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ORIGINAL ARTICLE

Efficacy of topical recombinant human platelet derived growth factor on wound healing in patients with chronic diabetic lower limb ulcers

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Abstract

Background Lower extremity ulcers are a serious complication of diabetes mellitus (DM). These ulcers show decreased angiogenic response and production of growth factors. Recombinant human platelet derived growth factor (rhPDGF) has been found to decrease the time to healing. This study was conducted to evaluate its efficacy in the treatment of diabetic foot ulcers.

Methods A total of 50 patients with type 1 or type 2 DM and chronic ulcers, of at least 4 weeks duration, were studied. They were randomised into two groups, of 25 patients each. The patients in group 'A' (test group) received treatment with topical application of rhPDGF gel and those in group 'B' (control group) were treated with local application of KY Jelly as a placebo. A standardised regimen of good wound care was provided to both groups. Healing or reduction in size of the wound, over a period of 10 weeks after commencement of treatment was recorded.

Results The mean age of the patients was 49.9 years in the control group and 56.2 years in test group. The median duration of ulcer at time of enrolment in the study was 6 weeks in control and 5 weeks in test group. Fifteen ulcers in control group belonged to IAET (International Association of Enterostomal Therapy) class III and 10 ulcers to class IV where as 16 ulcers were in IAET class III and 9 ulcers in IAET class IV in the test group. The mean size of the wounds was 26.5 ± 2.5 cm^2 in control group and 29.9 ± 3.4 cm^2 in test group. All patients tolerated the test medication well. At the end of 10 weeks, 18 (72%) ulcers had healed in control group and 15 (60%) in test group ($p > 0.05$). Three ulcers in control group showed >75% reduction in size compared to 2 in the test group ($p > 0.05$).

Conclusion This study did not show any statistically significant improvement in ulcer healing rates after the use of topically applied rhPDGF.

Keywords Chronic diabetic foot ulcer · Recombinant human platelet derived growth factor (rhPDGF)

Introduction

Diabetes is a dreadful affliction, not very frequent among men, being a melting down of the flesh and limbs into urine. The patients never stop making water and the flow is incessant…..''Life is short, unpleasant and painful''.

Aretaeus of Cappadocia

Modern clinicians can still identify with the sentiments, expressed so eloquently almost 2000 years ago, by the second century Greek physician Aretaeus of Cappadocia when he coined the term diabetes to describe an affliction

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with no known treatment [1]. The number of cases of diabetes mellitus (DM) worldwide is estimated to be around 150 million. This is predicted to double by 2025 with the greatest number of cases expected in China and India [2].

Lower extremity ulcers are a serious complication of DM and account for more than 60% of all non-traumatic lower leg amputations [3]. The risk factors for foot ulcers include: male sex, DM more than 10 years duration, peripheral neuropathy, abnormal structure of foot, peripheral arterial disease, smoking, history of previous ulcer or amputation and poor glycaemic control [4]. It is estimated that 15% of diabetic patients will develop a foot ulcer during their lifetime and that 6–40% of them may require an amputation [5, 6].

These ulcers exhibit decreases in both angiogenic response and the production of growth factors [7]. Some of these growth factors can be generated by recombinant DNA technology and can accelerate ulcer healing [8]. Recombinant human platelet derived growth factor (rhPDGF) was the first such growth factor to be approved by the US, FDA as a supplement for the treatment of chronic non-healing diabetic ulcers of the lower extremities [9]. It has been found to significantly decrease the time to healing [10].

We conducted a study to assess the efficacy of topical rhPDGF in Indian patients with chronic diabetic lower limb ulcers. We followed the IAET (International Association of Enterostomal Therapy) classification in this study because of its simplicity compared to the Meggitt–Wagner classification and the University of Texas Wound Classification System [11, 12].

Materials and methods

This study was conducted over a period of 2 years, from May 2006 to May 2008, at a tertiary level teaching hospital. Patients with type 1 or type 2 DM and chronic ulcers of at least 4 weeks duration of IAET stage III and IV were included. Patients with an ankle brachial pressure index (ABI) <0.9 were excluded from the study. They were randomised into two groups, each consisting of 25 patients, on the basis of computer generated numbers. The nature of medication to be applied topically was explained to the patient and informed consent obtained before enrolment.

