Evaluation of Recombinant Human Platelet Derived Growth Factor-BB in Healing of Chronic Diabetic Foot Ulcers

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ABSTRACT

Introduction: Diabetic foot problems are common throughout the world resulting in major economic consequences. Once a wound developed in diabetics it remains open for prolonged periods. Senescent and altered resident cells and certain growth factors deficiencies are incriminated for chronicity of wound. Growth factors are biologically active polypeptides that act to alter growth, differentiation and metabolism of targets cells. The present study was conducted with the aim to compare the effects of exogenous application of PGDF (platelet derived growth factor) on ulcer healing rate.

Material and Methods: All patients of age group 18-80 yrs with diabetic foot ulcer of more than 4 weeks duration were taken. Patients were randomised to one of two parallel treatment groups. In group 1, standard wound Care was given. Second group was treated with local applications of recombinant human PDGF-BB along with the required wound care. Primary study end points were complete healing of ulcers,12 weeks of duration, ulcer bed adequate for possible skin closure /skin grafting.

Results: Average time taken to achieve ulcer closure/skin cover at 12 weeks duration in PDGF group (38.5 days) was found to be less than in GWC (good wound care) group (63 days). Incidence of ulcer closure/skin cover at 12 weeks in patients with age less than 60 years (66.66) and non-smokers (68.18%) was found to be more than in patients with age more than 60 yrs or smokers(21.43%).

Conclusion: The incidence of ulcer closure / skin cover at 12 weeks duration in PDGF group was found to be more than in GWC group and this difference was statically significant.

Keywords: Diabetic foot, Growth Factors, Platelet Derived Growth Factor, Ulcer, Wound Healing

INTRODUCTION

Diabetic foot problems are common throughout the world resulting in major economic consequences for the patients, their families and society.[1]

The high rates of diabetes in many parts of the world make foot ulcers a major and increasing public health problems.[2,3]The cost of diabetic foot lesions is affected by interventions to prevent foot ulcers management strategy to heal ulcers and by management and care necessary for disability after amputation.[4] Diabetic have a tendency for the formation of chronic non healing foot ulcers and up to 70% of chronic wounds have been found to be due to diabetes mellitus, chronic venous stasis and pressure necrosis only.[5] There is predisposition for micro and macro vascular diseases in diabetics which leads to insufficient oxygen delivery to the tissue which impairs wound healing. Once a wound developed in diabetics it remains open for prolonged periods. Shunts in the microcirculation together with the presence of sympathetic nerve denervation and autonomic neuropathy leads to maldistribution of blood flow.[5] Senescent and altered resident cells and certain growth factors deficiencies are incriminated for chronicity of wound.[7]

Growth factors are biologically active polypeptides that act to alter growth, differentiation and metabolism of targets cells. The first recombinant cytokine growth factor or topical applications to wounds for the purpose of accelerating wound closure is platelets derived growth factors(PDGF).[6,7] In vitro study have shown that PGDF stimulate chemo taxis, proliferation and new gene expression in inflammatory cells.[6,10] In humans, clinical trial in pressure ulcer healing have shown that topical application result in a reduction in a wound volume.[11] Steed et al published a first study to show that PGDF significantly promoted healing in diabetic ulcers.[12] A significantly greater number of patients treated with PGDF demonstrate complete wound closure or at least faster healing when compare to placebo group or standard wound care alone.[13,14] The present study was conducted with the aim to compare the effects of exogenous application of PGDF on ulcer healing rate, its role in achieving complete wound closure and its ability to make wound bed adequate for possible skin closure/skin grafting in non healing lower extremities diabetic foot ulcers.

Study aimed at evaluation of efficacy of recombinant human platelets derived growth factors- PDGF in healing of chronic diabetic foot ulcers.

MATERIAL AND METHODS

All patients of age group 18-80 years with diabetic foot ulcer of more than 4 weeks duration were included. This was an open level parallel group and randomised study done in department of Surgery, Command Hospital Chandimandir

Exclusion criteria

Patients with osteomyelitis, patient on corticosteroid/ immunosuppressive and chemotherapeutic drugs, patients with grossly impaired RFT, known cases of malignancy, all

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death during study period were excluded.

Patients were randomised to one of two parallel treatment groups:

A. Controlled: Was subjected to good wound care (standard wound Care).
b. Study group: Was treated with local applications of recombinant human PDGF along with the required wound care.

Information was collected by questionnaire, clinical examination and laboratory investigations. The study was expected to have maximum of 12 weekly visits over a period of 12 weeks. Patients were applied a continuous thin layered of gel covered with moist saline gauze to the entire ulcer area once daily in study group patients.

Patients in control group had daily saline gauze dressings over target ulcer area. Efficacy and safety evaluation with photo documentations were performed at each visit.

Primary study end points were complete healing of ulcers,12 weeks of duration, ulcer bed adequate for possible skin closure /skin grafting.

