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Original Article

Pilot study on the effect of autologous activated platelet-rich plasma on diabetic foot ulcer wound healing and serum HbA1c levels

[Estudio piloto sobre el efecto del plasma rico en plaquetas activado autólogo en la cicatrización de la úlcera del pie diabético y los niveles séricos de HbA1c]

Dewi Fibrini[1]*, I Nyoman Ehrich Lister[2]

[1]Faculty of Medicine, Universitas Prima Indonesia, Jl. Ayahanda No.68a, 20118, Medan, Indonesia.
[2]Department of Biochemistry and Molecular Biology, Faculty of Medicine, Universitas Prima Indonesia, Jl. Ayahanda No. 68a, 20118, Medan, Indonesia.
*E-mail: dewifibrini@gmail.com

Abstract

Context: Autologous activated platelet-rich plasma (aaPRP) is a platelet-based therapy with high concentrations of growth factors that enhance the process of wound healing and glucose normalization.

Aims: To evaluate the safety and efficacy of systemic and local administration of autologous activated platelet-rich plasma in diabetic foot ulcer wound healing and patients' serum hemoglobin A1C.

Methods: Ten subjects were equally randomized to placebo and aaPRP treatment. The aaPRP was administered locally and intravenously. Wound surface area and serum HbA1c levels were recorded on days 0, 7, and 14.

Results: Injection of aaPRP for two weeks shows better clinical outcomes in reducing wound surface area non-significantly (40.11 ± 43.22 *vs*. -8.29 ± 49%; p = 0.136) and serum HbA1c levels non-significantly compared to the control group (2.16 ± 0.54 *vs*. 1.64 ± 2.218%; p = 0.635). However, patients in the aaPRP group had significantly better control of HbA1c within the first week of treatment (1.39 ± 0.84 *vs*. -0.08 ± 0.92; p = 0.030).

Conclusions: aaPRP could be considered a potential therapeutic strategy in patients with diabetic foot ulcers.

Keywords: autologous activated platelet-rich plasma; diabetic foot ulcer; hemoglobin A1c; wound surface area.

Resumen

Contexto: El plasma rico en plaquetas activado autólogo (aaPRP) es un tratamiento basado en plaquetas con altas concentraciones de factores de crecimiento que mejoran el proceso de cicatrización de heridas y la normalización de la glucosa.

Objetivos: Evaluar la seguridad y eficacia de la administración sistémica y local de plasma rico en plaquetas activado autólogo en la cicatrización de heridas de úlceras de pie diabético y en la hemoglobina sérica A1C de los pacientes.

Métodos: Diez sujetos fueron aleatorizados por igual a tratamiento con placebo y aaPRP. El aaPRP se administró por vía local e intravenosa. Se registraron la superficie de la herida y los niveles séricos de HbA1c los días 0, 7 y 14.

Resultados: La inyección de aaPRP durante dos semanas muestra mejores resultados clínicos en la reducción de la superficie de la herida de forma no significativa (40,11 ± 43,22 *vs*. -8,29 ± 49%; p = 0,136) y de los niveles séricos de HbA1c de forma no significativa en comparación con el grupo de control (2,16 ± 0,54 *vs*. 1,64 ± 2,218%; p = 0,635). Sin embargo, los pacientes del grupo aaPRP tuvieron un control significativamente mejor de la HbA1c en la primera semana de tratamiento (1,39 ± 0,84 *vs*. -0,08 ± 0,92; p = 0,030).

Conclusiones: aaPRP podría ser considerada como estrategia terapéutica potencial en pacientes con úlcera de pie diabético.

Palabras Clave: hemoglobina A1c; plasma rico en plaquetas activado autólogo; superficie de la herida; úlcera de pie diabético.

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AUTHOR INFO
ORCID: 0000-0003-1325-5208 (INEL)

INTRODUCTION

Diabetic foot ulcer (DFU) is a severe complication of diabetes mellitus. It is expected that 19-34% of patients with diabetes may develop diabetic foot ulcers during their lifetimes (Armstrong et al., 2017). Patients with DFU are correlated with a higher risk of mortality, morbidity, and healthcare expenditure, as well as lower quality of life and poorer physical adjustment (Skrepnek et al., 2017). The ultimate complication in DFU patients is lower leg amputation due to a non-healing wound or progressive infection, which is the cause of up to 88% of total procedures (Alvarsson et al., 2012).

