Platelet Derived Growth Factor in Healing of Large Diabetic Foot Ulcers in Indian Clinical Set-up: A Protocol-based Approach

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Abstract

AIM: To determine the effectiveness of topical recombinant human platelet derived growth factor (rh-PDGF- 100ug/ml) based dressing over conventional dressing for large chronic neuropathic diabetic foot ulcers.

Study Design: A prospective cohort study.

Methods: Diabetic patients with large chronic neuropathic foot ulcers were divided into conventional dressing group & rh-PDGF based dressing group. Once a day, topical rh-PDGF gel was applied in conjunction with standard wound care. The intervention was stopped on complete wound healing or at 10 weeks, whichever occurred first.

Results: Nineteen patients received PDGF-based dressings and 23 patients received conventional dressings. Data analysis showed that complete healing was significantly higher in the growth factor group (p value: <0.05, Fisher Exact Test). In addition, median reduction in ulcer surface area was also significantly high in rh-PDGF group at 4 & 6 weeks intervals (p value: <0.001 and <0.014 respectively).

Conclusion: Findings indicate that rh-PDGF based dressing is more effective than standard therapy. This effect is more pronounced in large severe wounds and wounds in immunocompromised patients. Unfortunately, large wounds and wounds in immunocompromised patients have not been evaluated in clinical trials of new agent interventions. Therefore, we encourage the inclusion of these patients in future trials.

Introduction

Diabetic foot ulcers are notoriously difficult to heal ulcers and its management frustrates surgeons of all ages, experiences, skills and nationalities. Despite advances in technologies and heroic efforts, 10 to 15% of diabetic foot ulcers remain non- responsive to standard wound care [1] and ultimately lead to amputation in more than 80% of the patients [2, 3]. The estimate says that every 30-second, a foot is lost somewhere in the world[4] and this frightening fact dominates our clinical thinking and forces even the recalcitrant devotee of the wound care to rethink that why diabetic foot ulcer get stuck in the phase of inflammation and don’t progress to the phase of proliferation and maturation. This fact remained as ‘brain-thirst’ for many researchers for many decades. But, now; we know that the wound environment of diabetic wounds are rich in serine proteases, matrix metalloproteinase’s (MMPs) and tissue inhibitors of MMPs, that lead to degradation of growth factors and subsequently lead to healing failure. In this regard, topical use of rh-PDGF has shown some promises as a healing protagonist in various clinical trials [5, 6]. However, many issues yet remain to be explored with its use in day-to-day clinical practices:

1. Most of the clinical trials have measured PDGF-efficacy, not effectiveness and both the terms are not synonymous. In addition, PDGF efficacy documented in small-randomized clinical trials cannot be translated to positive clinical experience because these studies are conducted under tightly controlled conditions, whereas clinicians encounter patients in actual practice rather than in the ideal world.
2. All these trails have excluded wounds of higher grade and ulcers in immunocompromised patients.

With the availability of this molecule in India at affordable cost and after knowing its excellent safety profile [7], we also planned to conduct a prospective comparative study to evaluate its healing power on Indian patients who mostly suffer from large diabetic foot ulcers.

Methods

Patients were divided into two treatment groups for prospective comparative study. First group received moist saline gauge based dressing (conventional arm) and the other growth factor based dressing (PDGF group). Both groups were evaluated and managed exactly the same way following a standard Institute’s protocol [Table-1]. Patients with type II diabetes were enrolled in the study with fulfillment of the criteria mentioned in Table 2.
Patients of chronic renal failure on dialysis and post-renal transplant patients on steroids and or immunosuppressive agents (on doses known to impair wound healing) were also included. If multiple ulcers were present, the largest ulcer was considered for the study after debridement of all the necrotic tissue.

