

Original Research Article

The efficacy of intralesional injection of autologous platelet rich plasma versus normal saline dressing in chronic non-healing ulcers

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ABSTRACT

Background: Platelet-rich plasma (PRP) can potentially enhance healing of chronic non-healing ulcer by increasing the delivery of various growth factors from the α -granules contained in platelets. Aim of this prospective randomized study was to evaluate the efficacy of autologous PRP versus normal saline (NS) at chronic non healing ulcer in relation to wound healing on the basis of ulcer size reduction, duration of healing, complete or partial healing and side effects

Methods: Fifty four patients with chronic non-healing ulcer were randomly divided into two equal groups: PRP group (treated with PRP) and NS group. Observations were made regarding pain, slough, discharge, granulation, reduction in ulcer size and volume on every 7th day till 4 weeks.

Results: Reduction in area and volume of ulcers at the end of treatment was 12.27 ± 4.10 cm² and 6.88 ± 5.26 cm³ in PRP group and 9.25 ± 1.89 cm² and 4.25 ± 1.05 cm³ in NS group. In PRP group 59.25% had no discharge, 74.08% had no slough, 62.97% had no pain while in NS group no patient was without discharge, 14.81% patient had no slough, 74.07% had minimal pain on 28th day. In PRP group 22.22% ulcers were completely healed while in NS groups all ulcers were partially healed.

Conclusions: PRP is more effective than NS on chronic non-healing ulcers as it causes more rapid healing, rapid relief from pain and early decrease in discharge and slough in all age groups and sex; irrespective of type, size, site, duration and etiology of ulcer.

Keywords: Chronic non-healing ulcer, Growth factor, Normal saline, Platelet-rich plasma

INTRODUCTION

Wound healing is a complex and dynamic physiological phenomenon and it is classically divided into three overlapping stages: Inflammatory, proliferative and remodeling.¹⁻³

Chronic ulcers or non-healing ulcers are unresponsive to initial therapy or that persist despite appropriate care and do not proceed towards healing in a defined time period with an underlying etiology due to lack of growth factors and cytokines which delay the healing process.^{4,5} There are many types of non-healing ulcers that may include venous, arterial, diabetic, pressure and traumatic ulcers.

The goal of ulcer treatment is to obtain wound closure as expeditiously as possible. Conventional treatment for non-healing ulcers includes wound cleansing, necrotic tissue debridement, prevention, diagnosis, and, if necessary, treatment of infection, mechanical offloading, management of blood glucose levels and local ulcer care with dressing application.⁵⁻⁷

However, there are certain risk factors like Local causes, such as presence of necrotic tissue, tissue hypoxia, and repeated trauma in the ulcer and systemic diseases, such as diabetes mellitus, medications such as steroids that commonly affect and contribute to poor wound healing.

A wide variety of advanced treatments for non-healing ulcer include hyperbaric oxygen therapy, skin grafting, VAC (vacuum assisted closure) and surgical management like angioplasty and reconstructive surgery as Needed.⁸⁻¹⁰

Platelet rich plasma (PRP) is, by definition, a volume of the plasma fraction of autologous blood having a platelet concentration above baseline.¹¹ Platelets play a central role in haemostasis and wound healing.

The use of platelet rich plasma was first promoted by Ferrari et al in 1987 as an autologous transfusion.¹²

Platelet-rich plasma can potentially enhance healing by the delivery of various growth factors like platelet derived growth factor (PDGF- $\alpha\alpha$, $\beta\beta$, and $\alpha\beta$ isomers), insulin like growth factor (IGF), transforming growth factor- β (TGF- β , $\beta 1$ and $\beta 2$ isomers), vascular endothelial growth factor (VEGF), platelet factor 4 (PF4), etc.¹³⁻¹⁷ and cytokines from the α -granules contained in platelets. The release of these growth factors is triggered by the activation of platelets that can be initiated by a variety of stimuli such as thrombin, calcium chloride, or collagen. Growth factors are involved in key stages of wound healing and regenerative processes including chemotaxis, cell proliferation, differentiation, and angiogenesis.

