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Role of Autologous Platelet Rich Plasma in the Treatment of Diabetic Foot Ulcer: A Comparative Prospective Study at Tertiary Care Centre

Dr. Rahul Rana[1], Dr J.L Kumawat[2], Dr Mit Patel[3], Dr Dixit Mithwani[4]

Resident Third Year

Abstract: ***This comparative prospective study investigates the efficacy of autologous platelet-rich plasma (PRP) in the treatment of diabetic foot ulcers. Conducted at Geetanjali Medical College and Hospital, Udaipur, India, the study involved 50 patients divided into two groups: one treated with PRP and the other with conventional dressing. PRP, rich in growth factors, is known to accelerate tissue repair and inhibit keloid and scar tissue growth. The study found that PRP dressing significantly improved wound contraction and healing rates in diabetic foot ulcer patients compared to conventional dressing. Therefore, PRP can be considered an effective adjunct to conventional dressings and debridement for diabetic wounds.***

Keywords: Platelet Rich Plasma, PRP, Diabetic foot ulcers, Wound healing

1. Introduction

Diabetes mellitus is a chronic illness caused by impaired insulin secretion or poor insulin action, affecting 300 million individuals worldwide.[1]

Diabetes foot is a serious and debilitating condition caused by socio-cultural and socioeconomic conditions, lack of information and resources for proper diabetic foot care, and 5% of diabetic patients have a history of foot ulceration.[2]

Diabetic foot has a 25 times higher risk of lower limb amputation than non-diabetics, but can be reduced with the right care and prevention strategies.[3]

Multidisciplinary team can reduce amputation rates and improve quality of life in diabetic foot ulcers. Novel therapeutics are needed to accelerate tissue repair, shorten recovery time, and inhibit the growth of keloids and retractile scar tissue, while also being affordable and well-tolerated.[4]

The optimal dressing should be devoid of contaminants, able to remove excess exudates, retain moisture, be impermeable to microorganisms, allow gaseous exchange, and be simple to remove and affordable to prevent infection and improve wound healing.[5]

Wound dressings have become a proactive component of wound care, providing cosmesis, haemostasis, protection, support and absorption. They should be simple to use, painless to remove and require less adjustments.[6]

Active dressings create an optimal micro environment for wound healing, allowing for oxygen transfer and epithelial migration. Wet wounds are ideal for cell movement and respiration, and growth factors (platelet-derived growth factor (PDGF), epidermal growth factor (EGF), and platelet-derived angiogenesis factor) released from platelets have been found to accelerate wound healing. Platelet extract has also been found to work well in treating non-healing ulcers.[7,8]

This study intends to evaluate the action of platelet-rich plasma (PRP) on the early wound healing trajectories of diabetic foot ulcers in a hospital setting. The physiological storage of a variety of growth factors with healing properties inside platelets, which actively take part in tissue regeneration, is the foundation of the healing properties of PRP. PRP therapy accelerates healing of diabetic foot ulcers, reduces ulcer size, and reduces infections due to its antibacterial activity against skin bacteria. PRP forms fibrin gel to prevent infection and promote wound healing. In this study we are trying to show the efficacy of PRP dressing.[9,10]

The study's objective is to compare the effectiveness of autologous platelet-rich plasma application to conventional dressing in the treatment of diabetic foot ulcers.

2. Material and Methods

This comparative prospective study was done on 50 patients **(**The Case group A (experimental group, n = 25) and case group B (control group, n = 25) were divided into two groups at random.) in Geetanjali Medical College and Hospital, Udaipur, India, from January 2021 to June 2022, after obtaining approval from the Institutional HREC (vide approval No. 2021/1883 ddt.1/2/2021). The patients or their legal guardians were given all the information they required to understand the study and written informed consent was taken from patients or their guardians, before proceeding with the study.

