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Efficacy of topical application of insulin versus platelet rich plasma versus normal saline dressings in the healing of diabetic foot ulcers: A study from a tertiary care center in India

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ABSTRACT

Background: Diabetic foot ulcers (DFU) are one of the major complications of diabetes. Despite proper insulin treatment and a strict diabetic diet, 15% of diabetic population develop non-healing ulcers which leads to amputation of the lower limb. Wound dressings represent a part of the management of diabetic foot ulceration. Normal saline (0.9%) wound dressings have been a useful adjunct in the treatment of open wounds. Topical insulin dressing improves wound healing by regulating oxidative and inflammatory responses. PRP dressing has emerged as an adjunctive and newer method for treating DFUs. Hence, the present study was undertaken to compare the effect of topical insulin, platelet-rich plasma (PRP), and normal saline dressing in healing of DFU. **Aims and Objectives:** The aim of the study was to study the comparison between topical application of insulin versus PRP versus regular normal saline dressing in healing of DFU. **Materials and Methods:** It is a duration based prospective comparative study including 60 patients divided equally into normal saline dressing group, topical insulin dressing group and PRP dressing group after they fulfilled all the inclusion and exclusion criteria and after obtaining the proper informed and written consent from relatives/patients. Ulcers at days 0, 7 and 14 in terms of size, depth and percentage reduction in area of wound were analyzed. **Results:** The mean ulcer size at day 14 in normal saline was 4.19 ± 0.95, in Insulin 2.64 ± 0.83 while 2.08 ± 0.47 in PRP group. The mean ulcer depth at day 14 in normal saline was 5.35 ± 1.18, in insulin 4.30 ± 1.38 while 2.35 ± 1.42 (mm) in PRP group, percentage reduction of mean ulcer size in normal saline was 27.02 ± 4.46, in insulin 50.31 ± 7.53 and 63.80 ± 5.75% in PRP group. **Conclusion:** PRP appears to be a promising agent in terms of faster wound healing, more significant reduction in the size of DFU as compared to topical insulin and other conventional dressings.

Key words: Diabetic foot ulcers; Normal Saline; Platelet rich plasma; Insulin; Wound healing

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INTRODUCTION

Diabetes mellitus is multifactorial multiorgan disease characterized by state of hyperglycemia in the body resulting from either defective insulin production or defective action of insulin over the peripheral tissues. There has been a continuous increase in the prevalence of diabetes worldwide at a frightening rate due to change in lifestyle, obesity, and physical inactivity. It leads to microangiopathy and macroangiopathy causing nephropathy, neuropathy, retinopathy, various lower limb complications, infections, peripheral vascular disease, ulceration, gangrene, Charcot's arthropathy, and non-traumatic lower limb amputations which leads to disability.[1]

Diabetic foot ulcers (DFU) are one of the major complications and considered as a major source of morbidity and cause of hospitalization in patients with

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diabetes.[2] Risk factors include diabetic neuropathy, peripheral vascular disease, smoking, poor glycemic control, previous foot ulcerations, and ischemia of large and small vessels. It is estimated that approximately 50–70% of all lower limb amputations are due to DFU. In addition, it is reported that every 30s, one leg is amputated due to DFU in worldwide.[3]

Diabetic ulcers are managed by offloading the wound using appropriate therapeutic footwear, daily dressings, serial debridement, antibiotic therapy, optimal control of blood glucose, correction of peripheral vascular insufficiency, assessment for neuropathy, bony deformity, and amputation if needed. Wound dressings represent a part of the management of diabetic foot ulceration. A wide array of dressings is now commercially available for treatment of DFU; thus, this study was done to compare the effect of topical insulin, platelet-rich plasma (PRP), and normal saline dressing in healing of DFU.

Aims and objectives

The objectives are as follows:

1. To study the efficacy of topical insulin on wound healing in DFU.
2. To study the efficacy of PRP on wound healing in DFU.
3. To compare the topical insulin dressing with normal saline dressing with PRP.

MATERIALS AND METHODS

The present hospital-based prospective comparative study was conducted in patients who presented with DFU to Surgical OPD and Emergency Department of GSVM Medical College, Kanpur, Uttar Pradesh. The study was pre-approved by the Institutional Ethics Committee (IEC) for the final permission. After obtaining, the permission of IEC the study was conducted. Study was done from December 2019 to October 2021 after all the inclusion and exclusion criteria were met and after obtaining proper informed and written consent from relatives/patients.

