Curas con factores de crecimiento (GF)

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Índice.

Factores de crecimiento.

- Son un conjunto de sustancias, la mayoría de carácter proteico, que desempeñan una importante función en la comunicación intercelular para la reparación de tejidos.

- Se encuentran en las plaquetas (gránulos α) y en el plasma.

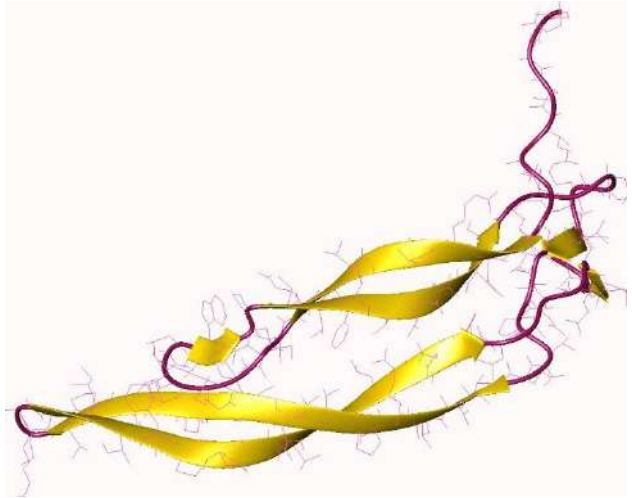


Figura 1: PDGF

Tipos de GF.

Growth factor	Cellular source	Target cells	Biologic activity
Activin	Fibroblasts, keratinocytes	Stromal cells	Granulation tissue formation, scarring
TGF-β_1 and TGF-β_2	Macrophages, platelets, fibroblasts, keratinocytes	Inflammatory cells, keratinocytes, fibroblasts	Chemotaxis, proliferation, matrix production (fibrosis)
TGF-β_3	Macrophages	Fibroblasts	Antiscarring?
TGF-α	Macrophages, platelets, keratinocytes	Keratinocytes, fibroblasts, endothelial cells	Proliferation
TNF-α	Neutrophils, mast cells	Macrophages, keratinocytes, fibroblasts	Activation of growth factor expression
PDGF	Macrophages, platelets, keratinocytes, fibroblasts, endothelial cells, vascular smooth-muscle cells	Neutrophils, macrophages, fibroblasts, endothelial cells, vascular smooth-muscle cells	Chemotaxis, proliferation, matrix production
FGF-1, FGF-2, FGF-4	Macrophages, fibroblasts, endothelial cells	Keratinocytes, fibroblasts, endothelial cells, chondrocytes	Angiogenesis, proliferation, chemotaxis
FGF-7 (KGF-1), FGF-10 (KGF-2)	Fibroblasts	Keratinocytes	Proliferation, chemotaxis
EGF	Platelets, macrophages, keratinocytes	Keratinocytes, fibroblasts, endothelial cells	Proliferation, chemotaxis
HB-EGF	Macrophages, keratinocytes	Keratinocytes, fibroblasts	Proliferation, epithelial migration, synergistic with IGF
IGF-1/Sm-C	Fibroblasts, macrophages, platelets	Fibroblasts, endothelial cells	Proliferation, collagen synthesis
IL-1α and IL-1β	Macrophages, neutrophils	Macrophages, fibroblasts, keratinocytes	Proliferation, collagenase synthesis, chemotaxis
CTGF/CCN2	Fibroblasts, endothelial cells	Fibroblasts	Downstream of TGF-β_1
VEGF	Macrophages, keratinocytes, fibroblasts	Endothelial cells	Angiogenesis

*Redundant biologic effects occur through both autocrine and paracrine mechanisms.
TGF-α, transforming growth factor-α; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor-α; PDGF, platelet-derived growth factor; FGF, fibroblast growth factor; KGF, keratinocyte growth factor; EGF, epidermal growth factor; HB-EGF, heparin-binding EGF; IGF-1, insulin-like growth factor 1; Sm-C, somatostatin C; IL-1, interleukin-1; CTGF, connective tissue growth factor; VEGF, vascular endothelial cell growth factor.
(Reproduced from Lorenz HP, Longaker MT. Wounds: biology, pathology, and management. New York: Springer-Verlag; 2000.)

Tabla 1: Lista con algunos GF.

- Tenemos diferentes tipos y cada uno tiene su función.
- Derivados de las plaquetas (PDGF)
- Transformante (TGF-beta)
- Endotelial vascular (VEGF)
- Insulínicos (IGF)
- …

Aplicación PRP.

