

Efficacy of recombinant human platelet derived growth factor in chronic diabetic foot ulcer

Syam Mohan¹, Mohammed Shafi^{1*}, Vipin C², Abdul Majeed¹

¹Department of General Surgery, Yenepoya Medical College, Yenepoya University, Mangalore, Karnataka, INDIA.

²Yenepoya Research Centre, Yenepoya University, Mangalore, Karnataka, INDIA.

Email: shaf_me@hotmail.com

Abstract

Background: The incidence of diabetes and its complications are significantly higher in diabetics as compared to non-diabetics. These diabetic ulcers are known to be resistant to conventional treatment. Chronic diabetic foot ulcer is the leading cause of amputations in these patients. Platelet derived growth factor (PDGF) is one of the growth factors which play a significant role in angiogenesis. **Objective:** To compare the efficacy of topically applied recombinant human platelet derived growth factor (rh-PDGF) in chronic diabetic foot ulcer. **Methodology:** A total of 50 patients were assigned. They are grouped into two by computerized randomization. Control group patients were treated with conventional dressing and study group was treated with rh-PDGF dressing and wound size was observed for 15 days. **Results:** The study group patients showed higher reduction in wound size of about 43.11% as against 13.64% of the control group which was significant at $p = 0.001$. **Conclusion:** Topical application of 100 $\mu\text{g/g}$ of rh-PDGF once daily significantly increases the incidence of wound healing in chronic diabetic foot ulcers.

Key words: rh-PDGF, diabetes mellitus, foot ulcer

*Address for Correspondence:

Dr. Mohammed Shafi, Associate Professor, Department of General Surgery, Yenepoya Medical College, Yenepoya University, Mangalore, Karnataka, INDIA.

Email: shaf_me@hotmail.com

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INTRODUCTION

Diabetes mellitus is characterized by chronic hyperglycemia with disturbances of carbohydrate fat and protein metabolism resulting from defects in insulin secretion, insulin action or both. The effect of diabetes mellitus includes long term damage, dysfunction and failure of various organs especially eyes, kidney, heart and blood vessels. Chronic complications are responsible for high morbidity and mortality and cause high number of hospital days.¹ The incidence of diabetes and its complications are significantly higher in diabetics as compared to non-diabetics.² Essential to mention here

that chronic diabetic foot ulcer is the leading cause of amputations in these patients, also that 15% of all diabetic develop diabetic ulcer and the most commonest site being the foot. Although the fundamental pathophysiologic factors leading to diabetic ulcer remain incompletely understood, the triad of neuropathy, ischemia and infections commonly are considered most important. These diabetic ulcers are known to be resistant to conventional treatment and may cause severe complications if not treated wisely.^{3, 4, 5} The wound environment contains a variety of growth factors. Platelet-derived growth factor is of particular relevance due to its chemotactic, mitogenic, angiogenic, and stimulatory effects leading to matrix formation and wound bed granulation. PDGF may be of significant benefit of diabetics as recalcitrant diabetic wounds have been found to be deficient in or absent of PDGF.⁶ Platelet-derived growth factor (PDGF) is one of the numerous growth factors, or proteins that regulate cell growth and division. In particular, it plays a significant role in angiogenesis. PDGF was discovered as a protein released from the alpha granules of platelets. Recombinant human PDGF-BB 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*.⁷ A series of animal experimental studies have shown that application of PDGF to a wound enhances the process of wound repair. PDGF has been demonstrated in preclinical studies to promote the formation of granulation tissue and thus stimulate cutaneous ulcer healing.⁸ Various human cellular studies have certainly established the fact that topical application of recombinant human platelet derived growth factor (rh-PDGF) can be a new pharmacologically active therapy for chronic neuropathic lower extremity diabetic ulcers.⁹ In phase II clinical trials, 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.^{10,11} A phase III randomized placebo controlled double blind study on 382 patients with diabetic foot ulcers supported that becaplermin gel 100 µg/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.⁷ Various phase II and phase III studies showed effectively the efficacy, i.e. complete reduction and the closure of the wound. PDGF promote tissue granulation and stimulate cutaneous ulcer healing. It stimulates the proliferation of a variety of mesenchymal cells including fibroblasts.^{12,13} In view of various 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.

MATERIALS AND METHODS

The present study was carried out at Yenepoya Medical College Hospital, Mangalore for a period of

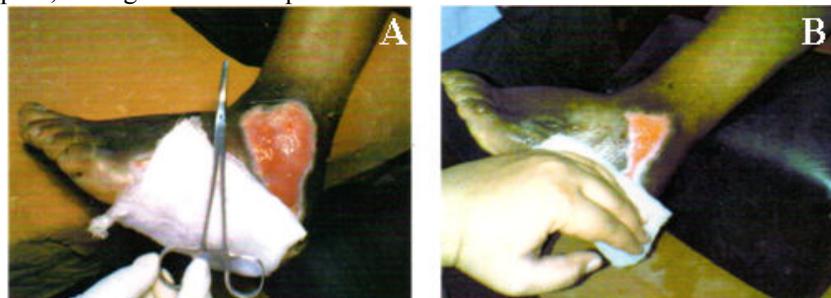


Figure 1: Improvement in wound healing with the treatment of recombinant human platelet derived growth factor. A) Before treatment, B) After treatment

This study showed that diabetic foot was commonest in the age group between 51-60 years of age (Table 1). It was observed that diabetic foot more commonly occurs on the plantar aspect (68.00%) of the foot as compared to

three years, 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, 25 were conventionally treated by normal saline dressings (control group) and the other 25 were treated with rh-PDGF dressing (study group). Off-loading of pressure from the affected area and adequate control of infection was maintained in both the groups. The initial wound area was recorded after sharp debridement by measuring length × width (ulcer should be less than 10 × 10 cm). The area of the ulcer was measured by planimetry using a transparent graph sheet.

