

ORIGINAL RESEARCH

A Comparative Study Of The Efficacy Of Autologous Platelet Rich Plasma With Autologous Platelet Rich Fibrin In The Management Of Diabetic Ulcers

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Abstract

Background: Diabetes mellitus is one of the most challenging health problems in the 21st century. Among the various complications which can occur in a diabetic individual, diabetic foot is a serious complication which aggravates the patient's condition and has a significant socioeconomic impact. Diabetic patients with poor glycemic control may show chronicity of ulcers due to delayed wound healing. In such chronic wounds, the standard practises such as surgical debridement, regular dressing of the ulcer, mechanical offloading may not be sufficient. Other treatment options including cellular therapy (Platelet rich plasma (PRP) and Platelet rich fibrin (PRF)), microsurgical flaps have shown good results in healing of such ulcers.

Objective: To compare the efficacy of Autologous PRP with Autologous PRF in the management of Diabetic ulcers.

Methods: The study was a random, non-blinded, prospective, comparative, hospital - based, therapeutic study where the outcomes of therapy with PRP and PRF were compared. A total of 60 subjects with diabetic ulcers were selected randomly and divided into 2 groups of 30 each. One group was treated with PRP therapy and the other group with PRF therapy. After each sitting of PRP or PRF, patients were followed up on a weekly basis for 4 weeks or till complete healing (whichever is early). At each follow-up, the ulcer measurements (area and volume) were recorded. The results of both groups were then compared.

Results: It was observed that patients treated with PRF therapy had significantly faster healing than those patients treated with PRP therapy. The response was statistically significant.

Limitations: This study included a small sample size, and the ulcers included were small in size. More studies are needed to study the efficacy of PRP and PRF in larger ulcers.

Keywords: Diabetes mellitus; Diabetic foot; Autologous Platelet rich plasma; Autologous Platelet rich fibrin

Introduction

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both. The chronic hyperglycemia of diabetes is associated with long term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart and blood¹.

Among the complications caused due to diabetes, diabetic foot ulcer, neuropathy, nephropathy, retinopathy are common².

The prevalence of non-healing diabetic foot ulcers is estimated to be between 4-10%, and probability of lifetime incidence is about 25%. Amongst those who develop such foot ulcers, an estimated 12% - 20% require amputation¹.

These ulcers become chronic as they lack the important growth factors which are needed for their healing.

Also, these ulcers usually become infected and healing is complicated by peripheral neuropathy, atherosclerotic peripheral arterial disease, leading to long term morbidities.

Standard treatment for diabetic ulcers includes debridement of necrotic tissue, infection control, local ulcer care, mechanical offloading, management of blood glucose levels and education on wound care. As the rates of recurrences and non-healing remain high, many other modalities have been tried in recent times including surgical such as microsurgical free flaps, local insulin. These are often termed “advanced wound care therapies”¹.

In recent times the cellular therapy led by platelet rich plasma (PRP) and platelet rich fibrin (PRF) have also come to forefront as successful treatment options. Also, as these methods are cost-effective, they are well-suited for patients in developing countries like India.

Hence this study was conducted to compare the efficacy of autologous PRP and autologous PRF in the management of diabetic ulcers.

Methods

The study was designed as an institution- based, prospective, comparative, therapeutic study. Prior clearance was obtained from the institutional ethics committee before the commencement of the study. The selected patients were counselled regarding the study and written consent was taken before enrolling them.

60 patients with diabetic ulcers were included, of which 30 patients were subjected to treatment with PRP therapy and the other 30 patients to PRF therapy. A detailed clinical history was taken including age, sex, occupation, duration of diabetes mellitus, site and size of ulcer.

The patients were selected based on the following inclusion and exclusion criteria:

Inclusion criteria

1. Diabetic ulcers of Grade 1 of Wagner’s classification of diabetic foot.
2. Diabetic ulcers of duration 4 weeks or more.
3. 60 Patients with well controlled diabetes mellitus having clean ulcers (showing no growth on culture). If the ulcer was infected, it was treated with appropriate antibiotics and then

included in the study after obtaining no growth on culture.

