



## STUDY TO EVALUATE THE EFFICACY OF PLATELET-RICH PLASMA INJECTION IN THE MANAGEMENT OF CHRONIC NONHEALING WOUNDS

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### ABSTRACT

**Objective:** The aim was to evaluate the efficacy of platelet-rich plasma (PRP) in treating chronic non healing wounds. **Background:** Non healing ulcers are a significant health problem with a high costs in terms of human and material resources. The application of autologous PRP has been a significant breakthrough for treating non healing ulcers, as it is an easy and cost-effective method and provides the necessary growth factors that enhance wound healing. **Methodology:** A prospective study was conducted from September 2018 to March 2020 at Narayana Medical college. A total of 30 cases with chronic non healing ulcers of various causes (traumatic, diabetic, pressure, venous ulcers), at least six weeks old with wound area measurement between 2 cm<sup>2</sup> and 10 cm<sup>2</sup> are injected with autologous platelet-rich plasma injection twice weekly. Wound contraction was measured every 4th day and represented as a percentage of healing wound area and followed up for 6 weeks. **Results:** The mean age  $\pm$  SD of the patients was 49.36  $\pm$  14.05. According to the etiology, non healing ulcers are again classified as traumatic, diabetic, decubitus ulcers, venous and others (postoperative wounds, Hansen's disease) which constitutes 40%, 27%, 17%, 3%, 13% respectively. The healing rates of the various ulcers were monitored in weekly intervals till the sixth week. Among 30 patients, 17 patients (57%) showed complete healing, 3 patients (10%) showed 99-90% healing, 5 patients (17%) showed 80-89% healing, 5 patients (17%) showed 80-89% healing, 4 patients (13%) showed 50-79% healing, 1 patient (3%) showed <50% healing. Area reduction was statistically significant (p-value is <0.001). **Conclusion:** Conventional therapies do not provide good healing for chronic nonhealing ulcers as they are not able to provide the necessary growth factors essential for the healing process. PRP is a safe, affordable, biocompatible, and simple OPD based procedure for treating nonhealing ulcers.

**KEYWORDS :** Autologous Platelet Rich Plasma, Chronic Wound, Growth Factors, Non Healing Ulcers

### INTRODUCTION:

Chronic non healing wounds are recalcitrant to primary wound care will deteriorate unless a clinical intervention or alternative care is provided. These wounds have been shown to halt in the inflammatory phase of wound healing and either do not heal or deteriorate. These stalled wounds have consistently high levels of matrix metalloproteinases and proinflammatory cytokines (i.e, tumor necrosis factor-alpha) and consistently low levels of tissue inhibitors of matrix metalloproteinases and growth factors (i.e, platelet-derived growth factor). Under the treatment of conventional debridement and dressing, the curative effect is low. With the aging of the population, chronic diseases such as diabetes and hypertension have increased. These diseases aggravate arteriosclerosis and excessive blood sugar which are not conducive for wound healing.

Platelets contain these growth factors, cytokines and chemokines which are crucial in the early stages of wound healing. Growth factors are a collection of soluble and diffusible polypeptide substances that control the growth, differentiation, proliferation and cellular metabolism of numerous cell types. They promote epithelial and endothelial regeneration, stimulate angiogenesis, collagen synthesis, soft tissue healing and hemostasis. Harnessing factors from platelets and applying them to a non healing wound could restart the healing process, moving the wound out of the inflammatory cycle into the proliferative phase of healing

Platelet-rich plasma (PRP) is an endogenous therapeutic substance that is attaining interest in regenerative medicine due to its capacity to stimulate and accelerate tissue healing. There are numerous growth factors which are known to be involved in the wound healing process like insulin-like growth factor (IGF1, IGF2) vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), epidermal growth

factor (EGF), fibroblast growth factor (FGF), transforming growth factor (TGF- $\beta$ ) and keratinocyte growth factor (KGF)<sup>(1)</sup>

For all the reasons mentioned above, this study evaluates the efficacy of platelet-rich plasma injection in managing chronic nonhealing wounds.

### METHODOLOGY

A prospective study conducted from September 2018 to March 2020 at Narayana general hospital on 30 patients with non healing ulcers. Ethical clearance was received before the beginning of the study from the Ethical Clearance Committee. Detailed history, including the name, sex, age, address, occupation, contact number and medication history was noted.