Inclusion Criteria:

- Patient with type 1 and type 2 DM.
- Chronic ulcers - foot ulceration for at least 4 weeks.
- Ulcer with minimum surface area of 4 sq cm^2 (length x width).
- Diabetic foot ulcer with Wagner's Grade 1 and Grade2.
- Hb >10gm/dL.
- Platelets count >100 $x10^9$/L.
- Screening - S. Albumin level of more than 3.5gm/dl

Exclusion Criteria

- Patient's with any bleeding disorder & malignancy.

- Patient known case or suspected c/o osteomyelitis.
- Patients with ulcer Wagner's Grade 3 and Grade 4.
- Patient undergoing hemodialysis, known immune disorder, liver disease, PVD and bleeding disorder.

Study Procedure

In this comparative prospective study, about 152 patients were distributed randomly into two groups, and 102 of them were eliminated (case: 63, control: 39) because they did not came for follow up or did not provide their agreement. Patients under inclusion criteria were informed of the study's methodology, results, and benefits and drawbacks. Patients were separated into two groups, one was managed with traditional dressing method and study group managed with PRP dressing, after receiving the required informed written agreement. Data from their follow-up was gathered. The Case group A (experimental group, n = 25) and case group B (control group, n = 25) were divided into two groups at random. Four weeks were spent studying two groups. All of these patients underwent an ulcer inspection, and the wound's features were evaluated and documented with photographs. By setting a meter scale from the wound's margins in its longest dimensions, the size of the wound was determined.

In Both groups, adequate wound debridement was done, and local infection was treated with systemic antibiotic therapy in addition to local antiseptic application.

In the conventional group, regular saline dressing is carriedout.

Patient in study group is treated with PRP .Platelet rich plasma is made manually by drawing10 ml of blood by venipuncture. 5ml of blood is put in a two test tube each, and adding anticoagulant citrate dextrose (ACD). Centrifuge for 10 minutes at 1000 rotation per minute. Three layers obtained as, top layer plasma, middle layer buffy coat, R BC at the bottom.

Plasma and the buffy coat layer was separated by pipet, and put in test tube mixed with calcium chloride (cacl2).Second centrifugation done for 10 minutes at 3000 rotation per minute. It resulted in three layers, as top platelet poor plasma (PPP), platelet rich plasma and at bottom , RBC. Before being used, platelet rich plasma was checked for all common blood- transmitted illnesses to avoid contamination with terrible viral infections. Ulcers assessed (length and width measured with a metric tape). The difference in wound healing between the two groups served as the outcome measure.[11] This process was repeated once a weekly for 4weeks. At every week follow up , the ulcer was examined for granulation tissue, area and volume which was calculated using BATES-JENSEN WOUND ASSESSMENT TOOL.[12]

3. Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics trial version 23 for Windows statistical software package (SPSS inc., Chicago, il, USA). The Categorical data were presented as numbers (percent) and quantitative data were presented as mean and standard deviation median interquartile Range. p-value of <0.001 was considered significant as mentioned in results of the study. All the data was systematically represented in a tabulated format and graphs.

