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Role of Autologous Platelet Rich Plasma in The Management of Chronic Non-Healing Ulcers

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Abstract

Background: Chronic non-healing leg ulcers are a major health problem worldwide and have great impact on personal, professional and social levels, with high cost in terms of human and material resources. The present study was conducted with an aim to demonstrate the efficacy of autologous platelet rich plasma (PRP) in chronic non-healing leg ulcers in comparison to conventional dressings.

Methods: About 50 patients presenting with chronic non healing ulcers to the surgical outpatient department in a tertiary care centre over a period of one year were included in the study, of which 25 patients received autologous PRP dressings other 25 patients received conventional dressings. Ulcer measurements were taken on day 1, 15, 28 and 42 days.

Results: The mean duration of healing of the ulcers was 3.9 weeks in PRP group and 6.2 weeks conventional dressing. PRP dressing group showed a reduction in ulcer size of about 45.50 percent as compared to 14.80 percent in conventional dressing group.

Conclusion: Chronic non healing ulcers are often difficult to heal because they lack the necessary growth factors to maintain the healing process. Conventional therapies do not provide satisfactory healing, since these treatments are not able to provide the necessary growth factors (PDGF, EGF, VGEF etc.) which are essential for the healing process. PRP is a safe, affordable, biocompatible and simple office based procedure for the treatment of non-healing ulcers.

Keywords: Platelet rich plasma, PRP, leg ulcers.

I. Introduction

Chronic non healing ulcers are defined as wounds, persisting beyond 6 weeks despite appropriate care due to several systemic and local factors. These ulcers affect the quality of life and productivity of the patients significantly. Hence there is a need to develop novel management strategies[1].This study will discuss the role of autologous platelet rich plasma in wound healing. Platelet rich plasma is a conglomerate of platelets, plasma, leucocytes and clotting factors with properties of healing and tissue regeneration.

The α granules of platelets contain various growth factors like PDGF, VEGF, TGF-β, IGF and FGF.PRP has mitogenic, angiogenic and chemotactic properties. These stimulate progenitor cells (human dermal fibroblasts) to proliferate and differentiate. It also has anti microbial activity to some extent due to the presence of leucocytes.PRP therapy helps to create a biological environment that is most conducive for restoration of tissue homeostasis[2].

Aim of the study

To evaluate the efficacy of Platelet Rich Plasma in the treatment of chronic non healing ulcers.

Objectives of the study

1. To compare the rate of healing among ulcers treated with autologous platelet rich plasma and conventional dressing.
2. To study safety of autologous platelet rich plasma in management of chronic non healing ulcers.

II. Materials And Methods

- **Type of the study**: This is a single centre randomized control trial with 2 study groups.

- **Source of Data**: Patients presenting with chronic non healing ulcers to Out patient department of S.V.R.R.G.G.H and patients admitted in general surgery wards.
  Eligible patients were randomized using odd and even sequence.

- **Study Duration**: 1 year

- **Sample Size**: **50** patients; 25 in each group
  Group A: Patients receiving PRP.
  Group B: Patients undergoing conventional dressing.

INCLUSION CRITERIA

- Patients above the age of 18 yrs.
- Cases with ulcer size <15 sq. cm.
- Patients with haemoglobin > 10g/dl.
- Ulcer duration >6 weeks.

EXCLUSION CRITERIA

- Patients with platelet count <1lakh/mm3
- Ulcers with signs of wound infection (presence of visible pus, copious wound exudates)
- Cases with cellulitis, ischaemia and gangrene.
- Patients with bleeding disorders.
- Cases of malignant ulcer.
- Ulcers with exposed bone, muscle and tendon.

STUDY METHODS

Autologous platelet rich plasma will be prepared from patient's whole blood by centrifugation in blood bank on the same day. Under aseptic precautions 20 ml of venous blood was drawn and added to a test tube containing acid citrate dextrose in a ratio of 9:1 (blood: acid citrate dextrose).

In the first spin the test tube is centrifuged at 5000 rpm for 15 min to separate the red blood cells from the platelets and plasma. After the first spin, 3 layers appeared. This is due to differences in the density of the blood components: the deep layer consists of red blood cells, the middle layer contains platelets and leukocytes, and the top layer is made up of platelet-poor plasma (Figure 1). The middle layer and top layer were collected directly by gentle aspiration with a pipette and transferred to a new, sterile centrifuge tube. And it centrifuged again at 2000 rpm for 5-10 min. **20** ml of whole blood yields **2-3** ml of Platelet Rich Plasma.

It is infiltrated into edges of the wound once every week, corresponding to ulcer size.Ulcer measurements were taken using ruler in cm at two largest perpendicular diameters and area of the ulcer is calculated by multiplying these two diameters.Depth is also measured, and volume of ulcer is calculated by multiplying area with depth.Rate of wound healing was calculated as the difference between area of primary wound on the day 1, 15, 28 and 42.End point of the study is complete wound epithelialization or appearance of granulation tissue which later lead to split skin grafting or by secondary healing whichever is earlier.