### Types of outcome measures

1. Total area epithelialized at the end of the intervention measured in cm<sup>2</sup>.
2. Wound complications: infection, necrosis.

### INCLUSION CRITERIA:

- Age between 18 to 70 years of age
- Chronic nonhealing ulcer of etiology (traumatic, diabetic, pressure, venous) is at least 6 weeks old
- Wound area (width x length) measurement between 2 cm<sup>2</sup> and 10 cm<sup>2</sup>
- Nonhealing ulcer without exposure to the bone

### EXCLUSION CRITERIA:

- Haemoglobin level < 10 g/dL
- Platelet count < 105000/uL
- Any history of allergic sensitivity to components of the PRP kit (calcium chloride, acid citrate dextrose solution A).
- Chronic kidney & liver disease patients
- Patient with known or suspected osteomyelitis

Described the treatment procedure to each patient and consent taken in the local language. Before PRP application, the wound bed was debrided (mechanical method), cleansing with normal saline. PRP is applied 2 times per week over the ulcer edges & onto the wound. Measurements were taken and recorded before each application. The length and width of the wound are measured using the standard "clock face" method detailed by Sussman<sup>(3)</sup>. Length was from 12:00 to 6:00 with 12:00 towards cephalad and width was from 9:00 to 3:00. Wound area is calculated using the formula for an ellipse: width × length × 0.7854. Wound contraction was measured every 4th day and represented as percentage of healing wound area. Percentage of wound contraction was calculated using the following formula:

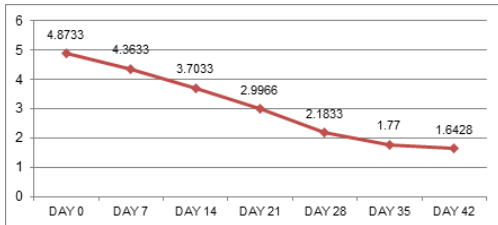
$$\% \text{ wound contraction} = \frac{(\text{Initial wound area} - \text{Specific day wound area})}{\text{Initial wound area}} \times 100.$$

**Preparation of PRP**

27 ml of blood was collected & ACD A solution added as an anticoagulant. Light spin centrifugation is 1500 rotations for 15 min. Heavy spin centrifugation is 3500 rotations for 7 min and thereby the platelets are spun down and get separated at the bottom of the tube and used as PRP<sup>(2)</sup>.

**RESULTS:**

The mean age of the patients was 49.36 ± 14.05. Percentage of males and females was 73% and 27% respectively. Based on the duration of the ulcers, classified into the <3,3 to 6,6 to 12 months and >1 year category which showed 5 (17%), 15 (50%), 4 (13%), 6 (20%) cases respectively. According to the etiology ulcers are classified as traumatic, diabetic, decubitus ulcers, venous, and others (postoperative wounds, Hansen's disease) which constitutes 40%, 27%, 17%, 3%, 13% respectively.



**Graph 1: Distribution according to Sum of the mean area of ulcers from baseline to the last visit**

The healing rates of the various ulcers were monitored in weekly intervals till 6<sup>th</sup> week. Among 30 patients, 17 patients (57%) showed complete healing, 3 patients (10%) showed 99-90% healing, 5 patients (17%) showed 80-89% healing, 4 patients (13%) showed 50-79% healing, 1 patients (3%) showed <50% healing.

There is a significant difference in change of area from pre PRP injection to post 6 weeks follow up (p-value is <0.001)



**IMAGE 1: Post traumatic nonhealing ulcer over right side lower end of tibia. Serial measurements show decrease in wound area and wound closure seen on 6th week.**

**DISCUSSION**

Chronic non healing ulcers come with significant cost and morbidity for the patients and society altogether. The main aim of any treatment modality is to obtain wound closure efficiently. The conventional treatment compromise adequate debridement, control of infection, avoidance of undue pressure on the wound and revascularization of ischemic tissue.