Exclusion criteria

1. Uncontrolled Diabetes Mellitus
2. History of bleeding disorders
3. Platelet count less than 1.5 lakhs/cumm
4. Patients on anticoagulants
5. Diabetic ulcers of Grade 0 and 2 to 5 of Wagner's classification of Diabetic Foot.

Procedure:

Patients were meticulously examined and ulcer size (length, width and depth) were measured by 'clock-face' method described by Sussman using a cotton tip applicator & ruler³.

Preparation of Autologous PRP :20 ml of venous blood was drawn and transferred to a vacutainer containing acid citrate dextrose and PRP was prepared by double centrifugation method. The first spin used was hard spin (5000 rpm for 15 minutes) which separated the blood into three layers: Plasma, buffy coat and red blood cells. The plasma and buffy coat were aspirated into a sterile test tube without an anticoagulant and subjected to a second spin (2000 rpm for 5 minutes) yielding a platelet rich plasma of 0.8ml – 1.5ml with the sediment of platelet at the bottom of the tube.

1 ml of PRP was aspirated and activated with 10% calcium chloride (0.3 ml for 1 ml of PRP) and injected to the ulcer and the edge of the ulcer⁴ and covered with non-absorbent dressing.

Preparation of Autologous PRF: 10 ml of the patient's blood was withdrawn into the vacutainer without any anticoagulant and immediately centrifuged (to prevent blood from clotting) at 3000 rotations per minute for 15 min. After 15 min, a fibrin gel was formed in the centre of the vacutainer in between the red blood cells which had settled at the base and acellular plasma above⁴. The PRF obtained was removed with the help of a toothed forceps and was placed on the ulcer after washing the adherent RBC's with normal saline. After applying the platelet rich fibrin, the ulcer was covered with a non-absorbent dressing.

After 1 week, the dressing was removed in both PRP and PRF treated patients and the ulcer was assessed for improvement. This process was repeated every week for 4 weeks or until the ulcer healed completely (whichever was early). At the end of every week, the wound area and volume was calculated by length × width × 0.7854 and length × width × depth × 0.7854 respectively⁴. Photographs were taken before each application and at the end of 4 weeks.

The treatment outcome was defined as a percentage improvement in area and volume of the ulcer.

Statistical analysis

The results were expressed in numbers and percentage for each category and were statistically evaluated. The parameters were analyzed by Chi square and student t test, p value of <0.05 was considered significant. SPSS software version 16 and Open Epi info software version 2.3 were used.

Results

60 patients with diabetic ulcers were taken up for the study, of which 30 patients were treated with PRP therapy and 30 patients with PRF therapy.

All the patients were followed up on a weekly basis and the results were tabulated as below.

Table 1: Age and Sex profile

Category	PRP Group	PRF Group	P value	Remarks
Age (years)				
Range	35 – 75	30- 88	0.653	Not significant
Mean	57.28	52.71		
Median (IQR)	15	15		
Sex				
Male	23 (76.67%)	22 (73.33%)	0.942	Not significant
Female	7 (23.33%)	8 (26.67%)		
Male: Female ratio	2.75:1			

Table 1 shows the age and sex distribution in both PRP and PRF groups. The mean age in PRP group was 57.28 years and that in PRF group was 52.71 years. This was seen to be statistically not significant indicating that the groups were matched. There was male predominance in both groups with a male: female ratio of 2.75:1.

Table 2:Diabetic status in both groups

Category	PRP Group	PRF Group	P- value	Remarks
Range of Duration of Diabetes	0-15 years	3months- 20years	6.40	Not significant
FBS levels in patients: Range (mg/dl)	101- 273	105- 261	0.727	Not significant
PPBS levels in patients: Range (mg/dl)	148- 304	104- 306	0.625	Not significant

Table 2 shows the diabetic status of patients in both PRP and PRF groups. It was observed that the duration of diabetes ranged from 0 to 15 years in PRP group and 3 months to 20 years in PRF group. The FBS levels varied from 101 to 273 mg/dl in PRP group and 105 to 261 mg/dl in PRF group. Also, the PPBS levels varied from 148 to 304 mg/dl in PRP group and 104 to 306 mg/dl in PRF group. The P-values were not statistically significant in all three categories indicating that both groups were matched with respect to glycemic status.

