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Case Series

Use of Autologous Plasma Rich in Growth Factors Membrane (Endoret) for Chronic Diabetic Foot Ulcers: A Case Series of Six Patients

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Abstract

Background and objectives: Diabetic foot ulcers (DFUs) are a significant source of morbidity, and pose great financial burden to the health service. Conventional treatments with dressings are often ineffective. Platelet-rich products have been used in recent years for the treatment of DFUs, with promising results. The present study aims to evaluate the efficacy of plasma rich in growth factors (PRGF) membrane therapy in the treatment of chronic non-healing DFUs, in order to improve wound healing and accelerate the epithelisation of chronic wounds.

Methods: A total of six diabetic patients with chronic non-healing foot ulcers were included in the present study. The Endoret procedure was used to isolate the PRGF from blood samples, resulting in the formation of a membrane clot, which was placed over the bed of the ulcer. A portion of the PRGF was also allowed to infiltrate around the ulcer edge. Patients were followed up in clinic at two weekly intervals, until full healing was achieved.

Results: All six patients (mean age: 60 years old) underwent successful treatment with the PGRF membrane. Full epithelisation of the ulcers was achieved for all patients, with a mean duration of eight weeks. No complications were noted throughout the treatment period.

Conclusions: The use of an autologous PRGF membrane is a secure and efficacious surgical treatment for chronic non-healing DFUs. The present study demonstrates that the PRGF fibrin membrane can be used to optimize surface regeneration in DFUs. Additional data and randomized studies are required to establish the effectiveness of this method in treating DFUs.

Introduction

Diabetic foot ulcer (DFU) healing is a major problem for healthcare worldwide. Approximately 15–20% of patients with diabetes develop foot ulcer during their lifetime.[1] DFUs are hard to heal due to inadequate vascularity and impaired sensation resulting from sensory neuropathy. These often become chronic intractable conditions, with significant financial burden. Furthermore, the National Health Service in the UK spends at least £10 billion a year on diabetes, which is equivalent to 10% of its budget, with 80% spent on treating complications.[2] Moreover, conventional treatments are ineffective for a number of patients, increasing the comorbidity associated with the DFU disease. In addition, approximately 7,000 lower limb amputations are performed for diabetes patients in England each year, and the likelihood that someone with diabetes will have any level of lower extremity amputation is approximately 23 times of that for a person without diabetes.[3]

Keywords: Diabetic foot ulcers; Plasma rich growth factors; Platelet-rich products.
Abbreviations: DFU, Diabetic foot ulcers; PRGF, plasma rich in growth factors; PTD, plasma transfer device.
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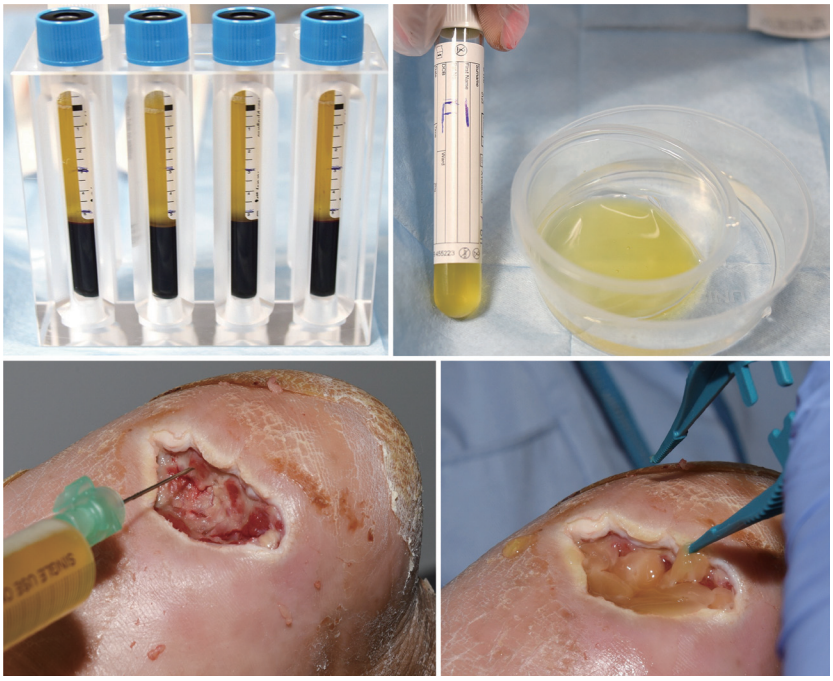

