

Study of Autologous Platelet-Rich Plasma in the Treatment of Non-Healing Ulcer in Comparison with Conventional Treatment

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ABSTRACT

Background: Non-healing ulcers are treated with platelet-rich plasma (PRP), a relatively new procedure. In spite of its effectiveness as well as less complication rates, data regarding its efficiency remains scarce. Therefore, the aim of the present research is to assess the probable healing outcomes of Autologous PRP on non-healing ulcers.

Method: The present analytical study was carried out between January 2021 and December 2022 at the S.R.T.R Government College, Ambejogai, and Department of General Surgery. All the patients' ulcers who visited the institute in the time period were included in the study. Clinical evaluation was used to diagnose and choose patients with non-healing ulcers.

Results: The study included 68% (n=34) males who received conventional treatment and 64% (n=32) who received PRP treatment. Among the 34 females, 32% (n=16) received conventional treatment and 36% (n=18) received PRP treatment. Among the conventional treatment group, 39 out of 50 patients did not experience ulcer recurrence, while all 50 patients in the PRP treatment group remained free of ulcer recurrence. The recurrence rate in the conventional treatment group was 22% (11 out of 50 patients), whereas the PRP treatment group had a 100% success rate in preventing ulcer recurrence.

Conclusion: Based on the outcomes of the study we can conclude that the group's recovery rates using PRP were more rapid and improved. The cases receiving PRP treatment demonstrated superior ulcer size and area reduction capacities. Moreover, rapid granulation tissue formation was also observed in the PRP group rather than the conventional group. The use of PRP had no negative effects or responses.

Keywords: Chronic ulcers, platelet rich plasma, conventional treatments

Introduction

Non-healing ulcers are known to be unresponsive in nature, especially to the initial treatments and are known to persist despite of appropriate treatment strategies and hence, fail to heal within a defined timeframe. The delayed healing could be attributed to a universal as an alternative indigenous disorder [1-2]. There are several distinct kinds of non-healing ulcers, comprising pressure, arterial, venous diabetic as well as traumatic ulcers. The three steps of the usual wound healing process are inflammation, tissue formation as well as tissue repair. If the normal healing process is disturbed, a lack of cytokines and growth factors, which slow down the healing process, could lead to an ulcer developing a chronic condition [3]. Chronic ulcers commonly affect the lower extremities,

particularly those caused by venous illness, diabetes or arterial disease [2].

An estimated 2 to 6 million people in the United States alone are thought to be affected by chronic non-healing ulcers [2,4] which have a prevalence of 1.9 to 13.1% worldwide[5,6]. In later life, chronic ulcers are more likely to develop due to atherosclerotic risk factors such as diabetes, obesity as well as smoking. A chronic wound is assessed to affect nearly 10% of the population in their whole lifetime. Although, advances in medical and instrumental therapy have reduced the mortality rate of patients with chronic wound to a certain extent, the mortality rate among hospitalized patients with chronic wound still remains to be as high as 2.5% [6].

Nowadays, autologous PRP is a commonly implemented treatment modality in several disciplines of medicine. Maxillofacial surgery, Dentistry, orthopedics, urology, dermatology, plastic, otorhinolaryngology and cosmetic surgery are a few of them with wound healing being a common binding link of them all. In addition to blood plasma, autologous platelets are a abundant source of growth factors. Concentrating and applying these autologous platelets to the surgical site will lead to a more predictable outcome. For the healing of soft tissues in any natural wound, the formation of blood clots is vital. PRP is the equivalent or same plan of action where platelet concentrate is produced, which untimely hastens up the complete healing process. Typical blood clot part contain white blood cell, platelets, red blood cells as well as fibrin strands, which were found to be in the sequence of 95%, 5% and 1% respectively [7].

According to a recent study using PRP therapy to heal chronic non-healing ulcers, it was found that PRP facilitates wound healing and ulcers in minor, difficult to heal chronic wounds also improved significantly [8, 9]. In addition, PRP treatment reduces infection platelet treated wounds, which exhibit antimicrobial activity contradictory to some bacteria on the skin [9]. It is therefore a feasible alternative to conventional ones cases of small, hard-to-heal ulcers because it has several advantages compared to other treatments [10]. Many studies demonstrate that PRP improves and expedites the healing of both soft tissue and hard tissue.. GFs, cytokines, chemokines as well as fibrin from the patient's blood make up the autologous PRP gel. [11]. The stimulation of typical wound healing responses at the molecular and cellular levels is assumed to be the PRP gel's mode of action [12]. In the management of persistent, non-healing ulcers, autologous PRP is a safe, simple as well as affordable technique with positive outcomes.

