Use of a platelet-derived growth factor gel in chronic diabetic foot ulcers

Rajendra Prasad Agrawal, Ashok Jhajharia, Niranjana Mohta, Rutba Dogra, Vineeta Chaudhari, Kailash Chandra Nayak

To improve outcomes for those with diabetic foot ulcers and, ultimately, to reduce the rate of lower-limb amputation, new treatment modalities are urgently needed. Platelet-derived growth factor may be an effective tool in the management of foot ulcers of diverse aetiologies. In this randomised control trial, participants with chronic diabetic foot ulcers who received platelet-derived growth factor therapy in addition to traditional wound care were found to be significantly more likely to progress to healing.

Article points

1. Platelet-derived growth factor (PDGF) is an adjuvant treatment for diabetic foot ulceration that has shown positive results in the wound care literature.
2. Participants were randomised to received either a PDGF or placebo gel in addition to traditional ulcer wound care.
3. A highly significant reduction in mean ulcer area from baseline to study end was seen in the group randmoised to received PDGF therapy.

Key words
- Chronic diabetic foot ulcer
- Diabetic foot unlcer
- Platelet-derived growth factor

Author details can be found on the last page of this article.

Diabetic foot disease, one of the complications of diabetes, is increasing in incidence and prevalence globally (Boulton et al, 2005); some 7–10% of people with diabetes will develop a foot ulcer during their lifetime (Apelqvist et al, 1994). The diabetic foot has been described as the "quiet dread" because it is often associated with long periods of hospitalisation, high expense, and the possibility of lower-limb amputation (Pendsey, 2003).

The diabetic foot is classically characterised by the triad of infection, ischaemia and neuropathy. Those with diabetic foot disease should be strictly managed for hypertension and hyperlipidaemia, and lifestyle measures should be adopted to reduce the risk of ulceration. Regular podiatrist visits are advised, and education about footwear should be provided (NICE, 2004). When ulceration of the diabetic foot does occur, it is responsible for more than 50% of all major limb amputations (Reiber et al, 1992). Intact local microcirculation and adequate arterial blood supply to the ulcerated area are crucial in progression to healing (Zimny et al, 2001).

Several adjuvant treatments are available to stimulate wound healing in diabetic foot

Page points

1. Platelet-derived growth factor (PDGF) is manufactured by recombinant DNA technology for therapeutic purposes and has shown a number of positive applications in the wound-care literature.
2. The aim of this study was to investigate the effect of recombinant human PDGF on the healing of chronic foot ulcers among people with type 2 diabetes.
3. Twenty-eight people with type 2 diabetes and one or more chronic foot ulcer were enrolled in the study.
4. People with liver disease, pulmonary tuberculosis, thyroid disorder, uraemia, alcoholism or renal insufficiency, and those undergoing vascular reconstruction or receiving steroid or anticoagulant therapy were excluded.

ulcers, including synthetic extracellular matrix proteins, bioengineered skin, hyperbaric oxygen therapy and platelet-derived growth factor (PDGF). PDGF is a potent chemo-attractant and mitogen for fibroblasts, smooth muscle cells and inflammatory cells and is now manufactured by recombinant DNA technology for therapeutic purposes (Katzung, 1998). PDGF has shown a number of positive applications in the wound-care literature (Steed et al, 1995), including:

- Improvements in the breaking strength of incisional wounds following a single PDGF dose in animal models.
- Increases in wound granulation.
- Promotion of macrophage activity, thereby attracting fibroblasts into the wound space and increasing epithelisation.
- Increasing neo-vascularisation at the wound site.

The aim of this study was to investigate the effect of recombinant human PDGF (rhPDGF) on the healing of chronic foot ulcers among people with type 2 diabetes.

Methods

Participants

Twenty-eight people with type 2 diabetes and one or more chronic foot ulcers were enrolled in an Indian diabetes clinic. Diabetes was diagnosed according to American Diabetes Association (2004) revised criteria. Participants were randomised to receive either treatment with an rhPDGF 0.01% gel (study group, n=14), or a placebo gel (control group, n=14), in addition to a standard regimen of high-quality care for both systemic (e.g. glycaemic control) and local factors (e.g. debridement, dressings, pressure relief).