At the outset, a detailed performa was filled noting down all the relevant history, medical examination and treatment received. Concomitant medications and their indications for use were also recorded. The diabetic status of the patient, including duration, type, and management, was noted with current activity level, ambulatory status, and history of ulceration or previous amputations. Blood test results included levels of glycosylated hemoglobin, glucose, albumin, creatinine, blood urea nitrogen, and liver function tests. Color arterial Doppler ultrasound was performed to assess the vascular status. Other tests included palpable ankle pulses and ankle brachial pressure index to assess foot perfusion. The wound area was measured by means of planimetry (the greatest length x the greatest width, measured in centimeters). The perimeter of the wound was traced using an acetate film and a fine-tipped permanent black ink marker. The target wound was assessed before and after cleansing and/or debridement for local infection and for wound condition (improving, stable, or deteriorating). Wound bed characteristics, margins, and the presence or absence of undermining or tunneling were also noted. Periodic sharp surgical debridement of nonviable or necrotic tissue (until healthy bleeding tissue was reached) was performed as and when necessary. The frequency of dressing changes varied according to the condition of the wound and the amount of drainage. A consistent protocol for patient management was followed. The protocol included:

1. To maintain hemoglobin >11 Gm%
2. Serum albumin > 3G/dl
3. Switch-over from oral hypoglycemic to Insulin therapy to achieve a tight blood sugar control
4. Deep tissue culture for both aerobic and anaerobic organisms
5. Systemic antibiotics according to culture sensitivity
6. Moist wound dressings
7. Off-loading [crutches, wheelchair, total contact cast and complete bed rest]
8. Periodic sharp surgical debridements.

Wound status was evaluated at 2 weeks to look for poor healing (<10-15% surface area). All patients having poor healing were randomly assigned into two groups: Control group (treated with moist saline gauge dressing) and Test group (treated with rh- PDGF gel 100 microgram/gm). Wound measurements were done at weekly intervals till 6 weeks and biweekly thereafter till 10 weeks and the results recorded. Effectiveness of both the treatment protocols was evaluated in terms of percentage healing or complete closure at 4, 6, 8, and 10 weeks. The end point of treatment was defined as complete closure of the wound. Anything less than 100% healing at 10 weeks was considered as failure to heal. The patients were considered non-compliant if daily dressings were missed for 2 days, offloading was not followed for more than 2 days and if patient failed to report for 2 consecutive visits during the follow up period.

### Statistical Analysis

Student's t-test for continuous data and a Pearson's chi-square test for categorical data were used for comparison between the two groups. A log rank test was used to compare the time to complete healing. Data were censured at 10 weeks (SPSS version 12.0).

### Results

One hundred and five patients were screened for this study. Sixty-five patients were excluded due to (a) non-salvageable limb (15 patients), (b) under standard care of treatment ulcers healed by >10-15% (18 patients) and (c) non-compliance (21 patients). Patient demographics are enumerated in Table 3. The difference in baseline profile was statistically not significant. Data were analyzed at 4, 6, 8 and 10-weeks. Twelve out of 19 patients (63.2%) in the PDGF group achieved complete healing at 10 weeks, which was significantly higher (p<0.05) in comparison to the control group (34.8%) on Fisher’s Exact Test [Table 4]. The median time to complete healing in the PDGF group was 56 days in comparison to the control group 63 days. The average percentage in ulcer size reduction was significantly higher in the PDGF group compared to the control group at 4 and 6 weeks (p <0.001 and <0.014 respectively) [Table 5]. Overall reduction in ulcer size was not statistically different at 8 and 10 weeks in both the groups. Interestingly when healing failure was compared, these were significantly lower (p< 0.05) in the PDGF (36.8%) group in comparison to the control group (65.2%) [Table 3]. The data suggests that PDGF gel based dressing not only healed a greater percentage of ulcers but also healed them faster.

### Discussion

Results from this study indicate that PDGF based interventions are superior to the standard therapy.
protocols. The difference in complete healing between the two groups was found to be statistically significant. PDGF-based dressing achieved complete healing in 63.2% of patients at 10 weeks [Figure 1-2], which was 28.4% higher than that observed in the standard dressing.