Therefore, this study primary aim to demonstrate therapeutic importance of PRP/allogenic platelet concentrates in the treatment of chronic non-healing ulcers.

Material and Methodology

This analytical study was piloted between the time period of January 2021 to December 2022 in the Department of General Surgery, S.R.T.R Government College, Ambejogai. All the patients during the study period are included. Patients having non-healing ulcers were diagnosed clinically and selected according to inclusion criteria. Those participants were involved who contented the following inclusion criteria:

Inclusion criteria:

1. Pressure ulcer patients or chronic foot ulcer patients
2. A pressure ulcer that has reached stage 3 or higher.
3. Patients with stable hemodynamics.
4. Both acute illness and infection.
5. Patients with reduced mobility or bedridden.

Exclusion criteria:

1. We excluded patients with active infection or sepsis.
2. In the case of anemia (hemoglobin less than 10 g/dL or active bleeding),
3. The cases with the Thrombocytopenia (platelet count less than 100, 000/mL or other platelet disorders)
4. Bacterial infection of the ulcer, clinically defined by purulent discharge, green discoloration or fever or positive culture
5. The patients with the malignancy were excluded in this study.

Method**Comparative study:**

This study, which compares results among cases treated with PRP (Group A, n=50) as well as cases treated conventionally (Group B, n=50) designed for various non-healing ulcer types, was analytically constructed. PRP was prepared from the patient's own peripheral blood samples as well as used to treat the ulcer after a week in Group A. In Group B, cases received standard care without the use of PRP.

All of the patients were allocated into two groups at random. Treatment for the intervention group (Group A) includes the application of PRP, traditional debridement as well as dressing covering. The conventional group (Group B) further had the same traditional debridement including dressing covering, but without the addition of PRP. The first half of the patients were divided into the control group as well as the second half of the cases were divided into the conventional group in order to prevent any allocation bias as well as because the cases were not treated at the equivalent time on the other hand instead after admission. The sub sequential statistical analysis only included patients who got care for at least two weeks. Patients who weren't followed up for the necessary amount of period were all eliminated. Altogether cases had their medical histories thoroughly documented, any underlying health conditions were attended to, and a clinical assessment of the ulcer was carried out. Also, the informed consent was signed by every patient.

The width, length, and depth of each ulcer were measured and recorded. When surgery was required, the ulcer was debrided, washed with sterile saline as well as samples were collected from the ulcer bed and ulcer borders to rule out the presence of cancer. In Group A, sterile paraffine gauze in addition to sterile gauze or pressure wound dressing were used to cover ulcer after a PRP clot or injection was administered (subject to availability). After the first two days, the dressing was left in place for two more days before being replaced with a regular dressing every other day. Every week, cases in Group B underwent a single repetition. Just debridement was performed on the patients in Group B as well as on alternate days, a standard dressing was used. If required, the debridement was performed every week.

Following was the method used for PRP preparation as well as application:

The technique is based on centrifuging red blood cells and other blood components to separate platelets from them. PRP also platelet-poor plasma (PPP) are formed by centrifuging the cases blood sample after which PRP can be scattered or else inserted onto the ulcer, otherwise a clot can form and be placed to the ulcer. There are various monetary marked PRP preparation methods existing. We employed GPS II system (gravitational platelet separation) as well as the RegenKit systems.

Blood from the patient is added to Solution A or anticoagulant citrate dextrose solution as needed by the GPS II system, which requires 27–108 ml. (ACD-A). After 15 minutes of centrifugation at 3,200 revolutions per minute, it tends to produce 3- 12 mL of platelet concentrate with a platelet count that is three to eight times higher than that of peripheral blood. Following that, a calcium solution might be used to activate the platelet. 23 mL of whole blood are added to ACD-A as well as centrifuged at 1,500 g (gravity force) for 6 minutes to make Regen PRP. It develops 8 mL of PRP within a platelet concentration that is 2 - 4 times higher than that of peripheral blood as well as 3 mL of thrombin for platelets. In order to treat small, shallow, or active ulcers, PRP is then injected into the ulcer's margins. For deep ulcers, the generated clot is subsequently placed into the ulcer cavity. The major epidemiologic information was reported for all patients. The main result was an ulcer that healed in 1 to 5 weeks. By taking three-dimensional measurements of the ulcers in both groups, the healing process was examined (length, width and depth). As per presumption that every ulcer has an elliptic shape, We determined ulcer's surface area (mm²). The healing rate was calculated using the variance in the mean areas during two consecutive weeks as a comparison measure healing rate (HR_|). Study Plan By measuring the three dimensions of the ulcer in both groups, the healing process was tracked (depth, width as well as length). According to supposition every ulcer has an elliptic shape, the area of ulcer (in mm²) is calculated in the current study. The healing rate was calculated using the variances in the mean areas during two consecutive weeks as a comparison measure HR.

