Autologous Platelet Rich Plasma Dressing VERSUS Normal Saline Dressing In Management Of Diabetic Foot Ulcers

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Category- original research paper

ABSTRACT

AIM OF THE STUDY: To test the efficacy of autologous platelet rich plasma in chronic diabetic foot ulcers in comparison to conventional dressing.
OBJECTIVES OF THE STUDY
1.   To assess the incidence of complete wound closure in the experimental and control groups.
2.   To compare the rate of wound healing during the study in either group.
3.   To evaluate the incidence of complications among the healing ulcers including adverse events and serious adverse reactions.
 MATERIALS AND METHODS From January 2018 to June 2019 patients presented with chronic diabetic foot ulcers recruited in this study. This was a prospective study conducted at ESIC Medical College PGIMSR, Bangalore. Total of 100 patients were assigned. They were grouped into two groups. Control group patients were treated with conventional dressing and study group patients were treated with autologous platelet rich plasma (PRP) dressing and observed for reduction in the wound size in a span of 21 days.
BACKGROUND: Chronic non healing diabetic foot ulcers are a common cause of amputation. Accepted therapeutic objectives and standards of care for diabetic foot ulcers include wound debridement, off- loading , etc. Apart from these conventional methods to facilitate wound healing various new methods are emerging such as cellular therapies which include platelet-rich plasma (PRP).Platelets releases multiple growth factors. These factors act locally on wound and hasten the healing process. This study intends to demonstrate the therapeutic role of autologous platelet rich plasma in healing of diabetic foot ulcers.
Results: The study group patients showed higher reduction in wound size of about 40.12%. as against 27.45%   of the control group with P value < 0.005.
Conclusion: Platelet rich plasma dressing significantly increases incidence of wound healing in chronic diabetic foot ulcers.

Key words: Platelet rich plasma, normal saline dressing, chronic diabetic foot ulcers, Growth factors.

INTRODUCTION

Chronic wounds are characterized by a long inflammatory phase that hinders regenerative wound healing. Chronic wounds, especially in patients with diabetes mellitus (DM), are a major health challenge. The goal of wound care in chronic ulcers is to facilitate healing and prevent lower extremity amputations using standardized protocols of wound care. The standard treatment algorithm includes a complete patient and wound assessment, history, physical examination, and a variety of diagnostic tests that determine the need for infection control intervention, revascularization, excision and debridement, skin graft/flap, wound protection, and education.[1]

Diabetic foot is defined as 'Infection, ulceration or destruction of tissues of the foot associated with neuropathy and/or peripheral artery disease in the lower extremity of a person with (a history of) diabetes mellitus.[2]

 Non-healing diabetic foot ulcers are a common cause of amputation and represent significant costs to health care system and reduce patient quality of life. The goal of diabetic foot ulcer treatment is to obtain wound closure as expeditiously as possible. Accepted therapeutic objectives and standards of care for diabetic foot ulcers include wound debridement, pressure relief in the wound area, appropriate wound management (e.g., moist wound healing), infection management, ischemia management, medical management of co-morbidities, and surgical management as needed.[3]

Apart from these conventional methods to facilitate wound healing various new methods are emerging such as cellular therapies which include platelet-rich plasma (PRP). This can have an adjunctive role in a standardized, quality treatment plan.[4]

Platelets release certain growth factors from alpha granules which are located in thrombocyte cell membrane which

include platelet derived growth factor (PDGF), epidermal growth factor (EGF), platelet derived angiogenesis factor and platelet factor.[5] These factors act locally on wound and hasten the healing process. Platelet extract has been used in many studies and has shown impressive results in healing of chronic non healing diabetic foot ulcers.

Since not all patients can afford commercially available recombinant platelet gel for dressing, platelet extract from the patient's own blood has been used in trials on chronic wound.

The purpose of this study is to evaluate how autologous platelet-rich plasma (PRP) affects initial wound healing trajectories of chronic, non-healing diabetic foot wounds in a hospital care setting.