The principles of diabetic foot ulcer management are well-established, but treatments are frequently challenging and prone to failure (Armstrong et al., 2017). Accordingly, over the recent years, significant progress has been achieved in DFU wound healing remedies, including platelet-based therapy. Autologous activated platelet-rich plasma (aaPRP) is a platelet-based treatment that contains high concentrations of growth factor (Martinez-Zapata et al., 2016). Platelets are believed to benefit the wound healing process by means of inducing granulation tissue and epithelialization, relieving inflammation, and exerting antimicrobial properties. Platelets in aaPRP can release a variety of growth factors in high concentration, such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β), epidermal growth factor (EGF), osteocalcin, and fibrinogen; all of which are essential to regulate the cellular processes in wound healing (Farghali et al., 2019; Lacci and Dardik, 2010; Yang et al., 2011).

In addition, a recent experimental study demonstrated that aaPRP injection was beneficial in regenerating and restoring pancreatic islet mass (El-Tahawy et al., 2017). Platelets and growth factors can stimulate the proliferation of β-cell and insulin production (Cirri et al., 2005). It has been investigated as a potential therapy for diabetes (Márquez-Aguirre et al., 2015; Pagliuca and Melton, 2013). Hemoglobin A1c (HbA1c; glycated hemoglobin) is a standard measurement to monitor glycemic control in diabetic patients. Some observational studies also showed a correlation between lower baseline HbA1c, faster wound healing, and lower amputation rate (Pscherer et al., 2012; Xiang et al., 2019).

To date, aaPRP has only been suggested to be used on unhealing DFU, which lacked a response to standard therapy (Picard et al., 2015). There is still lacking evidence to recommend the usage of aaPRP as the primary wound healing and therapy in diabetic patients. Therefore, we conducted a pilot study to evaluate the safety and efficacy of local and systemic administration of aaPRP in diabetic foot ulcer wound healing and patients' serum HbA1c levels before implementing it on a larger scale.

MATERIAL AND METHODS

Subjects

This pilot interventional study was conducted at the Royal Prima Medan Hospital (Medan, North Sumatra, Indonesia). The inclusion criteria for this study were as follows: 1) diabetic patients aged 40–70 years, 2) blood HbA1c >6.5%, and 3) presenting with a foot ulcer. Meanwhile, patients who refused to participate in the study were excluded. All patients provided their written informed consent for enrollment into the study. Ultimately, 10 patients were included in this pilot study and subsequently randomized equally into either the control or aaPRP groups. Data concerning the patients' sex, age, body mass index (BMI), the onset of ulcer, wound area, and HbA1c were collected.

Ethics statement

This study conforms to the Helsinki Declaration. The study protocol was approved by the Health Research Ethics Committee of Universitas Prima Indonesia (No. 016/KEPK/UNPRI/II/2022). The subjects in this study have been anonymized, and written informed consent was obtained from all subjects.

Preparation and administration of activated autologous platelet-rich plasma

The aaPRP was prepared according to a previously described protocol (Karina et al., 2021). For a single dose of aaPRP, 24 mL of venous blood was drawn from the patient and divided among 8 tubes containing sodium citrate (BD Vacutainer®, New Jersey, USA). The tubes were then centrifuged at 1000 rpm for 10 minutes. The resulting plasma was separated and centrifuged at 3000 rpm for 10 minutes. Afterward, the platelet-poor portion was discarded, and 2.5 mL of concentrate was left in each tube. Then, 0.15 mL of calcium activator was added to each tube to activate the PRP. The consequent clots formed by activation were removed, and 10 mL of normal saline was added to each tube. Finally, the aaPRP was photoactivated (AdiLight-1, AdiStem Ltd., Hong Kong) to clear the aaPRP of any platelets and leukocytes, making it safe for intravenous injection.

For patients in the control group, a placebo of 1 mL of normal saline was locally administrated via

injection into 10 points around the ulcer, and 100 mL of normal saline was administered systemically via intravenous infusion. For patients in the treatment group, 1 mL of aaPRP was injected into 10 points around the ulcer, and the rest of the aaPRP was administered systemically via intravenous infusion. The infusion took place for around 10–15 minutes. Other than the mentioned treatment, the patients also received standard therapy consisting of debridement and antidiabetics.

Measurement of wound surface area

Measurement of the wound surface area in cm^2 using imageJ (National Institute of Health, Bethesda, MD, USA) was done by an independent researcher. The patient and the rater were both blinded to the study allocation. The healing rate of the wounds **was** also measured and expressed in percentage. As described by El-Edel et al. (2019), it is calculated by subtracting the current wound area from an earlier wound area. The difference was then divided by the earlier wound area and multiplied by 100. A positive healing rate would signify an improvement in the wound area**,** while a negative healing rate would translate to a wider wound area. The wound surface at day**s** 0, 7, and 14 was measured along with the healing rate between days 0 and 7, days 7 and 14, and days 0 and 14.