All patients were admitted to the surgical ward and were subjected to detailed evaluation. A complete haemogram, renal and liver function tests were carried out in all patients. The ulcer area was calculated, by obtaining the impression of the ulcer floor on a sheet of cellophane paper and transferring the imprint on to a graph paper. This assessment of ulcer size was repeated once every week. Patients with evidence of local sepsis were subjected to repeated surgical debridement before starting topical treatment. Objective assessment of vascularity was done by careful palpation of peripheral arterial pulses and calculation of ABI. Colour Doppler imaging of the arterial circulation of lower limbs was done in patients with absent or feeble pulses. Presence of osteomyelitis was determined with the help of plain radiographs of the part. Neurological examination involved assessment of large fibre function with a 128 Hz tuning fork, small fibre function with hot and cold objects and testing of ankle reflexes.

Systemic antibiotics were administered based on culture sensitivity results. Insulin/oral hypoglycemic agents (OHA), as advised by the physician/endocrinologist were used to maintain a good glycaemic control. Once adequate glycaemic and infection control had been achieved topical therapy was commenced.

The patients in group ‘A’ (test group) received treatment with topical application of rhPDGF gel and those in group ‘B’ (control group) were treated with local application of KY Jelly (Ethnor) – a lubricating jelly containing glycerin 11.25% w/w, methylparaben 0.1% w/w and propylparaben 0.04% w/w. A proprietary preparation of rhPDGF gel 0.01% by the name PLERMIN (Dr Reddy’s Laboratories Ltd.) was used in the study. For calculating the dose of PLERMIN, the greatest length of the ulcer, in centimetres, was multiplied by the greatest width and surface area thus obtained was divided by four to give the length of gel, in centimetres, to be used. This appropriate amount of PLERMIN, thus calculated every week, was applied locally to the wound surface with the help of a cotton swab once daily and wound covered with moist dressing.

Pressure off-loading was carried out in patients with plantar ulcers. Healing or percent reduction in size of the wound over a period of 10 weeks after commencement of local application was recorded as the endpoint of the study. In those cases where the ulcer was still present after 10 weeks the patient was offered the option to continue with the topical application or to undergo a split skin graft. Simultaneously, these patients were also educated about various aspects of DM including dietary restrictions, exercise and foot care in order to prevent recurrence. Statistical analysis of the data was done using appropriate tests and p values calculated.

Results

A total of 50 patients were included in the study. Male-to-female ratio was 5:1. The mean age of the patients was 49.9 years in the control group and 56.2 years in test group. The mean BMI was 21.8 in control group and 22.9 in test group. No significant difference was seen between two groups as regards physical characteristics and risk factors as summarised in Tables 1 and 2.

The median duration of ulcer at time of enrolment in the study was 6 weeks in control and 5 weeks in test group. There were a, statistically significant, higher number of

Table 1 Efficacy of topical rhPDGF in chronic diabetic foot ulcers

Characteristic	Group	
	Controls (n = 25)	Test (n = 25)
Male:female ratio	23:2	19:6
Mean age (years)	49.92 ± 18.89	56.20 ± 11.34
Occupation		
Farmer	11	9
Ex-army personnel	3	8
Housewife	2	5
Soldier	2	2
Others	7	1
Onset		
Insidious	7	7
Local sepsis	4	7
Surgery	2	2
Trauma	12	9
Median duration of ulcer at presentation (weeks)	6.00	5.00
Moderate to severe pain	17	9
Impaired walking at presentation	20	15

Demographic Characteristics

Table 2 Efficacy of topical rhPDGF in chronic diabetic foot ulcers

Risk factors	Group	
	Controls (n = 25)	Test (n = 25)
Male sex	23	19
DM more than 10 years duration	9	8
Peripheral neuropathy	8	11
Peripheral arterial disease	0	0
Smoking	5	4
History of previous ulcer or amputation	1	1

Risk Factors for Ulcers

patients with moderate-to-severe pain in the control group as compared to the test group (p = 0.02). The median duration of OHA intake in control group was 10 years and in test group was 5 years (p = 0.51) while that of insulin intake in control group was 0.55 years and 0.33 years in test group.