Fig. 1. Endoret procedure. Top left: Processing of the Endoret. Top right: Activated F1. Bottom left: Infiltration of activated F1 around the wound. Bottom right: F2 clot on the bed of ulcer.

In recent years, there has been increasing interest in the use of autologous platelet rich products for the management of DFUs.[4–6] Topical growth factor products are typically used as adjuvant treatments, along with standard modalities, for the treatment of DFUs, with successful results.[7] The plasma rich in growth factors (PRGF)-Endoret technique involves a simple bedside procedure to obtain the autologous proteins and platelet-concentrated fibrin membrane rich in growth factors, which acts as a biological membrane.[8] The platelets are known to release different growth factors that enhance the repair process and vascular proliferation, ultimately helping in the biological wound healing.[8,9] This preparation has been successfully used in a variety of medical specialities, including dentistry, maxillofacial, ophthalmology and orthopedics.[8–11] The present study aims to test the PRGF clot membrane therapy in chronic non-healing DFUs, in order to improve wound healing and enhance the epithelization of chronic wounds. The investigators consider that this would be a useful method for treating chronic non-healing DFUs, which is under-reported in medical literature.

Methods

This case series comprised six patients, who met the following criteria: chronic non-healing DFU, previously failed the non-operative treatment with dressings, and the absence of ulcer infection. Exclusion criteria: ulcers of arterial aetiology, the presence of systemic or local infection, the presence of osteomyelitis, and active Charcot arthropathy. The present study followed the Case Report (CARE) guidelines (Supplementary File 1) and was performed in accordance with the ethical standards of the institutions to which we are affiliated and with the Declaration of Helsinki (as revised in 2013). An informed consent was obtained from each patient for the publication of the findings and associated images.

All participants were examined by podiatrists and diabetologists in the diabetic foot clinic, as a multidisciplinary team. An informed consent was obtained from all participants who met the inclusion criteria. Furthermore, the baseline medical history was obtained, and the physical examination was documented. One patient had type I diabetes, while five patients had type II diabetes, and their diabetic control was managed by a diabetologist. The medical photography of the ulcers was performed at the start of treatment, and on the final visit. The Endoret technique is comprised of a single treatment. Patients were followed up until the end point was achieved, which was defined as full epithelization of ulcer without drainage.

Endoret procedure

The ulcer was adequately cleaned with skin preparation. Blood was obtained by venepuncture from the antecubital vein. The blood was collected using the Endoret PRGF protocol in 9-millimeter sterile tubes, containing 3.8% (wt/v) sodium citrate. Using the patented Endoret technology, the collected blood was centrifuged for eight minutes at room temperature using the PRGF-Endoret system centrifuge to obtain the PRGF. Then, the PRGF was drawn off in two fractions which were labelled as, F1 and F2. F1 was injected around the wound margin. Two millilitres of F2, which contained the optimal concentration of platelets (2-3×) isolated above the erythrocytes and leucocytes, was drawn up using the plasma transfer device (PTD). Then, F2 was activated using calcium chloride. Upon completion of the Endoret protocol, a fibrin clot was formed and placed over the bed of the ulcer, and the remaining F2 was allowed to infiltrate around the edges of the wound. Adequate dressing was secured, and the patient was kept in non-weight bearing. The subsequent follow-ups were performed in clinic at two weekly intervals for the examination of the wound, dressing and medical photography by a trained nurse. For

Table 1. Patient characteristics, healing times and outcomes

Patient number	Age	Gender	Type of diabetes	Location of ulcer	Duration of healing	Outcome
1	38	Female	Type 2	Hindfoot	13 weeks	Epithelisation
2	51	Female	Type 1	Forefoot	6 weeks	Epithelisation
3	67	Male	Type 2	Midfoot	6 weeks	Epithelisation
4	69	Male	Type 2	Midfoot	8 weeks	Epithelisation
5	65	Male	Type 2	Midfoot	10 weeks	Epithelisation
6	70	Male	Type 2	Hindfoot	6 weeks	Epithelisation

all cases, the entire procedure was performed under one hour. The procedure steps are illustrated in Figure 1.