Similar findings [8-14] have been reported in various randomized controlled studies (complete healing 33% to 57.5%) at a cutoff time of 12-20 weeks. However, all these studies have included small ulcer size and applied PDGF on the ‘intention-to-treat’ group in contrary to our study where we intentionally selected large diabetic ulcers with associated co-morbidities, which is more common in our routine Indian clinical practice [Figure 3-5]. One of the important reasons for performing a randomized controlled trial is that it can essentially eliminate selection bias, because patients are randomly assigned to treatment. Purposeful selection raises suspicion that certain types of patients (those more or less likely to heal) are differentially chosen for treatment with PDGF. Therefore, the bias in observational study (case-control study or cohort study) could be that patients, treated with PDGF, might have wounds that are more or less likely to heal than patients not treated with PDGF gel based dressing. However, in our cohort study we attempted to control for selection bias by balancing factors (like age, duration of ulcer, grade and size of ulcer, glycemic control, vascular status and co-morbidities etc.) between the two treatment groups. One advantage of doing cohort studies over randomized controlled trials is that cohort studies measures effectiveness of two treatment modalities, whereas randomized controlled trials estimate efficacy of the treatment[15]. Effectiveness refers to the real-world ability of a treatment to provide benefit, whereas efficacy involves the potential benefits of a therapy under idealized conditions. Since, patients are rarely subjected to these idealized conditions, effectiveness estimates become more useful than efficacy estimates while deciding the best treatment option for individual patient.

Most of the published [8-14] series have used 10 or 20 weeks period for midterm evaluation. However, we attempted mid term evaluation at 4, 6, 8 and 10 weeks interval based on studies that reported healing of chronic wounds within 10-12 weeks [16]. The reason for opting short period was that, in India, people do not accept longer duration of treatment due to their poor socioeconomic status and do not prefer to become the part of study due to low literacy rate and it was the main reason for non-compliance in majority of our patients. Despite knowing the fact that wound size and wound duration are responsible for a wound being unlikely to heal within 8-10 weeks of care, we selected large and deep ulcers, because these large ulcers are more likely to progress to the point of amputation. We suggest possible explanation for the successful clinical outcome of PDGF-based dressing:

1. Aggressive serial debridements and twice daily dressing in the beginning was performed
2. Serum hemoglobin level of >11 gm% and serum albumin in the range of 3 to 4gm was maintained throughout the treatment course
3. Good vascular status (assessed by Doppler ultrasound) was assured
4. Proper off-loading of the wound site was provided
5. Early intervention of PDGF based dressing.

Most of the previously reported studies [17] have first attempted standard therapy for a minimum of 8 weeks in comparison to 2 weeks in our study. Reason for choosing 2-weeks observation period was: (a) we presume that two weeks observation gives enough time to select wounds struggling for healing and (b) majority of patients come from underserved part of the country lacking in primary health care, sanitation, transportation and safe water. Naturally, they have to depend on self-treatment or take help of other non-health care professional for long duration until their wound get worse. Therefore, the moment they reach to specialized centre, they request for quick intervention.

There are several limitations in our study. First, the small sample size limits significance. Second, two third of our patients had plantar ulcers involving the deep anatomical structure and dorsum of the foot. It is generally appreciated that ulcers in different region may have different etiologies or aggravating factors, making comparison between studies difficult. Third, the treating resident surgeon was not blinded to the treatment status of the patients. Therefore, it is possible that patients who received PDGF based dressing could have been treated in a more systematic and aggressive way from those that were treated with standard care alone. However, we think that this should not be a problematic issue because the covariates responsible for healing were homogenous in both the treatment groups. Lastly, this single center study includes large ulcers and ulcers in immune-compromised patients, therefore; requires validation with multi-center study.