Informed consent was obtained from each participant and the ethics committee of the institution approved the study protocol.

Inclusion criteria

- ≥30 years of age.
- A glycaemic target of HbA_{1c} ≤7.0%, but HbA_{1c} >7.0% was not an exclusion criterion.
- Ulcer stage I, II, III or IV according to the Wagner (1981) classification.
- Foot ulcer duration of >3 months, free of infection with an adequate lower-limb blood supply as demonstrated by a transcutaneous oxygen tension ≥30 mmHg.
- Free of peripheral vascular disease (PVD), or PVD to a moderate degree (diagnosed as described in the "Diagnosis and measurements" section below).

Exclusion criteria

- Active neoplastic disease.
- Diagnosis of active infection (purulent discharge from the ulcer or two local signs of infection [i.e. warmth, erythema, lymphangitis, lymphadenopathy, oedema or pain]).
- Those who had received immuno-suppressive therapy during the preceding 3 months.
- Those with liver disease, pulmonary tuberculosis, thyroid disorder, uraemia, alcoholism or renal insufficiency, and those undergoing vascular reconstruction or receiving steroid or anticoagulant therapy.

Diagnosis and measurement

Ulcer size was taken as the total circumferential area. All participants had neuroischaemic ulcers. Participants' baseline clinical, biochemical and anthropometric data are shown in *Table 1*.

Neuropathy was diagnosed by a history of numbness, paraesthesias, tingling sensation, burning sensation and confirmed by touch sensation using a 10 g monofilament, vibration sense by biothesiometer and ankle reflex.

PVD was diagnosed by definitive history of intermittent claudication or by the absence of one or both peripheral pulses of the feet and then graded according to ankle–brachial pressure index by Doppler (Multi Dopplex [R]-II; Huntleigh Diagnostics, Cardiff, UK).

Venous blood samples were taken. HbA_{1c} was measured by ion exchange chromatography. Lipid profiles were detected

by complete autoanalyser (Ark Diagnostics, Mumbai, India).

Treatment

The study group received rhPDGF 0.01% gel at a dose of 2.2 µg/cm^2/day. The control group received a placebo gel administered in the same manner. All participants also received daily moist dressing changes, appropriate debridement, effective off-loading and appropriate prophylactic antibiotic therapy. Treatment and assessment were continued for 12 consecutive weeks. Treatment was discontinued if the ulcer healed before study end.

Statistical Analysis

Data shown are the mean ± standard deviation, regardless of their distribution (Shapiro–Wilk test). Groups were compared using SPSS software, version 10.0 (SPSS, Chicago, IL, USA) and analysis of variance was calculated. Post hoc comparisons were made using the Newman–Keuls test and critical ranges were calculated. Healing response was evaluated using the Chi-squared test. *P*-values <0.05 were considered statistically significant.

Results

The study and control groups' demographic data were comparable for age (mean 54.38 and 56.24 years, respectively). The male:female ratio in both the study and control groups (9:5 and 10:4, respectively) showed a clear preponderance of males. Baseline characteristics of the two groups were well matched for all variables except sex and ulcer area (ulcer size was significantly [*P*=0.003] larger in the study group; *Table 1*).

Mean total circumferential ulcer area at baseline was 55.61 cm^2 in the study group.

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Page points

1. Mean total circumferential area of the ulcer at baseline was 55.61 cm^2 in the study group and 1.29 cm^2 at study end.
2. A highly significant (P<0.001) reduction in mean ulcer area was observed from baseline to study end in the study group.
3. At study end, participants were categorised according to the extent of ulcer healing achieved: complete responder, partial responder, non-complete responder, non-responder.

By week 5, the mean area was 3.50 cm^2, dropping to 1.29 cm^2 by study end. In the control group, the mean ulcer area was 33.75 cm^2 at week 1, 7.87 cm^2 at week 5 and 5.03 cm^2 at week 12. A highly significant (P<0.001) reduction in mean ulcer area was observed from baseline to study end in the study group (*Table 2*; *Figure 1*), but not in the control group.

