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Original Research Article

A clinical study of platelet rich plasma versus conventional dressing in management of diabetic foot ulcers

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ABSTRACT

Background: Diabetic foot ulcers continue to pose significant global issue despite the advances made in the management of diabetes. It causes major foot complications if they are not addressed properly. It needs multidisciplinary approach for its care. While several advancements has taken place in wound care management, platelet rich plasma and stem cell therapy promises to offer a new hope in its management, aiding in cellular and tissue regeneration. The purpose of the present study was to compare Platelet-Rich Plasma versus conventional dressing in the management of diabetic foot ulcers.
Methods: This prospective study was focused on 20 diabetic foot ulcers, carried out in a surgical unit of ACS Medical College and Hospital, Chennai, Tamil Nadu, from January 2018 to June 2018. Patients were divided into two groups; Group A received conventional ordinary dressing (N=10, 50%) and Group B received PRP dressing (N = 10, 50%). The mean follow-up period was 8 weeks.
Results: The estimated time of wound healing was 8 weeks and healing was found to be more effective for patients in group B compared to patients in group A; the PRP group was found to be more effective in wound healing with fewer complications, less infection, exudates and pain.
Conclusions: There have been considerable advances in the use of PRP in therapeutic processes in recent years in tissue regeneration therapy. PRP is a powerful tool for the treatment of chronic wounds and very promising for diabetic foot wounds; PRP enables healing, and reduces amputation rates, infection and exudates.

Keywords: Conventional ordinary dressing, Diabetic foot ulcer, Healing outcomes, Platelet-rich plasma

INTRODUCTION

One of the most common causes of chronic wounds is growth factor abnormality. Platelets are considered a rich source of growth factors. Platelet-rich plasma (PRP) enhances wound healing by either the barrier effect to prevent bacterial invasion into the wound or the growth factors stimulate wound healing.[1] About 15% of diabetic patients will develop chronic wounds and about 25% of these patients will have to undergo foot amputation. The healing process is impaired in part because of deficiency of growth factors.[2,3] Becaplermin, a recombinant human platelet-derived growth factor-BB, is the only growth factor preparation approved by the US Food and Drug Administration for the treatment of diabetes mellitus (DM) wounds, but it requires daily applications for weeks to months.[4] Cell therapy and cell-containing tissue-engineered skin represent a significant advancement in the treatment of difficult to treat wounds. Currently, there are two cell containing tissue-engineered skin products with US Food and Drug Administration approval available for use in the treatment of wounds. Apligraf and Dermagraft accelerate wound healing, but also require frequent weekly applications, have a short shelf-life, and

are expensive.[5] The use of adenovirus encoding human platelet derived growth factor formulated in bovine collagen gel (GAM501) for the treatment of small nonhealing diabetic foot ulcers has been reported. Despite these advanced researches, a more practical and effective therapy for nonhealing diabetic ulcers is clinically needed.[6,7] Plasma samples with platelet concentration above baseline values are referred to as PRP.[8,9]

The clinical efficacy of the PRP was discovered in the early 1990s when new 'biological glues' were being discovered. They are at present used extensively in many clinical and surgical fields requiring tissue regeneration such as orthopedics, dentistry, wound healing, and maxillofacial surgeries.[10] The therapeutic effect of PRP is attributed to the abundance of various growth factors such as platelet derived growth factor, transforming growth factor-β, fibroblast growth factor, insulin-like growth factor-1, insulin-like growth factor-2, vascular endothelial growth factor, epidermal growth factor, and also some cytokines primarily stored in alpha granules.[11,12]

PRP can be prepared either from an autologous or an allogenic source. The majority of studies documented have used autologous platelet preparations as they are more acceptable by the patient and have a lower risk of transmission of viral infections.[13] PRP is easy to produce, with minimal effort. In a two-step process, whole blood from the patient is first centrifuged to separate plasma from packed red blood cells (RBCs) and then further centrifuged to separate PRP from platelet-poor plasma (PPP). Clinically valuable PRP contains at least one million platelets per microliter.[14] Lower concentrations cannot be used to enhance healing and higher concentrations have not been shown to increase healing.[15] Blinded, multicentric, randomized-controlled studies with large sample sizes are urgently needed to establish their therapeutic efficacy. There are no universally established standards for the collection, quality control, and administration of the product.[16,17]

METHODS

After receiving approval from the ethical committee of ACS Medical College and Hospital and obtaining written fully informed consent from patients on the two methods of dressing and their benefits, risks, alternative interventions, and possible complications.

