Management of Diabetic Foot Ulcer with Recombinant Human Epidermal Growth Factor versus Conventional Dressing Method

R.C.L. Raj 1, A.R. Chand2, S. Kumar3, A.J. Philip4

1Assistant Professor, Department of General Surgery, Pondicherry Institute of Medical Sciences, Kalapet, Pondicherry. 2Associate Professor, Department of General Surgery, Pondicherry Institute of Medical Sciences, Kalapet, Pondicherry. 3Professor, Department of General Surgery, Pondicherry Institute of Medical Sciences, Kalapet, Pondicherry. 4Assistant Professor, Department of General Surgery, Pondicherry Institute of Medical Sciences, Kalapet, Pondicherry.

ABSTRACT

BACKGROUND
Diabetic foot ulcer is one of the major complications of diabetes mellitus. Normally, wound healing occurs mainly by the repair of extracellular matrix, but in certain cases physiological insult disturbs the wound healing process. One such metabolic disorder, diabetes mellitus, is found to impede the normal steps of the wound healing. At times, management of foot ulcers may be challenging and might require multidisciplinary assessment and treatments. The usual treatment for diabetic foot ulcers consists of appropriate dressings, antibiotics, and debridement.

METHODS
This study was conducted in Pondicherry Institute of Medical Sciences from November 2015 to May 2016, as a randomised control trial comparing the efficacy of recombinant human epidermal growth factor with that of conventional saline dressing in healing diabetic foot ulcers. The minimum required sample size was determined to be 30 in each of the treatment groups. Purposive sampling was employed in selecting the study participants and were followed up for minimum two weeks duration.

RESULTS
Among the study population, the rate of development of granulation, epithelialisation and reduction of the amount of wound discharge is faster in rhEGF group as compared to that of saline group of patients.

CONCLUSIONS
The effectiveness of recombinant epidermal growth factor (rhEGF) dressing over conventional saline dressing method was evaluated in the present study. The findings of the study suggest that rhEGF had significantly better effects on wound healing of diabetic foot ulcers in terms of faster rate of development of granulation, epithelialisation, and reduction of the amount of wound discharge.

KEYWORDS
Diabetic Foot Ulcer, Recombinant Human Epidermal Growth Factor (rhEGF), Saline Dressing, Granulation, Epithelialisation, Wound Discharge
BACKGROUND

Diabetes is a chronic disease, which occurs when the body cannot effectively use the insulin it produces, or pancreas does not produce enough insulin. Because of this phenomenon there is hyperglycaemia (increased concentration of glucose in the blood). Adults with diabetes mellitus are 2-3-fold increased risk of developing ischemic heart disease and stroke. In addition, diabetic neuropathy in the feet increases the chance of foot ulcers, infection and eventually leading to amputation of the affected limb. Diabetic foot ulcer is considered to be one of the major complications of diabetes mellitus. Normally wound healing occurs mainly by the repair of Extra cellular matrix, but in certain cases physiological insult disturbs the wound healing process. One such metabolic disorder, diabetes mellitus, is found to impede the normal steps of the wound healing. A prolonged inflammatory phase in diabetic wounds, which causes a delay in the formation of mature granulation tissue and a parallel reduction in wound tensile strength was reported by various researchers previously. Among patients with diabetes mellitus 15% tend to develop foot ulcers and 12%-24% of the individuals with foot ulcers require amputations. Education of diabetics regarding foot care combined with increased surveillance can reduce the incidence of serious foot lesions and ulcers. At times management of foot ulcers may be challenging and might require multidisciplinary assessment and treatments. The usual treatment for diabetic foot ulcers consists of appropriate bandages, antibiotics, debridement and serial dressings. Growth factors are substances that occur naturally in the body. They promote growth of new cells and healing of wounds. Treatment of diabetic foot ulcers with growth factors may improve the healing of ulcers. Evidence suggest that growth factors may increase the likelihood that people with diabetes will have complete healing of foot ulcers. Epidermal growth factor acts by binding with high affinity to epidermal growth factor receptors present in the cell surface, which in turn stimulates ligand-induced dimerization. It was reported that Recombinant human epidermal growth factor can be used effectively in the management of diabetic foot ulcers. Recombinant epidermal growth factors act by increasing the rate of wound healing in patients with diabetic foot ulcers.