Increased concentrations of these growth factors are likely the reason for the accelerated soft tissue wound healing, which is suggested to be at least 2-3 times faster than that of normal.¹⁸

Advantages of using an autologous PRP include no risk of cross reactivity, immune reaction or disease transmission.¹⁹

So we designed this randomized prospective study to evaluate the effect of intralesional application of autologous PRP versus normal saline at chronic non healing ulcer in relation to wound healing on the basis of ulcer area and volume reduction, duration of healing, complete or partial healing and side effects.

METHODS

This randomized Prospective study was conducted in department of General Surgery, Mathura Das Mathur Hospital, Jodhpur during October 2017 to September 2018.

Following approval of the institutional ethics committee and written informed consent, total 54 consecutive eligible male and female patients attending surgical outpatient department having chronic non healing ulcer and fulfilling inclusion criteria were enrolled.

Inclusion criteria

Patients with chronic non-healing ulcer and ulcer area less than 20 cm². Criteria for chronicity of ulcer included

ulcers with duration of more than 3 months, pale granulation tissue at the floor of ulcer and indurated base and edges.

Exclusion criteria

Patients with history of bleeding disorders or on anticoagulant medications, blood transmissible diseases, uncontrolled diabetes mellitus, pregnant and lactating mothers, immunosuppressive disorder/medication, psychiatric illness, ulcers with underlying osteomyelitis and/or bones exposed haemoglobin <11 gm% and platelet count <1.5 lacs/mm³ were excluded.

A careful and thorough pre-treatment history was taken regarding age, sex, occupation, etiological factors and associated medical conditions and thorough local and systemic examination with routine blood investigation was done. In local examination of ulcer include size which was recorded by direct impression of the ulcer over gauze piece/butter paper and later transferring the tracing over graph paper. Cotton tipped applicators and disposable scales were used to measure length, width and depth of the ulcer. Site of ulcer, discharge, margin, surrounding skin, granulation tissue, tenderness, temperature, regional lymph nodes etc. were noted.

Method of PRP preparation

Under aseptic precaution, 8-8.5 ml of blood aspirated by venipuncture using 18 G needle from antecubital fossa and collected in 10 ml sterilized vacuutainer tube containing 1.5 ml of anticoagulant acid citrate dextrose solution. Collected sample then put in centrifugation machine and first centrifuged with soft spin at 1200 rpm for 8 minutes at 20°C resulting in separation of whole blood into three layers; lower RBC region, middle buffy coat layer and upper straw colored plasma region. The separated buffy coat and platelet poor plasma (PPP) then aspirated with the help of pipette and collected into another no anticoagulant containing 10 ml sterilized collecting tube. This tube underwent a second centrifugation, hard spin at 2400 rpm for 4 minutes resulting into separation of the content into an upper portion of clear yellow supernatant serum, containing fibrinogen and very low concentration of platelets and lower bottom layer (red tinged) consists of highly concentrated PRP. The upper layer containing PPP was discarded with the help of pipette and the lower layer of PRP was taken for platelet count. Relying on the fact that collagen would activate PRP in vivo, allowed intralesional injections of unactivated PRP, which can be done with small gauge needle.

Patients were randomly divided into two groups (A and B) each group contain 27 patients. Group A: platelet rich plasma (PRP). Group B: normal saline.

All patients were treated with antibiotics whenever there was signs and symptoms of infection and receive the

same supportive treatment in the form of analgesics, proteins, iron, multivitamin etc. Observations were made regarding subjective complaints of pain, fever, discomfort, discharge, granulation, etc.

On admission ulcer was debrided if required. PRP was applied intralesionally on group A after every 7th day and normal saline dressing was done on group B on every alternate day.

Reduction in ulcer size was observed on every 7th day by size of ulcer: pre-treatment size (length, width and depth) of every ulcer was taken then ulcer size were measured again on 7th, 14th, 21st and 28th day or the day wound healed.

