

Original Research Article

Effect of autologous platelet-rich plasma in the promotion of healing of chronic ulcers

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ABSTRACT

Background: Chronic ulcers are a big health problem worldwide. Having a great impact at personal, social and professional levels. The use of autologous Platelet Rich Plasma (PRP) is a major advance in the treatment of these ulcers as an easy and cost-effective method. Platelets provide numerous growth factors enhancing tissue healing. The aim of this study was to evaluate the safety and efficacy of autologous platelet-rich plasma as a treatment of chronic non-healing ulcers.

Methods: Autologous PRP was prepared from whole blood by centrifugation and activated by 10% calcium chloride. Twenty-Four (24) patients with non-healing ulcers of different etiologies, whom they met our inclusion criteria, were treated with PRP injected every two weeks locally into their wounds until healing. The ulcer dimensions were measured every week. The follow-up period was 12 weeks after healing.

Results: The mean age of the study population 41 ± 21 years. Complete healing was achieved in all patients. The mean rate of healing (average decrease in ulcer dimensions) was 0.48 cm/week. The rate of healing was greater at the week following injection. The mean time for healing was 6.11 weeks.

Conclusions: Author witnessed the useful effects of PRP application on enhancing wound healing. The results from our case series showed that PRP is a safe and effective treatment for the promotion of healing chronic ulcers. Further research and controlled, randomized prospective clinical trials on larger patient population are important to validate our results.

Keywords: Autologous platelet rich plasma, Chronic ulcers, Healing, PRP

INTRODUCTION

Chronic ulcers are defined as spontaneous or traumatic lesions, mostly in the lower extremities that are non-responsive to initial conventional therapy or that persist despite adequate care, they do not proceed towards healing in a defined time and have an underlying cause related to a systemic or a local disease.^{1,2} There are different types of non-healing ulcers including venous, arterial, pressure, diabetic, and also traumatic ulcers. Wound healing is a dynamic and complex process mainly occurring in three distinct phases: inflammatory phase, tissue formation, and remodeling phase. But if this

process is interrupted, due to deficiency of growth factors and cytokines leading to a delay in the healing process. The ulcer will turn chronic in nature.³

The goal of ulcer treatment is to obtain wound closure as early as possible. Conventional treatment for non-healing ulcers basically includes wound cleansing, tissue debridement, prevention, and treatment of infection, mechanical off-loading, adjustment of blood glucose levels and local care with dressing application.^{4,5} The available treatment modalities for chronic ulcers consider these issues and provide optimal local ulcer care. Advanced treatment for chronic ulcers includes the use of

hyperbaric oxygen therapy, skin grafting, VAC (vacuum assisted closure) and surgery such as angioplasty and reconstructive surgery.^{6,7}

Platelets play the major role in the initiation of wound healing process. They adhere, aggregate, and release many growth factors, adhesive molecules, and lipids that control and enhance the migration, proliferation, and functions of keratinocytes, fibroblasts, and endothelial cells.⁸⁻¹⁰

Autologous platelet-rich plasma (PRP) is a platelet suspension in plasma derived from whole blood of the patient. It is frequently being used in the treatment of chronic nonhealing ulcers. The platelet concentration in PRP is from 2-6 folds higher than its concentration in whole blood.¹¹ The results achieved by PRP depends on the fact that platelets are the reservoir of numerous of growth factors, with healing function which has an active role in tissue regeneration.¹²

The advantages of PRP are apparent, being easy, cost-effective and more lasting if compared to other treatment modalities, moreover being autologous in nature, making it a safe therapeutic tool with good clinical outcome.¹³ The aim of the current study was to evaluate the safety and efficacy of autologous PRP in treating chronic nonhealing ulcers.

METHODS

The study was carried out at Cairo university hospitals kasr Al Aini from October 2014 to October 2015. After being approved by the ethics research committee of Cairo University. All included patients signed informed consents and agreed to get the treatment and to be involved in the research. This is case series 24 patients with chronic nonhealing ulcers. Inclusion criteria were an ulcer of at least 12 weeks duration with failure to achieve healing. Exclusion criteria were ischemic ulcers, exudating and discharging ulcers denoting infection, patients with uncontrolled diabetes, patients receiving drugs that negatively affect wound healing (such as steroids or chemotherapy), patients with known coagulation defects or thrombocytopenia, smokers or pregnant patients. Patient history, physical examination, and routine investigations were obtained, (complete blood count, coagulation profile, blood sugar etc...). Different ulcer etiologies were included like pressure ulcers, venous ulcers, and traumatic ulcers.