Hence, this study intends to demonstrate the therapeutic role of autologous platelet rich plasma in healing of chronic non-healing diabetic foot ulcers.

AIM OF THE STUDY

To compare the efficacy of autologous platelet rich plasma in chronic non-healing ulcers in comparison to conventional normal saline dressing.

OBJECTIVES OF THE STUDY

1. To assess the incidence of complete wound closure in the experimental and control groups.
2. To compare the rate of wound healing during the study in either group.
3. To evaluate the incidence of complications among the healing ulcers including adverse events and serious adverse reactions.

Type of study: prospective, time bound study.
Duration of study: 18months (January 2018 to June 2019)
Sampling procedure: simple random sampling

SAMPLE SIZE CALCULATION

100 patients of diabetic foot ulcer divided into 2 groups, 50 patients each. 1 group will undergo autologous platelet rich plasma dressing and other group will undergo normal saline solution dressing. The sample size has been calculated by considering the mean duration of healing (in weeks) in autologous PRP group (8.2±1.19) and in normal saline method (10.2±2.0, assumed) from published literature.

The sample size was calculated using G*Power version 3.1.9.2 software:
t tests – Independent t test,
Analysis: A priori: Compute required sample size
Input: Effect size f = 0.6 (1.2 weeks)
α err prob = 0.05
Power (1-β err prob) = 0.90

Number of groups = 2
Output: Noncentrality parameter λ = 13.1351351
Critical t = 3.0647607
Numerator df = 2.0000000
Denominator df = 94
Total sample size = 94
Actual power = 0.9043519

Calculated sample size was 94, it was round off to 100 (50 in each group).

Inclusion criteria

1. Age group of 18 to 80 years with long standing non healing diabetic foot ulcers
2. patients who had given written consent to be a part of study group
3. Ulcer ≥ 4 weeks duration.
4. Ulcer ≤ 15 cm^2 in size.
5. Hb ≥ 10 gm%.

Exclusion criteria

1. Screening platelet count < 100 × 10^9/l.
2. Patients with known or suspected osteomyelitis.
3. Patients with immunodeficiency.
4. Patients with serum creatinine above 1.5 mg/dl.
5. Severe infection (presence of visible pus or copious wound exudates).
6. Presence of cellulitis, inadequate perfusion, ischemia, gangrene.

METHOD

The present study was carried out at ESIC medical college PGIMSR,Bengaluru, where 100 patients with diabetic foot ulcer more than 4 weeks participated in the present study. Using a pretested and predesigned proforma the study population was randomized into either study group or control group using a computerized randomization chart. Out of 100, patients, 50 took treatment in the form of conventional normal saline dressings and 50 took treatment with autologous Platelet rich plasma dressing. Off-loading of pressure from the affected area were done in both the groups. Photographs of the ulcers before and after the dressings were taken, along with culture and sensitivity of the ulcers. After undergoing a detailed clinical examination, and relevant investigations, the initial wound area was recorded after sharp debridement by Measuring length x width. Both the groups were subjected to dressings. Platelet rich plasma dressing was done twice weekly. The patients were followed up a period of 3 weeks in both the groups. The outcome, that is the area of the target ulcer was

measured by using a metric tape. Results were calculated by using student 't' test.

DRESSING TECHNIQUE:

For conventional dressing: The ulcer was cleaned with normal saline and saline soaked gauze piece was kept over the ulcer which was covered with pad and roller bandage.

For platelet rich plasma dressing

The ulcer was cleaned with Normal Saline. Platelet rich plasma was prepared from patients blood and applied over the wound area twice weekly. At the end of 21 days the wounds in both the groups were inspected and the wounds were compared based on the following parameters. They are:

1. To assess the incidence of complete wound closure in the experimental and control groups.
2. To compare the rate of wound healing during the study in either group.
3. To evaluate the incidence of complications among the healing ulcers including adverse events and serious adverse reactions.

