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Efficacy of Platelets Rich Plasma as A Therapeutic Tool in Chronic Non-Healing Diabetic Foot Ulcers

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ABSTRACT

Background: One of the most prevalent and serious consequences in people with diabetes mellitus is diabetic foot ulcer (DFU). High management complexity, morbidity, and mortality are its defining traits. More efficient treatment methods are required since DFU therapy is still seen as frustrating and unsatisfying, even though new treatment alternatives are being developed. **Objective:** To assess the efficacy of using of platelet-rich plasma (PRP) on healing of DFUs in comparison to conventional therapy.

Method: A randomized controlled clinical trial was conducted on 92 diabetic patients with DFUs. Those patients were randomly divided into two equal groups either study group in which PRP was used and applied locally to the wound followed by Vaseline gauze and sterile dressing, and control group where patients received standard therapy in form of debridement and dressing. Patients were seen twice weekly throughout the treatment course and clinical evaluation was performed once weekly. **Results:** Both groups had insignificant differences as regard basic characteristics and laboratory data. Study group showed significant higher frequency of complete wound healing in comparison to the control group (73.8% vs. 30.4%; $p<0.001$). Percentage of wound reduction in the size of the ulcer at the end of the study in comparison to baseline size was significantly better in the study group. Mean time to complete healing was significantly lower among study group in comparison to the control group (8.15 ± 0.37 vs. 11.30 ± 0.17 (week); $p<0.001$). **Conclusion:** Autologous PRP significantly improved the complete ulcer healing in patients with DFUs. Well designed and adequately powered clinical trials are needed to confirm these findings.

Keywords: Autologous platelet-rich plasma, Diabetic foot ulcer, Healing rate, Diabetes mellitus.

INTRODUCTION

One of the most prevalent and painful consequences of diabetes is diabetic foot ulceration (DFU). It is estimated that a diabetic patient has a 25% lifetime chance of developing an ulcer. 84% of lower limb amputations are preceded by ulcers, which are a common cause of lower limb loss [1,2]. Diabetes ulcer (DU) is not only a major clinical issue that has an adverse effect on life quality and survival time, but it is also a financial burden that contributes significantly to expensive and drawn-out hospital stays. Additionally, non-healing diabetic cutaneous ulcers and the ensuing amputations may result in painful and pricy disability. However, more efficient therapies based on diabetes education may enhance DU healing and avoid the majority of amputations [3]. Despite the significant frequency and morbidity linked to DFUs, there are few available treatments at the moment. A surgical debridement procedure is currently used as the standard of care, followed by regular dressing changes and stringent infection and glycemic control. The risks of complications and amputation are still high despite this all-encompassing strategy. Platelet-rich plasma (PRP) has been a common supplementary treatment for DFUs [4,5]. First defined as plasma with a platelet count higher than that typically found in peripheral blood, PRP preparations were first introduced in the 1980s.

In comparison to whole blood, PRP has a 2–6 fold greater concentration of platelets [6,7]. In the current study, we aimed to evaluate effect of using of PRP in healing DFUs in diabetic patients in comparison to conventional therapy.

PATIENTS AND METHODS

A randomized controlled clinical trial was conducted on 92 diabetic patients with DFUs at Diabetic Foot Outpatient Clinic of Internal Medicine Department of Assiut University Hospitals. Those patients were randomly divided into two equal groups either study group in which PRP was used and applied locally to the wound followed by Vaseline gauze and sterile dressing and, control group where patients received standard therapy in form of debridement and dressing.

Selection criteria

Any diabetic patients with a foot ulcer for at least 4 weeks to be considered chronic which did not improve significantly after at least 4-week of standard treatments with ankle brachial index (ABI) value ≥0.9 was eligible for the study.

Exclusion criteria included; ulcer is due to non-diabetic etiology, the presence of an infected wound and/or osteomyelitis, and/or a completely necrotic ulcer, active oncological disease, systemic treatment medications like corticosteroids, immunosuppressive agents, as well as radiation or chemotherapy at the target sites .Decreased platelets count less than 100,000 mm^3, reduced haemoglobin less than 10.5mg/dl, and serum albumin level of less than 2.5g/dl, end stages renal diseases, haematological, collagen vascular disease and bleeding disorders.