III. Observations And Results

The present study was conducted in S.V.R.RG.G.H, Tirupathi in 50 patients with chronic non-healing uclers. These 50 patients were randomized into two groups based on odd and even sequence, Group A received PRP injections, whereas, group B patients underwent conventional dressing.

The present study included patients with age from **20 to 70** years. Maximum number of cases were in the age group 45-60 years. The mean age in group **A** is **50.50** and in group **B** is **52.45** years. In group A male to female ratio is **3:2** whereas in group B it is **2.57:1**.

Most patients presented with ulcer size of 10 – 15 sq. cm in the present study. Both the groups have maximum number of patients with ulcer size between 10 to 15 sq. cm.

The most common etiology of the ulcers in both grup A and B was diabetis followed by trauma in the current study.

Wound culture was sent for all the patients on day 1. Most of the ulcers of both groups were sterile. However , the most common organism isolated from ulcers of group A and group B were Staphylococcus aureus and Klebsiella pneumonia respectively.

The mean **duration of healing** of ulcers was **3.9** weeks in group **A** and **6.2** weeks in group **B**. PRP group showed a **reduction in ulcer size** of about **45.5%** as compared to **14.80%** in conventional dressing group.

Majority of the ulcers required 4 doses of PRP for complete healing

Table 1:Size Of Ulcers

	GROUP A	GROUP B
< 5 sq. cm	5	7
5-10 sq. cm	7	7
10-15 sq. cm	13	11

Table 2:Etiology Of Ulcers

Etiology	GROUP A	GROUP B
Diabetes	12	15
Traumatic	8	7
Venous	3	2
Trophic	2	1
Total	25	25

Figure 1:Organisms isolated on Day 1

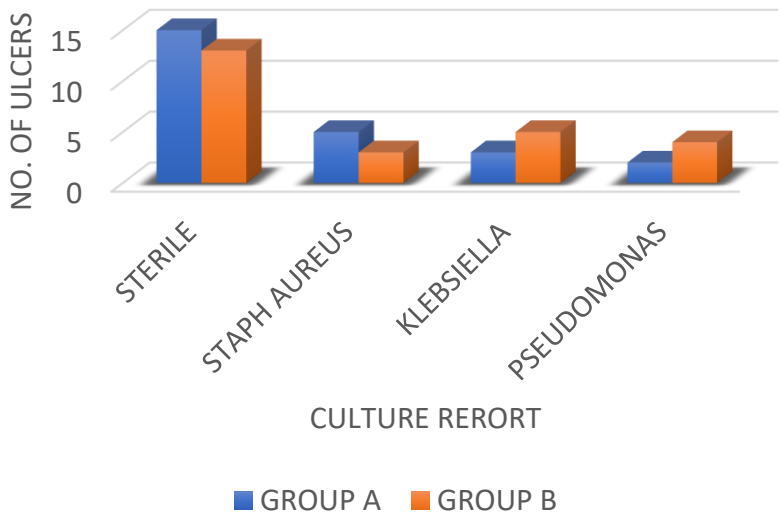

Figure 2:Mean ulcer size

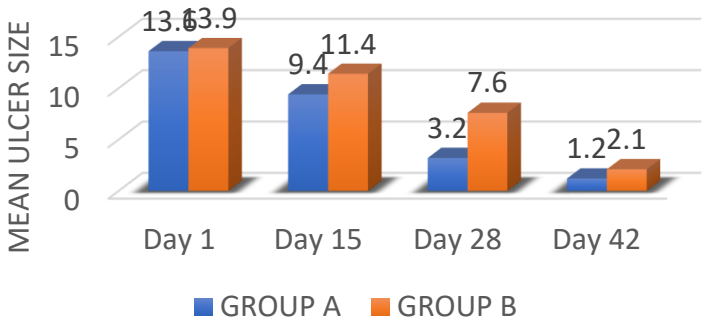

Figure 4: Ulcer at presentation **Figure 5: After 2 doses** **Figure 6: After 5 doses**