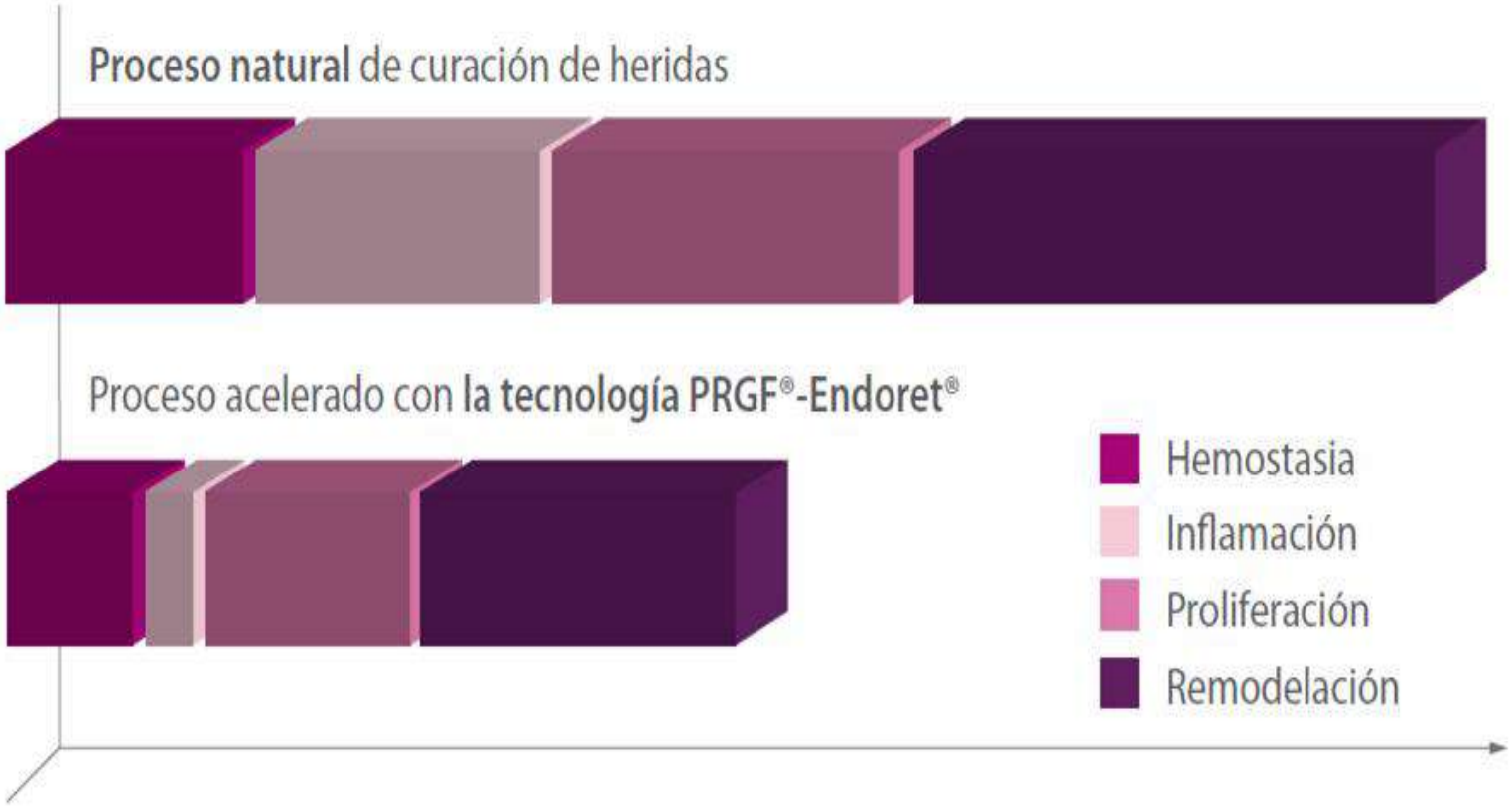


Figura 2: Proceso curación heridas

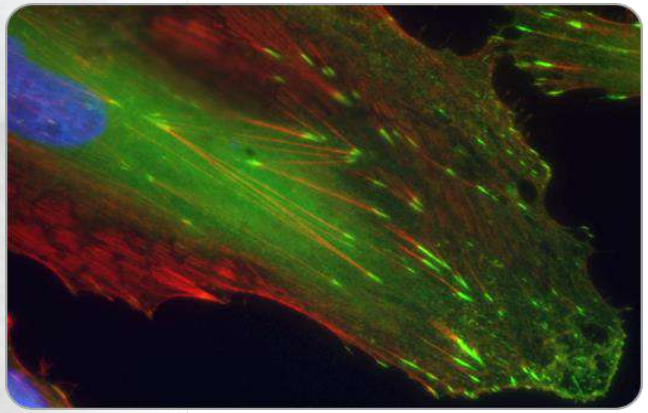
¿Qué requerimientos son necesarios para que tenga lugar el proceso de regeneración tisular?.

Requerimiento 1: Para optimizar el proceso de regeneración tisular son necesarios los factores de crecimiento y proteinas que regulan todos los mecanismos implicados

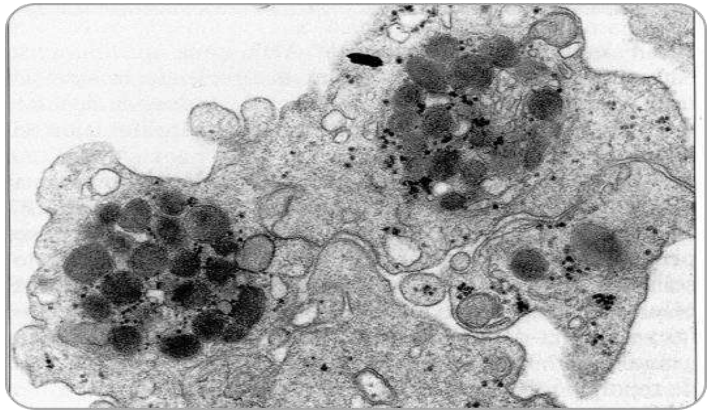
- Requerimiento 2: A su vez, es necesario que estos factores de crecimiento y proteinas sean aplicados en el lugar de la lesión manteniendo su actividad en el tiempo hasta la completa regeneración del tejido

Características principales.