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.

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 pad and roller bandage.

The dressings were changed daily morning in both control and study groups for 15 days and appearance of healthy granulation tissue is observed and the final area is measured on 15th day by planimetry using a transparent graph sheet and subjected to statistical analysis.

RESULTS

The results revealed that the recombinant human platelet derived growth factor dressing had better efficacy than conventional wound dressing. The topical application of 100 µg/g of rh-PDGF once daily significantly increased the incidence of wound healing in chronic diabetic foot ulcer (Fig 1).

the dorsal aspect (32.00%) (Table 2). Trauma is the most common cause of diabetic foot ulcer (72.00%) while only 28.00% were spontaneous in origin (Table 3). Most of participants were taking insulin for glycaemic control

(Table 4). The study group (43.11%) showed better area reduction as compared to controls (13.64%) (Fig 2). we also observed that patients with ulcers over the plantar aspect had lesser % of mean wound area reduction as compared to the participants with wound over the dorsal aspect when compared within the same group, that is, plantar wounds in the control group had lesser wound contraction (16.20%) as compared to participants who had ulcers over the dorsal aspect (12.37%) and likewise in the study group (Fig 3).

Table 1: Age distribution of participants

Age (years)	No. of Cases	Percentage
21-30	00	00
31-40	06	12
41-50	9	18
51-60	23	46
>60	12	24
Total	50	100

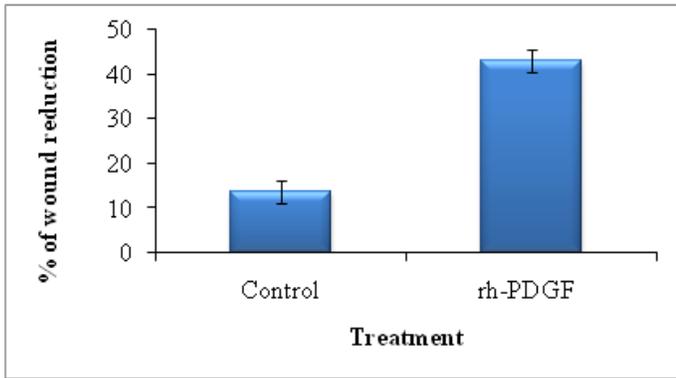


Figure 2: Wound contraction related to treatment

Table 2: Site of ulcer in the study group

Site	No. of Cases	Percentage
Plantar	34	68
Dorsum	16	32
Total	50	100

Table 3: Onset of diabetic foot ulcer

Type of Onset	No of Patients	Percentage
Traumatic	36	72
Spontaneous	14	28
Total	50	100

Table 4 : Anti diabetic agents used by participants

Anti Diabetic	No. of cases	Percentage
OHA	13	26
Insulin	37	74
Total	50	100

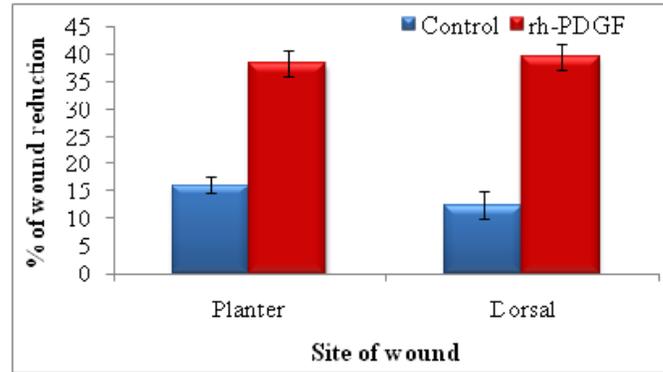


Figure 3: Wound healing related to site

Statistical analysis

Diabetic foot ulcers in the study group had better mean % of wound contraction of 43.11% as compared to control group which had mean % of wound contraction of 13.69 %, the difference in the mean 29.47% of area reduction of the two groups where studied using unpaired student t test was found to be significant (p<0.001).

DISCUSSION

Diabetic foot ulcers are chronic wounds, stuck in inflammation phase and shows cessation of epidermal growth.¹⁴ The present study was conducted at Yenepoya Medical College hospital, Mangalore to study the effect on chronic diabetic wound healing dynamics. In the present study it was observed that the incidence of diabetic foot ulcers were more in males (58.00%) as compared to females (42.00%). 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 in 1987, 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.¹⁵ The patients who had ulcers on the plantar aspect of the foot in the control group had mean wound contraction of 16.20% as compared to the dorsal wounds of the same group which had mean wound contraction of 12.37%, similarly the mean plantar wound contraction in the study group was 38.42% as compared to the mean dorsal wound contraction of 39.32% suggesting different wound healing dynamics in the two regions of the foot. In our study it was observed that participants receiving rh-PDGF (Plermin 0.01% gel) dressing had better wound contraction of 43.11% As compared to the group receiving only conventional dressing (normal saline dressing) in whom the mean

wound contraction was 13.64%, 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.

CONCLUSION

The wounds in subjects is treated with rh-PDGF dressing contracted more than the wounds in the non-treated group (43.11% vs 13.64%; $p = < 0.001$ significant) which indicates rh-PDGF dressing is an effective modality to facilitate wound contraction in patients suffering from diabetes and can be used as an adjunct to conventional mode of treatment (conventional dressings and debridement) for healing of diabetic wounds.

Thus, rh-PDGF dressing therapy in the treatment of diabetic foot ulcers was found to be more effective, safe, promoter of wound healing, and hence can be recommended for the treatment of diabetic foot ulcers as an adjuvant to the conventional mode of treatment.

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