EDITORS' PICK

Cite as: Archiv EuroMedica. 2024. 14; 3. DOI 10.35630/2024/14/3.331

Received 19 May 2024;
Accepted 6 June 2024;
Published 12 June 2024

EFFECTIVENESS OF AUTOLOGOUS PLATELET-RICH PLASMA FOR HEALING DIABETIC FOOT ULCERS

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ABSTRACT

Autologous platelet-rich plasma (APRP) is widely used to accelerate the healing of chronic wounds. However, the advisability of its use in patients with diabetic foot ulcers (DFU), which develop in various forms of the disease and are associated with complex metabolic conditions, is still being discussed. This study consisted in a comparative analysis of the effectiveness of local use of autologous platelet-rich plasma in the treatment of DFU in patients with neuropathic and neuroischemic forms of the disease. A total of 106 patients with type 2 diabetes mellitus undergoing hospital treatment were divided into a study group (n=48) and a traditional wound therapy group (n=58), similar in ankle-brachial index values and ulcer size. Systemic therapy in both groups of patients included measures to regulate metabolism and nutrition, and infection control. Treatment results were assessed by the area of foot wounds and duration of healing. The duration of therapy and the mean platelet concentration in autologous plasma did not differ between groups. The wound healing time in patients with the neuropathic form (60.4±23.77 days) and the neuroischemic form of the disease (64.8±29.6 days) during treatment with APRP was significantly shorter than in the subgroups of the comparison group with traditional treatment of DFU (85.11±40.7 and 90.40±47.12 days respectively) ($p<0.01$), but there was no significant difference between the subgroups receiving treatment with APRP. Although there was no significant difference in the average daily healing area among all subgroups ($p>0.05$), the rate of wound healing in the subgroups with APRP was higher (14.85±10.66 and 15.33±14.91 mm^2/day, respectively) than in the subgroups of the comparison group (8.39±6.02 and 8.79±7.13 mm^2/day, respectively), which confirms the effectiveness of local treatment with APRP in combination with traditional systemic therapy.

Keywords: autologous platelet-rich plasma, diabetic foot ulcer, neuropathic and neuroischemic forms of type 2 diabetes mellitus

INTRODUCTION

Diabetic foot ulcers (DFU) are one of the most common and serious complications of diabetes mellitus,

characterized by chronicity, refractoriness, high risk of lower limb amputation (in 40-88% of cases), which often leads to disability, socio-economic problems and serious deterioration of patients' life quality [1-4]. In this regard, the study of therapeutic technologies to accelerate wound healing will allow to develop new approaches to reduce disability and mortality [5, 6].

Routine first-line treatment for DFU used in the clinic includes monitoring blood glucose levels, traditional treatment (treatment of infection, surgical debridement, wound cleansing, dressing) and angioplasty for ischemic peripheral artery disease [7-9]. However, to date, the results of DFU treatment remain unsatisfactory, since in 20% of patients the average healing time of the tissue defect without surgical intervention exceeds one year, and the rate of disease relapse reaches 40%. In this regard, the development of rapid and effective treatment of DFU is an important public health task.

In a systematic review, OuYang et al. [10] showed that platelet-rich plasma has promising clinical results in wound healing: it contains a higher concentration of platelets than native plasma, and does not cause immunogenic adverse reactions, being of autologous origin (autologous platelet-rich plasma - APRP). Since platelets produce many growth factors and other biologically active substances necessary for the regeneration of damaged tissues, and also have antibacterial properties, APRP has attracted attention as a therapeutic agent that accelerates wound healing [11]. Over the past few decades, a large number of studies and clinical trials have been conducted to evaluate the role of APRP in wound healing and tissue regeneration [12, 13]. In recent years, many studies have made relevant analysis of the effectiveness of APRP in the treatment of DFU, but they are contradictory and limited to only a few indicators [14-16]. Therefore, further research is needed to objectify the effectiveness of APRP for DFU as a new method of treating tissue defects in patients with various forms of type 2 diabetes mellitus and concomitant diseases.

Purpose of the study: to compare the effectiveness of ulcer healing with local application of autologous platelet-rich plasma in patients with neuropathic and neuroischemic forms of diabetic foot.

MATERIAL AND METHODS

This prospective cohort, single-center, controlled clinical study was performed on 106 patients with DFU treated from September 2020 to August 2023 at St. Luke's Multidisciplinary Clinical Hospital, Simferopol. Patients were divided into the main group, with the use of autologous platelet-rich plasma (subgroup 1 - with neuropathic form, n=21, subgroup 2 - with a neuroischemic form, n=27), and a comparison group with traditional treatment of wounds (subgroup 3 - neuropathic, n=25, subgroup 4 - neuroischemic, n=33) which were similar in shape, ankle-brachial index (ABI) values and ulcer size.

