Contents lists available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

Brief report

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

Beatriz Orcajo [a,*], *Francisco Muruzabal* [b], *María Concepción Isasmendi* [a], *Nerea Gutierrez* [a], *Mikel Sánchez* [c], *Gorka Orive* [b], *Eduardo Anitua* [b]

[a] *Clinica Juber, Plaza San Antón 4, 01002 Vitoria, Spain*
[b] *Instituto Eduardo Anitua, c/Jose Maria Cajigal 19, 10005 Vitoria, Spain*
[c] *Unidad de Cirugía Artroscópica "Mikel Sánchez", c/La Esperanza, 01005 Vitoria, Spain*

ARTICLE INFO

Article history:
Received 17 December 2010
Accepted 4 April 2011
Published on line 5 May 2011

Keywords:
Diabetic foot ulcers
Plasma rich in growth factors
Platelet rich plasma
Mal perforant ulcer

ABSTRACT

A 71 year old person with diabetes with a severe *mal perforant* ulcer in the right foot was treated twice with autologous plasma-rich in growth factors (PRGF) obtained from her own blood. After PRGF treatment the severe *mal perforant* ulcer completely healed in 10 weeks.

1. Introduction

In some people with diabetes injuries caused by weight bearing remain painless due to the presence of poor vascularity and impaired sensation resulting from sensory neuropathy. Continued weight bearing and pressure of keratotic lesions on the underlying dermis eventually cause necrosis and ulceration [1]. Approximately 15–20% of people with diabetes may develop a foot ulcer during their lifetime [2]. Ulcers are the leading cause of amputation in the United States and the second leading cause of hospitalization of people with diabetes [3].

The management of a *mal perforant* ulcer is difficult, time-consuming, expensive and resource intensive requiring wound care treatments, offloading, and dedicated monitoring [4].

We report the use of autologous proteins and fibrin material obtained from plasma rich in growth factors (PRGF-Endoret) technology as a novel approach for the management of *mal perforant* ulcers. PRGF consists of a limited volume of plasma enriched in platelets that is easily obtained from the patient and which has potent wound healing and tissue regenerative potential together with an anti-inflammatory activity [5–7]. Apart from releasing a wide range of biologically active proteins, PRGF enables the development of a biocompatible fibrin material, which acts as a biological membrane

* *Corresponding author*. Tel.: +34 945257862; fax: +34 945160657.
E-mail address: clinicajuber@gmail.com (B. Orcajo).

Abbreviations: PRGF, plasma rich in growth factors; F1, fraction 1; F2, fraction 2; F3, fraction 3.

