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Role of platelet rich plasma in chronic non- healing ulcer: An observational study

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Abstract

Diabetic foot ulcer is a major complication of diabetes mellitus. Patients with poorly controlled diabetes, can develop ulcer around their feet for which amputation is the last resort and risk of re-amputation is high. Over the recent years, great progress has been made in the techniques of wound healing, among which autologous platelet-rich plasma (PRP) has attracted the most substantial attention. This was a prospectively designed study that evaluated the effect of PRP in patients with different types of ulcers. 70 patients with 82 non healing ulcers of various etiologies were treated with PRP at weekly intervals. The mean age of the patients was 42.5 years. the mean duration of ulcers was 4.75 months. About 100% improvement in the area was seen in 25 of the ulcers and 100% improvement in volume was seen in 24 of the ulcers at the end of the treatment. There was reduction in pain and discharge within 1 week. There were no side effects noted.

Keywords: chronic ulcer, platelet rich plasma, diabetic foot, healing

Introduction

Diabetic foot ulcer is a major complication of diabetes mellitus. Ulcer over of lower limbs is a common complication of a wide spectrum of pathologies that cause a negative impact on the quality of life of patients. Patients with poorly controlled diabetes, can develop ulcer around their feet for which amputation is the last resort and risk of re-amputation is high. Over the recent years, great progress has been made in the techniques of wound healing, among which autologous platelet-rich plasma (PRP) has attracted the most substantial attention. Platelets are known to start wound healing process through the release of locally activated growth factors(GF). For chronic ulcers, the conventional therapies may not be effective always and might need strict medical care and surgical correction in some cases.

Thus, this method of promoting wound healing by application of autologous platelet rich plasma membrane is an upcoming safe, easy and inexpensive modality as a treatment for chronic ulcers with no danger of allergic reactions.

Material and Methods

This was a prospectively designed study that evaluated the effect of PRP in patients with different types of ulcers. This is a hospital based observational study carried out in Department of General Surgery, Lata Mangeshkar Hospital, NKPSIMS .All patients were enrolled during a 2-year period following referral for surgical treatment of a pressure ulcer or a non-healing lower limb ulcer, and they remained in patients at the time of referral and during treatment.

The inclusion Criteria of enrolled patients were as follows:

- Patients who have given written and informed consent.
- Patients in the age group of 18-80 years.
- Wound duration of at least 6 weeks.
- Patients who have received conventional therapies for at least 6 weeks.
- Wound etiologies include diabetic, pressure, arterial or venous ulcer, surgical, or traumatic wound and other etiologies.

Exclusion Criteria

- Patients with history of bleeding disorders
- Patients on anti-coagulant medications
- Malignant ulcers

After taking written and informed consent from patients, detailed history including the name, age, gender, address, contact number, occupation, and history of medication was noted. Patients were thoroughly examined and ulcer size (length, breadth, and width) was measured by the wound's dimensions using a metric tape at the initial visit and then every week. When necessary, surgical debridement was performed. The ulcer was cleaned with sterile saline, and biopsies from the ulcer edges and ulcer bed were taken in order to exclude any malignancy.

Under aseptic precautions, according to the size of the wound, 10ml of venous blood was taken and anticoagulated by acid citrate dextrose. PRP was prepared by double centrifugation method.

The first spin used was hard spin (4000 rpm for 10 min) which separates into three layers: plasma, buffy coat, and red blood cells. The plasma and buffy coat was aspirated into a sterile test tube without an anticoagulant and subjected to a second spin (2000 rpm for 5 min); this centrifuge separates platelet-poor plasma (PPP) in the upper part and PRP in the lower part. PRP will be used for injection with 23-G needle subcutaneously inside and around the periphery of the ulcer after proper surgical debridement. The dressing was kept in place for 2 days, and after that, conventional dressing was applied on alternate days. The PRP treatment was repeated once every week.

PRP should be applied immediately onto wound as 70% of growth factors are released within 10 minutes and 90% within an hour. PRP can synthesis additional amount of growth factor for once about 8 days until depletion thus PRP application was repeated weekly. Dressing was removed after one week with normal saline and wound healing is assessed. PRP is then done weekly until the wound was healed.

Results

70 patients with 82 non healing ulcers of various etiologies were treated with PRP at weekly intervals. The mean age of the patients was 42.5 years. The duration of the ulcers ranged from 2 months to 1 year with the mean of 4.75 months. About 100% improvement in the area was seen in 25 of the ulcers and 100% improvement in volume was seen in 24 of the ulcers at the end of the treatment. There was reduction in pain and discharge within 1 week. There were no side effects noted.

Chronic wounds often lead to morbidity for patients along with its cost. Such wounds are found in all types of healthcare setup and are often challenging for healthcare providers. Conventional treatments like dressing, surgical debridement and even skin grafting do not provide satisfactory healing since these treatments are not able to provide the necessary GFs to modulate the healing process.

Platelet rich plasma enhances wound healing by promoting the healing process secondary to its GFs. These include platelet-derived GF fibroblast GF, vascular endothelial GF, epidermal GF, insulin like GF and transforming GF. These GF stimulate tissue re-generation. Due to presence of leukocytes which are at high levels in PRP, the anti-inflammatory factors in PRP also play a role in wound healing. Regardless of the rate and time of centrifugation a single spill cannot adequately concentrate platelet as RBCs will interfere with their fine separation. Chronic wounds lack the necessary GFs for healing, they are often difficult to heal and frequently complicated to

superinfection. Due to presence of high concentration of leukocytes in PRP, it prevents infection.