Inclusion criteria were as follows: a definite diagnosis of type 2 diabetes mellitus based on the 1999 World Health Organization Diabetes Diagnostic Standard, patients with mild to moderate lower limb ischemia (ABI greater than 0.5), and patients with at least one foot ulcer.

Exclusion criteria were diabetic ketoacidosis or hyperosmolar hyperglycemic state; uncontrolled systemic or local infection; dry or wet gangrene; severe coronary, cerebral and/or renal vascular diseases; malignant tumors; pregnant or lactating women and diseases of the hematological system. This study complied with the recommendations of the Declaration of Helsinki. Written informed consent was obtained from all patients.

All participants received systemic therapy and standard local diabetic wound care. Clinical treatment was carried out with the control of blood sugar, blood pressure and blood lipids levels. Systemic antibiotic therapy was used according to the results of a drug sensitivity test. All study participants were given the same neurotrophic and circulatory therapy (0.5 mg of mecobalamin three times daily and 100 mg of aspirin four times daily as needed). Local treatment in all patients was performed using similar procedures, which included primary debridement with removal of nonviable tissue, drainage with local dressing, or negative pressure wound therapy. Systemic and local therapy was continued until the end of the observation period. In patients of the comparison group (traditional wound treatment), systemic and local methods of treating diabetic wounds described above were used. When the wound beds were clean, without obvious necrotic tissue and purulent discharge, patients of the main group underwent local APRP - 1 ml/cm^2 along the edges and the bottom of the ulcer. If there was no specific discomfort after application, the dressing was changed every 5 days until the wound area was reduced by more than 80% of the original. The therapeutic effect of APRP in complex therapy was assessed by wound healing time, average daily healing area and adverse reactions (infection, itching, redness, pain, rash, etc.) and compared with the group of patients receiving traditional treatment.

A modified procedure was performed to prepare autologous platelet-rich plasma. Peripheral venous whole blood obtained from patients in a volume of 50-100 ml (depending on the size of the wound) was placed in sterilized centrifuge tubes with sodium citrate immediately on the day of treatment. The packed red blood cells were removed immediately after centrifugation in a freezing centrifuge (Beckman, Life Sciences, Indiana, USA) at 600 rpm for 15 min. The remaining plasma was further centrifuged at 1135 g for 7 min to isolate platelet-rich plasma. Platelet counts were counted using an automatic blood cell analyzer (Sysmex

XE-2100; Nigale, Chengdu, China).

The data obtained in the study were processed using the SPSS statistical software version 22.0 (IBM, Armonk, New York, USA). Continuous variables were described as means ± standard deviations. For normally distributed data variables, comparisons between two groups were made using t tests, comparisons across multiple groups were made using one-way analysis of variance, and further pairwise comparisons were made using Bonferroni tests. For variables that did not follow a normal distribution, multiple group comparisons were performed using the Kruskal-Wallis test and pairwise comparisons were performed using the Steel-Dwass test. Fisher's exact test was used for comparisons between groups. A p value <0.05 was considered statistically significant.

RESULTS

The clinical characteristics of all participants are shown in the Table 1. There were no significant differences in gender, age, duration of diabetes, smoking history, etc. among the four subgroups (p>0.05). There were no significant differences in comorbid conditions such as hypertension, coronary artery disease, hyperlipidemia (p>0.05).

After preparing APRP, the concentration of enriched platelets reached 985.9 ± 124.7 × 10^9/l.