Inclusion criteria

The following criteria were included in the study:

- Patients above 20 years of age, having DFU
- Patients with grade I and II ulcers of Wagner's classification.

Exclusion criteria

The following criteria were excluded from the study:

- Any infected wound
- Patients with Grades III, IV, and V ulcers of Wagner's classification
- Doppler showing gross atherosclerotic changes and venous abnormalities like varicosities
- Malnutrition and uncontrolled diabetes mellitus with HbA1c > 8
- Patients receiving corticosteroids other immunosuppressive agents, radiation or chemotherapy 1 month before entry into the study
- Patients with absent peripheral pulses such as(dorsalis pedis artery, posterior tibial artery, and anterior tibial artery)
- Patients not willing to enroll in the study.

A total of 60 patients were equally divided into three groups of 20 patients each:

1. Group A (n=20)- In this group, ulcers were cleaned with normal saline and covered with sterile gauzes and sterile dressing done.
2. Group B (n=20)- In this group, ulcers were cleaned with normal saline then irrigated with 4 units (0.1ml) of human soluble insulin (H. Actrapid) in 1 ml of normal saline (0.9%) for each 10 cm^2
3. Group C (n=20)- In this group, ulcers were cleaned with normal saline and covered with PRP. Dressing was done twice weekly.

Ulcers were evaluated at day 14 in terms of mean ulcer size, depth, percentage reduction of mean ulcer size in the three different dressing groups. The collected information was recorded in master chart.

Statistical analysis

Statistical analysis was done using IBM SPSS version 16. Data were expressed as mean±standard deviation (SD), or percentage, whichever was appropriate for the subject's characteristic description variable. Group differences was compared using the Pearson Chi-square test for testing the significance of groups for categorical variables, and the Student t-test for testing the significance of continuous variables. For testing individual subgroups of the two groups, z test was used. $P<0.05$ was taken as significant.

RESULTS

Mean age in normal saline was 56.75±12.81, in insulin 50.35±10.39 while in PRP group it was 49.8±8.92 years (Table 1).

Total number of males and females in normal saline group was 12 and 08, in insulin group 13 and 07, while in PRP group 16 were males and 04 were females out of total 20 patients in each group (Table 2).

Mean duration of diabetes in normal saline was 7.15±1.78, in insulin 6.37±1.92 while in PRP group it

Table 1: Age group distribution in the groups

Age group (years)	Normal saline (n=20)	Insulin (n=20)	PRP (n=20)	Total (n=60)
31–40	03 (15%)	05 (25%)	04 (20%)	12 (20.0%)
41–50	06 (30%)	05 (25%)	07 (35%)	18 (30.0%)
51–60	04 (20%)	05 (25%)	07 (35%)	16 (26.7%)
61–70	05 (25%)	05 (25%)	02 (10%)	12 (20.0%)
71–80	02 (10%)	00 (0%)	00 (0%)	02 (0.3%)
Mean±SD	56.75±12.81	50.35±10.39	49.8±8.92	52.30±11.11

SD: Standard deviation, PRP: Platelet rich plasma

Table 2: Gender distribution of patients in the groups

Sex	Normal saline	Insulin	PRP	Total
M	12 (60%)	13 (65%)	16 (80%)	41 (68.3%)
F	08 (40%)	07 (35%)	04 (20%)	19 (31.7%)
Total	20	20	20	60

was 6.55±1.95 years. This was non-significant (P=0.4151, χ^2=1.758) (Table 3).

Table 4 showing that mean ulcer size in topical insulin was 5.21±0.90 cm^2 at day 0,4.19±0.88 at day 7 and 2.64±0.83 cm^2 at day 14. The statistical difference in mean ulcer size (cm^2) in topical insulin group at days 0, 7 and 14 was highly significant (P<0.0001).

The mean ulcer depth in topical insulin group was 7.30±1.38 mm at day 0, 6.30±1.38 at day 07, and 4.30±1.38 at day 14. The statistical difference at days 0, 7 and 14 was highly significant (P<0.001) (Table 5).

Mean ulcer size in PRP was 5.71±0.62 at day 0, 4.13±0.58 at day 07, and 2.08±0.47 cm^2 at day 14. The statistical difference in mean ulcer size (cm^2) in platelet-rich plasma (PRP) group at days 0, 7 and 14 was highly significant (P<0.0001) (Table 6).