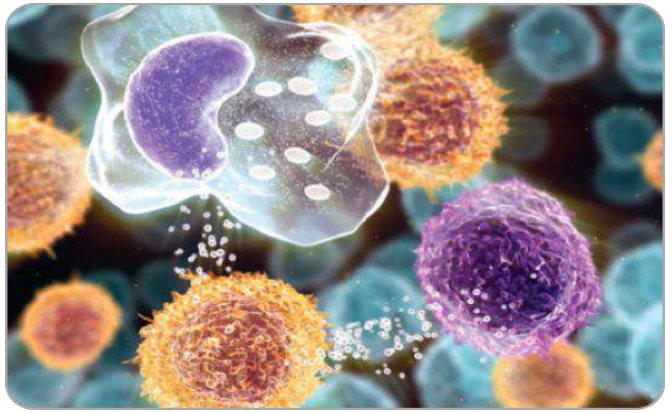
Concentración plaquetaria 2-3 veces



Uso de calcio para revertir la cascada de coagulación



Sin Leucocitos



Efectos Biológicos

. Regula la angiogénesis

. Aumenta la proliferación celular

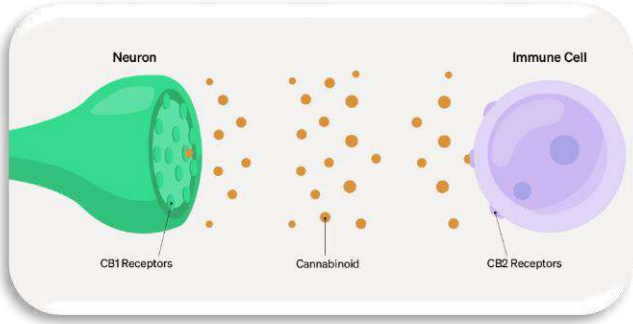
. Estimula la migración celular

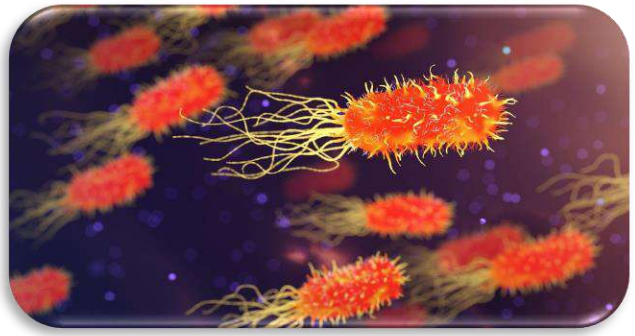
. Potencial antifibrótico

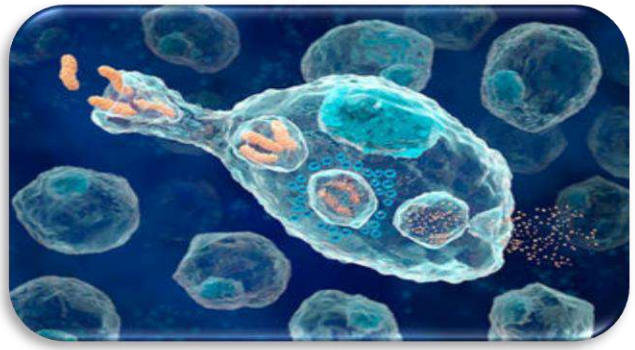
. Favorece la producción de MEC

. Disminuye la inflamación y el dolor

. Tiene potencial antimicrobiano



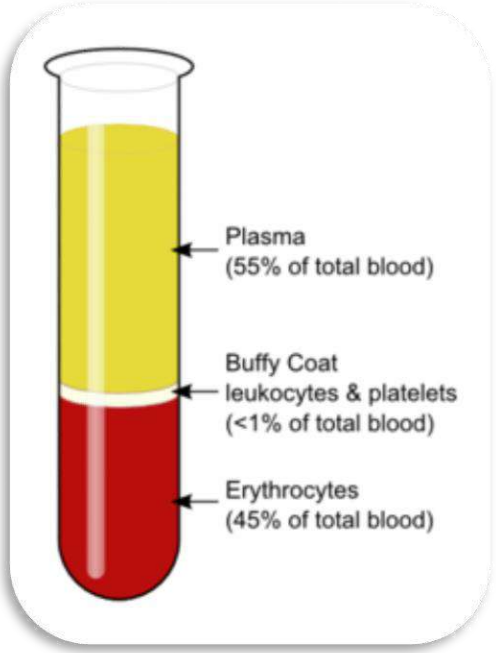




Protocolo elaboración.

- Se sigue un protocolo estandarizado, de los siguientes pasos:

1. Extracción de sangre del paciente.
2. Centrifugación para separar el plasma.
3. Recolección de las diferentes fracciones plasmáticas.
4. Activación.
5. Aplicación en la lesión.