Table 1. Clinical characteristics of patients of the study groups

	Main group		Comparison group		
Indicator	Subgroup 1 (n=21)	Subgroup 2 (n=27)	Subgroup 3 (n=25)	Subgroup 4 (n=33)	p-value
Gender (male/female)	16/5	19/8	14/11	20/13	
Age, years	63,3±20,8	61,5±7,1	65,2±10,8	66,6±14,2	$0,71^F$
Duration of illness (months)	105±51,4	116±76,3	121±88,7	129±90,9	$0,53^H$
Smokers (%)	9 (40,0)	11 (40,7)	13 (52,0)	18 (54,5)	0,42
Arterial hypertension (%)	12 (57,1)	18 (66,7)	18 (72,0)	24 (72,7)	0,19
Coronary heart disease	3 (14,3)	5 (18,5)	4 (16,0)	6 (18,2)	0,42
Hyperlipidemia (%)	4 (19,0)	13 (48,1)	7 (28,0)	14 (42,4)	0,08
HbA1c (%)	7,30±1,62	7,94±1,98	8,22±2,05	8,50±2,36	$0,68^H$
Leukocytes (10^9)	6,53±1,71	6,88±2,35	8,04±2,69	8,72±2,59	$0,08^F$
CRP (mg/l)	10,44±2,82	6,87±2,90	9,25±10,48	9,11±4,62	$0,15^H$
PCT (pg/ml)	0,04±0,02	0,06±0,03	0,10±0,09	0,13±0,09	$0,16^H$
ABI (left)	0,89±0,19	0,88±0,25	0,95±0,26	0,95±0,33	$0,85^H$
ABI (right)	0,90±0,22	0,93±0,24	0,91±0,18	0,94±0,15	$0,84^H$

Note: HbA1c - glycated hemoglobin; CRP - C-reactive protein; PCT - procalcitonin; ABI - ankle-brachial index. F: analysis of variance; H: rank sum criterion (Kruskal-Wallis test).

Before treatment, there was no significant difference between the area ofthe foot tissue defect and the number of ulcers among all subgroups ($p>0.05$). As for the healing time, no significant difference was found between the subgroups 1 and 2 - in the 1st (56.9 ± 29.22 days) and 2nd (55.6 ± 33.8 days) subgroups it was significantly shorter than in patients with DFU in the comparison group (88.0 ± 33.8 days) ($p<0.01$). Analysis of daily changes in the healing area showed an increase in the healing rate in the 1st and 2nd subgroups, by 16.77 ± 12.85 mm^2 and 14.31 ± 18.28 mm^2 respectively, and in the comparison group the indicator was significantly lower (9.90 ± 8.51 mm^2) (Table 2).

Table 2. Indicators of healing of diabetic wounds in all examined groups of patients

Indicator	Subgroup 1 (n=21)	Subgroup 2 (n=27)	Subgroup 3 (n=25)	Subgroup 4 (n=33)	*p*-value
Ulcer area (cm^2)	7,11±5,03	8,29±3,66	8,58±6,44	9,36±5,87	$0,19^H$
Number of ulcers	1,31±0,55	1,83±0,71	1,52±0,63	2,02±0,75	$0,12^H$
Ulcer healing time (days)	64,8±29,60	60,40±23,77	85,11±40,7	90,40±47,12	$0,002^H$
Average daily healing area (mm^2)	14,85±10,66	15,33±14,91	8,39±6,02	8,79±7,13	$0,12^H$

H: rank sum criterion (Kruskal-Wallis test).

Among the 48 patients treated with APRP, there were no adverse reactions such as local or systemic fever, periwound erythema, swelling, itching, rash, or burning.

DISCUSSION

Autologous platelet-rich plasma therapy for chronic wound healing is gaining immense popularity due to successful treatment results. In the present study, the effectiveness of APRP in the treatment of DFU was 77%. Our study is consistent with previously published data [17,18]. Although patients with DFU tend to be older and have a long history of diabetes mellitus, malnutrition, infections, thrombocytopenia, hypovolemia, anemia, immune dysfunction, and skin problems, our data support the effective and safe use of APRP for the treatment of foot ulcers.

The results obtained suggest that the use of APRP based on traditional wound treatment can accelerate the healing of ulcers in patients with both neuropathic and neuroischemic forms of the disease. The possible influence of total platelet count on treatment efficacy was eliminated by standardizing the APRP treatment time and using a similar mean platelet concentration.

The reparative potential of APRP is due to high concentrations of various growth factors resulting from the degranulation of concentrated platelets, including fibroblast growth factor, transforming growth factor, insulin-like growth factor, vascular endothelial growth factor and platelet-derived growth factor [19]. In clinical terms, APRP is a "biological antibacterial agent" for the treatment of diabetic skin ulcers with severe or multidrug-resistant infection. It is known that APRP can inhibit the growth of Pseudomonas aeruginosa, Staphylococcus aureus and Streptococcus faecalis through chemokine ligand-3, chemokine ligand-5 and chemokine ligand-1 (CXC) [20].

CONCLUSIONS

The study demonstrated that platelet-rich plasma injection was significantly more effective than a conventional dressing in treating diabetic foot ulcers, regardless of the type of diabetes. The use of APRP can provide effective and safe therapy in patients with DFU. Additional large-scale clinical trials are needed to evaluate the effectiveness of use of autologous platelet-rich plasma.

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