Before After PRP Dressing

Figure 1

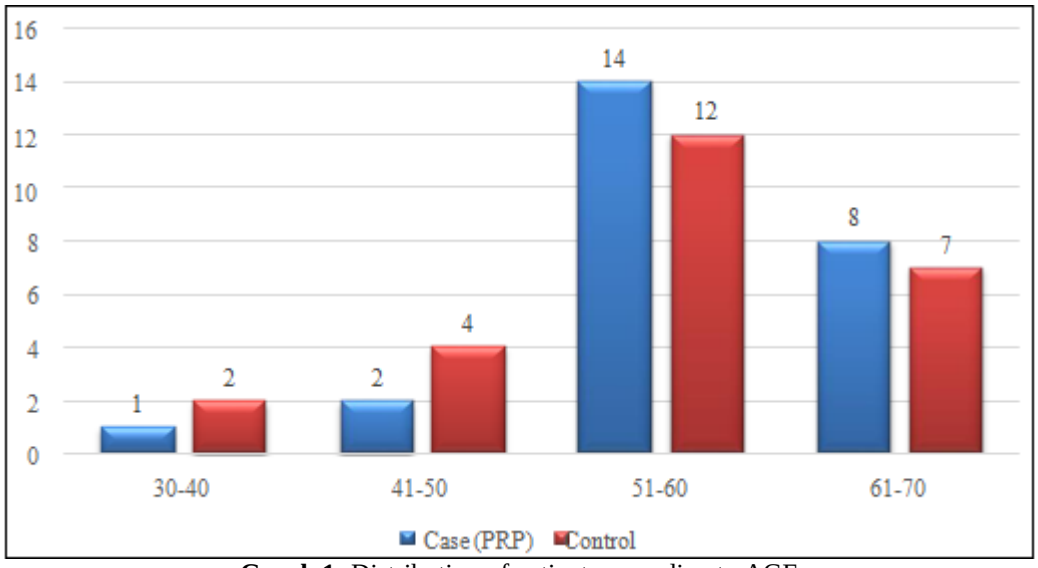
4. Result

Age Distribution:

Table 1: Distribution of patients according to AGE

	Case (PRP)	%	Control	%
30-40	1	4%	2	8%
41-50	2	8%	4	16%
51-60	14	56%	12	48%
61-70	8	32%	7	28%
Total	25	100%	25	100%
Mean	56.52		54.84	
SD	7.26		7.97	
P value	**0.43**			

In our study, it was shown that people between the ages of 51 and 60 had the highestprevalence of diabetic foot.



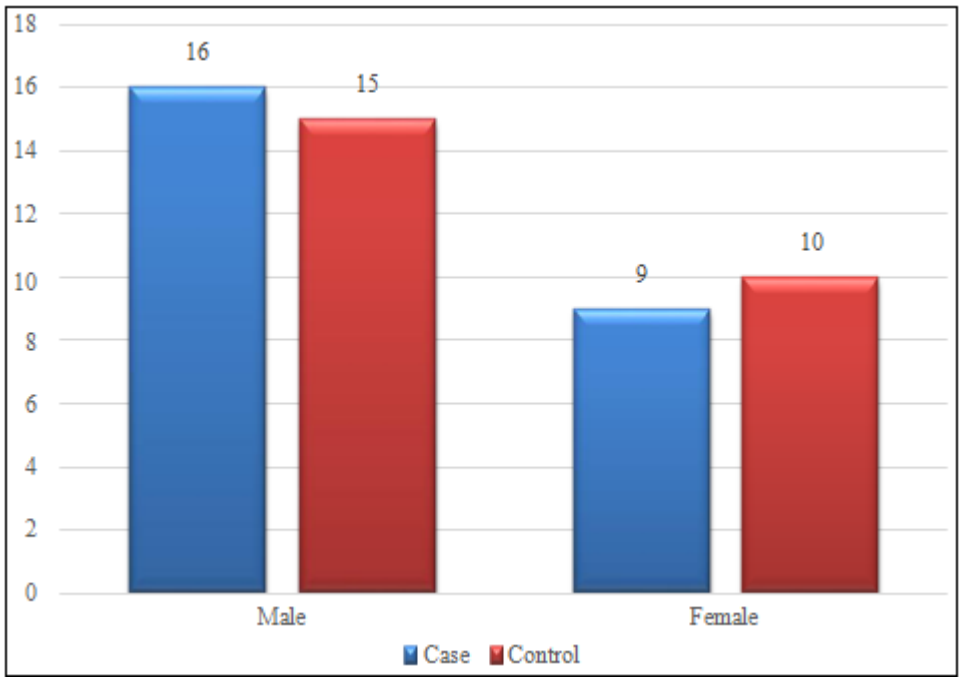
Graph 1: Distribution of patients according to AGE

Sex Distribution

Table 2: Distribution of patients according to Sex

Gender	Case	%	Control	%
Male	16	64%	15	60%
Female	9	36%	10	40%
Total	25	100%	25	100%

In our study it was observed that diabetic foot in control group male patient were 60% and female patients were 40% and in case was 64% of male and 36% of female patient.