We conclude that PDGF based topical interventions may be recommended for larger, higher-grade neuropathic diabetic foot ulcers and ulcers in immuno-compromised patients. The decision
regarding amputation should be postponed until PDGF
therapy option has been exhausted. Future studies
should include and perhaps focus on those patients
with the largest and deepest wounds, because these
wounds are more likely to progress to amputation.

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Illustrations

Illustration 1

Table 1: SGPGIMS Protocol for managing large diabetic foot ulcers

![Diabetic foot Management Protocol (SGPGIMS, Lucknow, India)](image_url)
Illustration 2

Table 2: Patients Enrolment Criteria

<table>
<thead>
<tr>
<th>Selection criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wagner grade III and IV</td>
<td>Ischemic ulcers</td>
</tr>
<tr>
<td>Ulcer with minimum surface area of 12 cm² (greatest length x greatest width in centimeter)</td>
<td>Presence of osteomyelitis</td>
</tr>
<tr>
<td>Ulcer of at least 4 weeks duration</td>
<td>Infective ulcers not well controlled on antibiotics</td>
</tr>
<tr>
<td>Largest ulcer if multiple ulcers (up to 3) were present.</td>
<td>Unwillingness of patient to walk using an off-loading device</td>
</tr>
<tr>
<td>Affordability with rh-PDGF therapy</td>
<td>Deformities like Charcot’s foot</td>
</tr>
</tbody>
</table>
Illustration 3

Table 3: Patients Demographics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Conventional (n=23)</th>
<th>PDGF-gel (100 ug/gm) (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>22</td>
<td>15</td>
</tr>
<tr>
<td>Female</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Age(Yrs)</td>
<td>54(35-82)</td>
<td>62(32-80)</td>
</tr>
<tr>
<td>Duration Of Diabetes(Yrs)</td>
<td>10(1-22)</td>
<td>12.5(5-42)</td>
</tr>
<tr>
<td>Chronic renal Failure</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Post renal Transplant</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Previous Minor Amputation</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Ulcer Grade(M-W Classification)</td>
<td>Grade -III: 8 pts</td>
<td>Grade -III: 5 pts</td>
</tr>
<tr>
<td></td>
<td>Grade - IV: 11 pts</td>
<td>Grade - IV : 18 pts</td>
</tr>
<tr>
<td>Ulcer Duration(Months)</td>
<td>1.5(1-6)</td>
<td>2.25(1-3)</td>
</tr>
<tr>
<td>Ulcer surface area (cm^2)</td>
<td>20(12- 40)</td>
<td>24(13- 42)</td>
</tr>
<tr>
<td>HbA1C( %)</td>
<td>7.4(5.10- 11.5)</td>
<td>7.5(5.5- 9.6)</td>
</tr>
</tbody>
</table>
Illustration 4

Table 4: Comparison of Percentage Healing and Healing failure in both treatment groups
Illustration 5

Table 5: Average reduction of ulcer surface area (in percent) at different weeks
Illustration 6

Figure 1: 52 year old man with type II diabetes, post renal transplant on immunosuppressive drugs with previous minor amputation of the digits, showing complete epithelialization of wound in 6 weeks period with PDGF (100microg/gm) gel application in conjunction with good wound care

Illustration 7

Figure 2: 58 year old female with type II diabetes, diabetic foot abscess with ulcer healed in 4 weeks with PDGF (100microg/gm) gel application in conjunction with good wound care
Illustration 8

Figure 3: 65 year old man with type II diabetes, on dialysis, almost completely epithelialised with the help of PDGF (100microg/gm) gel application in conjunction with good wound care in 10 weeks

Illustration 9

Figure 4: 62 year old man with type II diabetes, post renal transplant prepared for partial thickness skin graft with the help oh PDGF in 5 weeks, in conjunction with good wound care
Illustration 10

Figure 5: 48 year old female with type II diabetes, wound prepared for partial thickness skin graft with the help of PDGF in 7 weeks in conjunction with good wound care.
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