PRP will be prepared from the patient own blood (autologous PRP). Under complete aseptic conditions, 20 ml of venous Blood sample was drawn from the antecubital vein, Sample was added to sterile tubes containing 3.2% sodium citrate. Blood was centrifuged at 300xg during 5 minutes at 18°C to separate the red blood cells. The upper fraction (plasma and platelets) was isolated, without disturbing the buffy coat, and was transferred into another sterile tube then centrifuged

again at 700xg during 17 minutes at 18°C. The bottom layer (platelet pellet) obtained from centrifuged plasma was 2-3ml. Platelet activation was performed immediately by adding 0.3ml 10% calcium chloride for every ml of PRP.

The ulcer was rinsed with physiological saline. The injection was done immediately after activation in the ulcers edges and floor. A non-absorbent dressing was used and left closed for a week till follow up session. Reinjection of PRP was done every two weeks until complete healing. Follow up was weekly where photos and measurement of ulcers dimensions (length, width, and depth). The measurement was taken at the start of treatment and at the weekly follow up visits. Follow up was continued till complete healing occur and for 12 weeks later. Complete ulcer healing was defined as complete epithelization by inspection, measurements, and photography

The primary outcome was to evaluate the efficacy of autologous PRP in promoting chronic ulcer healing by measuring the decrease in ulcer dimensions. The secondary outcomes include the feasibility and safety of autologous PRP injections into ulcers.

RESULTS

Statistics were done by program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows (2006). Correlation between variables was done using Pearson moment correlation equation for linear relation in normally distributed variables and Spearman rank correlation equation for non-normal variables. P values less than 0.05 was considered significant. Data were statistically described in terms of mean±SD, median and range, or frequencies (number of cases) and percentages when suitable. We started our study with 24 cases. Four cases were excluded during the time of the study. One case excluded due to hyperlipidemia, two cases refused the idea of further blood withdrawal and injection, and one case did not continue to follow up.

The patient's ages ranged from 20 to 62 years old with a mean of 41±21 years, 40 %patients in this study were in the age group (41-60), 60% of patients were males. We found that sex and age were insignificant in correlation with the rate of healing (p value=0.51, 0.22 respectively). We performed full blood count for our patients prior to treatment, and patients with abnormal blood parameters were excluded. We found that there is no correlation significance between baseline platelet concentration and rate of healing (p=0.981).

Regarding the ulcer type, the majority of patients' ulcers were pressure ulcers 70% while the minority were traumatic ulcers 10% others including venous 20%. All patients' ulcers were in the lower limb most of them affecting the sole of the foot. We found that there is no

significance between ulcers type and site in correlation with the rate of healing (p value= 0.795, 0.845 respectively). Ulcers varied in dimensions. The least dimension was 1.2x1cm and maximal was 7x3cm. Size of ulcers was measured by the two perpendicular maximal diameters of the ulcer. For statistical reasons, we use the maximal diameter only.

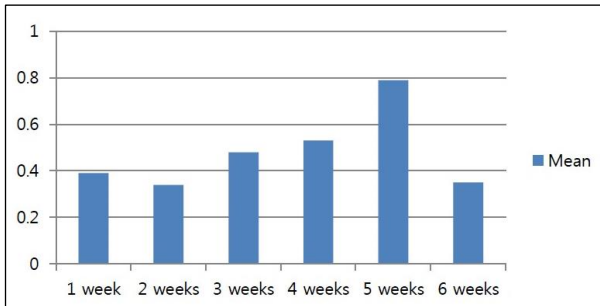


Figure 1: Average rate of healing in cm.



Figure 2: (A) before treatment, (B) 2 weeks after treatment, (C) 4 weeks after treatment, (D) 6 weeks after treatment.

The relation between the original size of ulcers and rate of healing was studied. It was found that there is a significant strong inverted correlation. (Pearson Correlation 0.879, p-value 0.001). There is a significant strong proportional correlation between the size of ulcers and treatment time (p=0.002) and there is a significant strong proportional correlation between the size of ulcers and the number of injections (p=0.040). The rate of healing (average decrease in ulcer dimensions) was 0.2cm/week as minimum average rate and 0.7cm/week as the maximal average rate with mean 0.48cm/week. We noticed that rate of healing was greater at the week

following injection. The minimum time was five weeks and maximum were 9 weeks with average 6.11 weeks.