The dressings were changed as described in both control and study groups for 21 days and appearance of healthy granulation tissue is observed and the final area is measured on 21st day by using a metric tape and subjected to statistical analysis.

OBSERVATION AND RESULTS

TABLE 1: DISTRIBUTION OF TYPE OF ONSET OF ULCER

		Cases	Controls	Chi square	p-value
Type of ulcer	Traumatic ulcer	34 (68.0)	33 (66.0)	1.84	0.445
	Spontaneous ulcer	16 (32.0)	17 (34.0)		
Total		50 (100.0)	50 (100.0)		

GRAPH 1- ONSET OF ULCER

ONSET OF ULCER
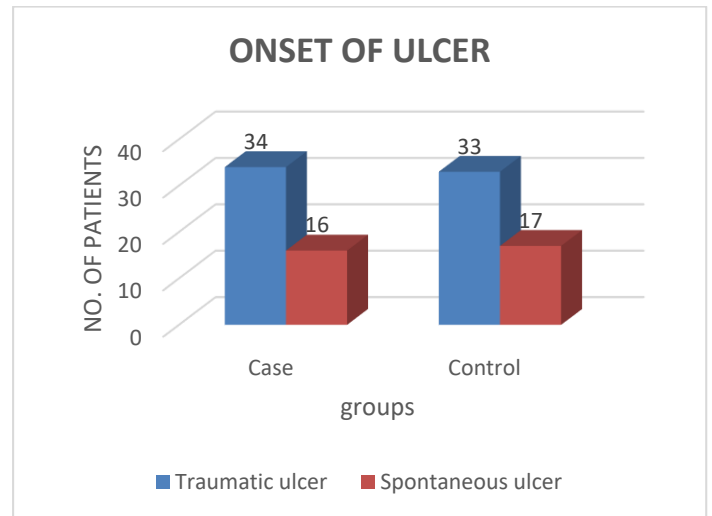
TABLE 2 : DEMOGRAPHIC DISTRIBUTION OF STUDY PARTICIPANTS

		Cases	Controls	test	p-value
AGE	<40 years	24(48.0)	22 (44.0)	2.22	0.25
	≥40 years	26 (52.0)	28 (56.0)		
	Mean age	45.0±11.0	45.8±13.6	1.05	0.44
GENDER	Male	30 (60.0)	35 (70.0)		
	Female	20 (40.0)	15 (30.0)	0.88	0.90

GRAPH 2- AGE DISTRIBUTION
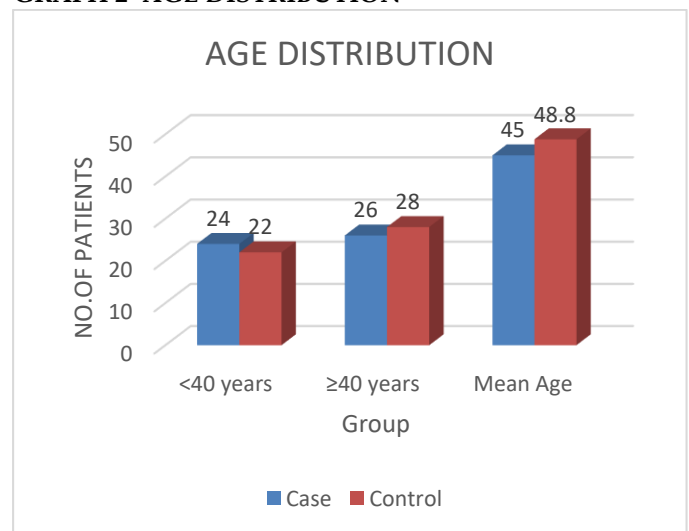
AGE DISTRIBUTION