Visual findings were recorded by taking photographs from a fixed distance, angle, focal length and illumination on every 7th, 14th, 21st and 28th day.

Statistical analysis

Sample size was calculated on basis of pilot study. Minimum of 10 patients were required in each group to evaluate the effect of application of autologous PRP versus Normal Saline at chronic non healing ulcer in relation to wound healing on the basis of ulcer size reduction, duration of healing, complete or partial healing and side effects, at a power of 80% and confidence interval of 95%. Randomization used as a sampling technique, so for this all the patients were randomly allocated into one of the two groups (Group PRP and Group NS) by chit in box method.

The statistical package for the Social Sciences (SPSS 24 for windows, SPSS Inc., Chicago) was used for the analysis of data. The baseline characteristics of the study patients were expressed as numbers and percentages for categorical variables and as means±standard deviations (SD) for continuous variables. Between and within group comparisons of efficacy variables were assessed by using the Mann-Whitney U test and the Wilcoxon signed rank for paired samples, respectively. Categorical variables were compared with the chi-square (χ^2) test.

RESULTS

The mean age in PRP group was 50.92±11.99 years and NS group was 51.62±9.22 years (Table 1).

Table 1: Demographic data of cases in both group.

	PRP group (n=27)	NS group (n=27)	P value
Mean age±SD (years)	50.92±11.99	51.62±9.22	0.810
Male	19 (70.37%)	21 (77.77%)	0.756
Female	08 (29.62%)	06 (22.22%)	

In PRP group out of 27 patients 19 patient (70.37%) were male and 8 patients (29.63%) were female. In NS group out of 27 patients 21 patients (77.77%) were male and 6 patients (22.23%) were female (Table 1).

Common occupation in male patients were shopkeeper (10 patients out of 40 male patients) then farmer (8 out of 40) and labour (7 out of 40) and female patients were mostly house wife (10 patients out of 14 female patients) in both groups (p value =0.956) (Figure 1).

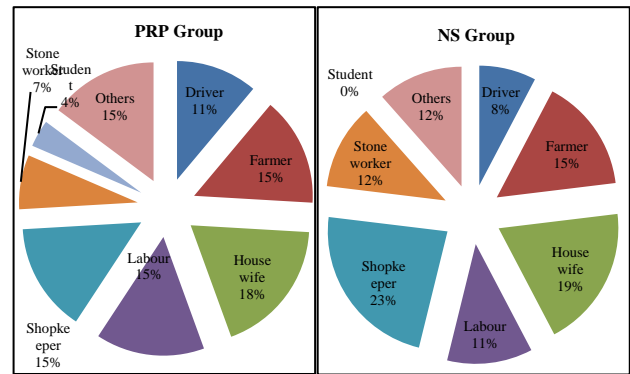


Figure 1: Occupation wise distribution in both group.

In PRP group most common type of ulcer is venous (29.62%). In NS group most common ulcers were post cellulitis (29.62%) and traumatic (29.62%) (Table 2).

Table 2: Etiology in both groups.

Type	PRP group (n=27)	NS group (n=27)	P value
Diabetic	07 (25.92%)	06 (22.22%)	0.719
Postcellulitis	06 (22.22%)	08 (29.62%)	
Traumatic	06 (22.22%)	08 (29.62%)	
Venous	08 (29.62%)	05 (18.51)	
Total	27	27	

Most common duration of ulcer in both groups were 3-6 months. In PRP group 81.48 % ulcers were of 3-6 months duration and 18.51% ulcers were of 6-12 months of duration. In NS group 88.89% ulcers were also 3-6 months old (Table 3).

Table 3: Duration of ulcer persisted before treatment in both groups.