Results

All six patients underwent successful treatment with the PGRF membrane, without any complications. The patient demographics, characteristics, and outcomes are summarized in Table 1. The mean age of patients was 60 years old (38–70 years old). The mean duration of ulcer healing was eight weeks (6–13 weeks). The patients were followed up in clinic every two weeks, until healing was achieved. All patients achieved full epithelisation of the ulcers (Figs. 2 and 3). No adverse events or complications were observed throughout the treatment period.

Discussion

DFUs are challenging to manage, and there is a plethora of local treatment options to choose from, with no consensus among medical fraternity. Plasma platelets have an important role in the initiation skin ulcer healing. These adhere, aggregate and release numerous growth factors, adhesive molecules, and lipids, which regulate the migration, proliferation and functions of keratinocytes, fibroblasts and endothelial cells.[9] Platelets release a variety of growth factors needed for tissue regeneration, angiogenesis and wound healing, including epidermal growth factor, fibroblast growth factor-2, transforming growth factor-β, vascular endothelial growth factor, and platelet-derived growth factor (PDGF).[12] In addition to the release of a range of morphogens, PRGF enables the development of a biocompatible fibrin scaffold, which acts as a biological membrane that maintains the controlled release of growth factors for several days.[12]

PRGF therapy has exhibited promising results in promoting tissue regeneration, and has been employed for the treatment of multiple musculoskeletal problems.[13,14] Recently, several studies have reported the effects of different platelet-rich products for diabetic ulcers, obtaining successful results in ulcer healing.[5,6,9,10] Orcajo *et al*. published a case report, in which the PRGF technique was used to treat chronic DFUs.[5] Furthermore, a large, randomized control trial (RCT) of autologous platelet gel reported the benefit in time to complete ulcer closure at 12 weeks, when compared to standard care.[10] A recent multicentric RCT[15] revealed the clinically and statistically significant benefit of the application of autologous immune cells, fibrin and platelet patches for DFUs. Although the trial results for autologous platelets may suggest the potential benefit in ulcer healing, the evidence remains inconclusive, including the optimal frequency

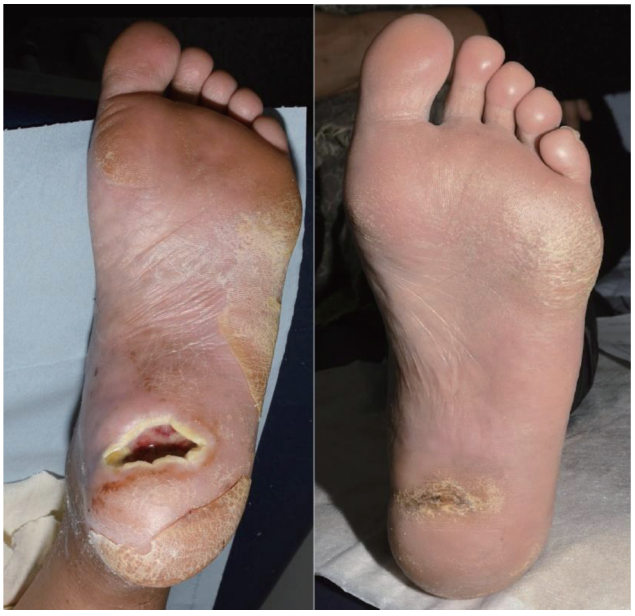

Fig. 2. Hindfoot ulcer: Pre-treatment and post-treatment at 13 weeks.

