



## ROLE OF PLATELET DERIVED GROWTH FACTOR (rhPDGF) IN HEALING OF DIABETIC FOOT ULCERS - A RANDOMIZED CONTROLLED TRIAL

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### ABSTRACT

**Purpose:** To study the effect of Platelet derived growth factor (rhPDGF) in healing of Diabetic foot Ulcers in study group.

**Method:** The present study was a randomized controlled Study. A Total of 50 patients were assigned. Control group patients (30) were treated with conventional dressing and study group patients (20) were treated with rh-PDGF dressing.

**Results:** The study group patients showed wound healing in 30% of patients against control group of 16.66%. Mean duration of time taken for complete ulcer closure in study group is 41.5 days against 54.8 days in controls. Total wound surface area reduction after 8 weeks is 71.54% in study group compared to 35.72% in control group. Ulcers with  $\geq 50\%$  surface area reduction in study group were 70% compared to 43.3% in control group.

**Conclusion:** Topical application of  $7\mu\text{g}/\text{cm}^2$  of rh-PDGF once daily significantly increases incidence of wound healing in chronic diabetic foot ulcers.

**KEYWORDS :** Rh-PGDF ; Topical application ; Diabetic foot ulcer ; Diabetes mellitus.

### INTRODUCTION

Diabetes mellitus affects more than 120 million people worldwide. As the "Diabetic Capital of the World" India, with its largest share of diabetic persons has an uphill task to care for its wide population. According to estimates, in year 2000, there were 31.7 million cases of Diabetes in India and the figure is expected to rise further to 79.4 million cases by year 2030<sup>1</sup>.

Lower extremity ulcers are a serious, debilitating complication of diabetes mellitus. It puts huge financial burden not only to the patient but also the family and society. In India the prevalence of foot ulcer is 2.1% to 12.4% among the diabetic population.

As the incidence of diabetes and its complications are on a rise, the risk of lower extremity amputations is 15 to 46 times higher in diabetics as compared to non-diabetics. Essential to mention here that chronic diabetic foot ulcer is the leading cause of amputations in these patients, also that 15% of all diabetics develop diabetic foot ulcer in their lifetime and about 14-24% of them may require an amputation. The annual prevalence of 6.3% of amputations has been reported in US population for diabetic foot ulcers.

### Diabetic Foot Ulcer

The 'diabetic foot' has traditionally been considered to result from the combination of:

- Peripheral neuropathy – Sensory, motor and autonomic.
- Arterial disease in the leg. Defects of the microcirculation (impairs oxygen and nutrient delivery to tissues).
- Infections
- Abnormalities of pressure loading on the sole and resulting callus formation.
- The role of hyperglycemia in reducing perfusion by producing glycation of basement membrane proteins, and thickening of basement membrane.

Management of the foot ulcer is largely determined by its severity (Grade) and vascularity, and the presence of infection. A systematic multidisciplinary approach to treatment should be taken for all diabetic foot lesions. However, the identification of the role of Platelet-derived growth factor (PDGF) in the formation of granulation tissue at the wound site and promotion of wound healing have given a

new impetus to the development of recombinant human PDGF. PDGF was discovered as a protein released from the alpha granules of Platelets, it was purified from platelets. Recombinant human PDGF-BB (Becaplermin) has been prepared and purified for use in clinical studies of wound healing. The recombinant human platelet derived growth factor (rh-PDGF) is produced by recombinant DNA technology by insertion of the human gene for the B chain of PDGF in the yeast *saccharomyces cerevisiae*<sup>7</sup> and also bacteria *E.Coli*.

In phase II studies, recombinant human PDGF-BB (rhPDGF-BB) was shown to have a positive effect on healing pressure ulcers and lower extremity ulcers in patients with diabetes.<sup>4</sup> A phase III randomized placebo controlled double blind study on 382 patients with diabetic foot ulcers supported that becaplermin gel 100  $\mu\text{g}/\text{g}$ , in conjunction with good wound care, significantly increased the incidence of complete wound closure and significantly reduced the time to complete closure of chronic diabetic neuropathic ulcers.<sup>2</sup>

In view of further studies regarding the efficacy of rh-PDGF in chronic diabetic ulcers, we undertook this study to know whether rh-PDGF applied topically over the chronic diabetic foot ulcers reduces the size of the wound effectively compared to conventional treatment alone (regular debridement, dressings and antibiotics).