Protocolo elaboración - Endoret PRGF

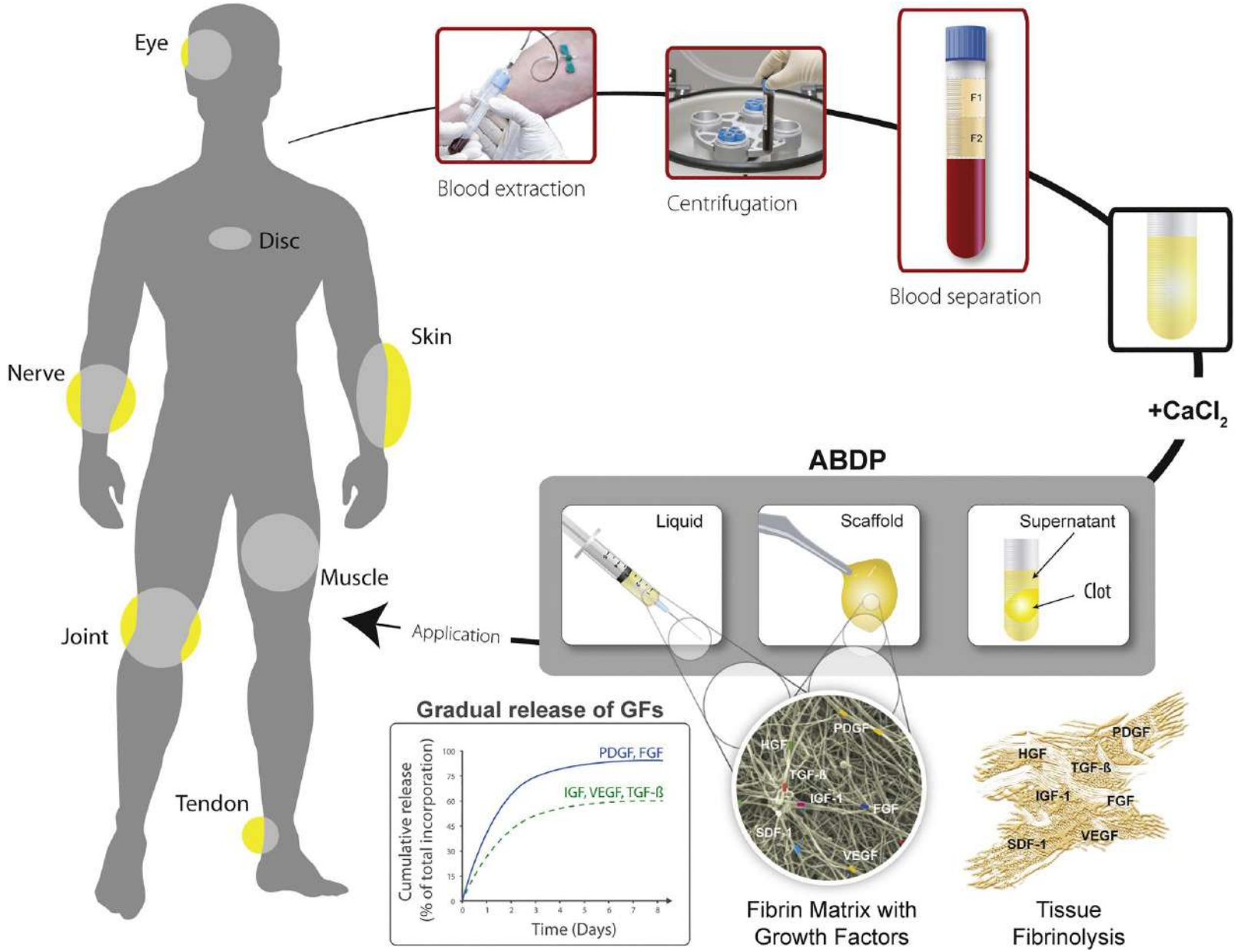


Figura 3: Elaboración Endoret

Evidencia clínica.

Effectiveness of Autologous Preparation Rich in Growth Factors for the Treatment of Chronic Cutaneous Ulcers

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Abstract: **Autologous Preparation Rich in Growth Factors (PRGF), a small volume of plasma enriched in platelets, is a novel therapeutic strategy for the acceleration of the wound healing of a wide range of tissues because of the continuous release of multiple growth factors, including PDGF-AB, TGF-β1, IGF-I, HGF, VEGF-A, and EGF. In this article, we have characterized the PRGF preparation and designed a randomized open-label controlled pilot trial to evaluate the effectiveness of PRGF in the treatment of chronic cutaneous ulcers. Results showed that at 8 weeks, the mean percentage of surface healed in the PRGF group was 72.94% ± 22.25% whereas it was 21.48% ± 33.56% in the control group ($p < 0.05$). These results, with the limitations of a pilot study, suggest that topical application of PRGF is more effective than standard therapy in helping a chronic ulcer to heal.** © 2007 Wiley Periodicals, Inc. J Biomed Mater Res Part B: Appl Biomater 84B: 415–421, 2008

Keywords: **chronic cutaneous ulcers; platelet; growth factors; PRGF; randomized trial**

INTRODUCTION

Cutaneous ulceration is a common clinical problem rising with the increasing median age of the population. The European Union allocates 2% of the yearly health budget to wound care[1] and it is estimated that in the United States the costs related to the care of patients with pressure ulcers is over $1.3 billion per year.[2] Absence of healing is not uncommon when predisposing factors, such as rheumatism, diabetes, peripheral vascular disease, or previous scars are present. In fact some comorbid conditions could be related to a deficiency of growth factors, such as platelet-derived growth factor (PDGF), epithelial growth factor (EGF), vascular endothelial growth factor (VEGF) in the ulcer site, resulting in the impairment of the healing process.[3] Additionally, matrix metalloproteinases (MMP's) have also been implicated with excessive extracellular matrix degradation in chronic venous ulcers with the resultant failure of completion of the healing process.[4,5]

The dynamic and efficient process of wound healing involves a complex dynamic series of events, including hemostasia, inflammation, granulation tissue formation, epithelialization, neovascularisation, collagen synthesis, and wound contraction. Blood platelets have a major role in initiation of cutaneous wound healing. They adhere, aggregate, and release numerous growth factors, adhesive molecules, and lipids that regulate the migration, proliferation, and functions of keratinocytes, fibroblasts, and endothelial cells. Some of the stored growth factors essential for wound repair include PDGF, transformed growth factor (TGF-β), VEGF, basic fibroblast growth factor, EGF, type-I insulin-like growth factor (IGF-I), and hepatocyte growth factor (HGF).[6–10] In fact, the potential therapeutic effects of some of these growth factors in promoting wound healing has been reported.[11,12] The key roles of growth factors in wound healing has stimulated significant research efforts aiming to test different platelet-derived products as therapeutic treatments to improve wound healing and to accelerate the closure of chronic wounds. Technology has evolved since the first applications of this concept. Initially a liquid product containing autologous platelet secreted molecules was

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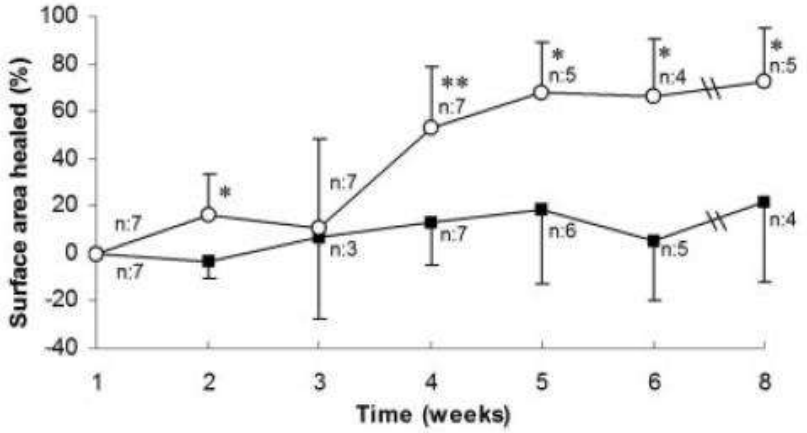

Figure 2. Percentage of surface area healed in the PRGF group (empty circles) versus standard care group (full squares). $^{*}p < 0.05$, $^{**}p < 0.01$.

