:** The patients with chronic and acute anal fissure were randomly divided into groups of A and B. Group A received PL hydrogel and Rectol, while group B received placebo and Rectol. Then, they were followed and evaluated for two weeks.

**Results:** Although it was anticipated that platelet growth factors would be effective in anal fissure healing process, no significant difference was observed between the control group and the case group after the treatment. Nevertheless, a significant difference was observed within the two groups after the treatment.

**Conclusions:** PL hydrogel does not seem to have beneficial effects compared to the placebo or Rectol on the healing of anal fissure.

**Keywords:** Platelet; Hydrogel; wound Healing

### 1. Background

Anal fissure is a painful longitudinal ulcer or tear in the anal canal. Every year, 235,000 new cases of anal fissure are diagnosed and anal fissure has been recognized as the main cause of severe anal pain (1). Etiology and pathophysiology of anal fissure is not clearly understood; however, increase in the resting pressure of internal anal sphincter (IAS) and local hypoperfusion and ischemia of anal canal mucosa are widely accepted etiologies among clinicians. Up to now, several successful medical and surgical treatments have been described based on these etiologies (1, 2). The treatments that are based on the pathophysiology of anal fissure have commonly focused on decreasing IAS pressure and consequently increasing local perfusion and decreasing the ischemic conditions in anal canal (specifically posterior anal commissure). Undoubtedly, several kinds of treatments, especially medical treatment and surgical sphincterotomy have been successful in reducing IAS pressure; however, these efforts are insufficient to heal the anal fissures entirely. On the other hand, growth factors play an important role in promoting and improving the wound healing cascade (3). According to this rationale, platelet was selected as a safe and cost-

effective source of growth factors (4). Platelet Lysate (PL) hydrogel is a hemoderivative pharmaceutical formulation that contains plenty of growth factors (5, 6). These growth factors can induce tissue regeneration and revascularization as well as fibroblast proliferation (7). These processes will result in enhancing collagen synthesis, especially in damaged tissues. In this study, we considered anal fissure as a non-healing wound disease with an alteration in wound healing process. However, the effects of PL hydrogel application on the treatment of fissure have been poorly documented.

### 2. Objectives

This study aimed to evaluate the healing effects of PL hydrogel on acute and chronic anal fissure.

### 3. Patients and Methods

The present study was conducted on the patients with proven anal fissure who had read and signed written informed consents. All the patients were female participants referred to Colorectal Ward of Shahid Motahari Clinic affiliated to Shiraz University of Medical Sciences

from February 2012 to March 2013, Shiraz, Iran. The patients were visited by colorectal surgeon to confirm their acute or chronic anal fissure. History taking and physical examination were performed. Anoscopy was not done in the patients with acute phase of anal fissure. Chronic anal fissure are described the unhealed ulcers more than 3 months. Demographic data forms were filled initially. Then, history and physical examination were performed and recorded. The symptoms such as painful defecation, bleeding, burning sensation, and itching were asked and recorded. High fiber diets, hydration and sitz bath were recommended to both groups. The exclusion criteria of the study were pregnancy or planning for getting pregnant, history of ischemic heart diseases, history of application of intra-anal drugs affecting the IAS tonicity such as nitroglycerin or diltiazem, history of previous anal procedure, anorectal diseases, and inflammatory bowel diseases. Skin disorders and migraine and the patients with stenosis need surgical intervention. The patients with unusual anal fissure (multiple, lateral ulcer) were also excluded after physical examination and anoscopy. The patients who fulfilled the inclusion criteria were grouped into arm (A) and (B) using permuted-blocked randomization method. Group A received PL hydrogel and standard treatment (Rectol, Khorraman Pharmaceutical co.), while group B received standard treatment and placebo. Finally, they were compared in terms of painful defecation, rectal bleeding, burning sensation and itching. The patients were instructed to apply the PL hydrogel or the placebo once daily for a week and not to apply Rectol within 12 hours after using PL hydrogel or placebo. High fiber diets with hydration and sitz bath were recommended for both groups. After two weeks of intervention, the patients were evaluated by other colorectal surgeon and the questionnaire was filled again.