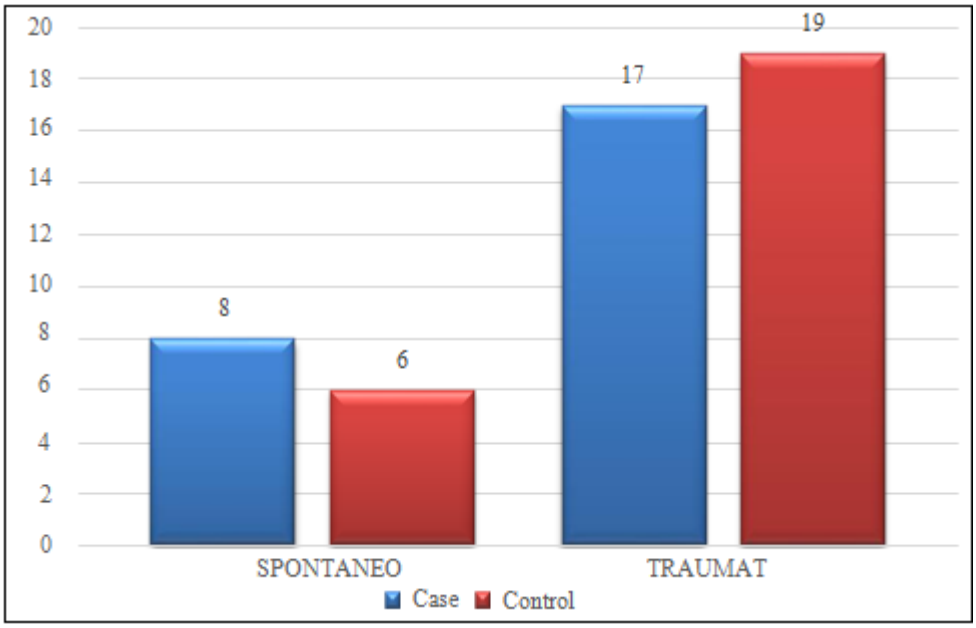
Graph 2: Distribution of patients according to Sex

Onset of Diabetic Foot Ulcer

Table 3: Distribution of patients according to onset of Ulcer

Onset	Case	%	Control	%
Spontaneous	8	32%	6	24%
Traumatic	17	68%	19	76%
Total	25	100%	25	100%

According to our study, 17 patients developed ulcer because of trauma, while 8 patients develop ulcer spontaneously, in case group. In control group 19 patients developed ulcer because of trauma, while 6 patients develop ulcer spontaneously.



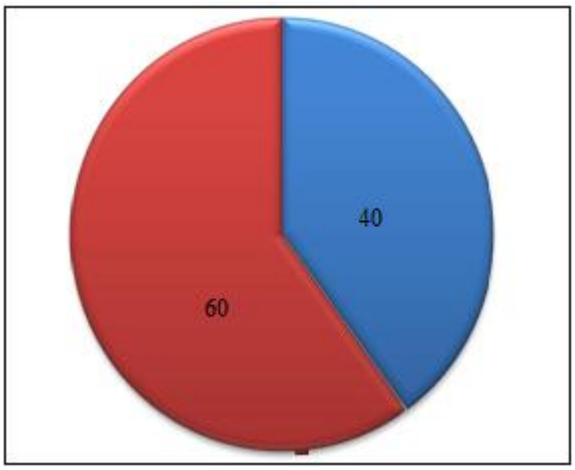
Graph 3: Distribution of patients according to Onset of ulcer

Site of Diabetic Foot Ulcer

Table 4: Distribution of patients according to Site of ulcer

Site	Case	%	Control	%
Dorsum	10	40%	8	32%
Plantar	15	60%	17	68%
Total	25	100%	25	100%

In our study, the case group included 10 patients with ulcers over the dorsum of the foot and 15 patients with ulcers over the plantar aspect, whereas the control group included 8 patients with ulcers over the dorsum of the foot and 17 patients withulcers over the plantar aspect.



