Section: General Surgery

Original Research Article

# THE EFFECT OF PLATELET DERIVED GROWTH FACTOR ON DIABETIC FOOT ULCERS: A PROSPECTIVE RANDOMISED CONTROL STUDY

**Jayalal. J. A.[1], EdwinKinsRaj.S[2], Baghavath.P.R.[2], Mahesh.L[3], Jonathan[3], Kiruba[3], Ajish[3]**

[1]Professor and HOD of General Surgery, Kanyakumari Govt. Medical College, India.
[2]Assistant Professor of General Surgery, Kanyakumari Govt. Medical College, India.
[3] Postgraduates in Department of General Surgery, KGMCH, India.

*Received* : 02/03/2023
*Received in revised form* : 27/03/2023
*Accepted* : 12/04/2023

*Keywords:*
*Diabetic foot ulcer, PDGF, Ulcers, Wound healing.*

Corresponding Author:
**Dr. Jayalal. J. A**
Email: lapsurgeon2001@yahoo.co.in

DOI: 10.47009/jamp.2023.5.3.109

Source of Support: Nil,
Conflict of Interest: None declared

*Int J Acad Med Pharm*
2023; 5 (3); 514-519

## Abstract

**Background:** The majority of the cost associated with the care of diabetics is attributable to chronic or non-healing lower extremity ulcerations, which are a substantial source of morbidity and mortality in diabetics. Several growth factors, some of which have numerous effects on various cell types, are involved in the complicated process of healing wounds. One important growth factor, platelet-derived growth factor (PDGF), is present throughout the entire healing process. The main cause of lower extremity ulcerations is neuropathy, and the aim of treating any wound is to restore tissue integrity as soon as feasible. PDGF application is better than good wound care alone. However, the evidence to demonstrate the safety profile and efficacy of PDGF in diabetic foot ulcers is minimal. **Aims and Objectives:** To evaluate the efficacy of PDGF over saline dressing in the healing of diabetic ulcers. **Materials and Methods:** Prospective randomized controlled trial design conducted in Kanyakumari medical college over a period of 8 weeks. 50 Patients with diabetic foot ulcers admitted to the septic ward were included in the study. Of them 25 patients were included in the study/treatment group, 25 patients were in the control group, randomized by lot method. **Results:** 25 patients in the control group have undergone conventional normal saline dressings and the remaining 25 patients were treated with rh - PDGF. All patients received appropriate methods daily. Optimal Glycemic control and appropriate control of infection were sustained in both groups. X-ray foot was taken for all patients to assess the bony involvement. The wound surface area measurement was taken weekly and granulation tissue was measured twice weekly, the final area measurement was on day 56 (week 8), and both groups were compared. An increase in the percentage of granulation tissue cover (80% vs 48%) and a decrease in wound surface area (7sq.cm vs 12sq.cm) was noted. **Conclusion:** The wounds in the study group treated with recombinant PDGF dressing contracted more with increased granulation tissue cover than the wounds in the control group which indicates PDGF dressing is an effective modality to facilitate wound healing in Diabetic foot ulcers. In terms of safety, and effective promotion of healing PDGF dressing is found to be better, and as an adjunct to saline dressing for healing of the diabetic wound, it gives good results. Healing of ulcers receiving PDGF was significantly faster as compared to ulcers receiving normal saline dressing with a statistically significant outcome ($p<0.01$).

## INTRODUCTION

Chronic hyperglycemia caused by diabetes mellitus (DM) can cause complications like retinopathy, nephropathy, and neuropathy. In addition, dyslipidemia plays a significant role in the development of arterial disease. The most frequent reason for non-traumatic lower limb amputations is diabetes. According to reports, between 1 and 4 percent of people with diabetes experience foot ulcers each year. Due to the development of multidrug-resistant organisms and microvascular complications, diabetic foot ulcers are invariably chronic and difficult to heal.[1,2] Deficits in wound healing are caused by more than 100 physiological variables in people with diabetes. Reduced or