Measurement of serum HbA1c levels

The subjects' HbA1c levels were analyzed by an independent lab using the boronate affinity high-performance liquid chromatography method. It measures the total glycated hemoglobin by using the binding property of *m*-aminophenylboronic acid**,** which binds to the cis-diol configuration formed by the glucose-bound hemoglobin (Little and Roberts, 2009)**.** Measurement was done using Wondfo HbA1c Rapid Quantitative Test (Wondfo, Guangzhou, China). The results were read with the Wondfo FIA Meter Plus fluorescence immunochromatographic analyzing system (Wondfo, Guangzhou, China) and expressed in percentage. The difference in HbA1c percentage was also calculated between day**s** 0 and 7, day**s** 7 and 14, and days 0 and 14. A reduction in HbA1c level was marked by a positive number, while an increase in HbA1c level was marked by a negative number.

Statistical analysis

Statistical analyses were conducted using IBM SPSS version 24 (IBM Corp., New York, USA) to analyze the difference in healing rate and difference in HbA1c between the groups. Analyses were also conducted for the patient's BMI and the days since the ulcer onset. Since the sample size was small, this study assessed for normality in distribution using the Shapiro-Wilk test. All normally distributed data were expressed in mean ± SD and analyzed using the independent t-test, while data not normally distributed were expressed in median (IQR) and analyzed using the Mann-Whitney test. A p-value of less than 0.05 was considered significant.

RESULTS

Demographics and onset of ulcer

The cohort consisted of 10 patients who were equally distributed to either the control group or the aaPRP group. Table 1 shows the sex, BMI, and onset of ulcer variables in the included patients. Statistical analyses showed no significant differences in BMI and days since the ulcer onset between the two groups.

Wound surface area

As shown in Table 2, the mean baseline wound surface area between the two groups was drastically different. However, the observed difference was statistically insignificant (19.90 ± 14.52 *vs*. 5.19 ± 6.27 cm^2). Nevertheless, we calculated the wound reduction rate instead of the difference to obtain a more objective result. It was found that after 2 weeks of therapy, the aaPRP group had a higher rate of wound healing than the control group, although the difference observed was not statistically significant (40.11 ± 43.22 *vs*. -8.29 ± 49%; p = 0.136).

Table 1. Subject characteristics.

Group	Sex		BMI (kg/m^2)	p-value	Onset of ulcer (days)	p-value
	Male	Female				
Control (n = 5)	3 (60%)	2 (40%)	29.44 ± 7.13	0.905	30 (30)*	0.421
aaPRP (n = 5)	4 (80%)	1 (20%)	30.07 ± 8.89		30 (31)*	

Data are expressed as mean ± SD. *median.

Table 2. Baseline wound area and wound reduction rates at various points between groups.

Group	Wound area baseline (cm^2) [mean ± SD]	p-value	Wound healing rate (%) Day 0–7 [mean ± SD]	p-value	Wound healing rate (%) Day 7–14 [mean ± SD]	p-value	Wound healing rate (%) Day 0–14 [mean ± SD]	p-value
Control (n = 5)	19.90 ± 14.52	0.088	-21.65 ± 44.54	0.068	10.71 ± 21.18	0.577	-8.29 ± 49	0.136
aaPRP (n = 5)	5.19 ± 6.27		28.81 ± 25.92		21.48 ± 35.58		40.11 ± 43.22	

Table 3. Baseline HbA1c and HbA1c difference at various points between groups.

Group	HbA1c baseline (%) [mean ± SD]	p-value	HbA1c difference (%) Day 0–7 [mean ± SD]	p-value	HbA1c difference (%) Day 7–14 [mean ± SD]	p-value	HbA1c difference (%) Day 0–14 [mean ± SD]	p-value
Control (n = 5)	10.52 ± 2.79	0.151	-0.08 ± 0.92	0.030	1.72 ± 2.41	0.437	1.64 ± 2.22	0.635
aaPRP (n = 5)	8.36 ± 1.22		1.39 ± 0.84		0.77 ± 0.95		2.16 ± 0.54	

Serum HbA1c levels

Patients in both groups have similar baseline serum HbA1c levels (p = 0.151), as shown in Table 3. After two weeks of therapy, patients receiving aaPRP treatment correlated with better overall serum HbA1c reduction than control (2.16 ± 0.54 *vs.* 1.64 ± 2.218%). However, the difference was not statistically significant (p = 0.635). The effectiveness of aaPRP in reducing serum HbA1c level was higher throughout the first week of treatment (1.39 ± 0.84 *vs.* -0.08 ± 0.92; p = 0.030).

