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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.

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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2. Materials and methods

An experimental prospective study with control group among individuals with venous ulcers who were randomly assigned to the study group (application of autologous PRGF) or control group (cures with saline) was designed with the aim of analysing the efficacy and safety of the use of Plasma Rich in Growth Factors (PRGF) to treat venous ulcers.

2.1. Subjects

A total of 58 patients with ulcers of venous aetiology from healthcare centres and surgical consultation from the Osuna Healthcare Area (Seville, Spain) were selected. Patients with venous ulcers which had not presented any clinical improvement or reduction in the ulcer area after six weeks of treatment with standard cures were chosen. After collecting informed consent, patients were randomly assigned according to their date of birth. It was decided to randomly assign subjects to each of the groups based on last digit of the year of birth. If this was "0 or an even number" was assigned to the experimental group (PRP therapy), and if the figure of the year of birth was "an odd number" was assigned to the control group (standard therapy). A total of 55 and 47 ulcers were assigned to the experimental (application of PRGF) and control (cure with saline) groups, respectively. Inclusion criteria were patients with venous ulcers of more than six weeks' clinical course with ankle/arm index 0.8–1.2 who had not been operated for their venous insufficiency with normal blood count and platelet count above 150,000 platelets/μL. Patients without long-standing treatment with non-steroidal anti-inflammatories, corticosteroids, anti-aggregates or anticoagulants. Patients non-suffering from cancer-related, liver or kidney disease in addition to poorly controlled diabetics ($HbA_1C > 7.5\%$). The study was performed between September 2009 and March 2014 and approved by the experimentation ethics committee of the University of Seville; it was registered in the Australian New Zealand Clinical Trials Registry under number ACTRN12615001112550.

2.2. Procedures

Prior to random assignation and with the purpose of achieving homogeneity of lesions treated in both groups, for two weeks all patients underwent washing with a chlorhexidine soap sponge, mechanical debridement of slough and fibrin, cover with gauze soaked in saline and subsequent cover with dry gauze and single layer compressive bandage. The rationale for surgical debridement focuses on removing nonviable tissue, reduced bacterial load and stimulation of epithelialization. Surgical debridement removes necrotic tissue, thereby promoting granulation [7]. The presence of necrotic or compromised tissue is common in chronic wounds that do not evolve towards healing. Non-vascularized tissue, bacteria and cells that impede the healing process (load cell) to obtain a medium which stimulates the formation of healthy tissue are suppressed [8]. The protocol used in this study is similar to that described for Anitua et al. [9].

In case of clinical infection systemic antibiotic therapy was commenced for 10 days. After assignment to each group patients from the experimental group underwent cleaning of the wound with soapy chlorhexidine and saline. The systematic review of O'Meara and Ovington [10] on the use of antibiotics in the treatment of venous ulcer cannot be concluded that definitive conclusions about the effectiveness of oral antibiotics and topical agents type antiseptics for the healing of venous leg ulcers.Therefore there is no evidence to support the routine use of systemic antibiotics to promote healing of venous leg ulcers. In our study, prior to starting treatment alone were treated with systemic antibiotics two patients in the control group and one experimental group.

To obtain PRGF applied to the experimental group, a sufficient volume of blood was drawn from each patient by means of intravenous infusion according to the area of the ulcer; treatment was according to the protocol proposed by Anitua et al. (PRGF Endoret®, BTI System, Vitoria, Spain) which unlike other methods and with one single centrifuge enables obtaining plasma-rich growth factor which is activated with 10% calcium chloride [11]. A graft of autologous platelet gel which is easy to handle is obtained. Once the graft was inserted into the wound bed, this was covered with a selective micro-adherence dressing comprised of an elastic network of silicon-covered polyamide (Mepitel® Mölnlycke Health Care, Madrid) which in turn was covered with a secondary dressing of gauze and single-layer pressure bandage. After 72 h a standard cure was applied with saline cleansing and application of another dressing. Ulcers from the experimental group underwent weekly application of PRGF for the time set out in the study (24 weeks). With the same treatment interval patients from the control group underwent cure with gauze soaked in saline with a second cover of dry gauze and single layer pressure bandage. The ulcer area at the start of treatment and after 24 weeks were calculated for all lesions included in the study. Pain perceived was evaluated by means of VAS scale at the start and end of the study. Any adverse event related to application of PRGF was recorded during the study follow-up period.

2.3. Data collection and analysis

The sample size necessary to estimate the difference in regard to the main study variable (area of the ulcer) between two independent samples was calculated assuming α error of 5% and β error of 20%. G*Power 3.1 (Faul, Erdfelder, Lang, & Buchner, 2007) was used to estimate the sample size. The result revealed that 43 lesions in each group were necessary. For the analysis of the main variable area of the ulcer at the start and end of treatment the Kundin method was used arising from applying the formula, Area = Length x Width x 0.785 (correction factor to compensate the lesion's irregularity). This method of measurement has turned out to be a useful tool to measure the area of wounds with validity similar to that of other methods [12].

Pain was measured at the start and end of treatment as a secondary variable for each one of the groups by record obtained by means of self-evaluation visual analogue scale. The Kolmogorov-Smirnoff test was used to estimate the normality of the variables. Contrast tests were performed by means of the Mann-Whitney *U* test. Comparative analysis of the secondary pain variable was performed by means of contingency tables with the Chi-square statistic. Statistically significant differences were considered for values $\alpha = 0.01$. Data were analysed using the statistical programme SPSS® version 20 for Windows (SPSS, Inc., Chicago, IL, USA.)

3. Results

A total of 102 venous ulcers from 61 patients who met the inclusion criteria were treated. Two patients from the control group were excluded; one because of hospitalisation for a worsened clinical situation and another because of non-compliance with the proposed treatment protocol. One patient was excluded from the experimental group because of intolerance to pressure therapy. The final study sample consisted of 102 ulcers from 58 individuals (15 men and 40 women) who completed 24 weeks' treatment (Fig. 1).

Both groups were homogeneous in regard to the age variable (mean age was not statistically different between groups $P = 0.712$). Nor were statistically significant differences found in regard to sex

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