ISSN (O): 2687-5365; ISSN (P): 2753-6556

impaired growth factor production, angiogenesis response, macrophage function, collagen accumulation, epidermal barrier function, amount of granulation tissue, keratinocyte and fibroblast migration and proliferation, the number of epidermal nerves, bone healing, and balance between the accumulation of ECM components and their remodeling by Matrix Metalloproteinases(MMP) are a few of these. The primary cause is due to an unbalanced relationship between MMPs and MMP inhibitors.[3] According to WHO report India today heads the world with over 32 million diabetic patients.[4]

In Present era the diabetic foot ulcers are treated with some physical therapies such as vacuum-assisted closure, high voltage pulsed current electrical stimulation, hyperbaric oxygen therapy (HBOT), and negative pressure wound therapy (NPWT), some biological therapies were also evaluated in diabetic foot ulcer treatment.[5,6] Some growth factors such as Epidermal growth factors.[7,8] granulocyte colony-stimulating factor, nerve growth factor, vascular endothelial growth factor, and activated platelet-rich plasma were evaluated in diabetic foot ulcers. Platelet-Derived Growth Factor (PDGF) is one of the growth factors important in angiogenesis and regeneration that is used in treating chronic ulcers.

PDGF is derived from platelets that contain alpha and beta granules. The rh-PDGF is produced by recombinant DNA process by inserting the human gene for the B chain of the Growth Factor in the yeast saccharomyces cevisiae8. Platelet-derived growth factor (PDGF) is a dimeric protein, composed of 2 disulfide–linked polypeptide chains. It exists in 3 different isomers the heterodimer PDGF –ab consisting of an a and b chain, and 2 homodimers, consisting of 2a or 2b chains (pdgf –aa and pdgf –bb) it has been shown in preclinical and clinical studies to promote the formation of granulation tissue at the wound site and to stimulate wound healing.[9] Microscopic examination of the wounds treated with topical PDGF showed a marked increased intensity of the inflammation phase of the wound healing cascade characterized by an increased presence of neutrophils, monocytes, and fibroblasts grossly. It is hypothesized that PDGF positively promotes angiogenesis indirectly through its activities on other inflammatory cells.

There is decrease in platelet function in patients with chronic diabetes. In type 2 diabetic individuals, the platelets adhere to the vascular endothelium and aggregate more easily in comparison to the healthy individuals. As the platelets here loose the sensitivity to normal restraint exerted by prostacyclin (PGI2) and nitric oxide (NO) produced by the vascular endothelium, it results in decrease in function of the platelet. The Platelet Rich Fibrin containing platelets with the alpha granules trapped in fibrin is expected to release some growth factors. Irrespective of the fact that, the platelets in Diabetic individuals will not have the usual efficacy of the function, the concentration of growth factors in PRF can still help in healing Diabetic Foot Ulcer (DFU).

Encouraging results have shown that PDGF is better than good wound care alone. The average time for healing was shorter with a greater reduction in ulcer size. Clinical trials conducted in western countries have demonstrated the safety and efficacy of PDGF in the management of diabetic foot ulcers but only a few trials are conducted in India hence the need for this study in our setup.

This study aimed to evaluate the efficacy of PDGF over saline dressing in the healing of diabetic ulcers of the foot, to compare and analyze the distribution of diabetic ulcers of the foot with age, and sex.

## MATERIALS AND METHODS

Ethical clearance for this proposed study was obtained from the college's ethical board. Both written and oral information in the local language were given to the participants of the study and then consent was obtained. Demography data and study data were collected. Participants were given the option to withdraw from the study at any time.

A prospective randomized controlled trial design was done for the study. 50 Patients with diabetic foot ulcers were admitted to septic wards in Government Kanyakumari medical college, Asaripallam over a period of eight weeks. 25 patients were included in the study/treatment group. 25 patients were in the control group.

Inclusion criteria were patients with diabetic ulcer of Wagner’s stage I, II more than1-week duration. Exclusion criteria were Wagner’s grade III, IV, radiological evidence of underlying osteomyelitis, ulcers resulting from any other cause (e.g., electrical, chemical, radiation, etc.) any concomitant disease (for example connective tissue disease), any medication affecting healing (e.g., steroid), pregnant women, ankle-brachial index <0.4, poor nutritional status, (<6.5gms% total proteins and albumin <3.5 gm%). If the patient had two ulcers one was randomized for the treatment group and the other for the control group before randomization the ulcer was debrided. Full medical history, complete examination, radiographs, and Doppler study of the lower extremity with other relevant investigations taken. Once eligibility was confirmed, particulars of target ulcers like surface area were measured.