The mean ulcer depth in PRP was 6.85±1.22 at day 0, 4.95±1.43 at day 07 and 2.35±1.42 (mm) at day 14. The statistical difference at days 0, 7 and 14 was highly significant (P<0.00001) (Table 7).

The mean ulcer size at day 7 in normal saline was 5.19±0.95, in insulin 4.19±0.88 while 4.13±0.58 in PRP group. The mean ulcer size at day 14 in normal saline was 4.19±0.95, in insulin 2.64±0.83 while 2.08±0.47 in PRP group. The difference in the mean size of ulcer at day 7 and day 14 between patients of Groups A, B, and C was highly significant (P<0.0001 and P<0.000001) (Table 8).

Table 9 showing that percentage reduction of mean ulcer size in normal saline was 27.02±4.46, in insulin 50.31±7.53, and 63.80±5.75% in PRP group. The statistical difference among patients of GroupsA, B, and C was highly significant (P<0.000001).

Table 10 showing that mean ulcer depth at day 07 in normal saline was 6.35±1.18, in insulin 6.30±1.38 while 4.95±1.43 (mm) in PRP group. The mean ulcer depth at day 14 in normal saline was 5.35±1.18, in insulin 4.30±1.38 while 2.35±1.42(mm) in PRP group. The difference in the mean ulcer depth at day 7 and day 14 between the patients of Groups A, B, and C was highly significant(P<0.001, P<0.00001).

In Table 11a, the statistical difference in distribution of granulation tissue of ulcers at day 7 in Groups A, B, and C was insignificant.

Table 11b showing that granulation tissue at day 14 in normal saline was healthy in 30%, in insulin 75% while in PRP it was healthy in 90%. The statistical difference of granulation tissue at day 14 between patients of Groups A, B, and C was highly significant (P<0.0001).

Table 12a showing that serous discharge at day 07 in normal saline was present in 25%, in insulin 50% while in PRP it was present in 65%. The serosanguinous discharge at day 07 in normal saline was present in 75%, in insulin in 50% while in PRP it was present in 35%. The statistical difference in distribution of discharge at day 7 between the patients of Groups A, B, and C was significant (P<0.05).

Table 12b showing that serous discharge at day 14 in normal saline was present in 40%, in insulin it was 60% while in PRP it was present in 85%. The serosanguinous discharge at day 14 in normal saline was present in 60%, in insulin it was 40% while in PRP it was present in 15%. The statistical difference in distribution of discharge at day 14 among patients of Groups A, B, and C was significant (P<0.05).

DISCUSSION

In normal saline and insulin group, 10 (50%) patients were in range of 41–60 years and in PRP group 14(70%) patients were in range of 41–60 years. Mean age in normal saline and insulin group was 56.75±12.81 years and

Table 3: Duration of diabetes in patients in the groups

Duration (years)	Normal saline	Insulin	PRP	Total	P value
0–5	05 (25%)	09 (45%)	07 (35%)	21 (35%)	>0.05 (0.4151)
6–10	15 (75%)	11 (55%)	13 (65%)	39 (65%)	
Mean±SD (years)	7.15±1.78	6.37±1.92	6.55±1.95	6.69±1.89	

SD: Standard deviation

Table 4: Mean ulcer size (cm²) in topical insulin dressing group

Ulcer size Mean±SD (cm²)	Day 0	Day 7	Day 14	P value
Insulin	5.21±0.90	4.19±0.88	2.64±0.83	<0.0001

SD: Standard deviation

Table 5: Mean ulcer depth (mm) in insulin dressings group

Ulcer depth Mean±SD (mm)	Day 0	Day 7	Day 14	P value
Insulin	7.30±1.38	6.30±1.38	4.30±1.38	<0.0001

SD: Standard deviation

Table 6: Mean ulcer size in PRP dressing group

Ulcer size (cm²) Mean±SD	Day 0	Day 7	Day 14	P value
PRP	5.71±0.62	4.13±0.58	2.08±0.47	<0.0001

SD: Standard deviation, PRP: Platelet rich plasma

Table 7: Mean ulcer depth (mm) in platelet-rich plasma (PRP) dressing

Ulcer depth Mean±SD (mm)	Day 0	Day 7	Day 14	P value
PRP	6.85±1.22	4.95±1.43	2.35±1.42	<0.00001