The current study was carried out at the General Surgery Department, ACS Medical College, from January 2018 to June 2018, to allow an 8-week follow-up period for the last patient dressed on. This prospective randomized-controlled study was carried out on 20 diabetic patients with chronic non-healing feet wounds. Patients were allocated randomly into two groups according to the dressing method used: Group A received conventional ordinary dressing (N=10, 50%) and Group B received PRP dressing (N=10, 50%). Patients included in this study had non healing foot ulcers and fulfilled the following criteria: patients aged between 45 and 60 years, both male and female gender, diabetic patients, both type I diabetes (insulin dependent) and type II diabetes (noninsulin dependent), with controlled blood sugar levels with nonhealing ulcers on their feet, persistent wound for 2-3 months, wound size of the foot ranging from 4 to 5 cm. The exclusion criteria were patients with severe cardiovascular disorders, hepatitis, HIV, patients who had received conventional skin grafting in the past, critically ill patients with immunological disturbances were excluded.

All patients with non-healing wounds on their feet were subjected to a formal assessment and investigations to determine the risk factors and treatment of diabetic foot disorders that required the expertise of a specialized practitioner to diagnose, manage, treat, and counsel the patient. Integration of knowledge and experience through a multidisciplinary team approach promoted more effective treatment, thereby improving outcomes and limiting the risk of lower extremity amputation. Intervention sharp debridement of heavily infected wounds or non-healing wounds was performed using a scalpel, curette, and scissors. Debridement converted a chronic or a heavily infected wound to one that was acute by removing nonviable tissue that could stimulate excessive inflammation and bacterial growth. Simple incisions were used to open the infected area. Excision of necrotic tissue was extended as deeply and proximally as necessary until healthy, bleeding soft tissue encountered. Any callus tissue surrounding the wound was removed. After debridement metronidazole gel was applied in the wound. The wounds should always be left open and inspected at fourth day.

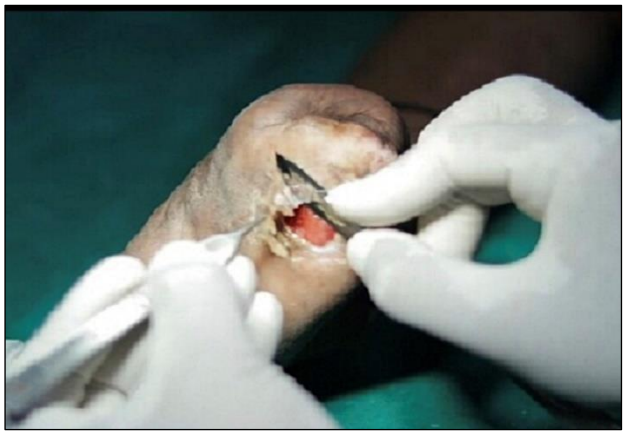

Figure 1: Surgical debridement and conventional.

Group A patients was treated by conventional ordinary dressing; surgical debridement was carried out for all necrotic tissues, and pus loculi were drained and the dressing material used was prepared. Irrigation of the wound was performed with saline, and a dressing was selected by matching the properties of the dressing (such as control of exudates) with the characteristics of the

wound and the patient, followed by packing of the wound. Appropriate dressing types were determined on the basis of wound location, depth, amount of slough present, amount of exudates, condition of the wound margins, and presence of infection. In general, betadine ointment were used as wound-dressing materials. This dressing was performed every day and sometimes twice per day (Figure 1).

Group B patients were treated by PRP therapy. The dressing protocol of these patients included PRP. PRP was injected about 3/4th of a cm away from the edge of the ulcer at a distance of 3/4th of a cm away from each injection site, after being prepared (within half an hour after preparation), followed by gauze and then dressing. The dressing was changed once in four days. This protocol was performed up to 8 weeks.

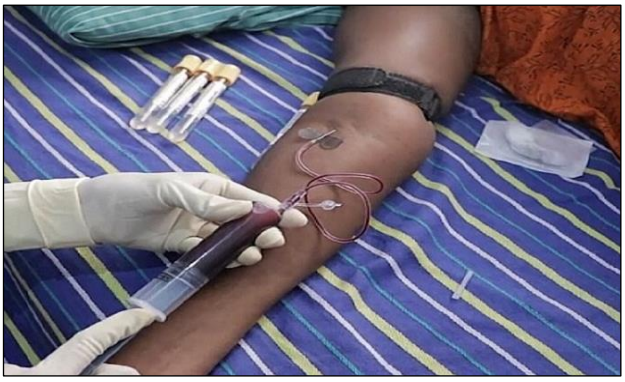

Figure 2: Drawing of patient's venous blood in syringe.