In this study, PRP was found to be useful in treating chronic leg ulcer.

Table 1: Showing age distribution

Age Group (Years)	Number of Patients	Percentage (%)
<20	0	0
21-30	15	21
31-40	9	13
41-50	18	26
51-60	28	40
>60	0	0
Total	70	100

Table 2: Showing gender distribution

Age Group (Years)	Number of Male Patients	Number of Female Patients
<20	0	0
21-30	9	6
31-40	8	1
41-50	14	4
51-60	22	6
>60	0	0
Total	53	17

Table 3: Showing duration of ulcer

Duration of Ulcer (Months)	Number of Ulcers	Percentage (%)
<3	12	15
3-6	40	49
6-9	15	18
9-12	15	18
Total	82	100

Table 4: Showing improvement of area of the ulcer in percentage at the end of sitting

Percentage improvement in area at the end of the sitting	Number of Ulcers	Percentage (%)
<60	13	16
61-70	0	0
71-80	15	18
81-90	0	0
91-100	54	66
Total	82	100

Table 5: Showing improvement of volume in percentage at the end of sitting

Percentage improvement in Volume at the end of the sitting	Number of Ulcers	Percentage (%)
<60	12	15
61-70	0	0
71-80	0	0
81-90	14	17
91-100	56	68
Total	82	100

Discussion

This study has found that the application of PRP on previously chronic non-healing ulcers has a beneficial effect as far as ulcer depth and healing are concerned.

Pressure ulcers pose a significant problem for the treatment of bed-bound patients, especially in the elderly, and they have a tremendous effect on their quality of life. Prevalence rates remain unacceptably high, ranging between 6% and 20%.

According to the recent National Institute of Care and Health Excellence Pressure Ulcers Quality standards, the National Reporting and Learning System (UK) found that pressure ulcers had the largest proportion of patient safety incidents in 2011–2012, accounting for 19% of all reports. Diabetic foot ulcer is another type of chronic non-healing ulcer. The most important factors underlying the development of foot ulcers are peripheral sensory neuropathy, foot deformities related to motor neuropathy, minor foot trauma, and peripheral arterial disease. Infection, tissue hypoxia, necrosis, exudate, and excess levels of inflammatory cytokines are the major risk factors that prolong the healing of chronic ulcers. Additionally, growth factors, cytokines, proteases, and cellular and extracellular elements play an important role in the different phases of the healing process, and alterations in one or more of these components may cause impaired healing.

Our study has shown that the use of PRP promotes the healing of chronic ulcers, although we could not evaluate its effect on each type of ulcers separately due to the small number of patients. The efficiency of this method is based on the local and continuous delivery of a wide range of PDGFs and proteins that mimic the natural healing process. Treatment with PRP seems to limit the noxious effect of deep tissue injury, preventing the spread of tissue necrosis. According to a recent study by Oomens *et al.*, a pressure-induced injury to muscle fibers, possibly at the cytoskeleton level, could in part be responsible for the development of pressure ulcers. Based on the findings of our study, we can assume that the growth factors are involved in the prevention of spread or even repair of such injury, and molecular mechanisms seem to be even more complex. However, data are still sparse, and more studies are required to shed light on those processes.

Our results indicate that PRP has the most pronounced effect on the depth of the ulcer concurring with other authors. Experimental models have provided substantial evidence to support that platelet-rich fibrin matrix – a variant preparation with similar properties – induces endothelial cell proliferation that may suggest an explanation for this type of effect [20]. Additionally, we have found a significantly higher HR in patients treated with PRP. Saad-Setta *et al.* have compared PRP with PPP in patients with chronic diabetic foot ulcers and also showed that healing with PRP was significantly faster. It seems that PRP promotes cell migration and proliferation, causing a rapid healing of chronic ulcers that could justify this effect. Finally, we have applied PRP only once a week in our study, although more authors seem to prefer a twice-a-week strategy.

Conclusion

According to the literature, PRP may improve the healing of foot ulcers associated with diabetes, but this conclusion is based on low-quality evidence from small randomized controlled trials. However, our study found that PRP was not associated with diabetes mellitus or other major outcomes. Regarding other confounding factors, we have also found that there is no correlation between hypoalbuminemia and major outcomes of PRP. This concurs with other studies as well. Ramos-Torrecillas *et al.* have found no association between the blood levels of albumin or total proteins and the PRP healing process, which is also consistent with the finding of de Leon *et al.*, that is, there is no relationship between serum albumin or hemoglobin levels and the effects of Plasma Rich in Growth Factors on chronic ulcers.

Finally, the limitations of our study include the small number of patients included in the study, although statistical significance

could be found. Due to study planning, blinded randomization was not feasible, as neither the healthcare provider nor the patients could be blinded. However, the randomization problem was addressed by allocating the first 20 patients to the treatment group and the last 20 patients to the control group, thus avoiding selection bias. Regarding the confounding factors, ulcer area size and depth could affect initial treatment decisions and increase potential bias, especially in correlation with ulcer's location. Therefore, a blind randomization would be optimal for safer results.

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