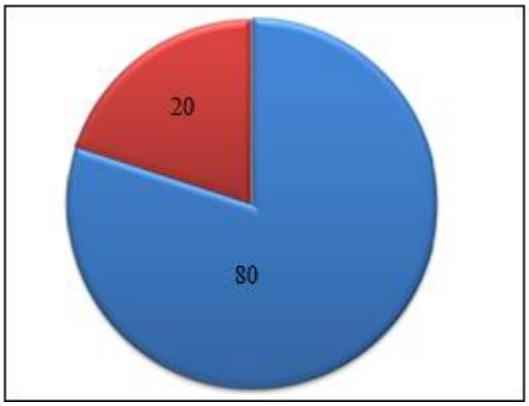
Graph 4: Distribution of patients according to Site of ulcer

Anti Diabetic Drugs

Table 5: Distribution of patients according to Anti Diabetic Drugs

Anti DM Drugs	Case	%	Control	%
Insulin	20	80%	19	76%
Oral Hypoglycemic Drugs	5	20%	6	24%
Total	25	100%	25	100%

In our study, 80% of patients in the case group and 76% of patients in the controlgroup, respectively, were using insulin to control their blood sugar.



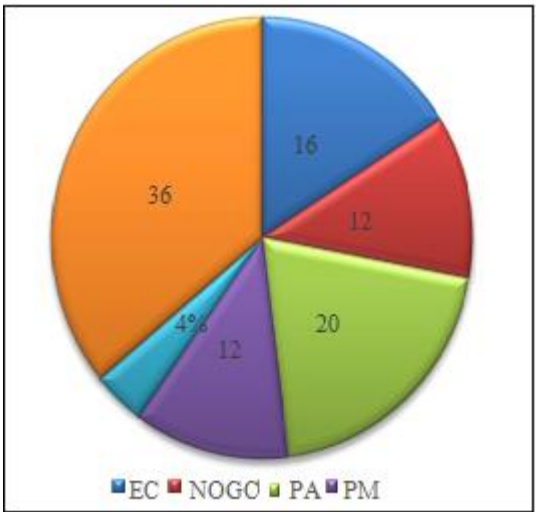
Graph 5: Distribution of patients according to Anti Diabetic Drugs

Wound Culture & Sensitivity

Table 6: Distribution of patients according to wound Culture & Sensitivity

Wound c/s	Case	%	Control	%
EC	4	16	2	8
NOGC	3	12	2	8
PA	5	20	4	16
PM	3	12	3	12
KP	1	4	3	12
SA	9	36	11	44
Total	25	100%	25	100%
Mean	4.16		4.16	
SD	2.47		3.13	
P'value	P = 1.0000			

- Staphylococcus aureus was the most often isolated bacteria from wounds (20 patients). Klebsiella Pnumoniae was the least prevalent isolated organism from the wound (4 cases).



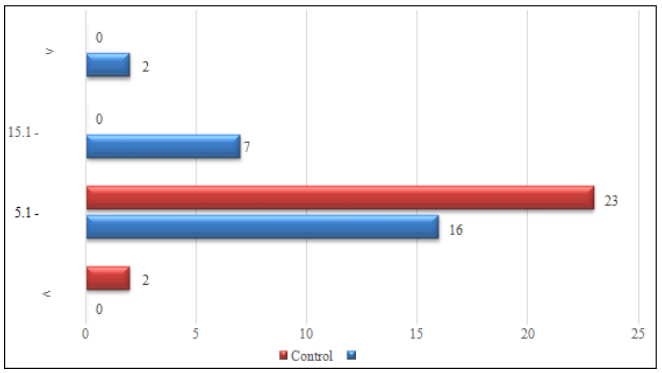
Graph 6: Distribution of patients according to Wound Culture and Sensitivity