### MATERIALS & METHOD

The present study was carried out at ACSR. Govt. Medical College & Govt. General Hospital, Nellore for a period of two years from July 2016 to June 2018, where 50 patients with diabetic foot ulcers 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 50 patients, 30 took treatment in the form of conventional wound care and 20 took treatment with rh-PDGF dressing. Off-loading of pressure from the affected area and adequate control of infection was maintained in both the groups. If culture grows organism, both control and study group cases would be treated with antibiotics as per culture sensitivity report. The initial wound area was recorded after sharp debridement by Measuring length x width (ulcer should be less than 10x10 cm). The outcome,

that is the area of the target ulcer was measured by Ruler method or Planimetry using a transparent graph sheet. Results were calculated by using student 't' test, Z-test.

**Inclusion criteria**

1. Type I and II Diabetes mellitus.
2. Diabetics between 18 to 80 years of age.
3. Have documented wound etiology resulting from complications of Diabetes mellitus.
4. Duration of the ulcer more than 4 weeks.
5. Size of ulcer less than 10x10 cm
6. Fasting blood glucose levels measured in two occasions 24 hours apart between 140mg/dl- 200mg/dl

**Exclusion criteria:**

1. Pulseless limb
2. Immunocompromised patients
3. Associated osteomyelitis.
4. Skin malignancy
5. Cellulitis
6. Diabetic Ketoacidosis.
7. Have exposed tendon or bone or presence of charcot joint.
8. Diabetic gangrene toe.
9. Pregnant & lactating women

**For rh-PDGF dressing**

The infected ulcer was cleaned with Normal Saline. rh-PDGF-BB gel (PLERMIN 0.01%) was applied on the gauze piece and put on the ulcer. It was then covered with saline moistened gauze, dry pad and roller bandage.

**DOSAGE**

The intended dose is around 7µg/cm<sup>2</sup> of ulcer per day in an average man of around 50kg weight for topical application. Thus the amount of PDGF gel to be applied varies depending upon the size of the ulcer. For calculating the adequate dose of PDGF gel, the greatest length of the ulcer should be measured and multiplied by the greatest width of the ulcer in centimeters. Surface area of the ulcer thus obtained is to be divided by a respective factor below to give the approximate length of the gel to be squeezed out from the tube.

Tube Size	Formula
7.5g/15 g tube	Length (cm) X width (cm) ÷ 4

The appropriate amount of PDGF gel is applied locally to the wound surface with the help of clean application aid. The dressings were changed daily in both control and study groups for 8 weeks and appearance of healthy granulation tissue, ulcer healing and size reduction is observed and the final area is measured on weekly basis upto 8 weeks and subjected to statistical analysis.

**OBSERVATIONS AND RESULTS**

**Table 1- Age distribution**

Age ( years)	No. of cases		Percentage
	Control	Study	
18-30	-	1(5%)	0.2%
31-40	5(16.66%)	2(10%)	14%
41-50	4(13.33%)	4(20%)	16%
51-60	13(43.33%)	7(35%)	40%
60-80	8(26.66%)	6(30%)	28%
<b>Total</b>	<b>30</b>	<b>20</b>	<b>100%</b>

In our study it is observed that Diabetic foot is commonest in the age group between 51-60yrs of age.