Table 3: Clinical profile of Ulcer

Category	PRP Group	PRF Group	P- value	Remarks
Duration of Ulcer				
Range	1.5-7 months	1.5-12 months	0.454	Not significant
Mean	3.25 months	3.13 months		
Area of ulcers				
Range	0.6-30 cm ²	0.5-20 cm ²	0.145	Not

Mean	4.69 cm ²	6.19 cm ²		significant
Volume of ulcers				
Range	0.5-60 cm ³	0.25-20.8 cm ³	0.298	Not
Mean	4.39 cm ³	4.51 cm ³		significant
Culture from ulcer				
Positive	5 (16.67%)	6 (20%)	0.739	Not
Negative	25 (83.33%)	24 (80%)		significant

Table 3 shows the clinical profile of the ulcers in PRP and PRF groups. The mean duration of ulcers in PRP group was 3.25 months and that in PRF group was 3.13 months. The mean area of ulcers in PRP group was 4.69cm² and that in PRF group was 6.19cm². The mean volume of ulcers in PRP group was 4.39cm³ and that in PRF group was 4.51cm³. The P- values in all three categories were not significant statistically, indicating that both groups were matched with respect to clinical profile of ulcers.

Table 4: Comparison of number of administrations required for PRP and PRF groups

Number of sittings	PRP	PRF
1	-	8 (26.67%)
2	8 (26.67%)	14 (46.67%)
3	16 (53.33%)	5 (16.67%)
4	5 (16.67%)	3 (10%)
>4	1 (3.33%)	-
Total	30	30

P-Value: 0.002 (Statistically significant)

Table 4 compares the number of interventions/ administrations required for healing of ulcers in both PRP and PRF groups. It was seen that 16 ulcers (53.33%) healed with 3 administrations of PRP and 14 ulcers (46.67%) in PRF group healed with 2 administrations only.

PHOTOGRAPHS

Treatment with PRP

Ulcer overlying the left metatarsophalangeal joint



Before PRP



After 2nd Sitting



Figure 1: 3 sittings of PRP showed complete healing of the ulcer

Treatment with PRF

Ulcer on the left side of upper back



Figure2:2Sittings ofPRFdoneonweeklybasis showedcompletehealing

Discussion

The data collected throughout the study from both PRP group and PRF group were compared with other studies and were grouped as below:

Age Distribution

In our study, the maximum number of patients with diabetic ulcers in both PRP (33.33%) and PRF groups (30%) were in the age group of 50 to 60 years.

This was similar to a study conducted by Dr. Murtuza Aliasger et al⁵. where the maximum number of patients with diabetic ulcers were in the age group of 45 – 60 years.

In the study conducted by Shwetha et al³., it was noted the maximum number of patients (37.5%) were in the age group of 51 – 60 years.

Sex Distribution

In our study, a male preponderance was seen in both PRP group (76.67%) and PRF group (73.33%). The male preponderance was also observed in previous studies conducted by Raslan MM et al⁶ (60% males), Driver et al⁷ (80% males) and Nelson R. Pinto et al⁸ (77.78% males).

Duration of ulcers

In our study, the average duration of the ulcers was 3.25 months in the PRP group while that in PRF group was 3.13 months. This was similar to the study conducted by Aymen Salem et

al⁹. where the average duration of the ulcers was 3.2 +/- 0.2 months.

Arearrange

The subjects in the PRP group had ulcers with an area range of 0.6 cm² to 30 cm². It was noted that 83.33% of subjects had ulcers with an area of ≤ 7.0 cm².

Driver et al⁷., had included cases with an area range of 0.5 cm² to 20 cm² and 88% of ulcers had a size range of ≤ 7.0 cm² in area and a volume of ≤ 2.0 cm³.

In our study, diabetic ulcers with an area of 0.5cm² to 20 cm² were included in the PRF group. Somani A et al¹⁰., had included ulcers with an area range of 1cm² to 24 cm² in their study.

Timerequiredforhealingofulcers

The subjects allocated into PRP group had diabetic ulcers varying from 1x0.6 cm to 6x5 cm. It was observed that the minimum and maximum time required for complete healing of the ulcer was 2 weeks and 7 weeks respectively, with an average of 2.9 weeks.