Wound Contraction

Table 7: Distribution of patients according to Wound Contraction

IA-FA= CA	Case	%	Control	%
< 5.0	0	0%	2	8%
5.1-15.0	16	64%	23	92%
15.1 -25.0	7	28%	0	0%
> 25	2	8%	0	0%
Total	25	100%	25	100%
Mean	14.64		7.24	
SD	5.66		2.45	
P'value	<0.0011Significant			

Mean percentage of area reduction was larger in the study group (14.64%) compared to the control group (7.24%), with a P value of <0.001 being considered significant.



Graph 7: Distribution of patients according to Wound Contraction

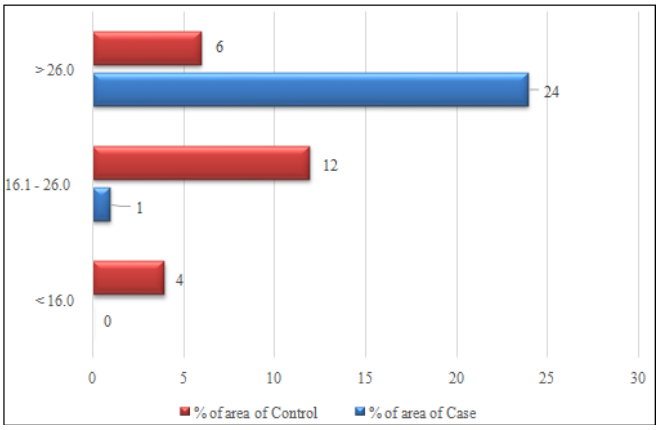
Wound Percent of Area of Reduction

Table 8: Distribution of patients according to Wound percent of area ofReduction

% of area of reduction	Cases	%	Control	%
<16.0	0	0%	4	16%
16.1 -26.0	1	4%	12	48%
>26.0	24	96%	6	24%
Total	25	100%	25	100%

Mean	47.43	22.44
SD	12.00	6.63
P'value	<0.001Significant	

The case group saw a greater mean percent area reduction (47.43%) than the controlgroup (22.44%).



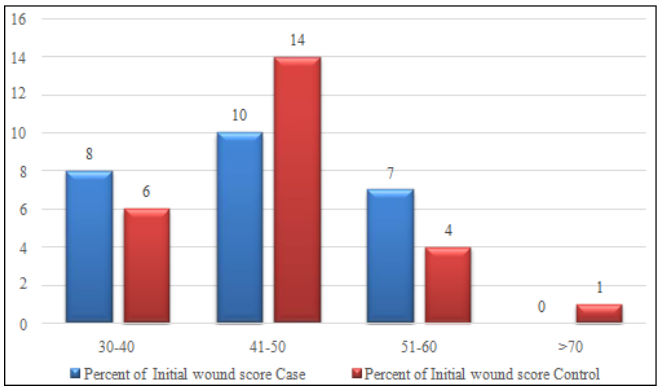
Graph 8: Distribution of patients according to Wound percent of areareduction

Initial Wound Score

Table 9: Distribution of patients according to Initial wound score

Percentage of Initial wound score	Case	%	Control	%
30-40	8	32%	6	24%
41-50	10	40%	14	56%
51-60	7	28%	4	16%
>60	0	0%	1	4%
Total	25	100%	25	100%

The percentage of initial wound score in the range of 41-50 group was found to be higher with the number of patients in the case group being 10(40%) and 14(56%); in the range of 51-60 in case group was 7(28%) and 4(16%); the range of >60 had no patient in case group and only 1(4%) in control group.