Sample size calculation

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G power program version 3.1.3 was used to calculate sample size. In order to detect a significant difference in proportion of healing between two groups under the study; PRP and control group assumed similar difference among diabetic patients with comorbidity with alpha error 0.05, power 80, allocation ratio 1:1. Forty-six subjects were needed in each group with total 92 subjects.

Patients who fulfilled the inclusion criteria were assigned randomly into either of the two groups under the study; PRP group and conventional therapy. Each patient was randomly assigned to his group using quick Calcs method for randomization (https://www.graphpad.com/quickcalcs/randomize1/) either the study or control group.

Methods

All patients were subjected to complete history including age, sex, duration of diabetes and ulcer. History of hypertension, obesity and ischemic heart disease was recorded. Clinical examination was done at each treatment visit, wounds were assessed and measured (length, width, and depth using a metric tape measure at each visit. Ulcer was categorized based on Sinbad score

The measurements and other wound variables including undermining or tunneling, characteristics of wound exudates (i.e., presence, color, amount, and odor), necrotic tissue, and granulation tissue and obtaining vital signs and follow up the ulcer. Ankle brachial index was assessed in all patients in addition to the following laboratory data complete blood count, glycosylated haemoglobin, coagulation profile, urea, creatinine, lipid profile and serum albumin.

Preparation of platelet-rich plasma

Venipuncture in acid citrate dextrose (ACD) was used to get an 8 ml whole blood sample for each patient. Depending on the size of the ulcer, we sometimes utilized to obtain two 8 ml whole blood samples for some patients. For 10 minutes, the blood was centrifuged at a gentle spin of 2000 rpm. Another sterile tube without anticoagulant was used to transfer the platelet-containing supernatant plasma (Kemico Z serum plain tube).

To obtain a platelet concentrate, the tube was centrifuged at a higher speed of 3000 rpm for 10 minutes. A pellet of platelets generated at the tube's bottom. After removing the platelet-poor plasma (PPP), a platelet pellet was vigorously mixed into 1 ml of PPP.

Depending on the size of the ulcer, each patient has two or more tubes. One tube is utilized right once, while the other is kept in a platelet agitator for three days at a temperature between 180°C and 250°C. PRP was administered locally to the ulcer after being combined with 10^{th} more calcium gluconate.

Dressing technique

Any callosities surrounding the area were debrided, along with the borders and top of the wound base. If necessary, this procedure was repeated. When PRP was employed, it was first given locally to the wound before being covered with sterile dressing and Vaseline gauze. The dressing protocol was followed for a maximum of 12 weeks or until healing was complete, whichever came first.

The conventional group and the PRP group both underwent the identical wound debridement and offloading procedures. A sterile dressing was applied after the wound had been treated with regular saline, and it was changed twice a week. The dressing protocol was followed for a maximum of 12 weeks or until healing was complete, whichever came first. Failure to heal was assumed if the wound had not healed by the end of the time frame.

Follow up

The patients were seen twice weekly throughout the treatment course and clinical evaluation was performed once weekly till three months. Clinical laboratory tests were performed every 4 weeks for all treatment groups. Evaluation of the rate of healing of the ulcer was carried out by measuring the ulcer's dimensions (length and width) using metric tapes at initial visit and then every week. Other wound variables including characteristics of wound exudates, necrotic tissue, infection and granulation tissue were documented.

Ethical consideration

The study was approved by the Hospital's Ethics Committee of Assiut University. The purpose of the study was explained to all participants, and written informed consent was obtained. The study was registered on clinicaltrials.gov with NCT 03890172. The study was conducted according to the Declaration of Helsinki.

Statistical analysis

SPSS was used to gather and analyse the data (Statistical Package for the Social Science, version 20, IBM, and Armonk, New York). Nominal data are presented as number (n) and percentage (%), while quantitative data was reported as mean (SD) and compared with Student t test. Such data were subjected to the Chi2 test. The Kaplan Meier analysis was used to estimate the length of time needed for healing in the examined groups. Since the confidence level was maintained at 95%, a P value of less than 0.05 was deemed significant.