At study end, participants were categorised according to the extent of ulcer healing achieved:

- Complete responder (complete healing).
- Partial responder (achieved a ≥50% reduction in ulcer area from baseline).
- Non-complete responder (<50% reduction in ulcer area from baseline).
- Non-responder (neither a reduction nor an increase in ulcer area from baseline).

Following 1 week of treatment, the study group consisted of two complete responders, five partial responders and seven non-complete responders. Following 1 week of treatment, the control group consisted of four partial responders and ten non-complete responders. By study end, the study group consisted of nine complete responders, four partial responders and one non-responder, whereas the control group consisted of three complete responders, two partial

Table 1. Baseline characteristics of study participants.

	Study group (n=14)	Control group (n=14)	P-value
Age (years)†	54.38 ± 8.77	56.24 ± 8.75	0.496
Males (n)	9	10	NS
Diabetes duration (years)†	10.69 ± 6.12	10.44 ± 5.08	0.900
BMI (kg/m^2)†	26.70 ± 2.98	24.78 ± 3.09	0.084
Waist:hip ratio†	0.98 ± 0.08	1.01 ± 0.13	0.449
Total cholesterol (mmol/L)†§	5.86 ± 0.97	5.53 ± 0.98	NS
HDL-cholesterol (mmol/L)†§	1.01 ± 0.19	0.95 ± 0.15	NS
LDL-cholesterol (mmol/L)†§	3.68 ± 0.54	3.79 ± 0.08	NS
VLDL-cholesterol (mmol/L)†§	0.99 ± 0.30	1.02 ± 0.33	NS
Triglycerides (mmol/L)†§	1.95 ± 0.21	1.84 ± 0.25	NS
FBS (mmol/L)†§	9.25 ± 4.11	8.93 ± 2.68	NS
HbA_{1c} (%)†	8.76 ± 0.98	8.83 ± 1.02	NS
Ulcer area (cm^2)†‡	54.32 ± 45.16	28.72 ± 21.77	0.003
Peripheral neuropathy (n)	14	12	NS

†Mean ± standard deviation; ‡Total circumferential area; §Study measurments in mg/dL, shown here converted to mmol/L.
BMI=body mass index; FBS=fasting blood sugar; HDL=high-density lipids; LDL=low-density lipids; NS=not significant (P>0.05); VLDL=very low-density lipids.

Table 2. Size of ulcer† in response to recombinant human platelet-derived growth factor **(study group) and placebo gel (control group) therapy.**

Study week	Study group‡	Control group‡	t-test	P-value
0	55.61 ± 4.45	33.75 ± 2.48	4.29	<0.001
1	30.62 ± 3.05	20.50 ± 2.18	2.71	<0.020
2	16.93 ± 2.95	16.06 ± 2.22	0.22	<0.900
3	8.75 ± 2.88	11.93 ± 2.19	0.88	<0.500
5	3.50 ± 0.12	7.87 ± 0.75	5.60	<0.001
12	1.29 ± 0.25	5.03 ± 0.21	11.68	<0.001

†Total circumferential area; ‡Mean ± standard deviation.