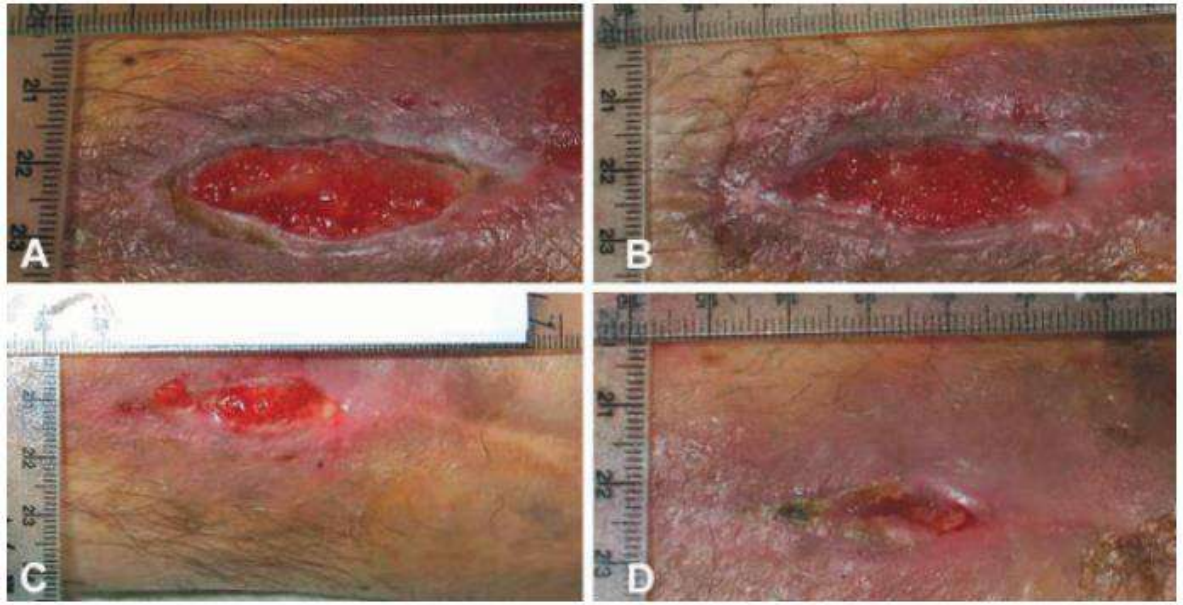

Figure 3. Evolution of a typical skin ulcer treated with PRGF: debrided ulcer before treatment (A), after 1 (B), 4 (C), and 8 (D) weeks, respectively. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Anitua E, 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

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Efficacy and safety of the use of platelet-rich plasma to manage venous ulcers

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ABSTRACT

Objectives: The aim of this study was to analyse the efficacy and safety of using platelet rich in growth factor (PRGF) as a local treatment for venous ulcers.
Methods: In a clinical trial 102 venous ulcers (58 patients) were randomly assigned to the study group (application of PRGF) or the control group (standard cure with saline). For both groups the healed area was calculated before and after the follow up period (twenty-four weeks). The Kundin method was used to calculate the healed area (Area = Length × Width × 0.785). Pain was measured at the start and end of treatment as a secondary variable for each group by record obtained by means of self-evaluation visual analogue scale.
Results: The average percentage healed area in the platelet rich plasma group was 67.7 ± 41.54 compared to 11.17 ± 24.4 in the control group ($P = 0.001$). Similarly, in the experimental group a significant reduction in pain occurred on the scale ($P = 0.001$). No adverse effects were observed in either of the two treatment groups.
Conclusions: The study results reveal that application of plasma rich in platelets is an effective and safe method to speed up healing and reduce pain in venous ulcers.
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1. Introduction

Venous ulcers affect 0.6%–3% of the population aged over 60; this increases up to 5% in those aged over 80 [1].Between 70% and 80% of all ulcers that affect the legs are of venous aetiology and almost one-third turn chronic. When the underlying pathology is not managed, it is estimated that approximately 45% of individuals with venous insufficiency and prior episodes of ulcer can be affected again throughout their life [2,3]. The application of suitable treatment protocols based on scientific evidence reveal that apparently 50% of ulcers heal within four months, 20% do not heal within two years, and approximately 8% do not heal even after five years [4]. Research on molecular mechanisms that control cellular signalling and lead to regeneration of tissues has enabled developing new therapeutic methods. The growth factors contained in platelet granules can act by favouring tissue repair mechanisms in chronic wounds because they act by regulating cellular proliferation, migration and differentiation in addition to synthesis of extracellular matrix. Recent studies reveal that healing both of chronic and acute wounds is modulated by growth factors and that cellular tissue receptors in the process of regeneration interact favourably with these [5].

In the last decade the use of so-called platelet-rich plasma (PRP) to treat chronic wounds has become more popular. The vast dissemination of the use of PRP in treating acute and chronic wounds contrasts with the little scientific evidence existing today. The few experimental studies together with the absence of standardisation in regard to systems to obtain and manage PRP and its application to wounds of different aetiology, hinder obtaining contrasted scientific evidence [5,6]. This study aimed to determine whether application of PRGF to the wound bed reduces healing time and improves local pain associated with this pathology; any adverse effect or reaction related to its application was also observed.