RESULTS

Baseline data of the studied groups (Table 1):

Mean age of PRP group was 49.87 (SD 10.78) years and majority (80.4%) of them was males while mean age of the control group was 52.09 (SD 14.07) years and majority (91.3%) of them also, was males. Both studied groups had insignificant differences as different baseline data (p>0.05).

Table (1): Baseline data of the studied patients

Variable	PRP group (n= 46)	Control group (n= 46)	*P* value
Age (years)	49.87 ± 10.78	52.09 ± 14.07	0.39
Sex			0.11
Male	37 (80.4%)	42 (91.3%)	
Female	9 (19.6%)	4 (8.7%)	
BMI (kg/m^2)	26.28 ± 2.21	25.98 ± 2.02	0.09
Type of DM			0.38
Type-1	6 (13%)	8 (17.4%)	
Type-2	40 (87%)	38 (82.6%)	
Type of therapy			0.79
OHD	11 (23.9%)	10 (21.7%)	
Insulin	31 (67.4%)	30 (65.2%)	
Both agents	4 (8.7%)	6 (13%)	
Duration of DM (years)	15.59 ± 6.84	12.65 ± 7.57	0.06
Level of education			0.53
Illiterate	18 (39.1%)	14 (30.4%)	
Primary level	23 (50%)	22 (47.8%)	
Secondary level	4 (8.7%)	8 (17.4%)	
College level	1 (2.2%)	2 (4.3%)	
CKD	11 (23.9%)	9 (19.6%)	0.40
HTN	9 (19.6%)	8 (17.4%)	0.50
IHD	6 (13%)	8 (17.4%)	0.38
Obesity	11 (23.9%)	10 (21.7%)	0.79

Data expressed as frequency (percentage), mean (SD). *P* value was significant if < 0.05. **PRP**: platelets rich plasma; **BMI:** body mass index; **DM**: diabetes mellitus; **OHD:** oral hypoglycaemic drugs; **CKD**: chronic kidney disease; **HTN**: hypertension; **IHD**: ischaemic heart disease.

Characteristics of DFU and baseline laboratory data among the studied groups (Table 2):

Both groups had insignificant differences as regard different characteristics of the DFU and baseline laboratory data ($p>0.05$) except significantly higher triglycerides level among the PRP group (183.89 ± 18.15 vs. 174.87 ± 18.82 (mg/dl); $p= 0.01$).

Table (2): Characteristics of diabetic foot ulcer and laboratory data studied patients

	Variable	PRP group (n= 46)	Control group (n= 46)	*P* value
Affected foot	Right foot	24 (52.2%)	28 (60.9%)	0.26
	Left foot	22 (47.8%)	18 (39.1%)	
Size (cm)		5.93 ± 0.98	6.13 ± 0.71	0.39
Depth (cm)		0.81 ± 0.15	0.87 ± 0.21	0.12
Site of ulcer	Toes	5 (10.9%)	7 (15.2%)	0.65
	MTH joint	11 (23.9%)	9 (19.6%)	
	Midfoot	13 (28.3%)	17 (37%)	
	Hindfoot	17 (37%)	13 (28.3%)	
Triglyceride (mg/dl)		183.89 ± 18.15	174.87 ± 18.82	**0.01**
LDL (mg/dl)		113.78 ± 6.48	107.17 ± 5.87	0.22
	HDL (mg/dl)	41.52 ± 10.21	38.40 ± 6.15	0.08
	Cholesterol (mg/dl)	202.61 ± 26.85	185.22 ± 27.41	0.30
Aspartate transaminase (U/l)		27.23 ± 5.30	27.96 ± 6.13	0.50
Alanine transaminase (U/l)		27.42 ± 4.21	26.45 ± 3.98	0.25
Albumin (mg/dl)		35.78 ± 2.72	36.46 ± 3.17	0.27
Leucocytes (10^3/ul)		7.43 ± 1.33	6.58 ± 1.30	0.34
Hemoglobin (gm/dl)		11.95 ± 1.22	11.18 ± 0.52	0.11
Platelets (10^3/ul)		352.02 ±8.00	323.30 ± 7.12	0.14
Glycosylated Hb (%)		10.20 ± 2.27	10.48 ±1.86	0.51
Urea (mg/dl)		5.76 ± 0.85	5.55 ± 0.84	0.84
Creatinine (mg/dl)		1.06 ± 0.2	1.03 ± 0.23	0.83
INR		1.01 ± 0.05	0.99 ± 0.01	0.23
Ankle brachial index		0.96 ± 0.15	0.94 ± 0.16	0.54