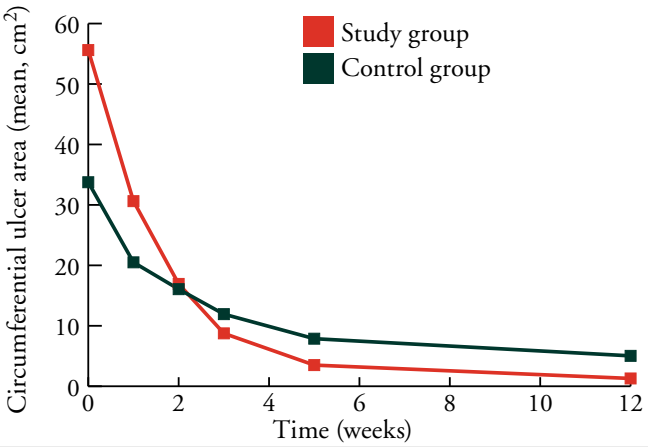

Figure 1. Effect of recombinant human platelet-derived growth factor therapy (study group, n=*14) and placebo (control group,* n=*14) on chronic diabetic foot ulcer mean total circumferential area during the study period. Note the signficantly (*P=*0.003) larger mean ulcer area at baseline of the study group and the rate of healing achieved in the study group during the first 2–4 weeks of therapy. Mean total circumferential ulcer area at baseline was 55.61 cm² in the study group, dropping to 1.29 cm² by study end.*

responders, four non-responders (*Table 3*). Five participants withdrew from the control group during the final week of the study period (week 12).

Ulcer healing may have been adversely affected by duration of diabetes, duration of ulcer or poor glycaemic control (*Figure 2*). There was no statistically significant difference in the biochemical profiles of participants from the study and control groups at the beginning of the study, or during weeks 1 and 3 (*Table 4*).

Side-effects reported during the study period are shown in *Table 5*. Side-effects associated with the use of the rhPDGF gel were infrequent and mild, including fever, local pruritis or burning, neutrophilia and arthralgia or myalgia.

Discussion

Various treatments are used to heal diabetic foot ulcers, including debridement, dressings and antibiotics (according to culture and sensitivity). Multidisciplinary management programmes that focus on prevention, education, regular foot examination, aggressive intervention, and optimal use of therapeutic footwear have demonstrated significant reductions in the incidence of lower-limb amputations (Larsson et al, 1995; Frykberg, 2002). However, to further improve outcomes for the diabetic foot, and ultimately to reduce the rate of lower-limb amputation, new treatment modalities are urgently needed.

Based on observations in the literature, rhPDGF may be an effective tool in the management of wounds of diverse aetiology

Page points

1. By study end, the study group consisted of nine complete responders, four partial responders and one non-responder, whereas the control group consisted of three complete responders, two partial responders, four non-responders.
2. Ulcer healing may have been adversely affected by duration of diabetes, duration of ulcer or poor glycaemic control.
3. Side-effects reported by study group participants were infrequent and mild (e.g. fever, local pruritis and neutrophilia).

Table 3. Healing response in study (*n*=14) and control (*n*=14) groups.

Study week	1		2		3		5		12			
Group	Study	Control	Study	Control	Study	Control	Study	Control	Study	Control†	Chi-squared	*P*-value
Complete responder (*n*)	2	0	3	1	5	1	6	1	9	3	2164	<0.001**
Partial responder (*n*)	5	4	11	7	9	8	8	11	4	2	0.622	<0.500
Non-complete responder (*n*)	7	10	0	6	0	5	0	2	0	0	10.36	<0.010*
Non-responder (*n*)	0	0	0	0	0	0	0	0	1	4	0.04	<0.900

*Statistically significant; **highly statistically significant. †Five control group participants withdrew from the study in week 12.