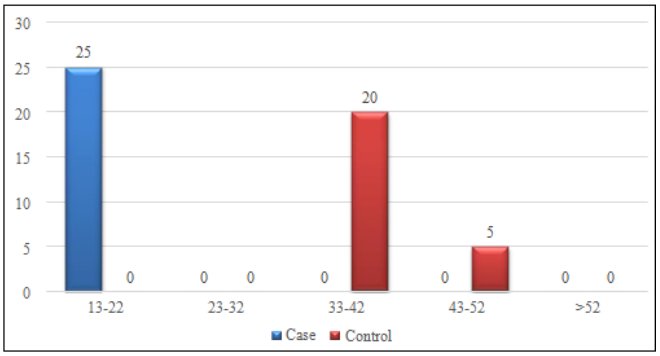
Graph 9: Distribution of patients according to Initial wound score

Final Wound Score

Table 10: Distribution of patients according to Final wound score

Final wound score	Case	%	Control	%
13-22	25	100%	0	0%
23-32	0	0%	0	0%
33-42	0	0%	20	80%
43-52	0	0%	5	20%
≥52	0	0%	0	0%
total	25	100%	25	100%
Mean	6.25		27.56	
SD	10.25		3.06	
P value	Significant <0.001			

Final wound evaluation results show that all patients in the case group had wound scores between 13 and 22 and those in the control group have wound scores between 33 and 42. In the case group, the maximum wound score was 21, while in the controlgroup, it was 33.



Graph 10: Distribution of patients according to Final wound score

5. Discussion

The patient's likely hood of developing a diabetic foot ulcer increases with age. Diabetic foot ulcer rate rises as people get older. **Hirase T et al**[13] found that the mean age of case group is 58.4 ±7.2 and in control group is 58.7±5.9. **Salem A et al**[14] found that the mean age of case group is 58.6 ±2.7 and in control group is 56.9±5.6. In our study case group had mean age is 56.52 ±7.26 and in control group is 54.84 ±7.97, which is similar with **Hirase T et al** [13] and **Salem A et al**[14] study.

Older patients are more likely to develop a diabetic foot ulcer. In our study maximum number of patients age were between 51-60 year out of which 14 were in case group and 12 in control group. Least number of patients was in 31-40 year age group, in which 1 patient in case group and 2 patients were in control group. Diabetic foot ulcers are mostly seen in 5th decade.

In our study, 31 patients were male and 19 patients were female and male to female ratio is 1.63:1. In study by **Goda AA et al** [11] 30 patients were male and 20 patients female and male to female ratio is 1.5:1, which is similar with our study. **Salem A et al**[14] 33 patients were male and 50 patients female and male to female ratio is 0.66:1, which is contrast to our study.

The most common cause for diabetic foot ulcer is trauma. In our study 17 patients developed ulcer because of trauma, while 8 patients develop ulcer spontaneously, in case group while in control group 19 patients were of traumatic and 6 patients spontaneously. Study conducted by **Srivignesh Kumar K et al** [15] 34 patients developed ulcer because of trauma and 16 patients spontaneously, in case group. In control group 33 patients developed ulcer because of trauma and 17 patients spontaneously. Study conducted by **Kumar V et al**.[16] 20 patients developedulcer after trauma, while 18 patients spontaneously. In control group 38 patients developed ulcer because of trauma, while 37 patients spontaneously. These findings are comparable to our study and this concludes that diabetic foot ulcer is more occur because of trauma.

In diabetic foot ulcer planter surface is commonly affected than dorsum of foot. In study conducted by **Orbanya et al 17** 23 and 1 patients had ulcer over planter aspect and dorsum of foot respectively and in control group 24 and 15 patients had ulcer over planter aspect and dorsum of foot respectively. **Elsaid A et al** [18] found that 4 and 3 patients had ulcer over dorsum of foot in case and control group respectively. While 8 and 9 patients had ulcer over planter surface respectively.