GRAPH 3- SEX DISTRIBUTON

SEX DISTRIBUTON
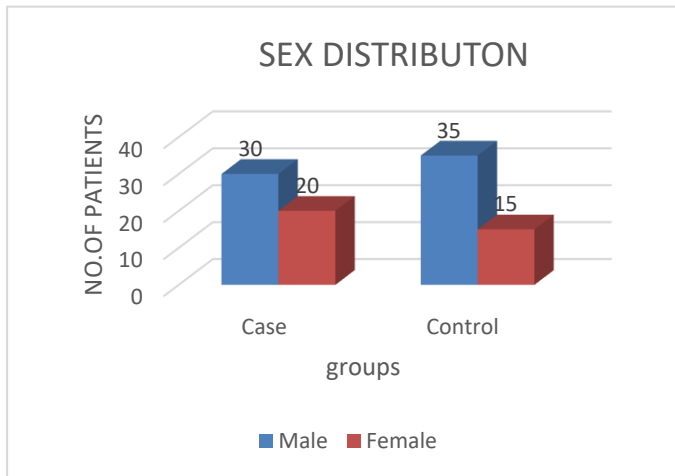
TABLE 4 : MEAN INITIAL AREA OF ULCER BEFORE PRP APPLICATION

	group	N	Mean	Std. Deviation	Std. Error Mean	t-test	p-value
Initial area of ulcers	Cases	50	1211.367	419.9419	76.6706	0.88	0.86
	Controls	50	1400.200	477.4922	87.1777		

TABLE 5: MEAN FINAL AREA OF ULCER AFTER PRP APPLICATION

	group	N	Mean	Std. Deviation	Std. Error Mean	t-test	p-value
Final area of ulcers	Cases	50	725.500	166.3647	30.3739	12.8	*0.002*
	Controls	50	1015.800	400.8606	73.1868		

TABLE 3: MEAN FASTING BLOOD SUGAR OF STUDY PARTICIPANTS

	group	N	Mean	Std. Deviation	Std. Error Mean	t-test	p-value
FBS	Cases	50	105.100	14.8750	2.7158	1.88	0.77
	Controls	50	104.167	13.7040	2.5020		

GRAPH 5- MEAN AREA OF ULCER

MEAN AREA OF ULCER

GRAPH 4- FASTING BLOOD SUGARS

FASTING BLOOD SUGARS
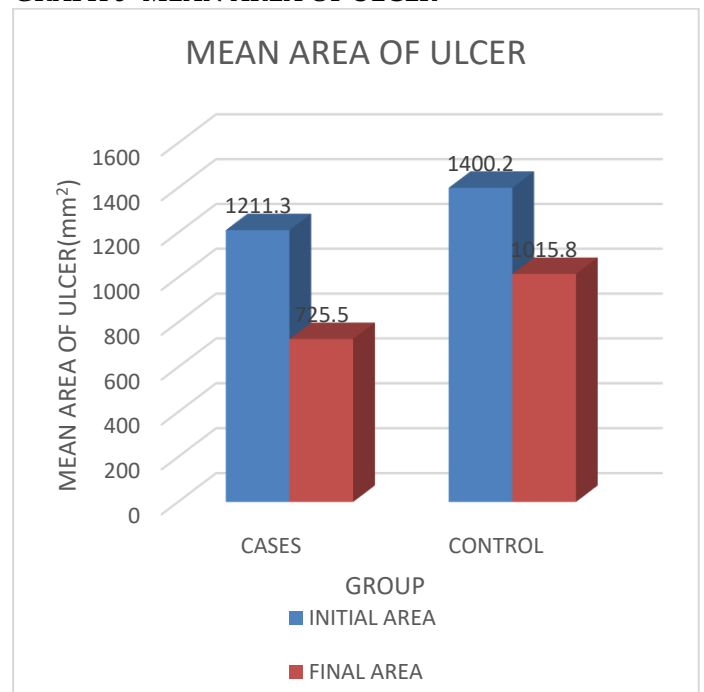
TABLE 6: MEAN DIFFRENCE AREA OF ULCER AFTER APPLICATION

	group	N	Mean	Std. Deviation	Std. Error Mean	t-test	p-value
Mean differe nce	Cases	50	485.867	415.5125	75.8618	10.5	*0.004*
	Controls	50	384.400	643.9781	117.5738		