PRP was prepared from the patient's own blood (autologous PRP). 20ml of venous blood were drawn in syringe (Figure 2) and mixed with an anticoagulant to avoid platelet activation and degranulation. Whole blood was centrifuged at 3000 RPM for 5 min at 23°C. The first centrifugation was called a 'soft spin', which enabled the separation of blood into two layers: the bottom most layer comprised RBCs, the top most layer comprised cellular plasma. The plasma thus separated and was transferred into a sterile tube without an anticoagulant, this was done using a pipette. This tube was subjected to a second round of centrifugation at 4500 RPM for 10 mins and was called a 'hard spin'. After the second spin the plasma gets separated in to platelet poor plasma and platelet rich plasma along with very few RBC'S which form the platelet pellets. The upper two third portion constitutes the PPP which is disguarded while the lower one third portion constitutes the PRP (Figure 3), which is used for the PRP treatment. The PRP thus separated is aspirated in a 1ml syringe with a 24-gauze needle and is injected all around the circumference of the ulcer (Figure 4). The injection is done about three fourth of a cm, away from the wound edge so as to prevent loss of PRP from the wound edge margin and from the floor. The direction of the needle is pointed downwards and towards the centre of the base as most of the regeneration takes place at the base of the ulcer. The distance between two injections is about two - third of a cm apart. All along the procedure care is taken to prevent loss of PRP from the floor by injecting it in deeper level. Dressing was done using metrogyl gel to preserve the moisture. The injection is repeated at four days interval and wound is not disturbed in between. The patient needed 6 to 8 doses according to the ulcer size.

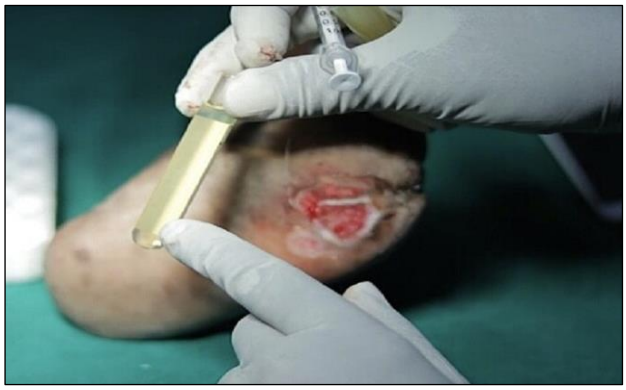

Figure 3: PRP at lower 1/3rd of the test tube after second spin.

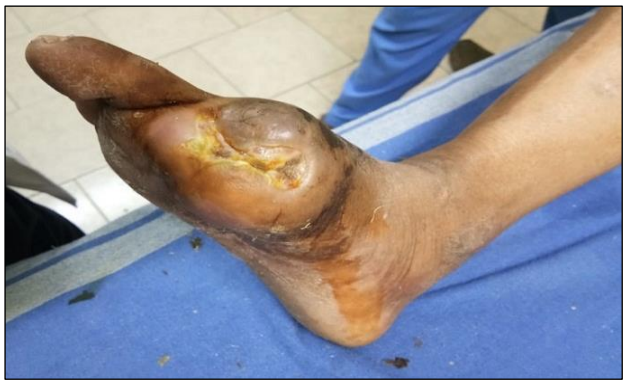

Figure 4: Injection of first dose of PRP around the circumference of ulcer.

Follow-up

Patients were advised to avoid pressure on the wound area. Appropriate off-loading footwear was given post procedure. Elevation of the feet was recommended when sitting or lying down to decrease edema. The patients were seen once in 4 days throughout the course of treatment. The patients were evaluated for the rate of wound healing in about 8 weeks and this evaluation was carried out by taking photos and measuring the wound's dimensions (length and width) using a metric tape at the initial visit and then every week. Characteristics of the wound such as exudates, necrotic tissue, infection, and granulation tissue were documented. The primary outcome evaluated: was reduction in the size of the wound, which was determined from photos taken every week. The secondary outcome parameters were the presence of infection, exudates, and pain. Statistical

analysis of data was carried out using Statistical Package for Social Sciences (SPSS) (version 17). Quantitative data were presented as mean and SD were analyzed using t-test to compare quantitative variables as parametric data SD <50% mean Qualitative data were presented as numbers and percentages and were analyzed using χ^2 and Fisher's exact tests. A P-value of less than 0.05 was considered significant.