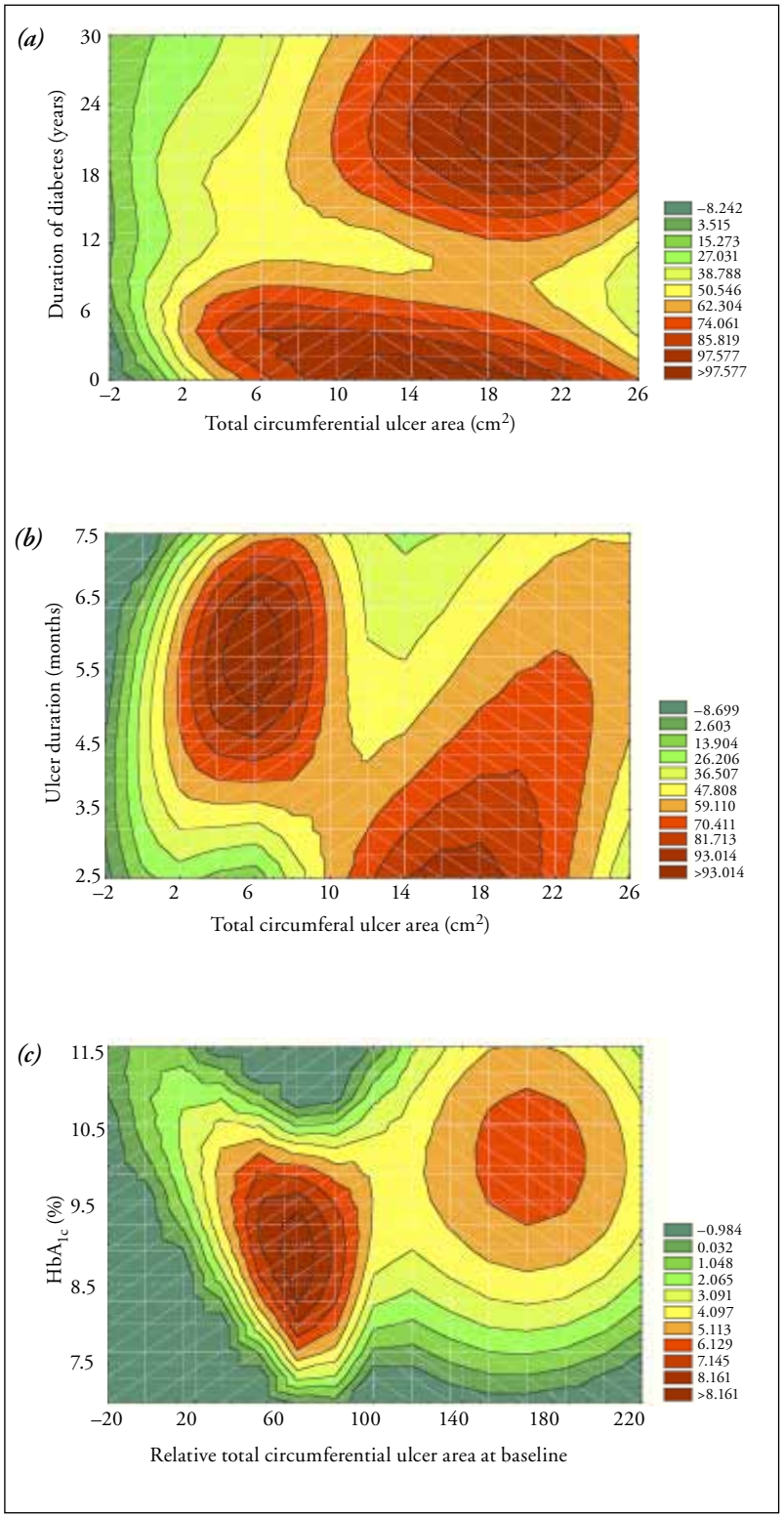

Figure 2. (a) The relationship between ulcer area at basline and study end in relation to the duration of diabetes. (b) The relationship between ulcer area at basline and study end in relation to ulcer duration. (c) The relationship between ulcer area at basline and study end in relation to HbA_{1c}.

in people with diabetes (Holloway et al, 1993), and especially in the management of diabetic foot ulcers (Knighton et al, 1986; Wieman et al, 1998a;b).

In the study reported here, participants receiving rhPDGF therapy showed a significant improvement in ulcer healing in comparison with the control group, and response to rhPDGF therapy was evident within 1 week of commencement. Sixty-four per cent of participants in the study group achieved complete healing and 29% achieved partial healing, while in the control group, only 21% achieved complete healing and 14% partial healing.

Similar results for the treatment of diabetic foot ulcers treated with rhPDGF were reported by Wieman et al (1998a;b). More than 20 years ago, Knighton et al (1986) reported successful treatment of chronic diabetic ulcers with an autologous platelet-derived product containing, among other factors, rhPDGF.