GRAPH 6-MEAN DIFFERENCE AREA OF ULCER (INITIAL AREA - FINAL AREA)

MEAN DIFFERENCE AREA OF ULCER (INITIAL AREA - FINAL AREA)
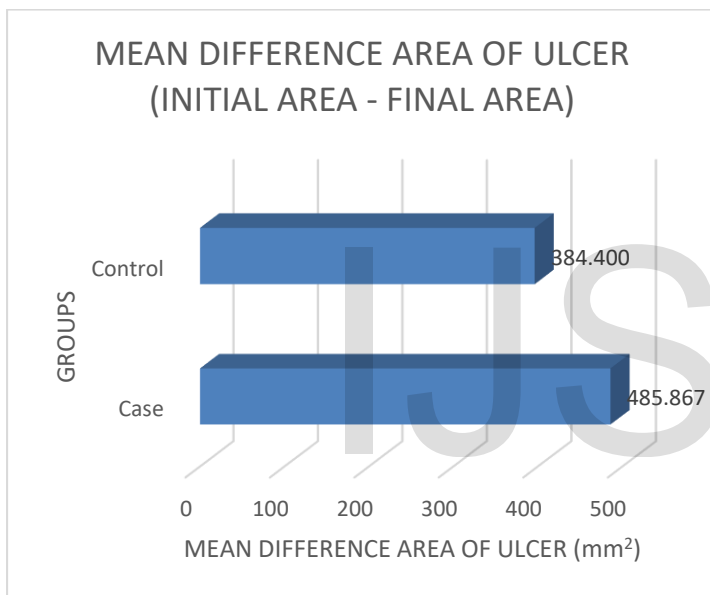
TABLE 7: MEAN DURATION OF HEALING

	groups	N	Mean	Std. Deviation	Std. Error Mean	t-test	p-value
Weeks for healing	Cases	50	3.253	.8378	.1530	8.74	*0.03*
	Controls	50	4.733	.8683	.1585		

MEAN DURATION FOR HEALING

TABLE 8: PERCENTAGE % AREA REDUCTION IN TWO GROUPS OF GROUPS

% area reduction	Cases	Controls	Chi square/t-test	p-value
<15	0 (0.0)	35(70.0)	11.24	*<0.001*
15-30	10 (20.0)	10(20.0)		
>30	40 (80.0)	5 (10.0)		
Total	30(100.0)	30(100.0)		
Mean ± SD	43.40±3.74	14.03±3.45	18.44	*<0.001*

