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Original Article

Topic platelet gel application in chronic diabetic foot ulcers

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ABSTRACT

In this observational study performed during 45 months we evaluated patients with chronic and recalcitrant diabetic ulcers who were treated with homologous platelet gel.

Methods: platelet gels were obtained from homologous platelet concentrates that were aliquoted and freezed, being then activated with calcium gluconate and applied in the ulcer after cleaning and debridement.

We evaluated patient's comorbidities, wound characteristics (size, tissue, inflammatory signs, pain), number and time of treatment as well as outcome (classified as complete epithelialization; partial improvement- 50% reduction in wound size or pain relief; no evolution).

Results: Fifty-two patients (42 males, 10 females), with a median age of 65 years (range 43–85) were proposed for platelet gel. The following associated comorbidities were observed: hypertension (n = 41), dyslipidemia (n = 29), polyneuropathy (n = 30), peripheral arteriopathy (n = 32), retinopathy (n = 21), nephropathy (n = 15), cardiac ischemic disease (n = 14), obesity (n = 9). Thirty-eight patients presented with 3 or more associated comorbidities. The more frequent ulcer locations were sole of the foot (n = 13) and heel (n = 10). The median number of applications was 16, during 8.5 weeks. Nineteen patients (44%) achieved complete healing, 3 patients (7%) had a partial response and 21 (49%) had no progression. We did not observe a statistically significant relationship between patient age and response nor between number of comorbidities and response. We observed a more favorable evolution in patients with good compliance and good glycemic control.

Conclusion: Platelet gel is an effective therapeutic alternative, provided compliance and effective metabolic control are ensured.

1. Introduction

Diabetic foot ulcers (DFU) are one of the most frequent and difficult complications in type 2 diabetes. The risk for a diabetic patient to develop an ulcer during his life is estimated as being 25% [1,2]. Ulcers are a frequent cause of lower limbs amputation and 84% of lower limb amputations are preceded by ulcers [3].

This represents a growing problem with undeniable economic and social repercussions. Platelet-rich plasma (PRP) and platelet gel (PG) healing properties have been known since the decade of '80s [3,4].

Recent interest has arisen in the application of PRP and PG in chronic and refractory DFU because it is a simple, effective, minimally invasive and cost-effective treatment [5,6].

In 2012 the Italian Society of Transfusion Medicine and Immunohematology published the guidelines for the use of blood components for non-transfusion use and proposed a 1B degree of recommendation for the use of PG in the DFU [7].

In 2016 the Spanish Society of Hematology and Hemotherapy also suggested the use of PG in diabetic wounds with the same 1B degree of recommendation [8].

The rationale for the use of platelets in the treatment of wounds relates to the content of alpha platelet granules, rich in growth factors (PDGF, TGF-β1, VEGF, bFGF, EGF) that promote the regeneration of tissues of mesenchymal origin, modulate the inflammatory response and have an anti-bacterial effect by its

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Abbreviations

DFU	Diabetic foot ulcers
PRP	platelet rich plasma
PG	platelet gel
PDGF	Platelet derived growth factor
TGF-β1	Transformed growth factor beta 1
b-FGF	Basic fibroblastic growth factor
VEGF	Vascular endotelial growth factor
EGF	Epidermal Growth factor

chemotactic capacity for macrophages and fibroblasts [3,9,10].

This is an observational study performed in patients with DFU and treated with PG to evaluate its effectiveness and safety.

2. Materials and methods

2.1. Patients

During a 45 months period, 52 patients with diabetic ulcers were selected for treatment with homologous PG.

Patients were being followed up at the Diabetic foot multidipliscinary Unit.

PG was usually proposed as a therapeutic option by the endocrinologist who followed the patient.

The Haematologist assessed the patient's eligibility, being the main inclusion criteria the presence of a chronic ulcer (more than 6 months of evolution) and refractory to conventional treatment measures.

Exclusion criteria were the presence of an infected wound and/or osteomyelitis, and/or a completely necrotic ulcer and/or active oncological disease.

All patients signed free and informed consent prior to the beginning of the treatment. For each patient we registered: demographic data, comorbidities, ulcer characteristics namely: dimensions, type of tissue (i.e. granulated tissue, with some necrotic zone, with epithelization, with fibrin), presence vs lack of inflammatory signs, associated pain (classified as mild from 0 to 3, moderate from 4 to 7, severe from 8 to 10 pontuation).

The number of applications, the treatment time (in weeks) and the evolution of the ulcer area was also documented. In particular, we classified the outcome as follows: complete healing, partial improvement (reduction in 50% of the wound area and/or improvement of pain if initially present) or absence of evolution.