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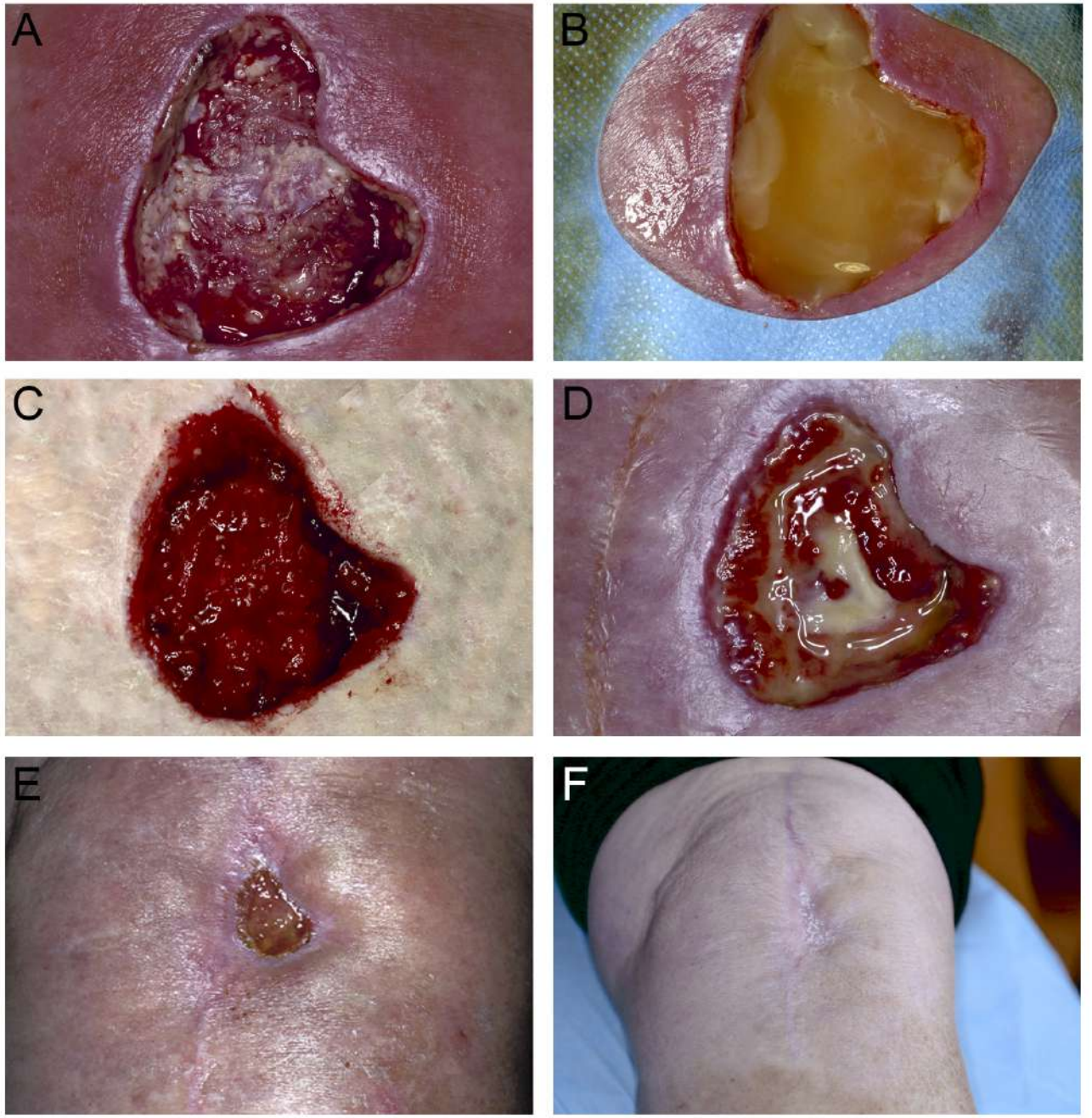

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CONTAMINATED PROBLEMATIC SKIN WOUNDS IN DIABETIC PATIENTS TREATED WITH AUTOLOGOUS PLATELET - RICH PLASMA (PRP): A case series study.

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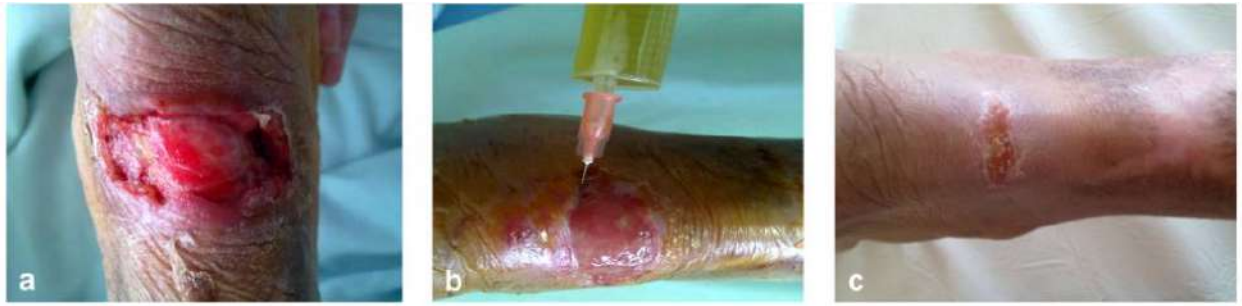
ABSTRACT

OBJECTIVE: To study the effect of platelet-rich plasma (PRP) on contaminated problematic skin ulcers in patients with diabetes.

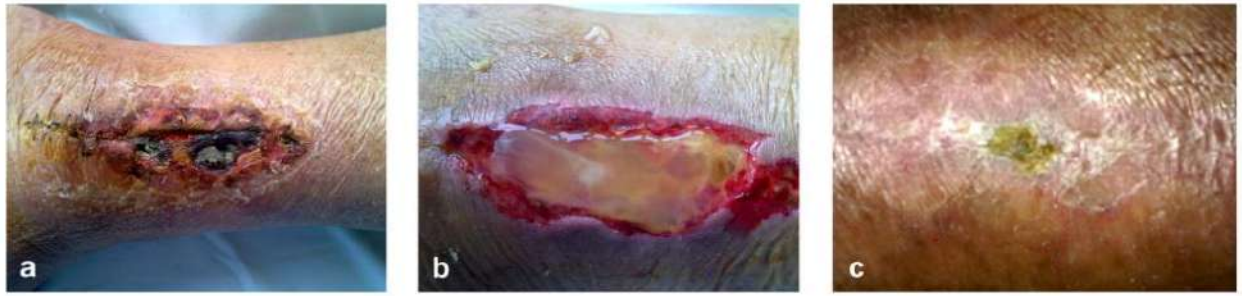
MATERIAL AND METHODS: A total of 6 patients had been treated within the period from 2012 to 2014; they had various types of problematic wounds and diabetes type 2. Patients' distribution by sex was as follows: 1 man and 5 women; mean age- 68 years. Ulcer types: acute (2 patients), hard-to-heal (2 patients) and chronic (2 patients) ulcers. The mean size of the skin and soft tissue defect was 9,5 cm^2. Pathogenic microflora was isolated in 4 patients - S. aureus in three and E. coli in one. Based on a scheme developed by us, all cases were treated by administering platelet-rich plasma, derived by PRGF Endoret system. Follow-up period was within 4 – 6 months (4,5 on average). We used platelet rich plasma derived by PRGF Endoret system, applied on the wound bed on a weekly basis.