For the saline dressing, the ulcer was cleaned with normal saline-soaked gauze piece was kept over the ulcer which was covered with a pad and roller bandage. For rh-PDGF dressing, the infected ulcer was cleaned with normal Saline. The wounds were covered with approximately a 1.5 mm layer of commercially available rh-PDGF_BB gel [HEALACE] (0.01%) and moist saline dressing. The dressings were changed daily in both groups and the appearance of healthy granulation tissue is observed. Adequate control of infection was done


ISSN (O): 2687-5365; ISSN (P): 2753-6556

by giving oral or injectable antibiotics and debridement was done where required.

The intended period of treatment was 8 weeks/ complete healing whichever was earlier. At each follow-up visit at an interval of 1 week for 8 weeks area of the target ulcer was assessed clinically for granulation, the percentage decreased in size, and culture sensitivity. The initial and final surface area of the ulcer are measured on the 1st and 56th day using a sterile gauze technique and findings are tabulated and subjected to statistical analysis. Continual variables were compared using the Independent sample t-test. Pearson chi-square test was used for the comparison of Categorical variables. Significance was defined by P values less than 0.05 using a two-tailed test. Data analysis was performed using IBM-SPSS version 21.0.

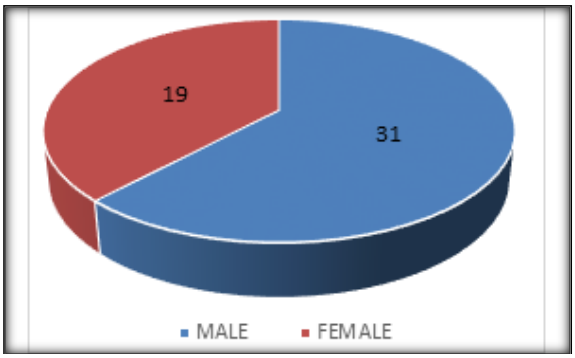
## RESULTS

### Age Distribution

Most of the patients are within the age group of 35 to 77 and the mean age of the test group is 56.9 and that of the control group is 55.1 and the p-value is p = 0. 221.hence the age distribution is statistically similar between the two groups.

### Gender Distribution

Male predominance was noted. In the test group, the male was 15 (60%), and the female were10 (40%). In the control group, the male was 16 (64%), and the female was 09 (36%). However, there was no statistical significance between the two genders between the experimental and control groups. The data are tabulated in. [Table 1.and Graph 1]




**Graph 1: Sex distribution**

**Table 1: Distribution of gender between groups**

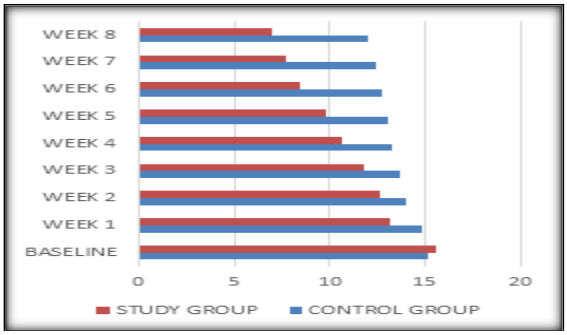
| Sex | Control | % | Test | % |
|---|---|---|---|---|
| Male | 16 | 64% | 15 | 60% |
| Female | 9 | 36% | 10 | 40% |
| Total | 25 | 100% | 25 | 100% |

### Wound Surface Area Distribution

The wound surface areas of the study group and control group were studied and values are summarised below. The mean wound surface area at baseline day was statistically not significant and was almost similar (15.2 cm2 in the control and 15.6 cm2 in the study group). But at the end of eight weeks mean WSA of control was 12.0 cm2 vs 7 cm2 in the study group which was statistically significant ($p<0.01$). The data are tabulated in [Table 2 and Graph 2].

