



TO COMPARE EFFICACY OF RECOMBINANT HUMAN PLATELET DERIVED GROWTH FACTOR DRESSING VERSUS NORMAL SALINE DRESSING IN WOUND REDUCTION OF CHRONIC DIABETIC FOOT ULCER AND THE EFFECT OF HbA_{1c} LEVEL ON HEALING OF CHRONIC DIABETIC FOOT ULCER

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ABSTRACT

Objectives: To compare the efficacy of topically applied recombinant human platelet derived growth factor (rh-PDGF) in chronic diabetic foot ulcer with conventional normal saline dressing and to determine the effect of HbA_{1c} level on healing of diabetic ulcer.

Method: The present study was a randomized controlled study conducted at Guru Nanak Dev hospital, Amritsar. Total of 60 patients with chronic diabetic foot ulcer were included and were divided in two groups of 30 each by randomization. The control group patients were treated with conventional dressing whereas the study group were treated with rh-PDGF dressing and observed over a period of 15 days for the efficacy of wound healing. Patients with pulseless limb, associated osteomyelitis, skin malignancy, cellulitis, diabetic ketoacidosis, pregnant or nursing mother, diabetic gangrene were excluded from the study. The initial wound area was recorded after sharp debridement. The area of target ulcer was measured and subjected to statistical analysis. The percentage of reduction of wound area was calculated. HbA_{1c} levels were measured in these patients and the effect of blood sugar control upon healing of diabetic foot ulcer was seen.

Results: In our study it was observed that mean healed area was significantly higher in study group 9.77±2.72 cm as compared to control group 3.29±0.88 cm and mean area reduction of wound in percentage was significantly higher in study group 38.99±3.30% as compared to the control group 12.41±2.12%. The p value was less than 0.001 indicating that there was significant difference between wound healing of healing of rh-PDGF treated patients and patients treated by conventional methods. It was also observed that HbA_{1c} level is a good predictor in assessing the response of host in healing of chronic ulcer. HbA_{1c} level of > 12 was associated with decreased rate of healing of chronic diabetic foot ulcer.

Conclusions: The results of this study suggest that within the setting of a comprehensive wound management, rh-PDGF gel has an excellent efficacy and is to be used by patients. Higher the HbA_{1c} level, it is associated with decreased neutrophil function, including leukocyte chemotaxis. Indeed, a greater elevation of blood glucose level PDGF gel increases the healing of lower extremity neuropathic ulcers in patients with diabetes. Moreover has been associated with a higher potential for suppressing inflammatory responses and decreasing host response to an infection and healing of chronic ulcer.

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INTRODUCTION

Diabetes mellitus refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. Depending upon the etiology of diabetes mellitus factors contributing to hyperglycemia include reduced insulin secretion, decreased glucose utilization and increased glucose production. The worldwide prevalence of diabetes mellitus has risen dramatically over the past two decades, from an estimated 30 million cases in 1985 to 285 million in 2010.¹

Based on current trends, the International diabetes federation projects that 438 million individuals will have diabetes by the year 2030.¹ Currently, 4.0-11.6 percent of India's urban population and 3 percent of the rural population above the age of 15 has diabetes.¹ India has been called The diabetes capital of the world, and it is estimated that 41 million Indians have the disease and Every fifth diabetes in the world is an Indian.¹ Diabetes mellitus is the leading cause of non traumatic lower extremity amputation in the United States. Foot ulcers and

infections are also a major source of morbidity in individuals with diabetes mellitus. Approximately 15% of individuals with type 2 diabetes mellitus develop foot ulcer and a significant number will ultimately undergo amputation.²