SD: Standard deviation, PRP: Platelet rich plasma

Table 8: Mean ulcer area size (cm²) in the different dressing groups

Ulcer size Mean±SD (cm²)	Normal saline	Insulin	PRP	P value
Day 0	5.69±0.95	5.21±0.90	5.71±0.62	>0.05
Day 7	5.19±0.95	4.19±0.88	4.13±0.58	<0.0001
Day 14	4.19±0.95	2.64±0.83	2.08±0.47	<0.000001

SD: Standard deviation, PRP: Platelet rich plasma

50.35±10.39 years, respectively. The males and females distribution in the normal saline was 60% and 40%, while in insulin group males and females were 65% and 35% of total 20 patients each. Most of the patients in normal saline and insulin group (75% and 55%) had duration of diabetes between 6–10 years, respectively, and the mean duration of diabetes in normal saline and insulin was 7.15±1.78 years and 6.37±1.92 years, respectively, which is similar to the study done by Sanjay et al.,[4] in which normal saline and insulin groups were 75.8±12.7 months and 70.8±7 months, respectively. In our study, in PRP group mean duration of diabetes was 6.55±1.95 years which is comparable to the study done by Prakasam et al.,[5] in which it was 9.35±1.59 years.

The mean ulcer area at the time of enrollment was 5.69±0.95 cm² in normal saline group and 5.21±0.90 cm² in insulin group, the mean depth of ulcer was 7.35±1.18 mm in normal saline group and 7.30±1.38 mm in insulin group. This was similar to the study conducted by Sanjay et al.,[4] had mean ulcer area of 5.35±0.6 cm² in normal saline group and 4.8±0.6 cm² in insulin group, the mean depth of ulcer was 8.4±0.7 mm in normal saline group and 8.6±0.9 mm in insulin group.[4] While in PRP group mean ulcer area and mean depth of the ulcer were 5.71±0.62 cm² and 6.85±1.22 mm respectively, similar to the study by Goda et al.,[6] in which mean initial ulcer area was 7.3 cm². In Group A at day 7,mean ulcer area was 5.19±0.95 cm² and mean depth of the ulcer was 6.35±1.18 mm. At day 14, the mean ulcer area was 4.19±0.95 cm² and mean depth of the ulcer was 5.35±1.18 mm similar to the findings of study of Sanjay et al.,[4] in which at day 7, the mean ulcer area was found to be 4.2±0.8 cm² and mean depth of the ulcer was 7.3±0.7 mm. At day 14, the mean ulcer area was found to be 1.9±0.5 cm² and mean depth of the ulcer was 5.8±0.8 mm.

In Group B at day 7, the mean ulcer area was 4.19±0.88 cm² and mean depth of the ulcer was 6.30±1.38 mm. At day 14, the mean ulcer area was 2.64±0.83 cm² and mean depth of the ulcer was 4.30±1.38 mm similar to the study of Sanjay et al.,[4] in which at day 7, the mean ulcer area was found to be 3.9±0.7 cm² and mean depth of the ulcer was 6.7±0.7 mm. At day 14, the mean ulcer area was 1.51±0.3 cm² and mean depth of the ulcer was 4.1±0.7mm.

In Group C At day 7, the mean ulcer area was found to be 4.13±0.58 cm² and mean depth of the ulcer was 4.95±1.43 mm. At day 14, the mean ulcer area was 2.08±0.47 cm² and mean depth of the ulcer was

Table 9: Percentage reduction of mean ulcer size in different dressings groups

% Reduction of ulcer size	Normal saline	Insulin	PRP	P value
Mean±SD (%)	27.02±4.46	50.31±7.53	63.80±5.75	<0.000001

SD: Standard deviation, PRP: Platelet rich plasma

Table 10: Mean ulcer depth (mm) in different dressings groups

Ulcer depth (mm) Mean±SD	Normal saline	Insulin	PRP	P value
Day 0	7.35±1.18	7.30±1.38	6.85±1.22	>0.05 (0.392)
Day 7	6.35±1.18	6.30±1.38	4.95±1.43	<0.001 (0.0017)
Day 14	5.35±1.18	4.30±1.38	2.35±1.42	<0.00001 (0.000004)

SD: Standard deviation, PRP: Platelet rich plasma

Table 11a: Granulation tissue in the groups (granulation tissue at day 7)

Granulation	Normal saline	Insulin	PRP	P value
Healthy	03 (15%)	06 (30%)	08 (40%)	>0.05
Unhealthy	17 (85%)	14 (70%)	12 (60%)	(0.21)
Total	20	20	20	