0168-8227/$ – see front matter
doi:10.1016/j.diabres.2011.04.008

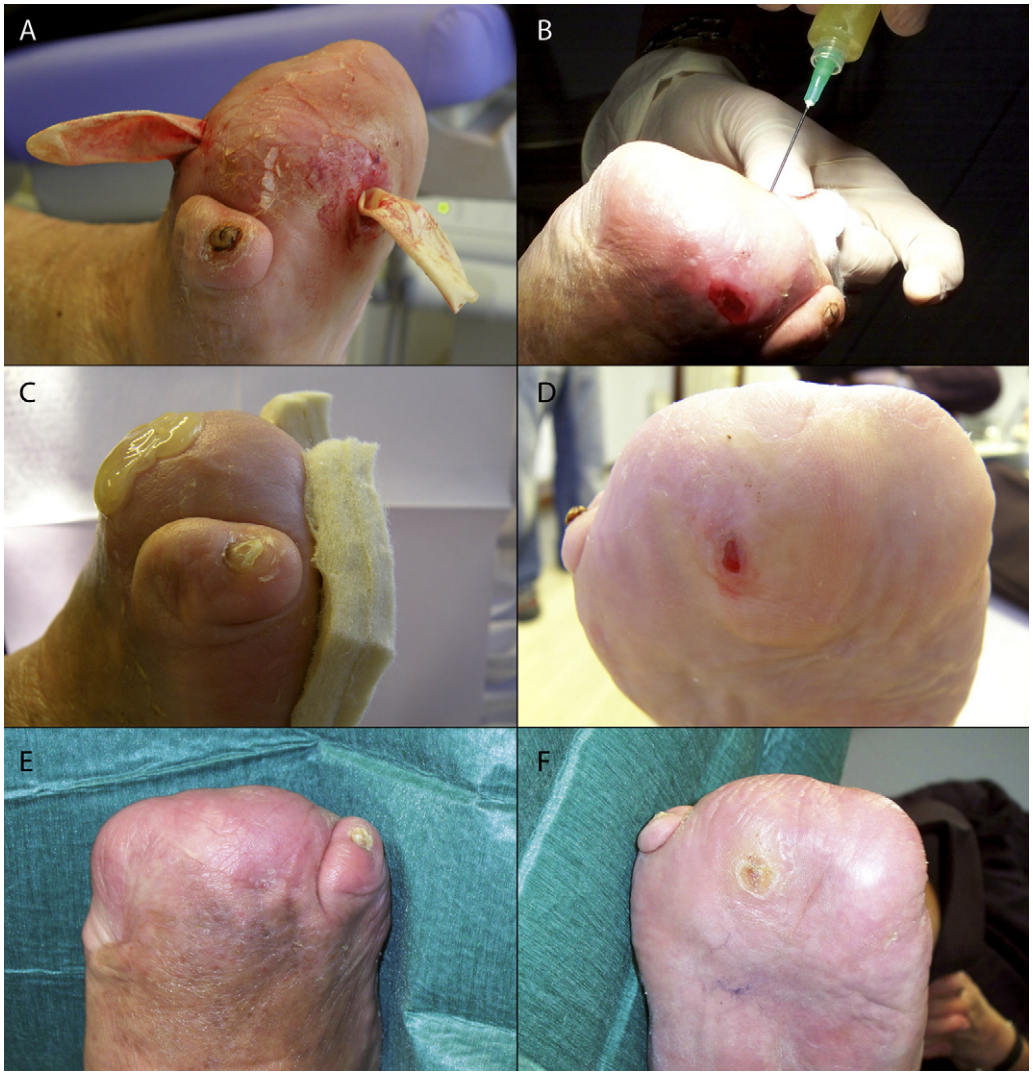

Fig. 1 – *Mal perforant* ulcer treatment with PRGF. (A) Drainage of the perforant ulcer. (B) Injection of plasma F2 in the borderline of the ulcer. (C) Treatment of the superficial ulcer with fibrin membrane and with an offloading. (D) Aspect of the ulcer after the first PRGF treatment. Appearance of the dorsal (E) and sole (F) of the foot after the second PRGF treatment. Note that the perforant ulcer is completely healed.

and as a growth factor slow delivery scaffold to regenerate soft tissues.

2. History and examination

Our patient was a 71 year old woman with type 2 diabetes, insulin treated since 2002 with microangiopathy and diabetic polyneuropathy. From 2002 to March 2009, the patient had amputations of the 1st, 2nd and 3rd toes of right foot due to persistent ulcers. In October 2009, she was admitted to the unit of vascular surgery of Santiago Apostol Hospital (Vitoria, Spain) due to a severe *mal perforant* ulcer on the right foot. An infection in the 4th toe caused an ulcer with bone exposed, which finally resulted in amputation of the toe. The *mal perforant* ulcer persisted, was associated with edema, and became deeper and approached the dorsal aspect of the foot.

Mal perforant ulcer is an easy portal of entry for bacteria, increasing the risk of soft tissue and bone infection. On November 12th, 2009, the patient underwent a dorsal incision at the foot to insert a drain to prevent ulcer infection (Fig. 1A). At that time, the perforant ulcer occupied a wide volume of the foot tissue, and a stiletto was easily introduced thought it. After drainage, a sample was taken to test the presence of infection, but this was negative.

On November 20th, 2009, 48 mL of blood were drawn from the patient and was centrifuged in order to obtain the PRGF formulation. The PRGF volume was drawn off in three consecutive fractions: fraction 1 (F1): the 2 mL volume of plasma located at the top of the tubes; fraction 2 (F2), the next milliliter of plasma below F1; and fraction 3 (F3) the milliliter of plasma located just above the sedimented red cells, avoiding collection of the buffy coat. Platelet enrichment of each plasma fraction (F1, F2, and F3) was 1.13, 1.56 and 1.72-fold, respectively.

To treat the *mal perforant* ulcer, F3 was activated with calcium chloride and collected with a 5 mL syringe. The syringe was connected to a sterile cannula and introduced into the *mal perforant* ulcer from the dorsum to the sole of the foot. The perforant ulcer was filled with the activated F3. The fibrin membrane obtained from the activation of half-volume of F1 was plug in the plantar ulcer to avoid the loss of F3. After that, the activated F2 was infiltrated around the borders of both exterior ulcers (Fig. 1B). Two fibrin membranes obtained from the rest of F1 were placed over external ulcers as a dressing (Fig. 1C). Throughout treatment, off-loading was also placed over the sole to reduce the load on the ulcer. Forty-eight hours after the treatment, there was some impediment to insertion of the stiletto in perforating ulcer, indicating that the tissue regeneration process had been initiated.

By December 12th, 2009, the *mal perforant* ulcer was completely healed and dermal ulcers were only present at the dorsum and sole of the foot (Fig. 1D). A second treatment with PRGF (prepared from 18 mL of blood) was applied. The remaining superficial ulcers were treated by border infiltrations with F3 and topically using a fibrin membrane from F1 as a dressing.