Statistical Analysis:

If the distribution of the continuous variables is normal, the independent ttest for those comparisons between groups was used; otherwise, the Mann Whitney U-test was used. For categorical variables, the relevant tests

were Chi-squared and Fisher's exact were performed. The mean and standard deviation for continuous data were displayed. Statistical significance is distinct as a p-value 0.05. The independent relationships between different risk variables and ulcer healing will be found using multivariate logistic regression. The proper tests were used at the conclusion of the investigation.

Results

Table-1: Distribution of sex and age group in study participants.

Gender	Conventional Treatment	PRP treatment
Female	16 (32%)	18 (36%)
Male	34(68%)	32 (64%)
Total	50	50
Age distribution (years)	Conventional Treatment	PRP Treatment
11-20	0	1
21-30	3	6
31-40	14	16
41-50	23	14
51-60	10	12
61-70	0	1

The study included 68% (n=34) males who received conventional treatment and 64% (n=32) who received PRP treatment. Among the 34 females, 32% (n=16) received conventional treatment and 36% (n=18) received PRP treatment. However, there were no statistically significant associations found in the group (p=0.17). Total, 100 patients with chronic non-healing ulcers found that the majority of patients were between 41-50 years old (n=37), followed by 31-40 (n=30) and 51-60 years old (n=22). The data suggests that older patients may be more resistant to initial treatments, with no specific time frame for healing. The statistical analysis shows a highly significant p-value of 0.000001.

Table-2: Clinical symptoms.

Clinical symptoms	Conventional Treatment	PRP treatment
Pain	43 (86%)	42 (84%)
Edema	50 (100%)	50 (100%)
Inflammation	50 (100%)	50 (100%)

In both treatment groups, all patients (100%) experienced edema and inflammation. For pain, 86% (43 cases) who received conventional treatment as well as 84% (42 patients) who obtained PRP treatment reported experiencing it.

Table-3: History of past habits.

Tobacco habit	Conventional Treatment	PRP treatment	P value
No	40	45	0.16 [NS]
Yes	10	5	
Smoking	Conventional Treatment	PRP treatment	P value
No	42	45	0.37 [NS]
Yes	8	5	
Previous Surgery	Conventional Treatment	PRP treatment	P value
No	45	49	0.09 [NS]
Yes	5	1	
History of Comorbidities	Conventional Treatment	PRP treatment	P value
No	41	43	0.58 [NS]
Yes	9	7	

Outcomes shows that there was no significant difference between the group A as well as group B including the PRP treatment group for (p=0.16) tobacco habit , (p= 0.37) smoking status , and (p= 0.58) history of comorbidities. However, for previous surgery, a borderline statistically significant difference was found (p=0.09), indicating that the proportion of patients who had not undergone previous surgery was greater in the PRP treatment group (49 patients) than in the conventional treatment group (45 patients). These findings suggest that the patients' characteristics were not significantly associated with the treatment received, except for the borderline significant association observed for the previous surgery.

Table-4: Distribution of etiology.

Etiology	Conventional Treatment	PRP treatment	P value
ARTERIAL INSUFFICIENCY	2	2	0.32 [NS]
BURN	8	9	
DM	1	2	
INSIDIOUS	6	5	
SNAKE BITE	2	7	
TRAUMA	31	25	
Total	50	50	

The study included all participants who developed chronic non-healing ulcer, which was reported to be caused by trauma in 56 cases, followed by 17 cases of burn injury and 11 cases with an insidious etiology. Snake bite, arterial insufficiency, and diabetes mellitus were found to be the causative factors in a lower number of cases,

with 9, 4, and 3 subjects, respectively.