Comorbidities found in our study were in the form of presence of Diabetes Mellitus (DM), Hypertension (HTN), and presence of mechanical factor exhibiting pressure at the site of the ulcer as congenital skeletal malformation (eg. talipes equinus), bed sore etc.). None of the study population suffered treatment related complications such as pain, skin irritation or allergic reactions.

DISCUSSION

Leg ulcers are classified as acute or chronic according to their duration, However, there is no definite time to define chronicity .¹⁴ The ultimate goal of any treatment modality is to obtain wound closure. The conventional treatment includes debridement, infection control, revascularization of ischemic tissue, and avoiding pressure on the wound. Skin grafting has shown some success, but they are not capable of providing the necessary growth factors to promote and regulate the healing process and are costly.¹⁵

In 1986, Knighton et al. demonstrated that the use of autologous platelet factors enhanced epithelialization of granulation tissue thus achieving healing of chronic ulcers. This was the first clinical trial that showed the promising role of locally acting factors derived from autologous blood in promoting healing of chronic nonhealing skin ulcers.¹⁶

Experimental studies on PRP suggested a potential benefit of PRP in enhancing the healing process by activating neovascularization in areas with poor vascularity.¹⁷ Another experimental model support that platelet-rich fibrin matrix (an alternative preparation of similar properties) enhances endothelial cell proliferation. This may provide an explanation of wound healing effect of PRP.¹⁸ Moreover PRP which was activated by 5% calcium chloride PRP stimulates the proliferation of human dermal fibroblast.¹⁹

Clinical studies regarding the role of PRP in chronic wound healing are increasing in number. Serra et al., compared the effect of platelet-rich gel with 32 patients serving as controls.²⁰ Healing rates were 96.15% in patients receiving platelet-rich gel against 59.37% in patients not receiving platelet-rich gel.

In the current study (a prospective case series on 24 patients with chronic leg ulcers) good results were achieved by applying standard PRP protocol for chronic lower limb ulcers. There was no correlation significance between the patient's Age and sex and healing rates of ulcers in the current study. Also, there was no correlation significance between the patients' baseline platelet concentration and rates of healing. In 2011 Saad Setta et al., conducted a study on 24 patients with chronic ulcers

with ages 40-60 years they concluded that sex and age are insignificant in correlation with the rate of healing of their ulcers moreover there was no correlation significance between baseline platelet concentration and rate of healing.²¹

Gui-Qiu Shan et al., in 2013 studied the effect of PRP on the healing of lower extremity chronic ulcers in which 21 patients with chronic ulcers are included in the study they concluded that, there no significance between type and site of ulcers in correlation with the rate of healing.²² This supports the results we found in our study.

A significant strong proportional correlation between the size of ulcers and treatment time (p=0.002), also a significant strong proportional correlation between the size of ulcers and the number of injections (p=0.040) was found. Many clinical trials concluded that the larger the ulcer the longer the time for treatment and the greater number of injections.²³ Most of our patient's ulcers (70%) healed within the six weeks. The average decrease in ulcer dimensions (rate of healing) was 0.48cm/week. The rate of healing was greater at the week following injection.

No complications or side effects were noticed in our study. A review of the literature pointed out that, generally, the application of PRP appears to be relatively safe. All the clinical trials found to record these complications reported no significant differences between the study group and control group, on the contrary, some of those studies reported a lower rate of complications in patients treated with PRP.²⁴

PRP is an autologous preparation, thus it a safe treatment modality if we compare to allogenic preparations with no risk of disease transmission. Moreover, PRP has no concerns regarding antibody formation, thereby preventing the risk of graft vs. host disease and leading to be more accepted by patients.²⁵

Diabetes Mellitus (DM) present in 80% of the cases. Other comorbidities present in our study in the form of presence of a mechanical factor in most of the patients (80%), Hypertension (HTN) in 40% of the patients. Surprisingly we found that DM and mechanical factor are insignificant in the relation to rate of healing. Mostly because all diabetic patients included in our study must be controlled with medical treatment before been included in the study, and we prevent patients with pressure ulcers from using their limbs, so no pressure exhibited at ulcers during treatment.

Post-healing follows up was done one month after complete healing. We noticed that recurrence occurred with one case only (case1) in the form of a small ulcer (0.4x0.5cm) after using his limb and exposure to mechanical trauma. No PRP injection was done, and spontaneous healing achieved after two weeks of classic treatment. This was case series reporting results in our

institute with some limitations. Small sample size, single institution setting, limited follow up period and data for ulcer recurrences in addition to the absence of a control group were of the drawbacks.

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