### 3.1. Platelet-Rich Plasma Preparation

PRP (Platelet-Rich Plasma) was obtained from Fars blood transfusion organization (Fars, Shiraz). PL was prepared by freezing PRP at  $-80^{\circ}\text{C}$  and subsequently defrosting at  $37^{\circ}\text{C}$  in a water bath (6). PL was loaded 1:1 into a pharmaceutical sterile vehicle (Carbapol 1%, ethylenediamine tetra acetic acid 0.05%, sodium metabisulfite 0.1%, sodium chloride 0.9% in adequate deionized water, all the percentages as w/v %). The vehicle pH was adjusted to 7.0 by sodium hydroxide 4N (8-15). For preparing placebo, the saline solution 0.9% (W/V) was replaced by PL. This study was approved by the Ethics Committee of Shiraz University of Medical Sciences, Shiraz, Iran. The code of RCT registration in Iran Registry of clinical Trials is 201304079936N4.

### 3.2. Statistical Analysis

The statistical analyses were performed by SPSS statistical software, version 20.0 (Chicago, IL, USA). Predeter-

mined variables for each group were compared before and after the treatment using the Wilcoxon signed-rank test. Besides, distribution of the confounding factors between the case and control groups was compared through chi-square test. Finally, Mann-Whitney test was utilized in order to compare the two groups regarding the treatment outcomes. All the tests were performed at 5% significance level.

## 4. Results

This study was conducted on 96 women with anal fissure who were divided into two groups (case and control). However, 15 patients were withdrawn from group A that received PL hydrogel and 5 individuals were excluded from the placebo group B (Figure 1). Chi-square test was performed for comparing the case and control groups regarding the distribution of confounding factors such as age, history of diabetes mellitus, diarrhea, constipation, hypertension, hypothyroidism, psychological diseases in need of medication, history and duration of anti-fissure medications, and anal fissure risk factors. The results showed no significant difference between the case and the control groups in these regards ( $P$  Value  $> 0.05$ ). Constipation was the most frequent underlying symptom (Figure 2) in both groups; 78.8% in the case group and 76.7% in the control group (Table 1). Furthermore, most of the patients, including 27 patients in the case group (81.8 %) and 33 patients in the control group (76.6%) had a history of anal fissure for longer than 3 months (Table 2). Wilcoxon signed-rank test showed a significant difference in measured outcomes before and after the intervention in both treatment and control groups ( $P$  Value  $< 0.05$ ). Mann-Whitney U test revealed no significant difference between the effect of treatment PL hydrogel or placebo in both groups. Therefore, we cannot distinguish PL hydrogel effect from Rectol or placebo. Finally, we compared the treatment outcomes between the case and placebo groups and the results revealed no significance difference between the two groups ( $P$  Value  $> 0.05$ ).

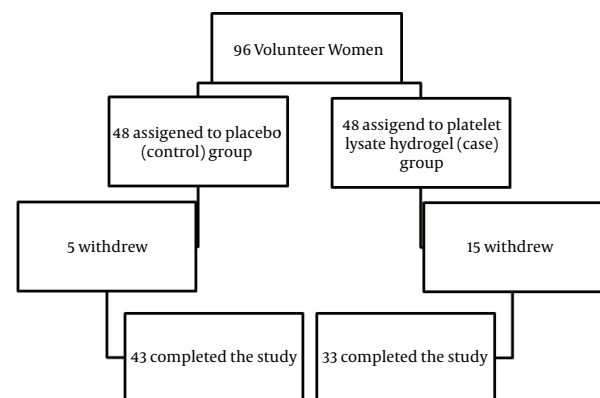
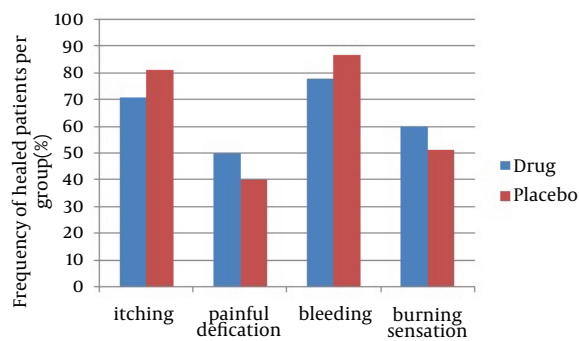