Group	PDGF (patient incidence)	GWC (patient incidence)	p value
Age 40-50 years	27.78%	22.22%	1
Age 50-60 years	27.78%	38.89%	0.479
Age 60-70 years	44.44%	38.89%	0.735
Ulcer duration>8wks	50%	38.89%	0.50
Ulcer duration<8wks	50%	61.11%	0.50
Diabetes>5yr	50%	38.89%	0.502
Asso. comorbidity	33.33%	27.78%	0.717
Drugs used	66.67%	55.56%	0.494
Foot deformities	33.33%	27.78%	0.717
Vascular insufficiency	0%	0%	_
Neuropathy symptom score> or equal to 3	16.67%	22.22%	1
Non vegetarions	61.11%	66.67%	0.728
Smokers	33.33%	44.44%	0.494
Alcoholics	38.89%	27.78%	0.597
Poor gen. condition	0%	0%	_
Poor nutrition	27.78%	22.22%	1
Debridement and dressings done	All	All	_
Off loading done	50%	44.44%	0.738
Antibiotics used	22.22%	33.33%	0.709
Deranged vitals	0	0	_
Systemic derangements	11.11%	16.67%	1
Abnormal temperature	27.78%	22.22%	1
Adverse events	05.56%	11.11%	1
Severe adverse events	0%	0%	_
Haematologic derangements	0%	0%	_
Biochemical derangements	0%	0%	_
Ulcer closer/skin cover	66.67%	33.33%	0.045

Table-1: Showing comparison between the two groups

Observations

No statistically significant difference was present regarding dietary and alcoholic habits along with general conditions built and nutrition of patients.There was no statistically significant difference in the incidence of lower limb vascular pathology and neuropathy, foot deformities and presence / absence of excessive slough with no granulation tissue at floor of ulcer, inflamed and oedematous skin changes and plenty of discharge from ulcer site (Table-1).

The incidence of ulcer closure/skin cover at 12 weeks duration in PDGF group (66.66%) was found to be more than in GWC group (33.33%),this difference between the two groups was found to be statistically significant(P=0.045),(Table-1).

Average time taken to achieve ulcer closure/skin cover at 12 weeks duration in PDGF group (38.5 days) was found to be less than in GWC group (63 days).This difference between the two groups was also found to be statistically significant (p=0.017), (Table-2).

Incidence of ulcer closure/skin cover at 12 weeks in patients with age less than 60 years (66.66) was found to be more than in patients with age more than 60 yrs.(26.67%) with statistically significant difference between these two groups (P=0.042), (Table-3).

The incidence of ulcer closure /skin cover at 12 weeks duration was found to be less in smokers(21.43%) than in non-smokers (68.18%).The difference in the incidence between the two groups was statistically significant as the p value was 0.017, (Table-3).

DISCUSSION

Diabetic foot is a major cause of morbidity throughout the world, resulting in major economic consequences not only for the patients and their families but also the society at large.[1] People with diabetes have 12-25% life time risk of developing a foot ulcer.[21] The cost of diabetic foot lesions is affected by interventions to prevents foot ulcers and managements strategy to heal ulcers which can shorten wound healing time and prevent amputation.[22] Historically wounds were treated

Group	PDGF	GWC	p-value
Av. Days for Ulcer closer/skin cover	38.5 days	63 days	0.017

Table-2: Showing difference in days of wound closure in both groups

Group			p-value
Ulcer closure/skin cover	Below 60 years 66.67%	Above 60 years 26.67%	0.042
Ulcer closure/skin cover	Smokers 21.43%	Non-smokers 68.18%	0.017

Table-3: Showing relationship of wound healing with age and smoking

with homespun remedies derived in part from ritualistic teaching and in part from careful observations.[10] It was not until 1865 we Dr. Joseph Lister first demonstrated the use of an antiseptic in surgery and his treatments of wound with dressing soaked in Carbolic Acid that germ theory and infection were understood. During 1920-30 Baer reported the successful treatment of osteomyelitis and chronic leg ulcers in over 90 patients by using maggots. Fine mesh gauze with its modest absorption but minimally adherent surface was introduced in 1944. Cytokines and growth factors were first described 50 Yrs ago.