A photographic record was taken in all patients at the beginning, during and at the end of treatment.

2.2. Platelet gel

Platelet gel was obtained from whole blood donations.

The donors were selected in accordance with the European directives 2002/98/EC, 2004/33/EC, 2005/61/EC and 2005/62/EC that were transposed into the national law number 185/2015 [11].

In addition, the selected donors should have platelet counts> 200×10^9/L and not being medicated with non-steroidal anti-inflammatory drugs or similars.

The whole blood was collected in quadruple bags with citrate, phosphate and dextrose (CPD) as anticoagulant and submitted to a first centrifugation (speed 1848 RCF, acceleration 8, brake B4, time 4.40 min, temperature 22 °C) to obtain an erythrocyte concentrate and PRP.

The PRP was subjected to a second centrifugation (RCF speed 393, acceleration 9, brake B6, time 6.30 min, temperature 22 °C) to obtain platelet-poor plasma and a layer of platelet and leucocytes which was subsequently resuspended in about 60 ml of plasma. The 60 ml platelet concentrate was aliquoted into 4 satellite bags (TeT® Kabi Fresenius bags 8002125) and frozen at −30 °C.

On the day of application, each aliquot was thawed at 37 °C and activated with 10% calcium gluconate (ratio of 1.5 ml of 10% calcium gluconate:15 ml platelet concentrate) to form a platelet gel constituted by activated platelets, leucocytes and fibrin.

After platelet activation, the maximum time for platelet gel application was defined as being 8 h.

The gel was applied to the ulcer after cleansing and debridement, in order to cover the entire area.

A non-adherent gauze (Adaptic®) was then applied and a patch was made.

2.3. Statistics

Patient data were entered a Microsoft Office Access 2007 database.

Data analysis was performed using Microsoft Excel 2007 software. The chi square test was used to compare groups. We considered significant p values < 0.05.

3. Results

Fifty-two patients (10 women and 42 men), with a median age of 65 years (range 43–85), were included in the present cohort study during a 45 months period.

All patients had chronic ulcers with more than 6 months of evolution.

In addition to diabetes, patients had multiple comorbidities, namely: arterial hypertension in 41 patients, dyslipidemia in 29, nephropathy in 15, distal sensitivomotor polyneuropathy in 30, retinopathy in 21, peripheral obstructive arterial disease in 32, obesity in 9 and ischemic heart disease in14 cases.

In particular, 38 patients had 3 or more co-morbidities simultaneously in addition to diabetes.

The location of ulcer in treated patients was: plantar in 13 cases, calcanear in 10, malleolar in 9, in a finger in 9, in the transtarsus or finger amputation stump in 9, in the leg in 2 patients.

The median area of the ulcer (length x width) at the beginning of treatment was 2.25 cm^2 (range 0.03–35).

Two of the 52 patients were considered initially suitable for treatment with platelet gel but they stopped treatment at the first application because they presented very large and exudative ulcers as well as uncontrolled glycaemia with medication.

Two out of the 52 patients applied the gel on 2 different ulcers with the same location in both the lower limbs.

The median number of PG applications per patient was 16 (range 1–67) during 8.5 weeks. The evaluation of efficacy of treatment was possible in 43 patients, with reepithelialization and complete response in 19 patients (44%), partial response in 3 patients (7%) and absence of response in 21 (49%) patients.

In relation to patients in whom efficacy assessment was not possible: 4 patients were still being treated at the time of writing this manuscript, 1 patient was lost in follow up after 2 applications, 1 patient suspended for poor compliance, 1 patient had 1 stroke and discontinued gel applications.

It should also be noted that 5 out of 43 patients initially applied the gel but had temporarily to stop because of inflammatory signs/infection in the ulcer. However, they restarted after management of the infection and 2 of them had a complete healing while 3 did not present favorable evolution.

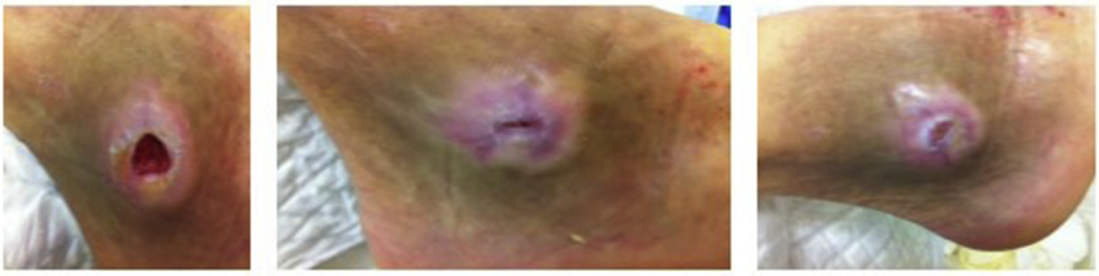

Fig. 1. (A,B,C): malleolar ulcer 1 × 1 cm before PG (A), during treatment (B) and after 14 applications (C).