The ulcer characteristics are as summarised in Table 3. Fifteen ulcers belonged to IAET stage III and 10 ulcers belonged to IAET stage IV in control group where as 16 ulcers were in IAET stage III and 9 ulcers in IAET stage IV in test group. The mean size of the wounds were 26.5 ± 2.5 cm^2 in control group and 29.9 ± 3.4 cm^2 in test group (p = 0.68). Depth of wound was 4.2 ± 2.1 mm in control group and 4.7 ± 3.5 mm in test group (p = 0.53). No significant difference between the two groups was seen.

At the end of 10 weeks, 18 (72%) ulcers had healed in control group and 15 (60%) in test group. In addition, 3 ulcers in control group and 2 ulcers in test group showed a 75% decrease in size; these underwent split skin grafting (Table 4). The remaining 4 ulcers in control group and 8 ulcers in test group had neither healed nor shown a 75% decrease in size. These patients opted to continue with topical application of the medications. All patients tolerated the test medication well. There was no instance of local or systemic side-effect in any patient.

Discussion

Diabetic foot ulcer is a major healthcare problem that is a significant cause of morbidity, mortality and financial

Table 3 Efficacy of topical rhPDGF in chronic diabetic foot ulcers

Clinical features	Group		Statistical significance
	Controls (n = 25)	Test (n = 25)	
Mean size of wound (cm^2)	26.50 ± 2.507	29.96 ± 3.494	p = 0.689
Depth of wound (mm)	4.24 ± 2.107	4.76 ± 3.597	p = 0.536
IAET class III	15	16	p = 0.771
IAET class IV	10	9	p = 0.771
Edematous surrounding skin	10	5	p = 0.123
Type of wound discharge			p = 0.189
No discharge	0	3	
Purulent	10	10	
Serous/ serosanguinous	15	12	

Ulcer Characteristics

Table 4 Outcome at 10 weeks

Results	Group	
	Controls (n = 25)	Test (n = 25)
Results at 10 weeks:		
Healed at 10 weeks	18	15
>75% reduction in size (opted for SSG)	3	2
Continued topical treatment >10 weeks	4	8

burden [13]. New research and technology have allowed the wound healing process to be understood at a cellular and molecular level, including the vital role of growth factors. Although it is not known precisely why chronic wounds do not follow the normal pattern of healing, diminished growth factor content and accelerated growth factor degradation may contribute to poor healing [14]. Growth factors are a major technological advance that promised to change the face of wound healing for chronic wounds like diabetic foot ulcers. The most important growth factors are: rhPDGF, granulocyte colony stimulating growth factor and insulin-like growth factor (IGF) [15]. rhPDGF is active in all stages of wound-healing and a number of studies have shown the benefit of rhPDGF in wound-healing compared to standard therapy [16–20] .

In a study of 922 patients with full thickness ulcers with a baseline area of <10 cm treated for up to 20 weeks, Steed in 2006, reported that patients treated with rhPDGF had a significant increase in complete healing compared to patients given placebo. It also decreased the time to complete healing by 30% [16]. An earlier meta-analysis by Schaffer in 2001, of the clinical studies with topical application of rhPDGF for neuropathic diabetic foot ulcers shows an increase in healing by 10–15% within 20 weeks of treatment [21]. In our study 15 (60%) ulcers treated with rhPDGF had healed, at the end of 10 weeks, compared to 18 (72%) in the control group. In addition, 2 ulcers in the test group showed >75% reduction in size at the end of 10-week period compared to 3 in the control group ($p > 0.05$). These results did not show any significant benefit following the use of rhPGDF. This could possibly be due to the small sample size and limited duration of application.

It is also likely that the sole application of rhPDGF may not be able to overcome multiple growth factor deficiencies and other vulnerabilities in these chronic wounds. In a study to investigate the mitogenic response of fibroblasts in response to various growth factors, Loot et al. have reported that a combination of rhPDGF and IGF may be more useful than rhPDGF alone for application in chronic diabetic wounds [22].

To conclude, the use of topically applied rhPDGF for treatment of chronic lower extremity diabetic ulcers is recommended only as a supplement to the standard methods of ulcer care. This study did not show any statistically significant improvement in ulcer healing rates after its use. Since wound-healing is a complex process that can be influenced, positively and negatively, by many factors, designing trials will always be difficult, and possibly a larger, randomised, multicentre trial may be appropriate.

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