DISCUSSION

The pathophysiology of diabetic foot ulcer (DFU) relies on a triad, namely neuropathy, arterial occlusion, and trauma with secondary infection. If healing is not achieved, ulcers may become infected, which usually ends in limb amputation (Bandyk, 2018). Hence, a rapid healing process is one way to resolve DFU and prevent the need for amputation. Autologous activated platelet-rich plasma (aaPRP) contains growth factors from activated platelets that can induce tissue regeneration. Being autologous, aaPRP virtually poses zero risk for rejection (Martinez-Zapata et al., 2016). Furthermore, aaPRP from diabetic donors was found to contain higher VEGF contents than those without diabetes. This makes aaPRP an excellent candidate for treating DFU (Karina et al., 2019). Besides the processes above, the role of oxidative stress has also been implied in the pathophysiology of DFU (Deng et al., 2021). A previous study by Gil-del Valle et al. (2019) has demonstrated the antioxidative capability of aaPRP. It is postulated that activation of aaPRP induces the secretion of growth factors, which ameliorates reactive oxygen species levels.

The mean BMI of the included patients in this study were 29.44 ± 7.13 and 30.07 ± 8.89 kg/m^2 for the control and aaPRP groups, respectively. There was no statistically significant difference between the two groups (p = 0.905). BMI has consistently been associated with the development of DFU. A previous study (Gebrekirstos et al., 2022) reported DM patients who were overweight and obese were respectively 3.1 and 3.6 times more likely to have DFU than their normoweight counterparts. A probable explanation is that obesity, being a part of metabolic syndrome, is associated with hypertension, dyslipidemia, poor glycemic control, and peripheral vascular disease, all of which are risk factors for developing DFU.

In this study, patients treated with aaPRP showed a greater wound healing rate than the control group, albeit the difference being statistically insignificant. Patients in the treatment group seemed to attain a consistent reduction in the wound surface area. While patients in the control group did experience a reduction in the wound surface area, a decrease in the mean wound healing rate was observed at one point. A representative illustration of wound reduction is available in Fig. 1. A previous systematic review of randomized controlled trials also concluded that aaPRP is safe and effective in treating DFU (Fibrini et al., 2022). However, a meta-analysis concluded that