By February 1st, 2010, the ulcers were completely healed (Fig. 1E and F) and the patient could return to her normal life.

3. Discussion

The optimal wound healing of foot ulcers includes debridement, control of possible infection, and maintenance of a moist environment [4]. However, when these actions fail and ulcer healing is impaired, additional therapies, such as cellular therapies, complementary therapies, dermal matrix equivalents, and exogenous growth factors may be considered [8–12].

In recent years, several studies have reported the effects of different platelet rich products in diabetic ulcers, obtaining successful results in ulcer healing [13–17]. However, none of these have reported the treatment of severe ulcers, such as *mal perforant* ulcers.

To our knowledge, this is the first report in the literature where autologous proteins from a platelet enrichment system were applied to heal a severe *mal perforant* ulcer. Although preliminary, this case report may shed light on the potential of PRGF for accelerating the healing of severe *mal perforant* ulcers.

Conflict of interest

The authors have a competing interest to declare. E.A., F.M. and G.O. are involved in a foundation that investigates the potential of plasma rich in growth factors in regenerative medicine.

REFERENCES

[1] Grunfeld C. Diabetic foot ulcers: etiology, treatment, and prevention. Adv Intern Med 1992;37:103–32.

[2] Brod M. Quality of life issues in patients with diabetes and lower extremity ulcers: patients and care givers. Qual Life Res 1998;7:365–72.

[3] Reiber GE, Boyko EJ, Smith DG. Lower extremity foot ulcers and amputations in diabetes. In: Harris MI, Cowie CC, Reiber G, Boyko E, Stern M, Bennett P, editors. Diabetes in America. Washington, DC: U.S. Government Printing Office; 1995

[4] Steed DL, Attinger C, Colaizzi T, Crossland M, Franz M, Harkless L, et al. Guidelines for the treatment of diabetic ulcers. Wound Repair Regen 2006;14:680–92.

[5] Anitua E, Sanchez M, Orive G, Andia I. The potential impact of the preparation rich in growth factors (PRGF) in different medical fields. Biomaterials 2007;28:4551–60.

[6] Anitua E, Sánchez M, Nurden AT, Nurden P, Orive G, Andía I. New insights into and novel applications for platelet-rich fibrin therapies. Trends Biotechnol 2006;24:227–34.

[7] Anitua E, Sánchez M, Orive G. Potential of endogenous regenerative technology for in situ regenerative medicine. Adv Drug Deliv Rev 2010;62:741–52.

[8] Blume PA, Walters J, Payne W, Ayala J, Lantis J. Comparison of negative pressure wound therapy using vacuum-assisted closure with advanced moist wound therapy in the treatment of diabetic foot ulcers: a multicenter randomized controlled trial. Diabetes Care 2008;31:631–6.

[9] Mutluoglu M, Uzun G, Yildiz S. Hyperbaric oxygen therapy in the treatment of diabetic foot ulcers – prudent or problematic: a case report. Ostomy Wound Manage 2010;56:32–5.

[10] Fernández-Montequín JI, Valenzuela-Silva CM, Díaz OG, Savigne W, Sancho-Soutelo N, Rivero-Fernández F, et al. Intra-lesional injections of recombinant human epidermal growth factor promote granulation and healing in advanced diabetic foot ulcers: multicenter, randomised, placebo-controlled, double-blind study. Int Wound J 2009;6:432–43.

[11] Steed DL. Clinical evaluation of recombinant human platelet-derived growth factor for the treatment of lower extremity ulcers. Plast Reconstr Surg 2006;117:143S–9S.

[12] Fang RC, Galiano RD. A review of becaplermin gel in the treatment of diabetic neuropathic foot ulcers. Biologics 2008;2:1–12.

[13] Driver VR, Hanft J, Fylling CP, Beriou JM. A prospective, randomized, controlled trial of autologous platelet-rich plasma gel for the treatment of diabetic foot ulcers. Ostomy Wound Manage 2006;52:68–70.

[14] Salemi S, Rinaldi C, Manna F, Guarneri GF, Parodi PC. Reconstruction of lower leg skin ulcer with autologous adipose tissue and platelet-rich plasma. J Plast Reconstr Aesthet Surg 2008;61:1565–7.

[15] O'Connell SM, Impeduglia T, Hessler K, Wang XJ, Carroll RJ, Dardik H. Autologous platelet-rich fibrin matrix as cell therapy in the healing of chronic lower-extremity ulcers. Wound Repair Regen 2008;16:749–56.

[16] Villela DL, Santos VL. Evidence on the use of platelet-rich plasma for diabetic ulcer: a systematic review. Growth Factors 2010;28:111–6.

[17] 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;84:415–21.