GRAPH 8- PERCENTAGE OF AREA REDUCTION OF ULCERS

PERCENTAGE OF AREA REDUCTION OF ULCERS

GRAPH 7- MEAN DURATION FOR HEALING
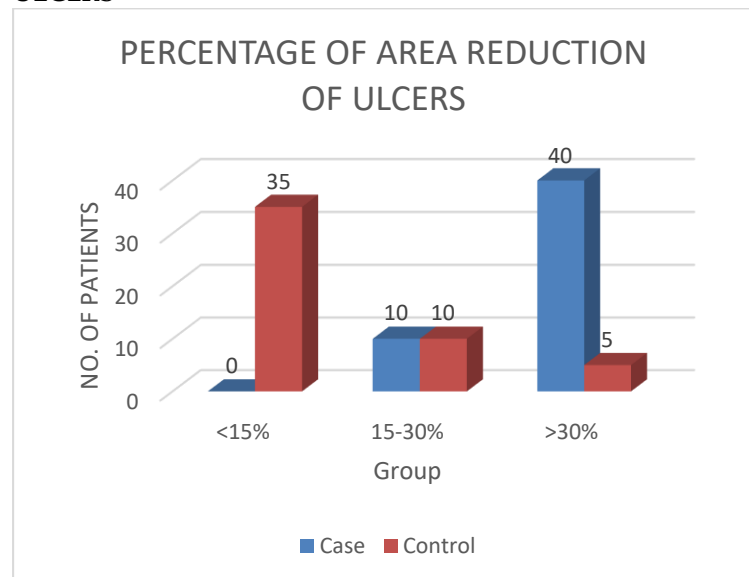
TABLE 9: DISTRIBUTION ACCORDING TO SITE

Site	Cases	Controls	Chi square	p-value
P	25 (50.0)	24 (46.6)	2.017	0.09
LM	5 (10.0)	04 (8.0)		
MM	8(16.0)	10 (20.0)		
D	12(24.0)	12 (24.0)		
Total	50 (100.0)	50 (100.0)		

DISCUSSION

Successful wound dressing should keep the wound moist and be devoid of any adverse reactions such as infection, maceration and allergy. It is every surgeon's desire that after dressing the wound, it should heal without any complications. Diabetic foot ulcers are chronic wounds, stuck in inflammation phase and shows cessation of epidermal growth.

The present study was conducted at ESIC Medical college and PGIMSR, Bengaluru to study the effect on chronic diabetic wound healing dynamics.

In the present study it was seen that the incidence of diabetic foot ulcers were more in males (65.00%) as compared to females (35.00%). The second national data source, NHDS documented higher hospital rates in males suffering from diabetic foot ulcer.

According to age, 54% cases are above 40years of age. 46% cases are below 40years of age. The prevalence of diagnosed diabetics increases with age (the diabetic foot). In this study patients with vascular complications such as pulse less limb and the patients with osteomyelitis were excluded.

In this study, 67.00% of the ulcers were traumatic in origin, trauma being the triggering factor secondary to neuropathy. 33.00% were spontaneous in origin secondary to blister rupture or unnoticed trivial trauma.

49 patients had ulcer on the plantar surface of the forefoot and 24 patients had ulcer on the dorsum of foot. Study conducted by Edmonds et al in 1986, (Edmonds) showed more foot ulcers were on plantar and fore foot areas. Most of the diabetic foot ulcers are invariably shoe related and due to gait abnormalities. They can be prevented by appropriate sized footwear. However in our study the incidence of ulcers over the plantar aspect of the foot were

not as high as postulated by Edmonds et al. Most of the patients (78.00%) were on insulin for control of sugar whereas only 22.00 % were on Oral Hypoglycaemic Agents.

In our study it was observed that participants receiving PRP dressing had better wound contraction of 40.12%. As compared to the group receiving only conventional dressing (normal saline dressing) in whom the mean wound contraction was 27.45%, these were found to be statistically significant on unpaired Student t test (p<0.004) suggesting that PRP dressing enhances wound healing in diabetic wounds. No patients underwent major amputations in both the groups.

Feasibility of this study:

In the present study we have taken 100 patients suffering from Diabetes Mellitus with foot ulcers. Patients were taken up for study based on inclusion and exclusion criteria. Out of 50 patients, 50 (30 males, 20 females) were study cases and 50 (35 males and 15 females) were control.

Participants included in the study group were treated with the PRP dressing biweekly for three weeks. All 50 patients selected for PRP treatment complied for the three weeks period of the study. The initial area measurement was taken on first week and final area measurement on third week was taken on transparent sheet. All 50 patients selected as a control complied for the three weeks duration period of the study. The initial area measurement on first week final area measurement on three week was taken on transparent sheet.