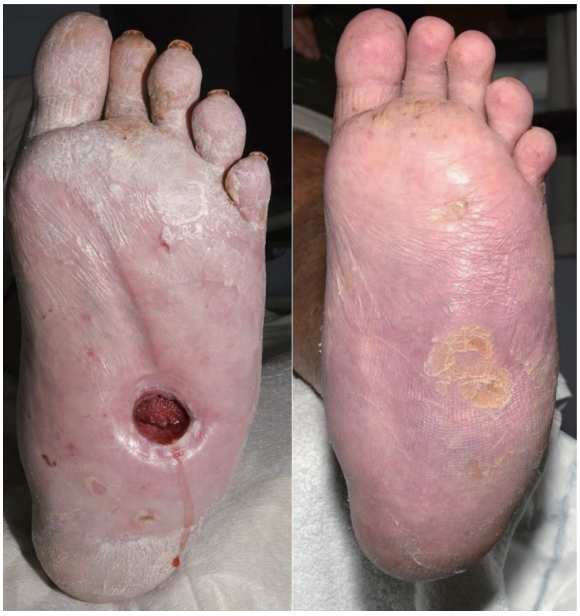

Fig. 3. Midfoot ulcer before and after treatment for 10 weeks.

of applying these products, and the determination of which ulcers may benefit the most from these.[16] The present study presented a unique case series, in which a fibrin membrane with autologous proteins from a platelet enrichment system was applied to heal DFUs.

Future directions

All six patients in the present study had promising results in the treatment of chronic DFUs. However, there were some limitations in the present study. First, a small sample size was used, thus, further studies with a larger number of samples are required to evaluate the efficacy of the PRGF membrane for DFUs. Second, the present study presented a prospective case series without any control group. Additional data and randomized studies are required to establish the effectiveness of topical PDGF in treating DFUs. Surgeons who treat DFUs can consider this mode of treatment as safe and effective.

Conclusions

The investigators successfully treated the chronic non-healing DFUs of six patients, without complications, using an autologous PRGF membrane. This biomaterial provides a safe and excellent vehicle for local growth factor delivery, functioning as a provisional matrix that supports the ingrowth of neovasculature and the migration of cells into the ulcer dead space, and regenerating the surrounding soft tissues.[9] This single treatment is a useful adjuvant to skin dressings for DFUs, which improves the outcome and decreases serious complications. The successful treatment of DFUs would decrease further diabetic complications, including amputations, and ultimately mortality.

Supporting information

Supplementary material for this article is available at https://doi.org/10.14218/ERHM.2021.00075.

Supplementary File 1. CARE checklist.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Study concept and design (NN and AP); Acquisition of data (NN, MN and MK); Analysis and interpretation of data (NN and MN); Drafting of the manuscript (NN, MN, MK and AA), Critical revision of the manuscript for important intellectual content (NN and AP), Administrative, technical, or material support (AP); Operating surgeons (NN and AP); Study supervision (AP). All authors have made a significant contribution to the study, and have approved the final manuscript.

Ethics statement

The study was performed in accordance with the ethical standards of the institutions to which we are affiliated and with the Declaration of Helsinki (as revised in 2013). An informed consent was obtained from each patient for the publication of the findings and associated images.

Data sharing statement

No additional data are available.