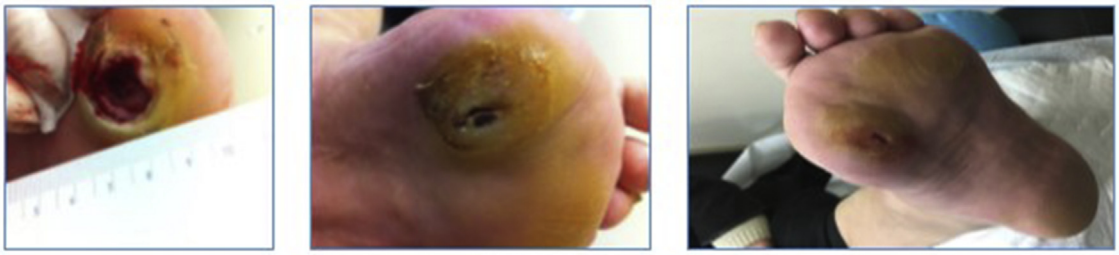

Fig. 2. (A,B,C): plantar 2 × 1,8 cm before PG (A), during treatment (B) and after 16 applications (C).

We did not observe any relationship between age (cut-off greater or less than 70 years) and outcome (Chisquare statistic 0.2867, p value 0.59). Moreover, the presence of multiple comorbidities (more than 3) was apparently unrelated to outcome (Chi-square statistic 0.0304, p-value 0.86).

There was also no relationship between presence/absence of peripheral obstructive arterial disease and response (Chi-square statistic 0.5604, p-value 0.45).

However, we must point out that the different patient subgroups were small to get a statistical power.

Figs. 1 and 2 represent the ulcers of 2 patients who presented a favorable outcome. Fig. 1 shows a right lateral malleolar ulcer in a 44-year-old man with hypertension, dyslipidemia, ischemic heart disease, nephropathy and diabetic neuropathy. The patient performed 14 applications in 7 weeks with complete healing.

Fig. 2 shows a plantar ulcer in a 53-year-old female, obese, with hipertension, diabetic neuropathy, already previously amputated in the 1st homolateral toe, which performed 18 applications during 8 weeks and completely healed.

Fig. 3 shows an extensive, malleolar ulcer in a Charcot foot of an 83-year-old man, who did not present favorable evolution and stopped the treatment after 4 weeks applications.

No adverse events or reactions were reported after topical application of platelet gel in none of the patients treated.

4. Discussion

A multitude of publications has arisen in literature in the last decade about the properties of PRP and PG in different settings, particularly in the treatment of wounds of various etiologies [12–14], in orthopedic surgery [15,16], in the treatment of sport injuries [17], in maxillo-facial surgery [18] and in aesthetic medicine [19].

The results of these studies are often contradictory and difficult to analyze, since methodologies for obtaining and applying platelet gel differ between studies and a comparative analysis is not possible.

In this study only diabetic foot ulcers were included. PG was obtained from whole blood donors, using a standardized processing method previously validated and used by other authors [2].

We consider that the topical application of homologous platelet gel has an overall benefic effect in refractory DFUs, reducing the average area of the wounds and contributing to their re-epithelialization.

However, individual biological characteristics in both patients and whole blood donors the PG is derived from could influence the final results.

Interestingly, the response to PG correlated more with the habits of the patient than with clinical variables, although this is not clearly objectified.

Fig. 3. (A,B,C): plantar ulcer 7,7 × 1 cm with no evolution after 5 application with PG.

The greater the degree of patient compliance with regard to hygiene, rest walking, diet compliance and metabolic control, the better and faster the documented response.

Patient adherence to therapy was good as PG is minimally invasive and easy to apply. No adverse reactions were reported. Some patients reported a decrease in pain evaluated in terms of decreased amount and frequency of ingested analgesics but that it was not possible to more objectively quantify this aspect.

In conclusion, we consider platelet gel a safe and effective therapeutic alternative, since compliance and proper metabolic control are ensured.

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