Figure 7:Mean Volume Assesment Of Ulcers

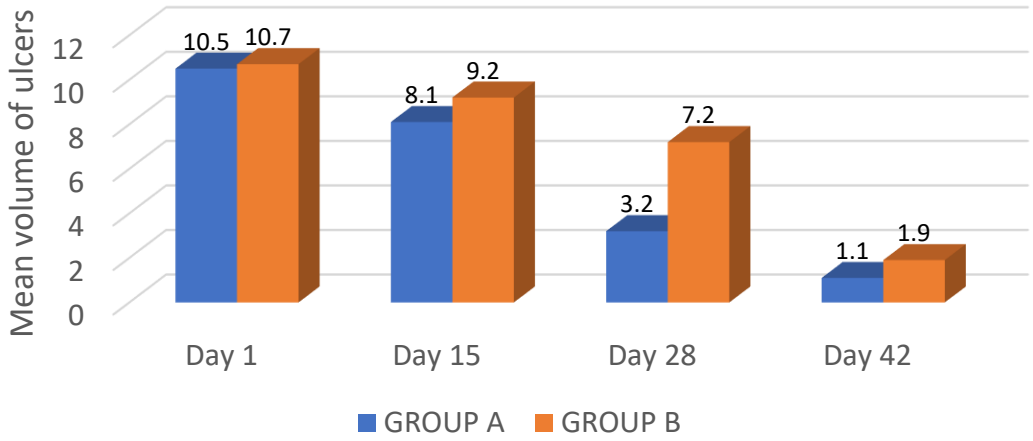

Table 3:Number Of Doses Of PRP Given

No. of ulcers healed	No. of doses of PRP given
2	2
5	3
9	4
5	5

IV.DISCUSSION

In 1970, hematologists created the term Platelet Rich Plasma and used it as transfusion product in patients with thrombocytopenia. Later, in 1986, Knighton et al. showed that use of autologous platelet factors accelerated epithelialization of granulation tissue[7].

A study conducted by Frykberg et al., on 49 patients with 65 non-healing ulcers showed that 63 of 65 ulcers responded with a reduction in area, volume and undermining of the ulcers in a mean duration of 2.8 weeks with 3.2 treatments [5]. Another study by Kakudo et al., treated five cases of intractable skin ulcer with autologous PRP, among which three ulcers healed completely within 4 weeks and epithelialiazation of wound occurred within 6.6 weeks on average[4].

A prospective, randomized, controlled, blinded multicenter study conducted by Driver et al., initially included 72 patients with diabetic foot ulcers who were treated with autologous platelet-rich plasma gel or control (saline gel). However, 32 patients were excluded from the final protocol because of protocol violations and failure to complete treatment. Their study results showed that significantly more wounds healed in patients treated with platelet-rich plasma gel (13 out of 16 or 81.3%) than patients treated with control gel (eight out of 19 or 42.1%). However, the study had several limitations including small sample size, protocol violations occurring during the study period, and high rate of patient dropouts.

Furthermore, Steenvoorde et al., conducted a study on 12 patients with 13 wounds, showing that seven of 13 wounds required more than one application, with a mean number of 2.2 applications and a mean treatment period of 4.2 weeks[6]. The results from our case series were concurrent with previously published studies in terms of healing time, even though in our study only a single dose of PRP was administered.

In our study mean duration of healing of ulcers treated with platelet rich plasma is 3.9 weeks contrary to 6.2 weeks in conventional group.Application of Platelet Rich Plasma enhanced the rate of healing.

PRP functions as a tissue sealant and drug delivery system, and platelets initiate wound repair by releasing locally acting growth factors via α-granules degranulation. α-granules of platelets contains: Platelet-derived growth factor (PDGF-AA, BB, and AB isomers), transforming growth factor-β (TGF-β), platelet factor 4 (PF4), interleukin-1 (IL-1), platelet-derived angiogenesis factor (PDAF), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), platelet derived endothelial growth factor (PDEGF), epithelial cell growth factor (ECGF), insulin-like growth factor (IGF), osteocalcin (Oc), osteonectin (On), fibrinogen (Ff), vitronectin (Vn), fibronectin (Fn), and thrombospondin-1 (TSP-1). These growth factors help in healing by attracting undifferentiated cells in the newly formed matrix and triggering cell division. PRP may suppress cytokine release and limit inflammation, interacting with macrophages to improve tissue healing and regeneration Promote new capillary growth. And accelerate epithelialization in chronic wounds.

A total of 32 diabetics were included in the study with mean blood glucose level of 109.4mg/dl.Few studies have shown efficacy of Platelet Rich Plasma is not associated with blood sugar level. However, in our study blood glucose levels of patients were under control.

In our study, administration of Platelet Rich Plasma didn't lead to any adverse effects, making autologous Platelet Rich Plasma, a safer alternative.

V.CONCLUSION

- Chronic non healing wounds have a pro inflammatory environment with high protease activity and reduced effective growth factors.
- Conventional therapies don't address the crux of issue.
- Platelet Rich Plasma being a physiological reservoir of various growth factors is a safe, affordable, biocompatible and simple office based procedure for the treatment of non healing ulcers.

Although there is lot of literature on PRP, there are several lacunae which needs to be filled. There is a need for development of a standard protocol for preparation of PRP. Few studies have reported PRP in decreasing pain, slough and discharge from the wound. Ramos-Torrecillas et al. have found no association between blood levels of albumin or proteins and PRP healing process.However, more evidence is warranted.

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