References

[1] Brod M. Quality of life issues in patients with diabetes and lower extremity ulcers: patients and care givers. Qual Life Res 1998;7(4):365–372. doi:10.1023/a:1024994232353, PMID:9610220.
[2] Whicher CA, O'Neill S, Holt RIG. Diabetes in the UK: 2019. Diabet Med 2020;37(2):242–247. doi:10.1111/dme.14225, PMID:31901175.
[3] Kerr M, Barron E, Chadwick P, Evans T, Kong WM, Rayman G, *et al*. The cost of diabetic foot ulcers and amputations to the National Health Service in England. Diabet Med 2019;36(8):995–1002. doi:10.1111/dme.13973, PMID:31004370.
[4] Driver VR, Hanft J, Fylling CP, Beriou JM, Autologel Diabetic Foot Ulcer Study Group. A prospective, randomized, controlled trial of autologous platelet-rich plasma gel for the treatment of diabetic foot ulcers. Ostomy Wound Manage 2006;52(6):68–70, 72, 74 passim. PMID:16799184.
[5] Orcajo B, Muruzabal F, Isasmendi MC, Gutierrez N, Sánchez M, Orive G, *et al*. The use of plasma rich in growth factors (PRGF-Endoret) in the treatment of a severe mal perforant ulcer in the foot of a person with diabetes. Diabetes Res Clin Pract 2011;93(2):e65–e67. doi:10.1016/j.diabres.2011.04.008, PMID:21546112.
[6] Villela DL, Santos VL. Evidence on the use of platelet-rich plasma for diabetic ulcer: a systematic review. Growth Factors 2010;28(2):111–116. doi:10.3109/08977190903468185, PMID:20001406.
[7] Margolis DJ, Kantor J, Santanna J, Strom BL, Berlin JA. Effectiveness of platelet releasate for the treatment of diabetic neuropathic foot ulcers. Diabetes Care 2001;24(3):483–488. doi:10.2337/diacare.24.3.483, PMID:11289472.
[8] Anitua E, Andia I, Ardanza B, Nurden P, Nurden AT. Autologous platelets as a source of proteins for healing and tissue regeneration. Thromb Haemost 2004;91(1):4–15. doi:10.1160/TH03-07-0440, PMID:14691563.
[9] Anitua E, Aguirre JJ, Algorta J, Ayerdi E, Cabezas AI, Orive G, *et al*. Effectiveness of autologous preparation rich in growth factors for the treatment of chronic cutaneous ulcers. J Biomed Mater Res B Appl Biomater 2008;84(2):415–421. doi:10.1002/jbm.b.30886, PMID:17595032.
[10] Li L, Chen D, Wang C, Yuan N, Wang Y, He L, *et al*. Autologous platelet-rich gel for treatment of diabetic chronic refractory cutaneous ulcers: A prospective, randomized clinical trial. Wound Repair Regen 2015;23(4):495–505. doi:10.1111/wrr.12294, PMID:25847503.
[11] Sabater AL, Mousa HM, Quinones X, Valenzuela F, Sanchez Avila RM, Orive G, *et al*. Use of autologous plasma rich in growth factors fibrin membrane in the surgical management of ocular surface diseases. Int Ophthalmol 2021;41(7):2347–2358. doi:10.1007/s10792-021-

01788-z, PMID:33745034.
[12] Barrientos S, Stojadinovic O, Golinko MS, Brem H, Tomic-Canic M. Growth factors and cytokines in wound healing. Wound Repair Regen 2008;16(5):585–601. doi:10.1111/j.1524-475X.2008.00410.x, PMID: 19128254.
[13] Anitua E, Sánchez M, Aguirre JJ, Prado R, Padilla S, Orive G. Efficacy and safety of plasma rich in growth factors intra-articular infiltrations in the treatment of knee osteoarthritis. Arthroscopy 2014;30(8):1006–1017. doi:10.1016/j.arthro.2014.05.021, PMID:24996872.
[14] Anitua E, Sanchez M, Nurden AT, Zalduendo M, de la Fuente M, Orive G, *et al*. Autologous fibrin matrices: a potential source of biological mediators that modulate tendon cell activities. J Biomed Mater Res A 2006;77(2):285–293. doi:10.1002/jbm.a.30585, PMID:16400654.
[15] Game F, Jeffcoate W, Tarnow L, Jacobsen JL, Whitham DJ, Harrison EF, *et al*. LeucoPatch system for the management of hard-to-heal diabetic foot ulcers in the UK, Denmark, and Sweden: an observer-masked, randomised controlled trial. Lancet Diabetes Endocrinol 2018;6(11):870–878. doi:10.1016/S2213-8587(18)30240-7, PMID:30243803.
[16] Vas P, Rayman G, Dhatariya K, Driver V, Hartemann A, Londahl M, *et al*. Effectiveness of interventions to enhance healing of chronic foot ulcers in diabetes: a systematic review. Diabetes Metab Res Rev 2020;36(Suppl 1):e3284. doi:10.1002/dmrr.3284, PMID:32176446.