Duration (in months)	PRP group (n=27)	NS group (n=27)	P value
3-6 months	22 (81.48%)	24 (88.89%)	0.701
6-12 months	05 (18.51%)	03 (11.11%)	
Total	27	27	

PRP group included 55.55% (15 out of 27 patients) patients that had ulcer surface area between 10 to 15 cm², 33.33% (9 out of 27 patients) patients had area less than 10 cm² and 11.11% (3 out of 27 patients) patients had

ulcer area between 15 to 20 cm². In NS group 59.25% (16 out of 27) patients had ulcer surface area between 10 to 15 cm², 37.03% (10 out of 27) patients had less than 10 cm² and 3.70% (1 out of 27) patients had ulcer area between 15 to 20 cm² (p value =0.581) (Figure 2).

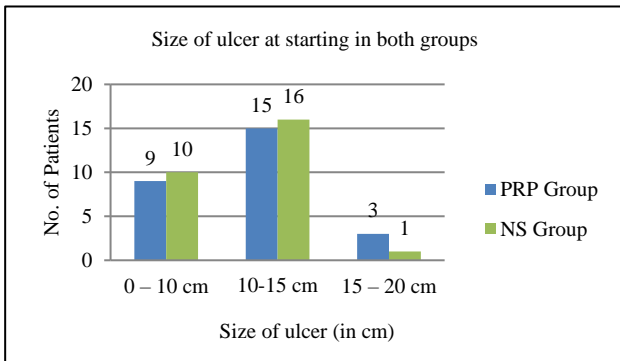


Figure 2: Size of ulcer at starting in both groups.

P value for age, gender, occupation of patients, pre treatment duration and size of ulcer, etiology of ulcer was more than 0.05 that means statistically significant difference was not found between PRP group and NS group for all these parameters.

The baseline mean area and volume of ulcer was 12.27±4.10 cm² and 5.05±2.45 cm³ in PRP group. The final mean area and volume of ulcer was 1.16±0.96 cm² and 1.10±2.28 cm³. Baseline mean area and volume in NS group was 12.36±3.19 cm² and 5.35±2.68 cm³. The final mean area and volume in NS group was 5.31±1.49 cm² and 2.27±1.11 cm³.

The mean reduction in area and volume of ulcer was 12.27±4.10 and 6.88±5.26 in PRP group whereas in NS group mean reduction in area and volume was 9.25±1.89 and 4.25±1.05. P value was set less than 0.05 and hence the results were found to be significant (Table 4).

Table 4: Reduction in area and volume of ulcer in both group at the end of final sitting.

At final sitting	PRP group (n=27)	NS group (n=27)	Total
Ulcer area (cm ²) Mean±SD; median (95% CI)	12.27±4.10; 12.00 (10.64-13.89)	9.25±1.89; 8.90 (8.50-9.99)	p=0.001
Ulcer volume (cm ³) Mean±SD; median (95% CI)	6.88±5.26; 5.00 (4.79-8.96)	4.25±1.05; 5.25 (3.83-4.66)	p=0.01

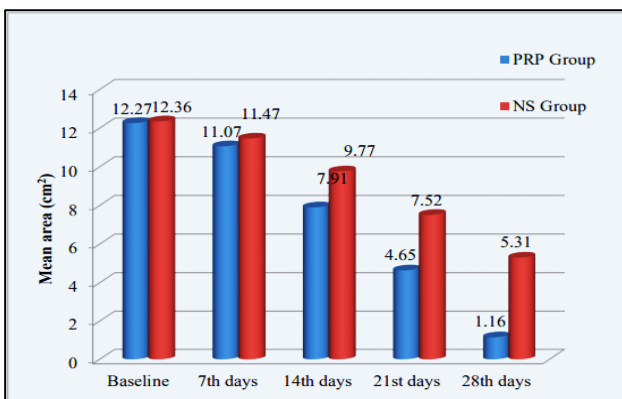


Figure 3: Mean area of ulcer during weekly followup.