In the study conducted by Raslan MM et al⁶., 24 patients with non- healing ulcers of different etiology were included. The sizes of the ulcers varied with the least dimension being 1.2x1cm and largest was 7x3cm. The minimum time required for complete healing was five weeks and maximum was 9 weeks with an average of 6.11 weeks.

In our study, the overall mean reduction in the ulcer area was 90% at the end of 3 weeks and all ulcers (100%) showed complete closure at the end of 4 weeks in PRF group.

The overall mean reduction in the ulcer area was 85.51% at the end of 4 weeks in the patients with PRF dressing in the study conducted by Somani A et al¹⁰. There was a complete closure of the ulcer in five patients (55.55%) in the same period.

When both the PRP and PRF groups were compared, the overall mean reduction in the ulcer area was 80% at the end of 3 weeks in PRP group while that in PRF group was 90%. This shows a better response and faster healing with PRF than with PRP therapy.

Conclusion

Wound healing in diabetes is impaired by various extrinsic and intrinsic factors. The prolonged inflammatory phase that occurs in diabetic ulcers results in delaying granulation tissue formation and decrease in tensile strength of the wound.

There are various treatment modalities available such as sharp debridement, mechanical offloading, treatment of secondary infections, regular dressing of wound. In many circumstances, these standard treatment methods are not sufficient and can lead to chronicity of the ulcers.

Autologous PRP and autologous PRF therapies represent safe, convenient, easy-to-use adjuvant therapies with significant potential for closing chronic wounds without adverse events. These platelet derived therapies enhance wound healing by providing the necessary growth factors and reducing the inflammation. Also, these therapies are very cost-

effective for the patients.

In our study, autologous PRF therapy was found to be more efficacious in healing of the diabetic ulcers when compared to autologous PRP therapy and was statistically significant.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil

Conflicts of interest

None

References

1. Shrivastava S, Mahakalkar C, Singh P, Chandak A, Tayde S. Platelet Rich Plasma as a Mono Therapy for Diabetic Ulcer. *J Tissue Sci Eng.* 2016;7:186
2. Tripathi K, Gupta P. Management of diabetic foot ulcers with platelet rich plasma: A clinical study. *National J Clin Orthop.* 2018;2(3):09-11
3. Suryanarayan S, Budamakuntla L, Khadri SI, Sarvajnamurthy S. Efficacy of autologous platelet-rich plasma in the treatment of chronic nonhealing leg ulcers. *Plast Aesthet Res.* 2014;1:65-9
4. Suresh DH, Suryanarayan S, Sarvajnamurthy S, Puvvadi S. Treatment of a nonhealing diabetic foot ulcer with Platelet-Rich Plasma. *J Cutan Aesthet Surg.* 2014;7(4):229-231
5. Calcuttawala MA, Bendre M, Menon N. Role of "Platelet Rich Plasma" in Treatment of Diabetic Foot Ulcers. *JMSCR.* 2017;5(4):19961-67
6. Raslan MM, Milad NM, AlAziz AA. Effect of autologous platelet-rich plasma in the promotion of healing of chronic ulcers. *Int Surg J.* 2018;5(1):15-9
7. Driver VR, Hanft J, Fylling CP, Beriou JM. A prospective, randomized, controlled trial of autologous platelet-rich plasma gel for the treatment of diabetic foot ulcers. *Ostomy Wound Management.* 2006;52(6):68
8. Pinto NR, Ubilla M, Zamora Y, et al. Leucocyte- and platelet-rich fibrin (L-PRF) as a regenerative medicine strategy for the treatment of refractory leg ulcers: a prospective cohort study. *Platelets.* 2017:1369–1635
9. Salem A, Tawfik AM. Role of Platelet Rich Plasma in Treatment of Diabetic Foot Ulcers. *Surgical Science.* 2016;7(6):272-277
10. Somani A, Rai R. Comparison of efficacy of autologous platelet-rich fibrin versus saline dressing in chronic venous leg ulcers: A randomised controlled trial. *J Cutan Aesthet Surg.* 2017;10(1):8-12