Cost-effective therapy

rhPDGF-based products are more costly than the consumables used as part of traditional wound care regimens. However, if the indirect costs associated with chronic diabetic foot ulcers are considered (e.g. extended periods of hospitalisation, lost earnings of individuals or families, quality of life, amputation, disability), this more expensive but effective addition to treatment regimens seems logical. A management strategy for the cost-effective treatment of chronic diabetic foot ulcers using rhPDGF-based topical preparations in Europe also took this position (Ghatnekar et al, 2001).

The study reported here was conducted in India. Current estimates suggest that people in that country with diabetic foot disease spend between US$1000 and US$2000 on diabetic foot ulcer treatments that ultimately result in a lower-limb amputation (Pendsey, 2003). When this figure is considered in the light of Indian gross per capita national income (less than US$500) and the low rates of private health insurance (Pendsey,

2003), the development of effective first-line therapies is essential for managing the burden of diabetic foot disease, whether in the developing or developed world.

Limitations

Limitations of this study are its small cohort, and the possible Hawthorn effect. There was a significant difference in mean ulcer area at baseline between the study and control groups, but this is unlikely to have affected the results.

Conclusion

Additional research is needed to define the specific indications for, and benefits of, rhPDGF therapy. Randomised controlled trials with large sample sizes would lend further strength to the growing body of evidence that suggests rhPDGF therapy improves clinical outcomes in chronic diabetic foot ulcers. ■

Rajendra Prasad Agrawal is Associate Professor, Ashok Jhajharia is a Senior Registrar, Niranjana Mohta is a Research Associate, Rutba Dogra is a Junior Research Fellow, Vineeta Chaudhari is a Senior Resident and Kailash Chandra Nayak is Professor and Head of the Department of Medicine, the Diabetes Care and Research Centre, SP Medical College, Bikaner, India.

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Apelqvist J, Ragnarson-Tennvall G, Persson U, Larsson J (1994) Diabetic foot ulcers in a multidisciplinary setting: an economical analysis of primary healing or healing with amputation. *J Intern Med* **235**: 463–71

Page points

1. The development of effective first-line therapies is essential for managing the burden of diabetic foot disease, whether in the developing or developed world.
2. Additional research is needed to define the specific indications for, and benefits of, platelet-derived growth factor therapy.
3. There is a growing body of evidence suggesting that platelet-derived growth factor therapy improves clinical outcomes in chronic diabetic foot ulcers.

Table 4. Mean haematological and biochemical profiles of study and control group participants.

Study week	0		1		3		12	
Group	**Study**	**Control**	**Study**	**Control**	**Study**	**Control**	**Study**	**Control**
Haemoglobin (× 10^9/L)	9.3	8.9	8.9	9.1	9.2	9.0	9.6	9.1
Leucocytes (× 10^6/L)	9530	8700	9800	8900	10200	9000	12500	8800
Neutrophils (× 10^6/L)	6000	6100	6400	6000	6900	6100	9100	6200
Lymphocytes (× 10^6/L)	2300	2100	2300	2400	2000	2100	2200	2100
Platelets (× 10^9/L)	160	170	165	177	167	170	160	165
Urea (mmol/L)†	11.4	10.0	8.9	9.3	8.6	8.9	9.3	8.2
Creatinine (µmol/L)‡	86.6	82.2	70.7	70.7	79.6	70.7	79.6	70.7
Uric acid (µmol/L)	404	390	410	396	420	425	415	425
Total protein (g/L)§	72	68	66	64	65	68	64	66

†Study measurments in mg/dL, shown here converted to mmol/L. ‡Study measurments in mg/dL, shown here converted to µmol/L. §Study measurments in g/dL, shown here converted to g/L.

Table 5. Adverse effects reported by study and control group members.

	Study (*n*=14)	Control (*n*=14)	*t*-test	*P*-value
Fever or malaise	2	0	2.14	<0.20
Local pruritis or burning	3	0	3.36	<0.10
Neutrophilia	6	0	7.62	<0.01*
Arthralgia or myalgia	1	0	1.04	<0.50
Allergic reaction	1	0	1.04	<0.50

*Statistically significant.

"... the development of effective first-line therapies is essential for managing the burden of diabetic foot disease."

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