Data expressed as frequency (percentage), mean (SD). *P* value was significant if < 0.05. **PRP**: platelets rich plasma; **MTP:** metatarsophalangeal joint; **LDL**: low density lipoproteins; **HDL**: high density lipoproteins; **Hb**: hemoglobin; **INR**: international randomized ratio

Ulcer healing and percentage of wound reduction among the studied groups (table 3):

PRP group showed significant higher frequency of complete wound healing in comparison to the control group (73.8% vs. 30.4%; *p*< 0.001). Percentage of wound reduction in the size of the ulcer at the end of the study in comparison to baseline size was significantly better in the study group.

In majority (91.3%) of PRP group, percentage of wound reduction exceeded 81% (17.4% had 81-90% percentage of reduction and 73.9% had > 90% percentage of reduction) while out of the control group; only 25 (54.3%) patients had percentage of wound reduction exceeded 81% (41.3% had 81-90% percentage of reduction and 13% had > 90% percentage of reduction).

Table (3): Ulcer healing and percentage of wound reduction among the studied groups

Variable	PRP group (n= 46)	Control group (n= 46)	*P* value
Complete healing	34 (73.9%)	14 (30.4%)	**< 0.001**
Wound reduction*			**0.002**
> 90%	34 (73.9%)	19 (41.3%)	
81-90%	8 (17.4%)	6 (13%)	
71-80%	3 (6.5%)	13 (28.3%)	
61-70%	1 (2.2%)	5 (10.9%)	
< 60%	0	3 (6.5%)	

Data expressed as frequency (percentage). *P* value was significant if < 0.05. **PRP**: platelets rich plasma.
*reduction in the wound size at the end of follow up compared to baseline size.

Time to complete healing among the studied groups (Table 4, Figure 1):

Mean time to complete healing was significantly lower among PRP group (8.15 ± 0.37 vs. 11.30 ± 0.17 (week); *p*<0.001) in comparison to the control group.

Table (4): Time to complete healing among the studied groups

Variable	PRP group (n= 46)	Control group (n= 46)	*P* value
Time to healing (weeks)			**< 0.001**
Mean (SD)	8.15 ± 0.37	11.30 ± 0.17	
95%CI	7.42 to 8.88	10.97 to 11.64	

Data expressed as mean (SD). *P* value was significant if < 0.05. **PRP**: platelets rich plasma; **CI**: confidence interval.