RESULTS: Application of PRP allowed successful closure of all wounds. There were no complications associated with treatment of PRP. Epithelialization of the wound took 15 weeks on average for all patients. One patient presented with hyperkeratosis. Initial score of followed wounds, based on the scales are as follows: Total wound score – 10 p. Total anatomic score – 8 p. Total score – 15 p. at the initial stage. At the end of the treatment period scores were as follows - 0 p., which means excellent results

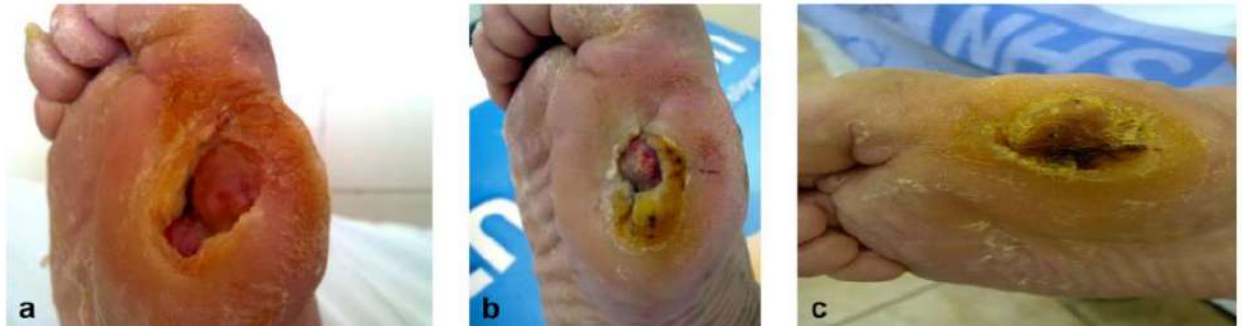
CONCLUSION: We believe that the application of PRP may become optimal therapy in the treatment of contaminated problematic skin wounds in diabetic patients group; patients with concomitant diseases which make reconstructive surgery impossible are also included. Problematic skin wounds include acute, hard-to-heal wounds and chronic wounds. Acute skin wounds located in the area of adjoining tendons, joints, the plantar surface of foot and bony prominence are also difficult to treat, especially in the event of a skin defect. Acute wounds are defined as disruptions in the integrity of the skin and sometimes the underlying tissues, where the healing process follows consecutive biological stages. Hard-to-heal wounds are considered those that do not heal after the fourth week of their appearance after being treated with standard methods for the particular pathology. Chronic is a wound that is not healing for a period of three months. Tests of the material obtained from chronic wounds show a significant reduction of the amount of growth factors as compared to acute wounds. A rapid metabolization of growth factors is observed in chronic wounds due to wound proteases, which may be of a bacterial or cellular origin. These problematic wounds cause patients severe emotional and physical stress. Besides the above mentioned reasons, reduction of growth factors in diabetic wounds results from the presence of fibrin sequestering around capillaries [2]. In recent years, there have been many attempts for the development of new therapeutic approaches and technologies in the field of regenerative medicine, tissue engineering and the use of autologous proteins and growth factors in order to support and accelerate tissue healing and regeneration. For this reason, additional biological stimulation of wound defect with platelet-rich plasma (PRP) is applied recently, where

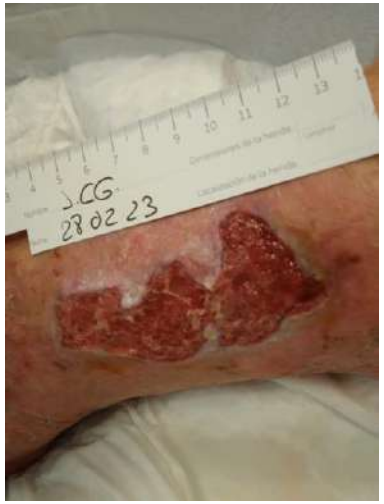


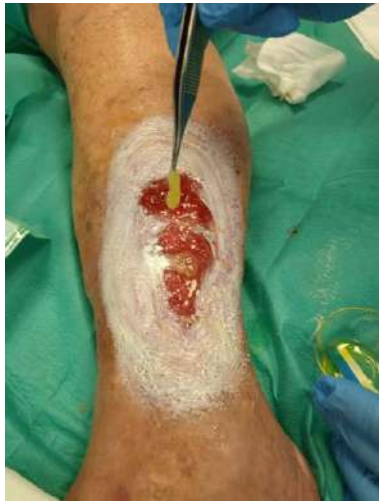
Woman, aged 62, with diabetes mellitus type 2, with a lateral malleolus fracture and metal osteosynthesis. After removal of the synthesis, skin necrosis on the wound edges presented on the 20 postoperative days. E. coli was isolated from the wound. Wound debridement was implemented and a skin defect with area of 12 sq. cm occurred. Treatment with PRP was started on the second postoperative day. Final score on the 12th week - full epithelization of wound. a) initial stage, b) necrectomy and fibrin clot, c) 12th week (fig. 2).