RESULTS

This was a prospective study that included 20 diabetic patients with nonhealing foot ulcers recruited from ACS Medical College and Hospital and were followed up for 8 weeks; patients were divided according to the dressing performed into two groups: Group A included 10 patients who received conventional ordinary dressing. Group B included 10 patients who received PRP dressing. Their ages ranged from 45 to 60 years, with a mean of 52.2±4.94 years. All patients presented with non-healed foot ulcers and none of them presented with any other symptoms; the majority of patients were men 11 (55%) (Table 1).

Table 1: Patient's demographic data.

Data	Findings
Age (years) strata	
45-50	10 (50%)
51-55	6 (30%)
56-60	4 (20%)
Mean±SD	52.2±4.94
Sex	
Female	9 (45%)
Male	11 (55%)
Performed dressing	
Group A: conventional ordinary dressing	10 (50%)
Group B: PRP dressing	10 (50%)
Duration of diabetes [range (mean±SD)] (years)	7-12 (9.35±1.59)
Size of the wound [range (mean±SD)] (cm)	4-5 (4.52±0.27)

The wound was mostly present on the sole of the foot. The duration of diabetes in the patients ranged between 7 and 12 years with a mean of 9.35±1.59 years, and the size of the wound ranged between 4 and 5 cm with a mean of 4.52±0.27cm. PRP was shown to be more effective than conventional dressing after the second week [4 (40%) patients vs. 3 (30%) patients, respectively]. The same result was found at the fourth week [6 (60%) cases versus five (50%) cases, respectively]. In terms of the rate of healing (cm^2/week), after the second week, there was a higher rate of healing per week in group B versus group A. At the fourth week, the highest healing rate was found for both groups, but was better for the PRP group B. At the sixth and eighth weeks, a higher healing rate was found for the PRP group B (Figure 5). However, for the conventional group, the lowest rate of healing was reported at the eighth week.

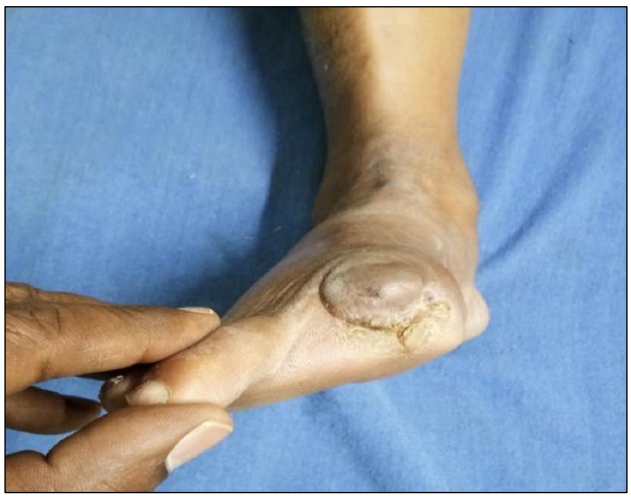

Figure 5: Higher healing rate at eight weeks after injection of PRP.

There was a statistically significant difference between both groups. The total rate of healing (cm^2 /week) was higher in Group B than Group A.

DISCUSSION

DISCUSSION: Diabetic foot wound is a common clinical problem. Because of population aging and an increase in risk factors and comorbidities such as tobacco use, obesity, hypertension, and atherosclerosis, there is a clear trend toward increased risk of chronic wounds. The social and economic effects are inevitable.[18] PRP is defined as a proportion of the plasma fraction of autologous blood with a platelet concentration above the baseline. PRP is also known as platelet-enriched plasma, platelet-rich concentrate, and autologous platelet rich plasma. PRP have been used to treat wounds since 1985.[19]

For more than 20 years, the PRP has been used to promote wound healing. Autologous PRP is composed of cytokines, growth factors, chemokine, and fibrin scaffold derived from a patient's blood. The mechanism of action of the PRP is believed to be the molecular and cellular induction of normal wound-healing response similar to that found with platelet activation. The present study was carried out to evaluate the effectiveness of PRP in promoting healing of diabetic foot wounds, preventing infection, and reducing exudates, besides its preventive action by reducing amputation rates. There have been considerable advances in the use of PRP in therapeutic processes in recent years in tissue regeneration therapy. On the basis of the last 10 years of research, the results of the systematic review with meta-analysis published by Carter et al, suggest that PRP therapy can positively impact wound healing and associated factors such as pain and infection in both chronic and acute cutaneous wounds.[20] The current study was carried out on 20

patients with diabetic foot wounds; the patients' ages ranged from 45 to 60 years, with the majority of patients were men. The study of Saad et al was carried out on 24 patients with chronic ulcers ranging in age from 40 to 60 years, they concluded that sex and age are insignificant in correlation with the rate of healing of their ulcers.[21]