**Table 2: Distribution of wound surface area**

| Mean wound surface area | Control group (cm2) | Test group (cm2) |
|---|---|---|
| BASELINE | 15.2 | 15.6 |
| WEEK 1 | 14.8 | 13.2 |
| WEEK 2 | 14.0 | 12.6 |
| WEEK 3 | 13.7 | 11.8 |
| WEEK 4 | 13.3 | 10.7 |
| WEEK 5 | 13.1 | 9.8 |
| WEEK 6 | 12.7 | 8.5 |
| WEEK 7 | 12.4 | 7.7 |
| WEEK 8 | 12.0 | 7.0 |




**Graph 2: showing the decrease in the wound surface area**

GRANULATION TISSUE ASSESSMENT

The presence of granulation tissue over the wounds was assessed once in every 2 weeks and a score was given from 1 to 4 according to the percentage of granulation tissue observed.

SCORE FOR THE PERCENTAGE OF GRANULATION TISSUE COVER. [Table 3]


ISSN (O): 2687-5365; ISSN (P): 2753-6556

**Table 3: *WSA- wound surface area.**

| SCORE | PERCENTAGE OF GRANULATION TISSUE COVER |
|---|---|
| 1 | No granulation tissue |
| 2 | <25% OF WSA |
| 3 | 25-74% OF WSA |
| 4 | 75-100% OF WSA |

There is no significant difference in the granulation of tissue at baseline between both groups. [Table 4]

**Table 4: Baseline wound surface area**

| GRANULATION TISSUE | | STUDY | | CONTROL | |
|---|---|---|---|---|---|
| | | N | % | N | % |
| BASELINE | 1 | 19 | 76% | 20 | 80% |
| | 2 | 5 | 20% | 4 | 16% |
| | 3 | 1 | 4% | 1 | 4% |
| | 4 | 0 | - | 0 | - |

The granulation of tissue at week two in the test group was < 25% of the wound in 20(80%), 26-75% of the wound in 4 (16%), and 76-100% of the wound in 1(4%) of patients. In the control group, no Granulation in 4 (16%), < 25% of the wound in 16 (64%), and 26-75% of the wound in 4 (16%) of patients.

**Table 5: Granulation tissue cover at week 4**

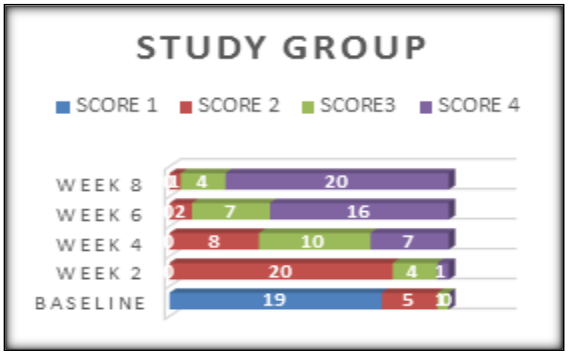
| GRANULATION TISSUE | | GROUP | | | |
|---|---|---|---|---|---|
| | | STUDY | | CONTROL | |
| | | N | % | N | % |
| WEEK 4 | 1 | 0 | - | 1 | 4% |
| | 2 | 8 | 32% | 15 | 60% |
| | 3 | 10 | 40% | 6 | 24% |
| | 4 | 7 | 28% | 3 | 12% |

The granulation of tissue at week six in the test group, < 25% of the wound in 2 (8%), 26-75% of the wound in 7(28%), and 76-100% of the wound in 16(64%) of patients. In the control group, no granulation in 1 (4%), < 25% of the wound in 6(24%), 26-75% of the wound in 11(44%), and 76-100% of the wound in 7(28%) patients. At week six statistically significant granulation tissue cover was noted in the test group (p<0.01).

**Table 6: Granulation tissue cover at week 8**

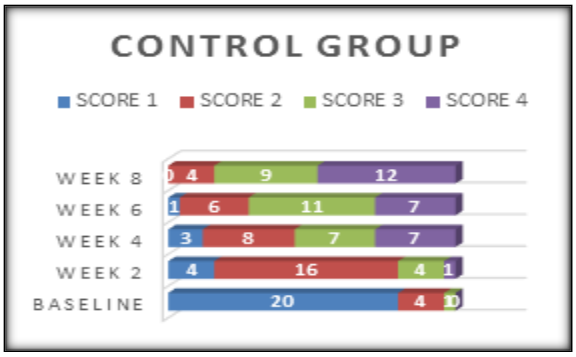
| GRANULATION TISSUE | | GROUP | | | |
|---|---|---|---|---|---|
| | | STUDY | | CONTROL | |
| | | N | % | N | % |
| WEEK 8 | 1 | 0 | - | 0 | - |
| | 2 | 1 | 4% | 4 | 16% |
| | 3 | 4 | 16% | 9 | 36% |
| | 4 | 20 | 80% | 12 | 48% |