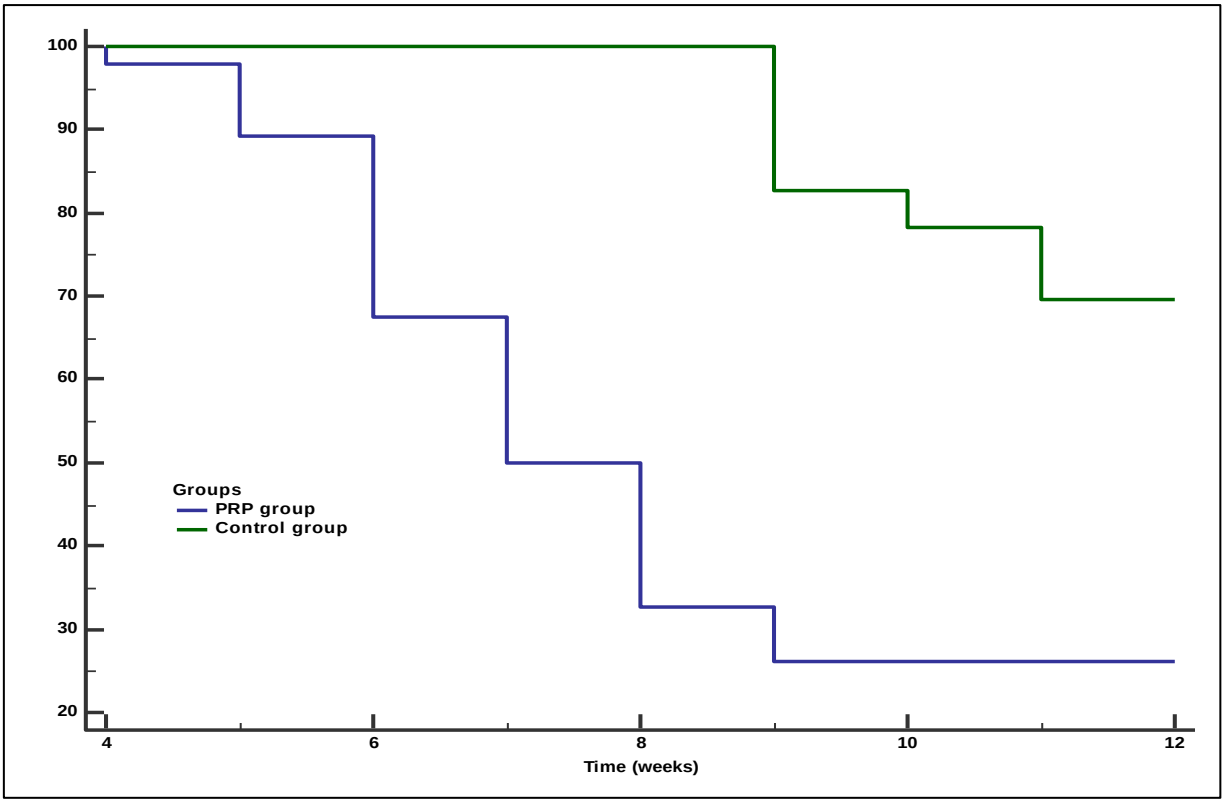

Figure (1): Time to complete healing among the studied groups.

DISCUSSION

The most common reason for amputations of the legs worldwide is diabetic foot ulcer sores. The progression of foot ulcer ulcers is caused by neuropathy, peripheral artery disease, foot abnormalities, and undiagnosed mild injuries. Since the foot ulcer is a conduit for infection that frequently results in limb amputation in individuals, healing must be completed very quickly after the foot ulcer lesion manifests [8].

Depending on the pathophysiology of wound healing in diabetes, using platelet-rich plasma to treat diabetic foot ulcer wounds may be an effective strategy; however, a strong indication in favor of such a treatment is lacking. After receiving conventional care, diabetic foot ulcer ulcers that have not healed should be treated with platelet-rich plasma [9].

Here, in the current study a total of 92 diabetic patients with chronic non-healing DFU were enrolled aiming at assessment the efficacy of PRP in patients with chronic non-healing DFU. Those patients were randomly subdivided into groups; either treated with PRP (PRP group=46 patients) or treated with conventional therapy (control group=46 patients).

We found that both groups had insignificant differences as regard baseline data. Mean age of PRP group was 49.87 (SD 10.78) years and majority (80.4%) of them was males while mean age of the control group was 52.09 (SD 14.07) years and majority (91.3%) of them also, was males. Similarly, **Elsaied *et al.*** [10] enrolled 12 patients in each group and found that both groups had comparable baseline data.

Also, in this study was found that both groups had insignificant differences as regard different characteristics of the DFU (p>0.05). Also, there were insignificant differences between both groups as regard size of the ulcer (5.93 ± 1.95 vs. 6.13 ± 1.64 (cm); p= 0.12) and depth of ulcer (0.81 ± 0.15 vs. 0.87 ± 0.21 (cm); p= 0.12). In line with the current study, **Li *et al.*** [11] stated that both studied groups had similar ulcer's characteristics.