SD: Standard deviation, PRP: Platelet-rich plasma

Table 11b: Granulation tissue in the groups (granulation tissue at day 14)

Granulation	Normal saline	Insulin	PRP	P value
Healthy	06 (30%)	15 (75%)	18 (90%)	<0.0001
Unhealthy	14 (70%)	05 (25%)	02 (10%)	(0.00018)
Total	20	20	20	

SD: Standard deviation, PRP: Platelet rich plasma

Table 12a: Type of discharge in the groups (discharge at day 07)

Type	Normal saline	Insulin	PRP	P value
Serous	05 (25%)	10 (50%)	13 (65%)	<0.05
Serosanguinous	15 (75%)	10 (50%)	07 (35%)	(0.0375)
Total	20	20	20	

Table 12b: Type of discharge in the groups (discharge at day 14)

Type	Normal saline	Insulin	PRP	P value
Serous	08 (40%)	12 (60%)	17 (85%)	<0.05
Serosanguinous	12 (60%)	08 (40%)	03 (15%)	(0.0135)
Total	20	20	20	

2.35±1.42mm comparable to the study by Goda etal.,[6] which showed 0.6388±0.0009 healing area at day 7 and 0.66±0.04 ulcer healing rate per week.

In our study, the percentage area of reduction in normal saline group was 27.02±4.46%, in insulin group was 50.31±7.53% which is similar to the study done by Kanase et al.,[7] in which area of reduction was found to be 19.2% and 49.7% in both the groups, respectively, and in our study in PRP group it was 63.80±5.75% which is comparable to the study by Elsaid et al.,[8] in which percentage of reduction in PRP group was 43.2±34.4% in maximum longitudinal diameter and 42.3±37.5% in maximum horizontal diameter.

In our study,at day 7, in normal saline group 15 (75%) patients had serosanguinous discharge and 5 (25%) serous discharge. At day 14, 12 (60%) had serosanguinous and 8 (40%) had serous discharge comparable to the study of Sanjay et al.,[4] in which at day 12, 11 (55%) had serosanguinous and 5 (25%) had serous discharge.

At day 7, in insulin group 10 (50%) patients had serosanguinous discharge and 10 (50%) serous discharge. At day 14, 8 (40%) had serosanguinous and 12 (60%) had serous discharge comparable to the study by Sanjay et al.,[4] in which at day 12, 6 (30%) had serosanguinous and 14 (70%) had serous discharge.

At day 7, in PRP group 07 (35%) patients had serosanguinous discharge and 13 (65%) serous discharge. At day 14, 3 (15%) had serosanguinous and 17 (85%) had serous discharge.

In our study, at day 7, in normal saline group granulation tissue was healthy in 3 (15%),at day 14, in 6 (30%) patients.

In our study, at day 7, in insulin group granulation tissue was healthy in 6 (30%), at day 14 in 15 (75%) patients, similar to the study by Sanjay et al.,[4] in which at day 12, 14 (70%) had healthy and 6 (30%) had unhealthy granulation tissue.

In our study at day 7, PRP group granulation tissue was healthy in 8 (40%). At day 14,18 (90%) had healthy granulation tissue comparable to the study by Lone et al.,[9] who showed 62.85% patients developing granulation

tissue by the end of 2nd week.The statistical difference in distribution of granulation tissue on at day 7 and day 14 between the patients of Groups A, B, and C was significant ($P<0.05$).

Limitations of study

Sample size was small therefore need further more research including these three groups so that it can be relevantly projected to the whole population.

CONCLUSION

In our study, among three groups, PRP appears to be promising agent as it shows significant difference in ulcer at days 0, 7, and 14 in terms of size, depth, and reduction in percentage area. It also helps in production of granulation tissue and reduction in discharge which ultimately helps in faster healing, better wound closure, and prevent occurrence of complication. This study also shows benefits of insulin dressing over normal saline in reduction in ulcer size and depth. Further research is needed and prove the best dressing so that mankind can be helped and get better treatment.

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Author's Contribution:
VK-Concept and design of the study and prepared first draft of manuscript; **AKV-** Interpreted the results; **YM-**Reviewed the literature and manuscript preparation; **PS-** Concept, coordination and interpretation of results; **MG-**Statistical analysis and interpretation, preparation of manuscript, and revision of the manuscript.

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