The granulation of tissue at week eight in the test group, < 25% of the wound in 1(4%), 26-75% of the wound in 4 (16%), and 76-100% of the wound in 20(80%) of patients. In the control group, < 25% of the wound in 4 (16%), 26-75% of the wound in 9 (36%), and 76-100% of the wound in 12(48%) patients. (Table 5). In week 8, 32% of patients form study group showed better granulation tissue than control group and the difference was statistically significant (p < 0.01).




**Graph 3: Diagram showing the percentage of granulation formation once in every 2 weeks in the study group**


ISSN (O): 2687-5365; ISSN (P): 2753-6556




**Graph 4: Diagram showing the percentage of granulation formation once in every 2 weeks in the control group**

**Figure 1: Ulcer at Day 0 and end of week 2**

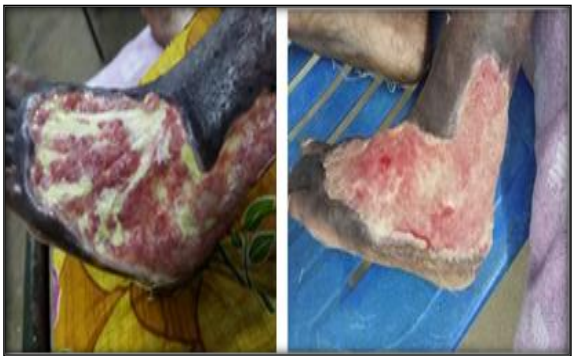


**Figure 2: Ulcer at end of week 4 and week 8**

## DISCUSSION

Diabetes-related foot ulcers are chronic sores that exhibit a prolonged phase of inflammation and epidermis growth cessation. Invariably diabetic foot ulcers are resistant to healing because of multidrug-resistant organism growth and microvascular complications. The purpose of the current study was to determine the impact of PDGF usage on diabetic foot ulcers. The present study was conducted at the Kanyakumari government medical college, Asaripallam for a period of 8 weeks. In the current study, it was discovered that men [64%] had a higher incidence of diabetic foot ulcers than women [36%]. The NHDS, the second national data source, showed that males were more likely than females to have diabetic foot ulcers, and more common in the sixth decade.

In our study, it was observed that participants receiving rh-PDGF dressing had better wound contraction. As compared to the group receiving only conventional dressing (normal saline dressing) it was found to be statistically significant suggesting that rh-PDGF dressing enhances wound healing in diabetic wounds.

It was also observed that the contraction of wounds in the study group (55%) is more than that of the control group (21%). On applying unpaired student t-test p=0.001 which is statistically significant. These results were found to be similar to an original article by Purushothaman R et al.[10] From our study, we can say that rh-PDGF dressing therapy facilitates wound healing in patients suffering from diabetes mellitus.

The mean age which was in the 6th decade in our study was almost similar to most of the studies. The majority of the patients were in the 6th decade according to Margolis et al.[11] Male-to-female ratio was 1.84:1. This finding was similar to the study done by Hardikar et al.[12] Higher incidence of males over females could be because females have a largely indoor existence in our society. Percentage healing in ulcers was almost 50% better in the group receiving drug 2 (PDGF). Most of the ulcers were neuropathic in this study, our findings are similar to those of Mam et al.[13] And the overall study reproduced similar outcomes to the studies by Wieman et al, Margolis et al, Embill et al and Nagai et al.[14-16]

## CONCLUSION

The wounds in the study group treated with rh-PDGF dressing showed more granulation tissue and contraction in the wound surface area than the wounds in the control group (80% versus 48%; 7sq.cm vs 12sq.cm: P<0.01- statistically significant) which indicates rh-PDGF dressing is an effective modality to facilitate wound granulation and wound contraction in patients suffering from diabetes. Rh-PDGF dressing is found to be a more effective, safe promoter of wound healing and can be used as an adjunct to saline dressing for healing diabetic wounds. Healing of ulcers receiving PDGF was significantly faster as compared to ulcers receiving saline dressing.