**TABLE 2- Sex distribution**

Sex	No. of cases		Percentage
	Control	Study	
<b>Male</b>	<b>26 (86.66%)</b>	<b>16 (80%)</b>	<b>84.00%</b>

<b>Female</b>	<b>4 (13.33%)</b>	<b>4 (20%)</b>	<b>16.00%</b>
<b>Total</b>	<b>30</b>	<b>20</b>	<b>100%</b>

In our study it is observed that Diabetic foot is more common in the males (84.00%) as compared to females (16.00%)

**Table 3- Site of ulcer in the study**

Site	No. of cases		Percentage
	Control	Study	
<b>Plantar</b>	<b>20(66.66%)</b>	<b>14 (70%)</b>	<b>68.00%</b>
<b>Dorsum</b>	<b>10(33.33%)</b>	<b>6(30%)</b>	<b>32.00%</b>
<b>Total</b>	<b>30</b>	<b>20</b>	<b>100%</b>

In our study it is observed that diabetic foot more commonly occurs on the plantar aspect (64.00%) of the foot as compared to the dorsal aspect (32.00%)

**Table 4- Ulcers healed in 8 weeks followup**

Group	No. of cases	Percentage
<b>Control (30)</b>	<b>5</b>	<b>16.66%</b>
<b>Study (20)</b>	<b>6</b>	<b>30%</b>

In our study it is observed that ulcers healed in 8 weeks followup were 16.66% in control group as compared to 30% in study group. P value is 0.001.

**TABLE 5- Duration of complete healing of ulcers**

Group	Mean in days	SD
<b>Control</b>	<b>54.8</b>	<b>1.6733</b>
<b>Study</b>	<b>41.5</b>	<b>7.4229</b>

The mean time taken for complete healing of the ulcers were 41.5 days in study group as compared to 54.8 days in control group. P value is <0.001

**Table 6- Ulcers with ≥ 50% area reduction after 8 weeks**

Group	No. of Cases	Percentage (%)	PValue
<b>Control (30)</b>	<b>13</b>	<b>43.3%</b>	
<b>Study (20)</b>	<b>14</b>	<b>70%</b>	<b>&lt;0.0001</b>

In our study it is observed that ulcers with ≥ 50% of surface area reduction was higher in study group (70%) as compared to the controls (43.3%).

**Table 7- Total ulcer area reduction after 8 weeks follow-up**

Group	Mean % of reduction	SD	P value
<b>Control</b>	<b>35.72%</b>	<b>19.9675</b>	
<b>Study</b>	<b>71.54%</b>	<b>23.0296</b>	<b>&lt;0.001</b>

In our study it was observed that Mean % of total ulcer area reduction was higher in study group (71.54%) as compared to the controls (35.72%).

**DISCUSSION**

In the present study it was seen that the incidence of diabetic foot ulcers were more in males (84.00%) as compared to females (16.00%). Diabetic foot ulcers are most commonly seen in 6<sup>th</sup> decade (40%), the next common being in above 60 years (28%). While 18% of the patients were in the fifth decade. We had only one patient below third decade (2%). Older the patient more the chances of having diabetic foot ulcer. The prevalence of diagnosed diabetics increases with age (the diabetic foot).

In this study, 72.00% of the ulcers were traumatic in origin, trauma being the triggering factor secondary to neuropathy. 28.00% were spontaneous in origin secondary to blister rupture or unnoticed trivial trauma. More than half (68.00%) of the patients had ulcer on the plantar surface of the forefoot and the remaining (32.00%) had 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 as same as postulated by Edmonds et al.

Most of the patients (84.00%) were on insulin for control of sugar whereas only 16.00 % were on Oral Hypoglycaemic Agents. In our study it was observed that participants receiving rh-PDGF (Plermin 0.01% gel) dressing had better ulcer area reduction of 71.54% (S.D;23.0296), as compared to the group receiving only conventional dressing (normal saline dressing) in whom the mean wound area reduction was 35.72% (S.D;19.9675). These were found to be statistically significant on unpaired Student t test ( $p < 0.001$ ), suggesting that rh-PDGF dressing enhances wound healing in diabetic wounds.

All 30 patients selected as a control complied for the eight weeks duration period of the study. The initial area measurement on day 01 final area measurement on completion of 8 weeks was taken on transparent sheet. The area measurement was done using Ruler method & planimetry.

We have applied the following formula to calculate % reduction in area of wound after 8 weeks period in both cases and control groups.