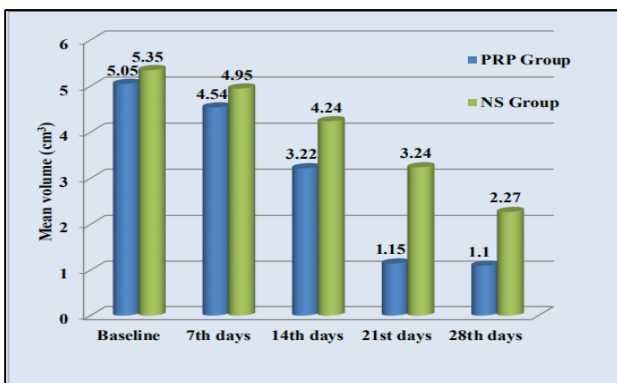


Figure 4: Mean volume of ulcer during weekly followup.

The declining trend in mean area and volume of ulcer at weekly follow up in PRP and normal saline group is shown in Figures 3 and 4.

Table 5: Slough, pain in ulcer, discharge, granulation tissues on ulcer at the end of treatment.

At final sitting	PRP group	NS group	P value
Minimal Slough	07 (25.92%)	21 (77.78%)	<0.0001
Mild slough	00 (00.0%)	02 (7.40%)	
Moderate slough	00 (00.0%)	00 (00.0%)	
Absent slough	20 (74.08%)	04 (14.81%)	
Minimal granulation	00 (00.0%)	08 (29.62%)	<0.0001
Mild granulation	04 (14.81%)	19 (70.37%)	
Moderate granulation	23 (85.18%)	00 (00.0%)	
Absent granulation	00 (00.0%)	00 (00.0%)	
Minimal pain	09 (33.33%)	20 (74.07%)	0.0003
Mild pain	01 (3.70%)	05 (18.51%)	
Moderate pain	00 (00.0%)	00 (00.0%)	
Absent pain	17 (62.97%)	02 (7.40%)	
Minimal discharge	11 (40.74%)	21 (77.77%)	0.0004
Mild discharge	00 (00.0%)	03 (11.11%)	
Moderate discharge	00 (00.0%)	00 (00.0%)	
Absent discharge	16 (59.25%)	03 (11.11%)	

In PRP group 74.08% patients had no slough from ulcers whereas in NS group only 14.81% patient had no slough from ulcers at end of treatment (Table 5).

Mostly patients (62.97%) in PRP group were pain free at end of treatment. In NS group 74.07% had minimal pain and only two patient had no pain (Table 5).

In PRP group mostly patients (59.25%) had no discharge and 40.74% patients had minimal discharge at the end of treatment. In NS group 77.77% had minimal discharge, 11.11% patients had mild discharge and 11.11% patients had no discharge (Table 5).

P value for declining trend of slough, discharge from ulcer and pain was less than 0.05 and hence the results of these parameters were found to be significant.

Moderate granulation tissue developed in 85.18% cases and mild granulation tissue in 14.81% cases in PRP group. In NS group 70.37% cases had mild granulation tissue and 29.62% had only mild granulation tissue. Significant difference found in both group (p value <0.0001) (Table 5).

In PRP group 22.22% ulcers were completely healed and 77.78% ulcers were partial healed. In NS groups all ulcers were partial healed. Statistically significant difference found between both group in healing of ulcers. (p value =0.022) (Table 6).

Table 6: Final outcome.

Final outcome	PRP group (n=27)	NS group (n=27)	Total	P value
Complete healing	06 (22.22%)	00	06 (11.11%)	0.022
Partial healing	21 (77.78%)	27 (100%)	48 (88.89%)	
Total	27	27	54	



Figure 5: Pre and post PRP healing of ulcer.

There was no side effect of therapy noted in both groups. The before and after therapy photographs are shown (Figure 5).

DISCUSSION

Chronic nonhealing ulcer management has been a challenging task in the medical field since mankind's efforts are being regularly directed to achieve satisfactory results.