In India, the prevalence of foot ulcer is 2.1% to 12.4% among diabetes.² Early detection and appropriate treatment of these ulcers may prevent large number of these amputations. The development of smart biomaterials for tissue regeneration has become the focus of intense research interest and platelet derived growth factor is one important biomaterial which play a significant role in angiogenesis. Topically applied recombinant human platelet derived growth factor is a new pharmacologically active therapy for chronic diabetic ulcers, resistant to conventional mode of treatment. Platelet derived growth factor is mainly secreted by the platelets, alpha granule, but is also produced by other cells involved in early healing wound healing, ie, macrophages, endothelial cells, fibroblasts and keratinocytes. PDGF is a powerful chemoattractant and mitogen, exerting its action on fibroblasts, smooth muscle cells, and endothelial cells. It also induces production of fibronectin and hyaluronic acid. There is a synergistic effect between PDGF and EGF, as well as TGF-beta, and so PDGF has a pivotal role at all stages of wound healing. At present, recombinant PDGF is produced by DNA technology via incorporation of the gene for the beta chain of human PDGF into the yeast *saccharomyces cerevisiae*. PDGF is a dimer consisting of A and/or B chains, held together by a disulfide bond. Three isomers (AA, BB and AB) have been isolated. The most common and potent isomer is the BB isomer. Therefore this isomer is one used in the management of foot ulcers.³ The best indicator of glucose control over a period of time is HbA_{1c} level. This test measures the average blood sugar concentration over a 90-d span of the average red blood cell in peripheral circulation. The higher the HbA_{1c} level, the more glycosylation of hemoglobin in red blood cells will occur.⁴

MATERIALS AND METHODS

The present study was a randomized controlled study conducted at our institution, which is a teaching and tertiary hospital located at Amritsar, Punjab. Total of 60 patients with chronic diabetic foot ulcer were included and were divided in to two groups of 30 each by randomization. The control group patients were treated with conventional dressing whereas the study group patients were treated with rh-PDGF dressing over a period of 15 days for the efficacy of wound healing. The initial wound area was recorded after sharp debridement by recording the length and width. The outcome that is the area of target ulcer was measured. The dressing were changed daily in the morning for both the groups for 15 days and the appearance of healthy granulation tissue was observed and the final area was measured on the 15th day and subjected to statistical analysis. HbA_{1c} levels were measured in both study and control group.

OBSERVATIONS AND RESULTS

In our study it was observed that mean healed area was significantly higher in study group 9.77cm as compared to controlled group 3.29cm. The p value was less than 0.001, indicating that there was significant difference between wound healing of rh-PDGF treated patients and patients treated by conventional methods. Wound area reduction was maximum in patients with HbA_{1c} level 6-8 (40%), HbA_{1c} level 8-10 had

15% reduction, HbA_{1c} >10-12 had only 2% reduction in wound area irrespective of the dressings applied.

DISCUSSION

The present study was conducted at Guru Nanak Dev Hospital, Amritsar with an aim to compare the efficacy of topically applied recombinant human platelet derived growth factor(rh-PDGF) in chronic diabetic foot ulcer with conventional normal saline dressing. The study group ulcers were dressed with Becaplermin and control group ulcers received conventional normal saline dressing. The patients were assessed at 7th and 15th day respectively for reduction in wound area. In our study mean healed area was significantly higher in study group 9.77+2.72cm as compared to control group 3.29+0.88cm and percentage area of reduction was significantly higher in study group (38.99%) as compared to control group (12.41%) and (34.6%) in those receiving placebo. Study conducted by Basavaraj G V concluded that Becaplermin treated patients did achieve a slightly higher healing rate (44.1%) in comparison with carboxymethylcellulose treated patients (35.7%) and those receiving standard wound care alone (22%).⁵