In our study 10 patients had ulcer over dorsum of foot and 15 patients had ulcer over planter aspect, and in control group 8 patients had ulcer over dorsum of foot and 17 patients over planter aspect. These findings are comparable with above mention study.

In diabetic patient blood sugar control is most important factor for the healing of any ulcer. They are managed by either oral hypoglycemic agents or insulin. In our study majority of patients were on insulin which constitute 75% and 76% in case and control group respectively. **Sakthivel Velayutham S et al**[19] also found that majority of patients were on insulin which was 78% and 81% in case and control group respectively which is similar to our study.

PRP is defined as the Platelet rich plasma. It contains a high level of platelets and a full complement of clotting and growth factors. These growth factors contribute to the healing process of chronic wounds.

PRP may inhibit cytokine release and reduce inflammation, working in conjunction with macrophages to enhance tissue repair and regeneration, encourage the creation of new capillaries, and quicken epithelialization. Additionally, it appears that the activated platelets have potential antimicrobial actions that could aid in wound healing. PRP helps in wound contraction which is calculated with following formula.[20]

1. $To\ calculate\ surface\ area\ of\ wound\ (cm^2) = Logenst\ Length^*\ (cm) \times Width\ (cm)$

2. $Rate\ of\ Contraction\ of\ Wound\ after\ four\ weeks\ of\ treatment = \frac{(Initial\ area - Final\ Area)}{Initinal\ Area} x100$

A study conducted by **Kumar V et al** [16]found that mean of wound contraction was 38.19± 5.86mm^2 and 19.63±6.83mm^2 in case and control group respectively. **Sakthivel Velayutham et al**[19] also found that mean of wound contraction was 34.42±2.52 mm^2 in case group and 13.52±2.55mm^2 in control group. In our study case group mean is 14.64±5.66 mm^2 and control group mean is 7.24±2.45 mm^2,Which shows that individuals who received PRP dressing had improved wound healing but in our study wound contraction was 14.64±5.66 mm^2 and 7.24±2.45 mm^2 in case and control group respectively.

According to our study percentage area of reduction range, mean value is 47.43 ±12%in case group and in control group 22.44±6.33% which is very similar to study conducted by **Srivignesh Kumar K et al**[15] in which showed 43.4±3.74% in case and 14.3±3.45% in control group. According to **Elsaid A et al**[18] study mean value is 43.2±34.4% in case group and 4.1±12.4% in control group.

In our study, case drop out was 20, 27 and 30 in 1st 2nd and 3rd week respectively. While 11, 8 and 6 in control group respectively.

The Bates-Jensen Wound Assessment Tool is a 13 item objective assessment createdto evaluate the condition of the wound and monitor healing. It helps to gauge how quickly wounds are healing.[114] In our study this tool used for initial and final assessment of wound. Majority of patients had score of >40 on initial assessment in case and control group which was 10 and 14 respectively. Maximum Bates Jensen wound score was 60 in case and 62 in control group. On final assessment of wound, wound score of all the patients in case group ranges between13 to 22 and in control group between 33 to 42.Maximum value of wound score on final assessment in case group was 21 and in control group was 33. According to this scoring system better improvement is noticed in case group as compared to control group.

According to our study, Staphylococcus Aureus is the most common culprit organism.

Patient's satisfaction score was 4 in 19, 3 in 5, 2 in 1 patients in case group, while incontrol group 4, 12, 9 cases respectively.

6. Conclusion

PRP dressing can be considered as an effective intervention to facilitate wound contraction in diabetic foot ulcer patients. PRP dressing was found to be more efficient than conventional dressing in diabetic foot ulcer. It increases the rate of wound healing; hence it can be used as an adjunct to conventional dressings and debridement for diabetic wounds.

7. Limitation

1) Main limitation was fewer number of patient because of limited period of study and more drop out cases.
2) This study did not assess the associated costs.

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