Table-5: Complications in patients

Pain	Conventional Treatment	PRP treatment	P value
Yes	5(10%)	4 (8%)	0.52 [NS]
No	45(90%)	46 (92%)	
Secondary infections	Conventional Treatment	PRP treatment	P value
No	44	50	0.001*
Yes	6	0	

Above table displayed the differentiation between the group A and group B with respect to pain and secondary infections. The findings show that there was no statistically significant variance in the levels of pain among the two treatment groups (p=0.52). Among patients who received conventional treatment, 5 (10%) reported experiencing pain, while 4 (8%) patients in the PRP treatment group reported the same. However, for secondary infections, the results show a statistically significant difference (p=0.001). Specifically, out of the 50 patients who received PRP treatment, none reported secondary infections, while only 6 patients in the conventional treatment group reported secondary infections, indicating a higher risk of secondary infections in the conventional treatment group.

Table-6: Ulcer size before and after treatment in different groups

Ulcer dimension	Conventional Treatment	PRP treatment	p value
	Mean SD	Mean SD	
Post- treatment	33.28 13.29	30.04 12.61	0.21
After 1 month	27.34 12.54	21.36 9.51	0.009*
After 2 months	22.2 11.45	12.02 7.07	0.0001*
After 3 months	16.94 10.28	5.91 5.99	0.001*

The results show that there was no statistically significant variance among the two treatment groups in post-treatment ulcer dimension (p=0.21). However, at one month post-treatment, the mean ulcer dimension inside the PRP treatment group was significantly lesser than that in conventional treatment group (21.36 ± 9.51 vs 27.34 ± 12.54, p=0.009). This difference was even more pronounced at two months post-treatment, with the mean ulcer dimension in the PRP treatment group being significantly lower than that in the conventional treatment group (12.02 ± 7.07 vs 22.2 ± 11.45, p=0.0001). At three months post-treatment, the mean ulcer dimension within PRP treatment group was also significantly inferior than that in conventional treatment group (5.91 ± 5.99 vs 16.94 ± 10.28, p=0.001). These findings suggest that PRP treatment may be more effective than conventional treatment in reducing ulcer dimension over time.

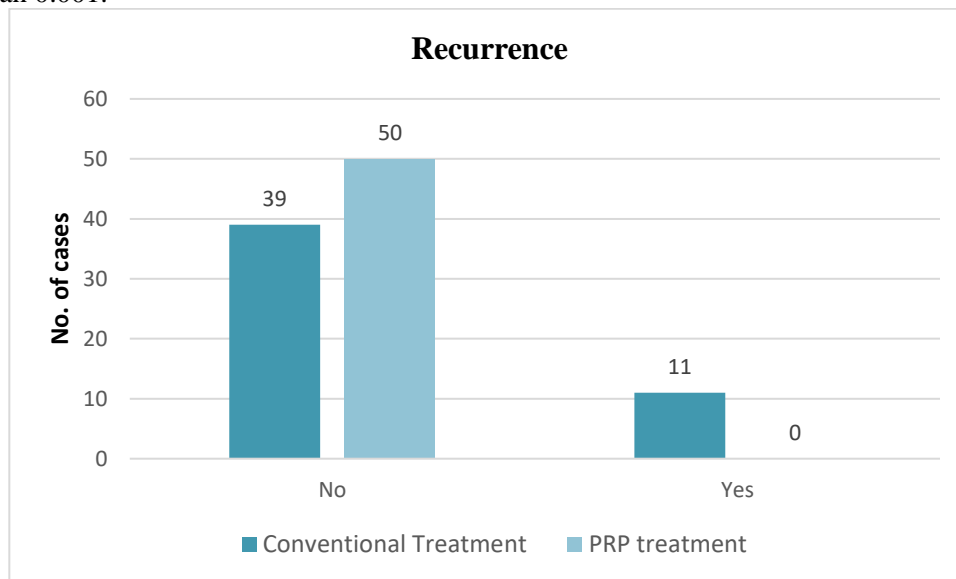
Table-7: Average no. of days of healing completion.

Healing time (in days)	Conventional Treatment	PRP treatment
Mean	111.4	88.78
SD	8.74	18.88
N	50	50

p value

0.001*

The healing time of wounds was shorter in the PRP treatment group (mean=±88.78 weeks) compared to the control group (mean=±111.4 weeks). The statistical analysis showed that this difference was significant with a p-value of less than 0.001.



Graph-1: Patients recurrence in study groups

Among the conventional treatment group, 39 out of 50 patients did not experience ulcer recurrence, while all 50 patients in the PRP treatment group remained free of ulcer recurrence. Therefore, the recurrence rate in the conventional treatment group was 22% (11 out of 50 patients), whereas the PRP treatment group had a 100% success rate in preventing ulcer recurrence. The p-value of 0.004 suggests that the difference in recurrence rates between the two groups is statistically significant.