Efficacy evaluations carried out by Hardikar J.V. *et al* at 10 and 20 weeks showed that a significantly higher percentage of patients i.e. (40%) higher at 10 weeks and (32%) higher at 20 weeks in the rh-PDGF gel treated group achieved complete healing compared to the placebo treated group.⁶ Kumar N *et al* also conducted a study in which 19 patients received PDGF based dressing and 24 patients received conventional dressing.⁷ Data analysis showed that complete healing was significantly higher in the growth factor group as compared to the control group. In conclusion, the results of this study suggest that within the setting of a comprehensive wound management programme, rh-PDGF gel increases the healing of lower extremity neuropathic ulcers in patients with diabetes. Moreover, rh-PDGF gel has an excellent efficacy and is easy to be used by patients. Chemotaxis induces vascular endothelial growth factor (VEGF) expression at the transcriptional level and consequently promotes angiogenesis and stimulates fibroblast proliferation while also possessing antioxidant action, protecting the local wound milieu from oxidative stress. A total of 2 trails reported healing rate in different treatment period, and the pooled results have no statistical difference. A total of 2 trails reported healing area of wounds and the result revealed that the efficacy in honey dressing is better than that of control group. The acidification of the alkaline environment of chronic non-healing ulcers by honey has also been proposed as another mechanism by which honey induces healing, and acidification inhibits protease activity, induces fibroblast proliferation and establishes an aerobic environment, all of which aid in the healing process.⁸ GFs have been shown to stimulate chemotaxis and mitogenesis of neutrophils, fibroblasts, monocytes, and other components that form the cellular basis of wound healing.⁹ Evidence for adjunctive therapies such as negative pressure wound therapy, skin substitutes, and platelet-derived growth factor can help guide adjunctive care but limitations exist in terms of evidence quality.¹⁰

Studies showed 58% of collagen-treated wounds completely healed (weighted mean 67%). Only 23% of studies reported control group healing with 29% healing (weighted mean 11%) described for controls. Collagen-based wound dressings can be an effective tool in the healing of diabetic foot wounds.¹¹ Alginate or hydrocolloid dressing in terms of healing, a meta-

analysis of trials in which people with neuropathic ulcers received good wound care reported that 24% of ulcers attained complete healing by 12 weeks and 31% by 20 weeks.¹²

Our study showed that in study group, increased HbA1c level 6-8 had wound area reduction upto 40%, HbA1c level 8-10 had wound reduction upto 20%, and HbA1c level >10-12 had wound reduction upto 5% and in control group, increased HbA1c level 6-8 had wound area reduction upto 10%, HbA1c level 8-10 had wound reduction upto 5%, and HbA1c level >10-12 had wound reduction upto 1%. Other Studies have shown that HbA_{1c} level of > 12 is associated with decreased neutrophil function, including leukocyte chemotaxis. Indeed, a greater elevation of blood glucose level has been associated with a higher potential for suppressing inflammatory responses and decreasing host response to an infection. In addition, it's indicated that a 1% mean reduction in HbA_{1c} was associated with a 25% reduction in micro vascular complications.⁴ It has been shown that for every 1% increase in HbA_{1c}, there is an increase of 25%-28% in the relative risk of PAD, which is a primary cause of DFU.⁴ A study by Al-Lawati showed that for each 1.0% point increase in HbA_{1c}, the daily wound-area healing rate decreased by 0.028 cm²/day (95% CI: 0.003, 0.0054, p=0.027). Its results suggest that glycemia, as assessed by HbA_{1c}, may be an important biomarker in predicting wound healing rate in diabetic patients.¹³ Only elevated HbA_{1c} was significantly associated with poor wound-area healing rate per day. Study by Zubair suggested that hyperglycemia, as assessed by HbA_{1c} is associated with slower wound healing in patients with diabetes, particularly for neuropathic foot wounds.¹⁴

CONCLUSION

Platelet derived growth factor dressings proved to be more effective than normal conventional saline dressings as it promotes healing by stimulating chemotaxis and mitogenesis of neutrophils, fibroblasts, monocytes, and other components that form the cellular basis of wound healing. HbA_{1c} level has a direct correlation with healing of a chronic wound or ulcer. Higher the HbA_{1c} levels, lower the rate of wound healing.

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