Funding: No funding sources


ISSN (O): 2687-5365; ISSN (P): 2753-6556

Conflict of interest : None declared

Ethical approval : The study was approved by the institutional ethics committee.

## REFERENCES


1. The expert committee on the diagnosis and classification of diabetes mellitus. Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care. 1997;20:1183- 97.
2. Reiber GE, Ledous WE. Epidemiology of diabetic foot ulcers and amputations: evidence for prevention. In Williams R, Herman W, Kinmonth .The evidence base for diabetes care. London : John Wileyand Sons; 2002:641.665
3. Ravari H, Modaghegh MH, Kazemzadeh GH, Johari HG, Vatachi AM. Sangaki A, et al. Comparison of vaccumassiated closure and moist dressing in the treatment of diabetic foot ulcers. J Cutaneous Aesthetic Surg. 2013;6(1):17-20.
4. Shrivastava SR, Shrivastava SP, Ramasamy. Role of self-care in management of diabetes mellitus. Journal Diabetes Metabolic. 2013;12:14
5. Zhang J, Hu ZC, Chen D, Guo D, Zhu JY, Tang B. Effectiveness and safety of negative pressure woundtherapy for diabetic foot ulcers: a meta-analysis. Plastic Reconstructive Surg. 2014;134(1):141-51.
6. Polka A, Franek A, Taradaj J. High-voltage pulsed current electrical stimulation in wound treatment. Advances Wound Care. 2014;3(2):104-17.
7. Thambi Durai David, J. A. Jayalal, and Selwyn J. Kumar. "The Role of Epidermal Growth Factor Cream in Healing of Diabetic Foot Ulcer-Comparative Analytical Study in South India." (2019), International Journal of Health Sciences & Research (www.ijhsr.org) 1Vol.8; Issue: 6; June 2018
8. Heldin CH. Structural and functional studies on platelet-derived growth factor. EMBO J. 1992;11(12):4251-9.
9. Single S, Singla S, Kumar A, Siggla M. Role of epidermal growth factor in healing of diabetic foot ulcers. Indian J Surg. 2012;74(6):451-5.
10. Purushothaman R et al, Prospective study of platelet derived growth factor in wound healing of diabetic foot ulcers in Indian population; Int Surg J. 2017 Jan;4(1):194-199; http://dx.doi.org/10.18203/2349-2902.isj20164428
11. Margolis DJ et al, Effectiveness of platelet release rate for the treatment of diabetic neuropathic foot ulcers. Diabetes Care. 2001;24:483-8.
12. HardikarJV, ReddyC, BungDD, VarmaN, PrakashPS, PrasadED, et al. Efficacy of recombinant human platelet derived growth factor(rhPDGF)based gel in diabetic foot ulcer, a randomized, multicenter, double-blind, placebo-controlled study in India. Wounds. 2005;17(6):141-52.
13. Mam MK, Dhar KL, Pawar I. Some observations on diabetic foot. Indian J Orthopaedics. 1998;33:197-9.14.Rio T, Green J, Kirsner RS. Vascular endothelial growth factor delivery via gene therapy for diabetic wounds: first steps. J Investigative Dermatol.2009;129(9):2084.
14. Margolis DJ, Kantor J, Berlin JA. Healing of diabetic neuropathic foot ulcers receiving standard treatment. a meta-analysis. Diabetes Care. 1999;22(5)692-5.
15. Embill JM, Papp K, Sibbald G, Tousignant J, Smiell JM, Wong B. Becaplermin for healing chronic lower extremity diabetic ulcer; an open lable clinical evaluation of efficacy. Wound Repair Regeneration. 2000;8(3):162-8.
16. Nagai MK, John ME. Becaplermin; recombinant platelets derived growth factor, a new treatment of healing diabetic foot ulcers expert opinion. Biological Therapy. 2002;2(2):211-8.17.




ISSN (O): 2687-5365; ISSN (P): 2753-6556