Another study found that there were no statistically significant differences between the treatment group and the control group regarding patient demographic and ulcer characteristics. The authors also, found that both groups had insignificant difference as regard duration of ulcer (5.25 ± 3.4 vs. 5.58 ± 2.7 (months); *p*= 0.79) [10].

In the current there were no significant differences between both groups as regard baseline laboratory data with except significantly higher triglycerides level among the PRP group. This is difference in triglycerides level may be secondary to selection bias in the study but in general had no effect on the outcome. In line with the current study, **Elsaied *et al.*** [10] found that both groups had comparable laboratory data included HbA1C, RBS and albumin level.

The main findings in the current is that PRP group showed significant higher frequency of complete wound healing in comparison to the control group (73.8% vs. 30.4%; p<0.001). Percentage of wound reduction in the size of the ulcer at the end of the study in comparison to baseline size was significantly better in the study group.

In majority (91.3%) of PRP group, percentage of wound reduction exceeded 81% (17.4% had 81-90% of reduction and 73.9% had >90% of reduction) while out of the control group; only 25 (54.3%) patients had percentage of wound reduction exceeded 81% (41.3% had 81- 90% of reduction and 13% had >90% of reduction).

Also, we noticed that three patients exhibited percentage of reduction <60% and all of them were from the control group. Mean time to complete healing was significantly lower among PRP group (8.15 ± 0.37 vs. 11.30 ± 0.17 (week); p<0.001) in comparison to the control group.

According to a prior research, individuals who received PRP experienced better wound contraction-33.74%-than those who solely received conventional therapy, which had a mean wound contraction of 12.82%. Additionally, compared to the conventional dressing group's requirement of 6.188 cm, the PRP group's requirement of 4.488 cm was shorter for wound contraction [12].

A recent study included 50 cases with DFU were with peri-ulcer autologous PRP applications once weekly. All the patients showed signs of wound healing with a reduction in wound size, and the mean time duration of ulcer healing was 6.75 (SD 1.47) weeks [13]. These were comparable with many previous studies as regard time to healing as **Yilmaz *et al.*** [14] (4.82 weeks), **Crovetti *et al.*** [15] (10 weeks), and **Ahmed *et al.*** [16] (3.87 weeks).

Margolis *et al.* [17] investigation into the effectiveness of PRP gel in the treatment of neuropathic DFU found that 43.1% of patients had recovered after 32 weeks of treatment. Our investigation, however, revealed that more than 90% of the therapy group's patients experienced some degree of recovery, whether complete or partial. There may be a difference in the healing percentage between our study and the other study because only neuropathic ulcers were included in the earlier study.

Also, a recent study revealed that PRP gel group and control group cure rates were 93.3% vs. 50%, respectively. The healing rate per 2 weeks was significantly higher in the PRP gel than in the control group (0.78 ± 0.05 vs. 0.43 ± 0.04). There was no statistically significant difference in the platelets, haemoglobin, albumin, and HbA1c levels in the treatment and control groups [18].

The patients who received treatment had an average age of 62.5 years and 13.53 years, according to **Suthar *et al.*** [19] analysis, and they were followed up

for 24 weeks. The average amount of time it took for an ulcer to heal was 8.2 weeks, and every patient showed signs of wound healing, including shrinkage of the wound. Additionally, a final PRP product made with the quick point-of-care equipment had an average five-fold increase in platelet concentrate, and patients received an average platelet dosage of $70.10 \text{ X } 10^8$.

This study compared the effects of platelet-rich plasma and conventional care on diabetic foot ulcer wound healing. However, more research is still required to clarify these potential connections and assess the impact of platelet-rich plasma vs control on the outcomes under investigation.

Study limitations, include a relatively small sample size, single-center study design, and brief follow-up time. Due to the fact that the current trial was an open-label study and the investigators were aware of the treatment given, bias may arise and could be another study drawback. However, the key advantage of the current study is that it was conducted prospectively with randomized patient subgrouping.

CONCLUSION

In conclusion, PRP plasma gel could improve the complete ulcer healing rate, shorten the healing time, with no increasing the incidence of adverse events. Future studies are warranted to confirm these findings.

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