Chronic ulcers or non-healing ulcers are defined as spontaneous or traumatic lesions, typically in lower extremities that are unresponsive to initial therapy or that persist despite appropriate care and do not proceed towards healing in a defined time period with an underlying etiology that may be related to systemic disease or local disorders.^{20,21}

Conventional therapies such as dressing, debridement and grafting cannot provide satisfactory healing because these treatment unable to provide the necessary GFs to modulate the healing process.²²

PRP therapy is an advance therapy which have a concentration of platelets. Platelets contain a large number of growth factors and cytokines that play key roles in inflammation and tissue repair, by stimulate mesenchymal cell recruitment, proliferation, extracellular matrix degeneration, and cell differentiation for tissue regeneration. These characteristics of platelets have led to the idea of using platelet rich plasma as a therapeutic tool to promote wound healing, particularly in patients whose tissue repair is significantly impaired or delayed.^{23,24} These factors are released from α granules in response to platelet activation by inducers of platelet aggregation.²³

In addition, PRP having high concentration of leukocytes which are helpful in preventing infections.²⁵

PRP is an autologous preparation, making it a safe treatment modality as compared to allogenic preparations and is free from concerns over transmissible diseases.^{26,27}

In our study out of 54 patients, 27 patient in PRP group who treated with intralesional PRP application on ulcer average reduction in area of ulcers at the end of treatment was 12.27 ± 4.10 cm² in PRP group and 9.25 ± 1.89 cm² in NS group. Average volume reduction in chronic ulcers at the end of treatment was 6.88 ± 5.26 in PRP group and 4.25 ± 1.05 in NS group.

Reduction in pain, discharge and slough from ulcer with more granulation tissue on ulcer surface was observed in all the patients of PRP group post-treatment without any side effect. The results demonstrated the safety and efficacy of autologous PRP in treating chronic non-healing ulcers.

In 1986, Knighton et al showed that the use of autologous platelet factors accelerated epithelialisation of granulation tissue leading to complete repair of chronic non-healing ulcers.²⁷ In this study, the time to 100% healing after initiation of platelet derived wound-healing factors (PDWHF) was 7.5±6.5 weeks. There was a direct correlation between the initiation of PDWHF therapy and 100% healing. The age of the patients and the location of the ulcers had no statistically significant effect on PDWHF-stimulated wound repair.

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 epithelialization of wound occurred within 6.6 weeks on average.²⁸

Driver et al conducted a prospective, randomized, controlled multicenter trial in the United States on 72 patients with chronic diabetic foot ulcer.²⁹ In this study, investigators compared the effectiveness of autologous PRP gel to that of normal saline gel for 12 weeks. The authors found that 68.4% (13/19) of patients in the PRP group and 42.9 percent (9/21) in the control group had wounds that healed. Wounds in the PRP group healed after a mean of 42.9 days (SD-18.3) versus 47.4 days (SD-22.0) in the control group.

Suthar et al performed a case series to evaluate effect of autologous platelet rich plasma in treatment of chronic non-healing ulcers.³⁰ Twenty Four (24) patients with non-healing ulcers of different etiologies, who met the inclusion criteria, were treated with single dose of subcutaneous PRP injections along with topical application of PRP gel under compassionate use, followed-up for a period of 24 weeks. All the patients showed signs of wound healing with reduction in wound size, and the mean time duration to ulcer healing was 8.2 weeks.

Several studies have been conducted on the use of PRP for the treatment of non-healing ulcers and the results have been promising, however, currently there is a paucity of critical scientific data regarding the beneficial effects of PRP in clinical procedures.

In the current study, PRP was found to be useful in treating chronic non-healing ulcers. However, further controlled randomized prospective clinical trials of large size are necessary to definitively demonstrate its efficacy.

This study has certain limitations. Some patients cannot be included in this study like: patients with large size ulcer, patients with history of bleeding disorders or on anticoagulant medications, with hemodynamic instability, patients with immunosuppressive disorder or on medication, patients with psychiatric illness, patients with uncontrolled diabetes mellitus, ulcers with underlying osteomyelitis or deeper ulcers with tendons and/or bones exposed, study was conducted on small group of patients

so to apply on general population large group study is require.

CONCLUSION

Present study showed that PRP is more effective than NS on chronic non-healing ulcers as it causes more rapid healing, rapid relief from pain and early decrease in discharge and slough in all age groups and sex; irrespective of type, size, site, duration and etiology of ulcer.

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