Growth Factors and wound Healing

The healing of a wound requires a well or striated integration of the complex biological and molecular events of cell migration, cell proliferation and extracellular matrix deposition.[6] In diabetics atherosclerosis and vessels wall damage cause impaired blood flow to distant tissue resulting in reduced delivery of oxygen and nutrient to the cell in a wound. Inflammation is prolonged, angiogenesis is impaired and there is decreased synthesis of collagen.[11]

Factors that impairs wound healing should be evaluated when a patient present with a non-healing wounds. These factors can be classified into 2 categories as extrinsic and intrinsic.[8] Some earlier studies, have revealed that time taken for non healing, lower extremities diabetic foot ulcers, is shorter when treated with exogenous application of PDGF.[14-17]

Bennett and Schultz reported that mastectomy drainage fluid promoted cell replications whereas chronic wound exudates inhibited it.[23] Further worked has revealed that levels of endogenous growth factors including PGDF and TGF-b recovered by dextranomer beads placed in chronic wound were significantly lower than those reported in acute wound[24] The processes of wound healing is complex and involved a series of interaction between platelets and macrophages.[10] Within the alpha granules of human platelets are multiple growth factors that are released when platelets are activated and degranulate.These include PGDF,TGF-b,FGF,EGF,PF4.[10]

Trials with growth factors

Trials with various growth factors have shown their role in wound healing. Steed et all published the 1st study to show that PDGF significantly promoted healing in diabetic ulcers.[12] This study with 118 patients showed healing incidence in PDGF group – 48% and placebo gel-25% (P=0.01).

Several studies till now have shown the ability of PDGF to promote wound healing.[14-20]

DL conducted a study with 922 patients with full thickness diabetic neurotropic foot ulcers which revealed 30% decrease healing time in PGDF group than with placebo gel.[14]

Wieaman TJ,Smiell JM, Suy[15] conducted trial including 382 patients in which closure time decreased by 32% with PDGF (P=0.013). Smile JM, Wyman TJ, Steed DL, Perry BH Sampson AR, Schwab BHA[16] conducted analysis of studies in which PDGF decrease healing time by 30% than placebo gel (P=0.01). Kantor J, Margolis DJ[19] observed that incidence of healing ulcers with PDGF gel was 43% while with standard care 30.9% with platelet release 36.8% and specialised wound care 35.6%. Ghatnekar O, Persson U, Willis M, Odegaard K[20] conducted a study to estimate the cost effectiveness of treating Diabetic foot ulcers with PDGF + Good wound care (GWC) compared with GWC alone in variety of European health care setting. PDGF was found to be a cost effective treatment. Saba AA,Freedman BM, Gaffeield JW, Mackay DR, Ehrlich HP[25] conducted studies to investigate effects of PDGF on wound healing in animal and human models. Wounds with PDGF healed faster. Sibbald RJ, Torrance G, Hut N, Attard C,Milkovich N[26] evaluated cost effectiveness of adding PDGF to a regimen of best clinical care on 251 patients with diabetes. Adding PDGF resulted in 26 less ulcer days/patients/year. Freedman BM, Oplinger EH, Freedman IS[27] conducted trial on occupationally related finger tip injury in 50 men. PDGF group had early return to work, less average functional impairment and less associated treatment cost, all statistically significant. A study was conducted by Keswani SG et al[28] on 3 different diabetic model of mice which showed that PDGF use was positively correlated with neo vascularisation and wound healing. A study undertaken by Cheng B,Liu HW,Fu XB,Sun TZ, Sheng ZY[29] to investigate the possible signalling mechanism by which PDFG improved healing of four full thickness skin wound in diabetic rats. PDGF accelerated rate of re-epithelisation compared with vehicle treated or untreated group at 7 days after wounding.

In our study, we found that the incidence of ulcer closure / skin cover at 12 weeks duration in PDGF group was found to be more than in GWC group and differences statically significant. PDGF is the 1st recombinant cytokine growth factor for topical applications to wounds for accelerating wound closure.[8,9] At wound site PDGF results in endogenous production of the growth factor and extracellular matrix synthesis, fibroblast proliferation and eventually collagen production. A significantly greater number of patients treated with PDGF with diabetic foot ulcer demonstrate complete wound closure or at least faster healing when compare to placebo group or standard wound care alone.[14-16] In this study the incidence of ulcer closure /skin cover at 12 weeks duration in PDGF group was found to be more than in GWC group and differences statically significant. Various earlier studies have reported the higher incidence of healing with PDGF and on comparison with other methods of wound care its demonstrate has been documented[12,14-16,19] average time taken to achieve ulcer closure /skin cover at 12 weeks duration in PDGF group was found to be less than in GWC group and difference was statistically significant.

CONCLUSION

The aim of this study was to evaluate the safety and efficacy of PDGF for the treatment of non healing, lower extremity diabetic foot ulcers this open labelled parallel group and randomised study had aged and morbidity matched study group. Trial with various group growth factors have shown their role in wound healing. In conclusion, the results of

this study showed that the daily exogenous application of PDGF is efficacious and safe in healing of lower extremities non healing diabetic foot ulcers. Its topical application over non healing diabetic foot ulcers increases the incidence of ulcer closure, reduces the time to archive ulcer closure, and enhances granulation tissue formation at ulcer site

ABBREVIATIONS

PDGF- platelet derived growth factor, GWC- good wound care, RFT -renal function test, TGF-b - transforming growth factor, FGF- fibroblast growth factor, EGF- epidermal growth factor, PF4- platelet factor 4

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