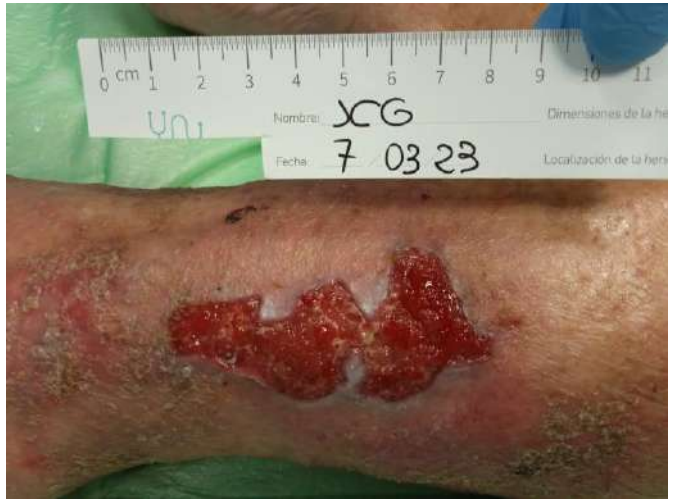


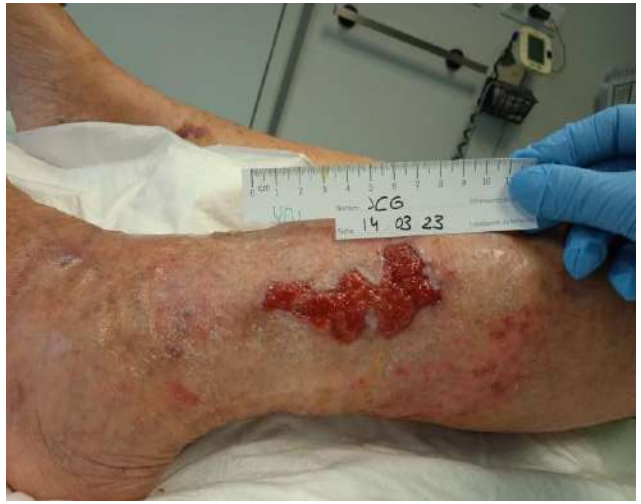
Woman, aged 73, with diabetes mellitus type 2, chronic decubitus wound on the foot, with Parkinson's disease; S. aureus was isolated from the wound. Because of the concomitant diseases she could not use aids, and continued stepping on her foot, thus hindering treatment. Wound debridement was implemented and a skin defect with area 7 sq cm occurred. Treatment with PRP was started on the second postoperative day. Final score on 16th week - full epithelization of wound. a) initial stage, b) 8th week, c) 16th week (fig. 3).

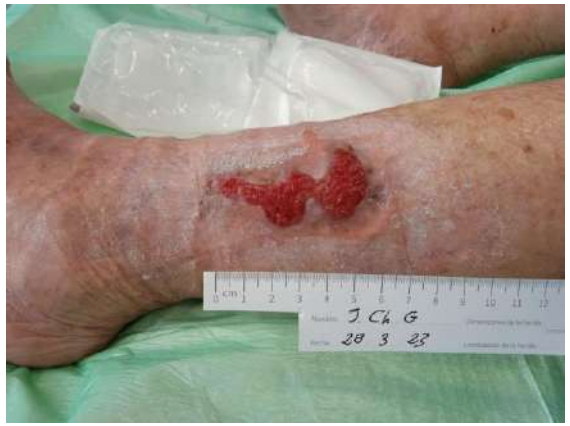


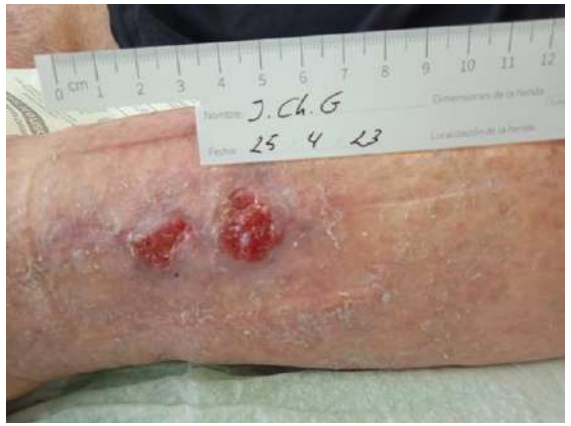


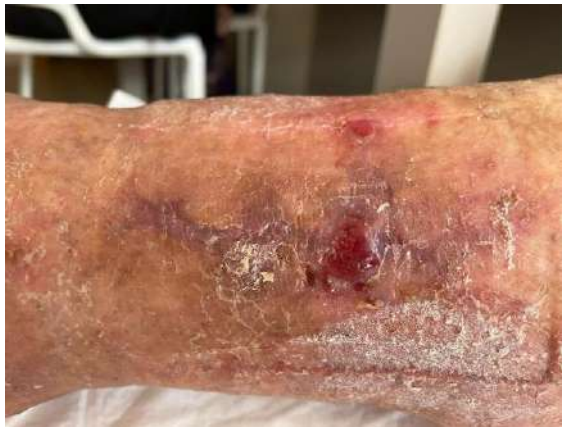


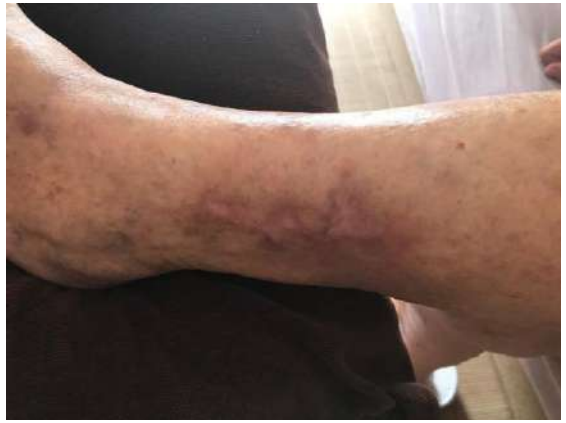












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Conclusiones.

El uso de Factores de crecimiento, mediante técnica de PRP, para heridas complejas, consigue:

- Aumenta la proliferación celular.
- Reducimos el tiempo de curación y optimizamos el restablecimiento de la arquitectura de los tejidos.
- Reducción del dolor y mejoría de la calidad de la vida del paciente.
- Potencial antibacteriano.
- Autólogo.
- Sin leucocitos.

Muchas gracias por vuestra atención.