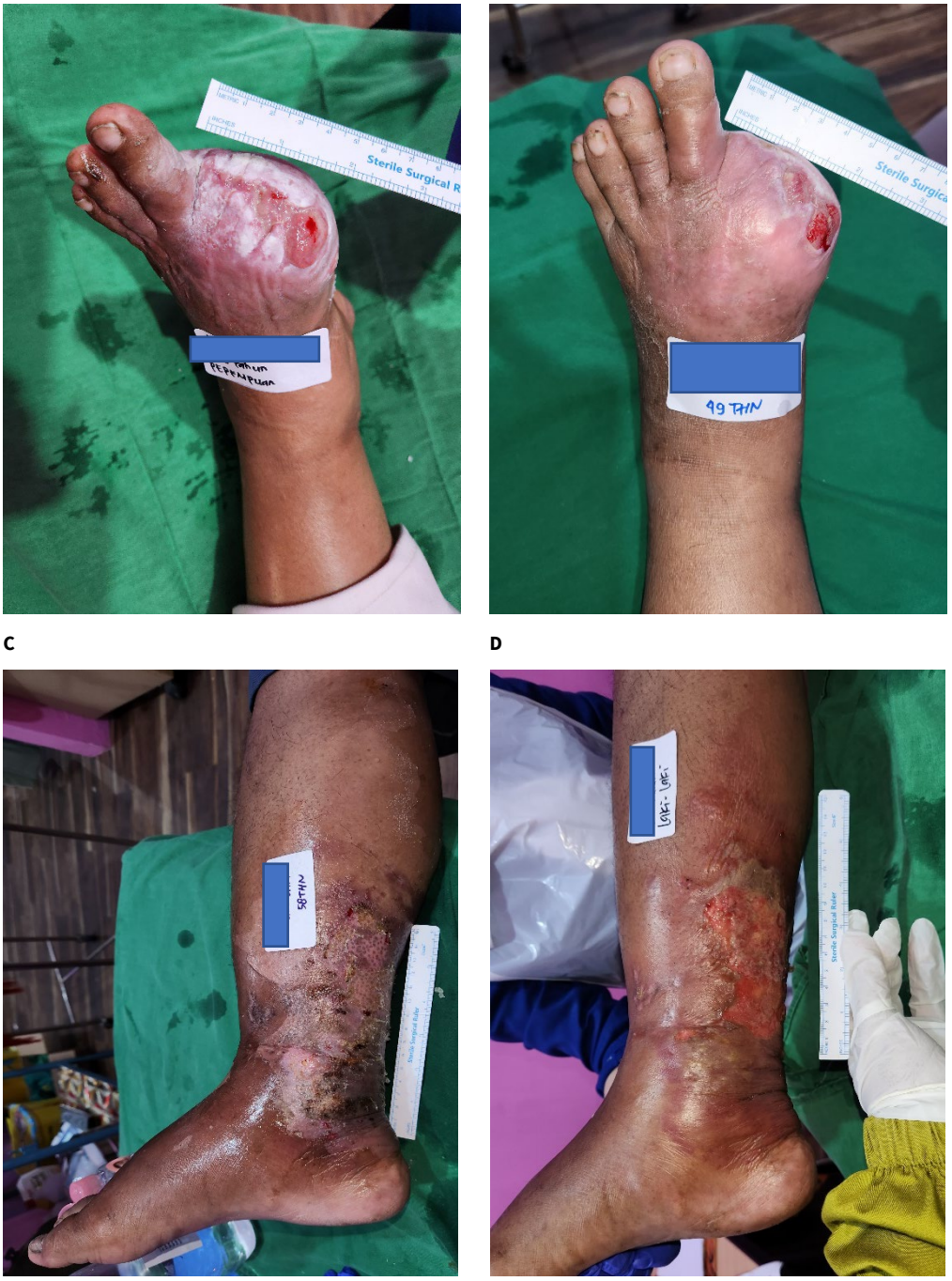

Figure 1. Representative illustrations of the ulcers.

(A) Representative patient's ulcer at day-0 from the aaPRP group. **(B)** Representative patient's ulcer at day-14 from the aaPRP group. **(C)** Representative patient's ulcer at day-0 from the control group. **(D)** Representative patient's ulcer on day-14 from the control group.

current evidence for the utilization of aaPRP for non-healing DFU is still poor due to methodological flaws in the included studies. Nevertheless, the results did suggest that aaPRP is beneficial for the healing of DFU (del Pino-Sedeño et al., 2019).

Our study found that aaPRP treatment correlated with better HbA1c reduction than the control. HbA1c provides valuable information about the diagnosis and prognosis of diabetes. As previously mentioned, the presence of hyperglycemia promotes the development of DFU. In this study, all patients had HbA1c >7%, indicating their uncontrolled glucose level. During the measurement, we found rapid HbA1c normalization in all patients, even three subjects successfully achieved normal HbA1c (<6.5) on day 14. These may indicate the potential rapid effect of PRP injection in blood glucose reduction in diabetic patients. Howev-

er, as a long-term indicator of glucose level, further confirmation of these findings are warranted.

The evidence of PRP injection in reducing human blood glucose levels is still lacking. A study by Ullah et al. (2022) demonstrated that both PRP and control groups were correlated with decreasing trend of HbA1c level. After 180 days, PRP treatment showed a better reduction of HbA1c (12.3 ± 4.5 *vs*. 7.3 ± 2.9) compared to the control (11.9 ± 4.2 *vs*. 7.8 ± 2.5). In other experimental studies (El-Tahawy et al., 2017; Zarin et al., 2019), PRP injection in diabetic rats significantly decreased blood glucose levels compared to the control. The study proved that PRP treatment correlated with increased pancreatic islet insulin production, lower pancreas oxidative stress, enhanced antioxidant activity, and regulated plasma insulin and glucose levels in diabetic rats. Considering that HbA1c represents the mean blood glucose levels in the past three months (Saudek and Brick, 2009), we hypothesize that the current study's follow-up period was too short. Hence, changes in the HbA1c levels were not detected within the 14 days of observation. A study with a longer time frame should be carried out to obtain more solid results.

CONCLUSION

Autologous activated platelet-rich plasma (aaPRP) could be a potential therapeutic strategy in patients with diabetic foot ulcers. Intravenous and local injection of aaPRP for two weeks showed better clinical outcomes in reducing wound surface area significantly and serum HbA1c levels, although statistically insignificant compared to the control group. Future studies should be conducted with more participants, a longer follow-up duration, and a more rigorous methodology.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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AUTHOR CONTRIBUTION:

Contribution	Fibrini D	Lister INE
Concepts or ideas	x	
Design	x	
Definition of intellectual content	x	
Literature search	x	x
Clinical studies	x	
Data acquisition	x	
Data analysis	x	
Statistical analysis		x
Manuscript preparation	x	x
Manuscript editing	x	x
Manuscript review	x	x

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