Rate of contraction of wound after 8 weeks of treatment =  
(Initial area – Final Area)

----- X 100  
Initial area

We have found 35.72% (S.D; 19.9671) contraction of wounds in the control groups as compared to 71.54% (S.D; 23.0296) contraction of wounds in study group. Ulcers healed in study group were 30% as compared to 16.66% in controls. Mean duration of complete healing of ulcers in study group is 41.5 days compared to 54.8 days in control group. Ulcers with  $\geq 50\%$  of surface area reduction after 8 weeks follow up were 43.3% in controls versus 70% in study group.

Therefore, study groups are having more % of wound healing as compared to control group. On applying unpaired student t test p value is  $< 0.001$  which is significant. Mean duration taken for complete wound healing is 41.5 days in study group compared to 54.8 days in controls which is 13.3 days (approx 2 weeks) less with rh PDGF gel therapy. PDGF gel decreased the time to achieve wound healing by 24% ( $p < 0.001$ ). This result indicates rapid wound contraction by PDGF gel facilitates patient by lesser hospital stay and lesser expenditure.

Our study is in comparison with the previous studies using rhPDGF gel 0.01%. i.e.,

1. A Phase – III randomised double blind controlled trail by **Wieman TJ, MD, FACS, Janice MS, MD, Yachin Su.** – in 382 patients 50% (61 of 123) who received PDGF Gel 0.01% achieved complete wound healing compared to 35% (44 to 127) with placebo ( $p = 0.007$ ).
2. **Hardikar JV, Reddy Y, Chiranjeev, Bung DD et al.** Efficacy of recombinant human platelet-derived growth factor (rh-PDGF) - based gel in Diabetic foot ulcer: A multicentric, double-blind, Placebo-controlled randomized study in India.- in 113 patients consisting of 58 patients in the placebo group and 55 patients in drug group nearly 71% of ulcers in PDGF arm were completely healed vs. 31% in the Placebo arm a difference of 40% at the end of 10 weeks. ( $p < 0.001$ )

Thus from our study, we can say that rh-PDGF dressing therapy facilitates wound healing in patients suffering from diabetic foot ulcer.

## CONCLUSION

The ulcers in subjects treated with rh-PDGF dressing healed & contracted more than the wounds in the conventionally treated group ( $P = < 0.001$  Significant) which indicates rh-PDGF dressing is an effective modality to facilitate wound healing in patients suffering from diabetes and can be used as an adjunct to traditional mode of treatment (conventional dressings and debridement) for healing of diabetic foot ulcers.

## SUMMARY

In our study 50 patients of diabetic foot ulcers were studied. They were divided into two groups of 30 as control & 20 as study groups. One group received rh-PDGF and the control group received treatment in the form of conventional therapy. A comparative study was done between both groups regarding percentage area wound reduction and healing. Patients were between 18-80 years of age. Males were more affected than females. 82.00% males Vs 16.00% females. 72.00% of the ulcers were traumatic in onset. Plantar aspect (68.00%) was most common site.

Most of the patients were on insulin (84.00%) compared to the oral hypoglycaemic agents (16.00%). In our study it is observed that participants receiving rh-PDGF had better wound contraction of 71.54% as compared to the group receiving only conventional treatment in whom the mean wound contraction was 35.72%. These were found to be statistically significant on unpaired Student T test ( $p < 0.001$ ), suggesting that rh-PDGF enhances wound healing in diabetic wounds.

Ulcers healed in study group were 30% as compared to 16.66% in controls. Mean duration taken for complete wound healing is 41.5 days in study group compared to 54.8 days in controls which is 13.3 days (approx 2 weeks) less with rhPDGF gel therapy. PDGF gel decreased the time to achieve wound healing by 24% ( $p < 0.001$ ).

Ulcers with  $\geq 50\%$  of surface area reduction after 8 weeks follow up were 43.3% in controls versus 70% in study group. Thus, rh-PDGF dressing therapy in the treatment of diabetic foot ulcers was found to be more effective, safe, promoter of wound healing Hence it can be recommended for the treatment of diabetic foot ulcers as an adjuvant to the conventional mode of treatment.

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