We have applied the following formula to calculate % reduction in area of wound after three weeks period in both cases and control groups.
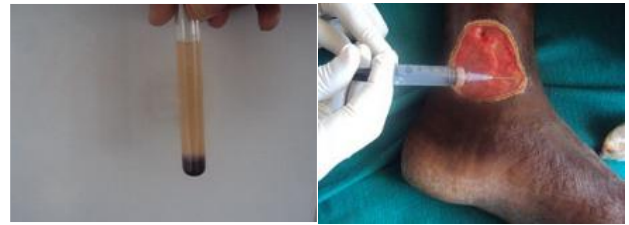
Rate of contraction of wound after 21days of treatment =

$$\frac{(Initial\ area - Final\ Area) \times 100}{Initial\ area}$$

We have found 40.12% rate of contraction of wounds in the control groups as compared to 27.45% contraction of wounds in study group. Therefore, study groups are having 12.67 % more wound contraction as compared to control group. On applying unpaired student t-test p<0.004 which is significant.

CONCLUSION

From our study, we can conclude that PRP dressing therapy promotes wound healing in patients suffering from chronic non-healing diabetes foot ulcers. The wounds in subjects treated with PRP dressing contracted more faster than the wounds treated with (40.12%. Vs 27.45% ;   P = <0.005 Significant) which indicates PRP dressing is an effective modality to promote   wound contraction in patients suffering from diabetic foot ulcers and can be used as an adjunct to conventional mode of treatment (conventional dressings and debridement) for healing of diabetic foot ulcers.
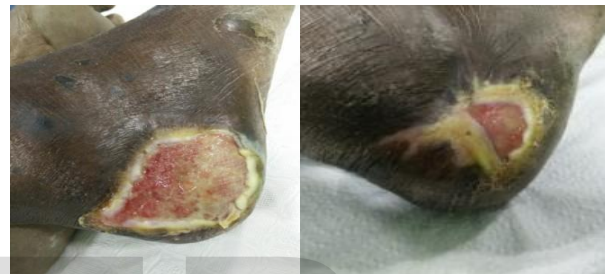
Fig 1.11- CENTRIFUGE

Fig 1.12- BLOOD COLLECTED IN TEST TUBE WITH ACD AND AFTER FIRST CENTRIFUGE

Fig 1.13-AFTER SECOND CENTRIFUGE AND PRP INJECTED IN WOUND SITE

PRP APPLICATION FOR 21 DAYS (Figure 1.16)

Before   **After**

Before   **After**

Before   **After**

NORMAL SALINE DRESSING FOR 21 DAYS   (Figure 1.17)

Before   **After**

Before   **After**

were treated with normal saline dressing and study group patients were treated with autologous platelet rich plasma (PRP) dressing and observed for reduction in the wound size in a span of 21 days. Outcome was assessed in terms of the incidence of complete wound closure in the experimental and control groups, the rate of wound healing during the study in either group, incidence of complications among the healing ulcers including adverse events and serious adverse reactions. We have found 40.12% rate of contraction of wounds in the control groups as compared to 27.45% contraction of wounds in study group. Therefore, study groups are having 12.67 % more wound contraction as compared to control group. On applying unpaired student t-test $p < 0.004$ which is significant. Also we concluded that autologous platelet rich plasma dressing significantly increases incidence of wound healing in diabetic foot ulcers.

SUMMARY

Number of diabetic foot ulcer cases are increasing day by day and Diabetic foot non-healing ulcers are a common cause of amputation and represent significant costs to health care system and reduce patient quality of life. The goal of diabetic foot ulcer treatment is to obtain wound closure as expeditiously as possible. Apart from these conventional methods to promote wound healing various new methods are emerging such as cellular therapies which include platelet-rich plasma (PRP). The purpose of this study is to evaluate how autologous platelet-rich plasma (PRP) affects initial wound healing trajectories of diabetic foot non-healing wounds in a hospital care setting. . This was a prospective study conducted at ESIC MC PGIMSR, Rajaji nagar, Bangalore -10. Total of 100 patients were included, 50 patients to each group. Control group patients

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