The mean age of patients in this study was 49.36 ± 14.05 comparable to Atef et al<sup>(4)</sup> who had an average age was 48 ± 7.38 years. In this study, younger patients and older patients showed the same rate of healing. The number of wounds taken into this study was 30 of different etiologies. Studies conducted by Weed et al. 2004<sup>(5)</sup>, Anita et al. 2008<sup>(6)</sup> are also done on different etiologies. In this study, 89% of wounds showed a positive response within four treatments over 2 weeks. Frykberg et al.<sup>(7)</sup> showed 97% of different etiology wounds improved over 3 weeks. de Leon et al.<sup>(8)</sup> showed that a good response was seen in 86.5% of ulcers of various etiologies within 2.2 weeks.

In this study, PRP was injected on 30 wounds. The number of wounds in studies conducted by Suthar et al.<sup>(9)</sup>, Bernuzzi et al.<sup>(10)</sup> was around 20 Wounds. In this study, the ulcer's duration on which PRP was injected was around 3 -15 months. The duration of ulcer in studies conducted by Suthar et al.<sup>(9)</sup>, Mohammadi et al.<sup>(11)</sup>, Bernuzzi et al.<sup>(10)</sup>, Yilmaz et al.<sup>(12)</sup>, Kontopodis et al.<sup>(13)</sup> was around 4 months. Regarding the effect of duration of ulcers on the healing rate, this study showed a positive correlation between healing rate percent and duration of ulcers. That may be due to the short duration of all ulcers (<12 months). Margolis et al.<sup>(14)</sup> showed that ulcer healing rate was higher in cases whose duration of the ulcer was within one year compared to ulcers longer than one year. It was explained by time-dependent changes occurring in the ulcer micro environment, making the healing process difficult.

In this study, the mean size of the wounds was 4.87 cm<sup>2</sup> which is comparable to other studies like Kontopodis et al.<sup>(13)</sup>, Yilmaz et al.<sup>(12)</sup>, Mohammadi et al.<sup>(11)</sup>. There was a significant and firm proportional correlation between the size of the wounds and treatment duration—the larger the surface of wounds, the longer the duration to heal. Although the percentage healing rate decreased with increased wound size, absolute healing rates increased enormously with initial wound size. In this study, chronic non healing wounds of larger size showed a better response to a greater number of injections. There was a significant and firm proportional correlation between the size of the wounds and the number of PRP injections. Many studies concluded that the larger the ulcer, the longer the duration required for treatment and the greater the number of injections.

**Table 1: Similar studies showing efficacy of PRP**

Name	Number of Wounds	Duration in Months	Mean Area Cm <sup>2</sup>	Application duration	Wound Improvement
Frykberg et al <sup>(7)</sup>	65	12 (0.75-65)	19	Mean 2.8 weeks with 3.2 applications	Volume reduction, mean 51%. PRP gel can reverse nonhealing trends
de Leon et al <sup>(8)</sup>	285 wounds	12	28	2.2 weeks with 2.8 treatments	PRP gel can restart the healing process.
Suthar et al <sup>(9)</sup>	24	4 (1.25-6)	NIL	PRP system, one single application, gel and intra lesional	PRP is safe and efficient in chronic wounds
Bernuzzi et al <sup>(10)</sup>	17	Minimum 1 month (mean duration unspecified)	43 (36-96)	Mean weekly treatments: 14.5 (4-25)	Considerable variability in clinical outcomes exists
Mohammadi et al <sup>(11)</sup>	50	4.6-11	6.11 (0.2-15.12)	weekly topical applications	PRP may be considered a suitable treatment for recalcitrant diabetic foot ulcers
Yilmaz et al <sup>(12)</sup>	19	1.75-6.6	8.61±3.44	weekly until complete wound healing (mean 3.57±1.83 sessions)	Effective in promoting healing, especially in deep venous ulcers
Kontopodis et al <sup>(13)</sup>	72	Minimum 1 month	4.1±3.9	PRP for 16 weeks	PRP could serve as a useful adjunct therapy

**Strength of the study**

As it is autologous, it presents no risk of immunogenic reactions or human to human disease transmissions like HIV or Hepatitis B, thus making it a safe modality of treatment.

**Limitations of the study**

- No control group was used

- Single centre study

## CONCLUSION

With the use of autologous PRP dressings for the treatment of chronic nonhealing ulcers the following conclusions were derived

- Area reduction was statistically significant (p-value is <0.001)
- There were no adverse effects or reactions seen
- It is a cost-effective procedure and easy to use
- Showed faster and better healing rates

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