In the present study, the site of diabetic feet wounds was generally the sole of the foot. The duration of diabetes ranged between 7 and 12 years, it was observed that there was no correlation between the site and the rate of healing. This result was reported by Gui-Qiu et al, who studied the effect of PRP on healing of lower extremity chronic ulcers in 21 patients, they concluded that 'there was no significant difference between type and site of ulcers in correlation with rate of healing'.[22] In this study, wounds varied in size and ranged between 4.9 and 8.6 cm, with a mean of 6.4±0.7 cm. It was observed that there was a significant and strong inverse correlation between the rate of healing and the size of the wounds, and there was a significant and strong proportional correlation between the size of the wounds and treatment duration (P=0.001).

Also, there was a significant and strong proportional correlation between the size of the wounds and the number of injections. Many trials concluded that the larger the ulcer, the longer the duration required for treatment and the greater the number of injections.[23,24] Upon review of risk factors and co-morbidities, diabetes represents a worldwide public health issue, affecting 5% of the population of the USA. Its high prevalence places this disease among one of the main pathologies that can progress to chronic ulceration.[25] Other risk factors found in this study included diabetic related comorbidities, foot angiopathy, and retinopathy, which affected wound healing and care, and smoking in 48 (60%) patients, which might have impaired wound healing directly or indirectly through vascular bad effect of smoking.[26,27]

In the current study, PRP was found to be more effective than conventional dressing after the second week. The same effect was reported at the fourth week. This could be explained by the fact that during wound healing, platelets are activated by contact with collagen and released into the bloodstream after endothelial injury. Platelets secrete stored intercellular mediators and cytokines from the cytoplasmic pool and release their α-granule content after aggregation. More than 800 different proteins are secreted into the surrounding media, exerting a paracrine effect on different cells. This secretion is intense in the first hour and platelets continue to synthesize more cytokines and growth factors from their mRNA reserves for at least another 7 days.

However, all systematic reviews have shown that PRP can stimulate healing of wounds. Gui-Qiu et al, recruited 21 patients with refractory diabetic lower extremity ulcers who showed no response to conventional treatments, these patients were treated with homologous PRP. Their data indicated that homologous PRP was effective in enhancing and accelerating healing of diabetic lower extremity wounds. Martinez-Zapata et al, reported that the percentage of total healing in PRP-treated wounds increased compared with the controls. In a meta-analysis of chronic wound studies, Carter et al, confirmed that the use of PRP treatment promotes complete healing compared with control care. Villela et al, also reached the same conclusions.[27]

All the above-mentioned studies concluded that on the basis of the meta-analysis and scientific evidence of consistent favorable outcomes, PRP is a treatment of choice for the care of wounds.[28] This could be attributed to the fact that PRP functions as a tissue sealant and drug-delivery system, with the platelets initiating wound repair by releasing locally acting growth factors by α-granule degranulation. These growth factors aid healing by attracting undifferentiated cells to the newly formed matrix and triggering cell division and by interacting with macrophages to improve tissue healing and regeneration, promoting new capillary growth, and accelerating epithelialization in chronic wounds.[29]

Most of the wounds healed within the estimated time of healing (8 weeks); all these cases showed more than 50% healing after the first 4 weeks. These results were confirmed by Gelf et al, who stated that 'it is generally accepted that a reasonable goal is healing by 12 weeks.'[30] Healing rates at 4 weeks predict overall healing rates, and a 10-15% area reduction weekly suggests an excellent prognosis'. The use of antibiotics was more frequent in Group A because of infection.

Paola et al, reported that the fewer complications in Group B could have been because of the fact that platelets exert anti-inflammatory and analgesic effects, which was confirmed by Asfaha et al. They reported PAR4- mediated analgesic effects in vitro. Also, ElSharkawy et al, studied platelet secretions and their effect on macrophage cultures, concluding that 'platelet concentrates function as an anti-inflammatory agent, because of the high RANTES and LXA4 concentrations'. Also, the anti-inflammatory effect of platelets could be explained by the fact that 'PRP may suppress cytokine release and limit inflammation'.[31]

CONCLUSION

There have been considerable advances in the use of PRP in therapeutic processes in recent years in tissue regeneration therapy. PRP is a powerful tool for the treatment of chronic wounds and very promising for diabetic foot wounds as it enables healing, and reduces amputation rates, infection and exudates.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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