Figure 1. Sample Distribution in Case and Control Groups



**Figure 2.** Frequency of Anal Fissure Symptoms

**Table 1.** Comparison of the Frequency of Underlying Diseases Between Two Groups

Disease/Symptom	Frequency in Case Group, % (n = 33)	Frequency in Control Group, % (n = 43)	P Value
Neuropsychological Disease	3	0	> 0.05
Constipation	78.8	76.7	> 0.05
Diabetes Mellitus	0	0	-
Diarrhea	12.1	2.3	> 0.05
Hypertension	3	2.3	> 0.05
Hypothyroidism	0	2.3	> 0.05

**Table 2.** Frequency of Duration of Anal Fissure in the Case and the Control Group Compared With  $\chi^2$  ( $P = 0.05$ )

Duration of Anal fissure	Frequency in Case Group %	Frequency in Control Group, %	P Value
Less than 1 month	9.1	7	> 0.05
1-3 months	9.1	16.3	> 0.05
More than 3 months	81.8	76.7	> 0.05

## 5. Discussion

PRP preparations like PL hydrogel played an important role both theoretically and practically in wound healing processes, overshadowing wound healing, and regenerative medicine (8, 9). PRP preparations have been widely used in the treatment of diabetic foot ulcers, chronic ulcers, coronary artery bypass graft-associated foot ulcers, surgical ulcers, and corneal surgeries (10-16). PRP applications extend beyond cutaneous wounds; healing properties of platelet growth factors have been evaluated in gastrointestinal wounds, as well (11-15). There is some evidence associating the gastric ulcers healing to platelets activation and release of their growth factors in the body (16). Thus, we decided to assess the effect of PL hydrogel in the anal fissure. This drug is theoretically potential for

healing anal fissure ulcers. Despite the evidence that support the ability of PL hydrogel in healing anal fissure, this study showed no benefits in this regard. In order to figure out the reasons for the failure of PL hydrogel in healing anal fissure, the following scenarios should be taken into account: a) Rectol as a standard treatment of anal fissure has a prominent effect (equal to or more than that of PL hydrogel) on anal fissure cure in a manner that blurs PL hydrogel effect, and b) Placebo has the same effect as PL hydrogel without any healing effects on anal fissure.

The first scenario could be true because Rectol is the standard treatment for anal fissure and is widely used by the patients in Iran because of its satisfactory effects. The other scenario could also be true, owing to the following reasons: the content of platelets and growth factors may be insufficient, or the method of platelets activation may be inefficient (4), the PL hydrogel pharmaceutical vehicle may be inappropriate, and finally PL hydrogel treatment may be pharmacologically ineffective in healing anal fissure. In order to address the mentioned ambiguity about PL hydrogel effectiveness in healing anal fissure, we suggest another randomized double-blinded clinical trial to be conducted on PL in such a way that the effect of PL hydrogel can be distinguished from that of the placebo or Rectol. The findings of the present study indicated that PL hydrogel showed no beneficial effects on healing of anal fissure compared to the placebo or Rectol.

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## Authors' Contributions

Study concept and preparation of PRP: Akram Jamshidzadeh, Sleiman Mohammadi, Seyed Mojtaba Seyed Raoufi; Writing the manuscript: Zeinab Mardani; Study design: Leila Ghahramani; Statistical analysis: Alireza Safarpour; and Final edition: Ahmad Izadpanah, Alireza Safarpour, Leila Ghahramani, Seyed Vahid Hosseini, Masoumeh Rahimi.

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