Discussion

Patients and society are both affected by chronic wounds [13]. Non-healing ulcers are most commonly caused by growth factor abnormalities. Often, they are difficult to treat. Treatments, such as surgical debridement, dressings as well as even skin grafts, cannot delivered acceptable healing because they don't offer the growth factors needed for controlling the healing procedure [14]. Platelets and wound macrophages are two sources that are essential for wound repair during the healing process. A significant source of GFs is thought to be platelets. PRP has significant amounts of leukocytes, which contribute to its anti-inflammatory properties, which contribute in wound healing [14]. Therefore, the main aim of present research is to demonstrate the therapeutic importance of PRP/allogenic platelet concentrate in the treatment of chronic non-healing ulcers.

Many researches have emphasized the use of autologous PRP in contrast to this one. The first prospective, randomized, controlled multicenter experiment on the application of autologous PRP for the treatment of diabetic foot ulcers was conducted by Driver et al. [15] While Mehta et al.[16] had success using autologous PRP to treat a persistent lower extremity wound.

In the present study, several subcutaneous injections of PRP were administered to 50 individuals of control group, each of whom had one wound or ulcer. The mean duration for ulcers to heal in patients who underwent conventional treatment was 8.74 weeks and 18.88 weeks in patients receiving PRP treatment. A consistent phenomenon associated with the overall population was a reduction in wound size. Following therapy, all patients experienced a decrease in pain and their quality of life was greatly improved. The outcomes showed that

autologous PRP was both safe and effective in treating persistent ulcers that wouldn't heal. Innumerable studies were carried out to further assess the time period required by the PRP recipients to heal completely. One of the studies being the study carried out by Frykberget al.[17] who examined 65 chronic non healing ulcers in 49 patients. Amongst which 63 ulcers healed via size reduction in 2.8 weeks. Similarly, Steenvoorde et al.[18] also conducted a study on 13 ulcers in 12 patients, out of which 7 ulcers healed within a time frame of 4.2 weeks with an average need of repeated application accounting to 2.2. Another literature by Kakudo et al.[19], particularly focusing on non-healing ulcer, with a sample of five cases, using autologous PRP, three ulcers totally recovered in just four weeks and the wound epithelized was observed within 6.6 weeks.

In the present study included 68% (n=34) males who received conventional treatment and 64% (n=32) who received PRP treatment. Among the 34 females, 32% (n=16) received conventional treatment and 36% (n=18) received PRP treatment. At one month post-treatment, the mean ulcer dimension in the PRP treatment group was significantly less than that in the conventional treatment group (21.36 ± 9.51 vs 27.34 ± 12.54 , $p=0.009$). At three months post-treatment, the mean ulcer dimension in the PRP treatment group was also significantly less than that in the conventional treatment group (5.91 ± 5.99 vs 16.94 ± 10.28 , $p=0.001$). These findings suggest that PRP treatment is more effective than conventional treatment in reducing ulcer dimension over time. The study conducted by Ramakrishna RG, [20] revealed the average amount of time required for an ulcer to completely heal was 3.68 weeks in the group using PRP dressings, compared to 6.2 weeks in the group using traditional dressings (p value 0.0001). In the PRP dressing group, the ulcer size was reduced by 43.96%, compared to 13.81% in the traditional dressing group (p 0.0001). It was found that the PRP dressing group exhibits quicker wound healing and wound contraction. Prabhu et al.[20] reported that 98 (94.23%) of the 104 patients treated with PRP showed good healing. Over the course of five weeks, the ulcer's mean surface area consistently decreased. Along with healing, they also noticed a decrease in pain.

The present study has some limitations which are followings:

1. The sample size was too small.
2. There hasn't been enough follow-up to determine whether PRP can effectively and permanently cure ulcers.
3. To further validate the efficiency of PRP dressings, more randomized controlled trial studies are necessary.
4. Since there is currently no standardization of the method in the literature, it is also necessary to design excellent procedure for the preparation of PRP.

Conclusion

Based on the outcomes of the study we can conclude that the group's recovery rates using PRP were more rapid and improved. The cases receiving PRP treatment demonstrated superior ulcer size and area reduction capacities. Moreover, rapid granulation tissue formation was also observed in the PRP group rather than the conventional group. The use of PRP had no negative effects or responses.

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