We wanted to evaluate the effectiveness of recombinant epidermal growth factor (rHEGF) dressing over conventional saline dressing method, compare the time taken for the diabetic foot ulcer to heal and assess the granulation tissue formation as a percentage of the total surface area of the diabetic foot ulcer following the dressing with recombinant human epidermal growth factor and conventional saline dressing.

METHODS

The present study is a randomised control trial conducted at Pondicherry Institute of Medical Sciences, Pondicherry, South India, from November 2015 to May 2016. The sample size was determined to be 30 in each of the treatment groups. The study population was selected from the surgical OPD attendent of Pondicherry Institute of Medical Sciences, who were willing for admission in hospital and follow up for the stipulated study period of minimum of two weeks duration. Purposive sampling was employed in selecting the study participants from all the all the eligible patients who attended the hospital

Inclusion Criteria

Patients of both gender above 18 years of age with diabetic ulcer (Wagner’s classification I and II).

Exclusion Criteria

Patients who were diagnosed with vascular disease.

Treatment Groups

Intervention group received topical recombinant human epidermal growth factor. Control group received conventional saline wound dressing. The above treatments therapies were approved by Drug Controller General of India (DCGI) for use in the management of diabetic foot ulcers.

Randomization

Study participants selected based on inclusion and exclusion criteria were randomized to rhEGF group and saline group. Informed written consent for participation was obtained before randomization.

Procedure

After randomization patients received appropriate wound dressings based on the groups to which they are randomly allocated. Wound size and characteristics were noted at the time of enrolment and also at regular intervals. There was no loss to follow up or non-compliance observed during the course of the study period among any of the study participants until 14 days. Parameters studied were wound size, presence of granulation, presence of wound discharge, appearance of epithelialization Control of Glycaemic status of the study participants was ensured throughout the study duration by using appropriate hypoglycemic agents used in the treatment of diabetes mellitus.

Statistical Analysis

Data entry was done using MS Excel 2013 and statistical analysis was done using SPSS version 21.0. Means and proportions were calculated and describing the base line characteristics. Repeated measure ANOVA test was used to measure statistical significance in difference of means between the two treatment groups. Chi square test was used to compare statistical difference in proportions between the two groups. A p value of <0.05 was considered statistically significant.

Ethical Considerations

Institute ethical committee approval and clearance was obtained before the study was started. Informed consent
was obtained from all the patients in their own language before starting protocol wise treatment and data collection.

RESULTS

**Figure 1. Distribution of Study Groups Based on Reduction in Ulcer Size at Different Time Intervals**

**Figure 2. Proportion of Study Participants Who Showed Presence of Granulation at Various Time Intervals**

**Figure 3. Proportion of Study Participants Who Showed Presence of Epithelialization at Various Time Intervals**

Males and females were equally distributed between the intervention and control groups, with 22 and 8, males and females respectively in each of the groups. The mean area of ulcer in rhEGF group was 38.1 cm² and in saline group the mean area of ulcer was 26.4 cm². After 6 days on an average wound size reduced by 9.73% in rhEGF group and 1.3% in saline group. This difference was found to be statistically significant. After 14 days on an average wound size reduced by 25.82% in rhEGF group and 6.06% in saline group. This difference was found to be statistically significant. Rate of reduction in ulcer size is faster in rhEGF group as compared to that of saline group of patients. Among the patients who were treated with rhEGF the rate of development of granulation tissue was much faster as compared to the patients who were treated with conventional saline dressings. Proportion of patients with signs of epithelialization in the wounds increased significantly with time in the rhEGF group when compared to those patients who are treated with saline dressings, at various different time intervals.

**Table 1. Distribution of Study Participants Based on Gender**

<table>
<thead>
<tr>
<th>Gender</th>
<th>rhEGF Group n (%)</th>
<th>Saline Group n (%)</th>
<th>Total n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>22(50)</td>
<td>22(50)</td>
<td>44(73.3)</td>
</tr>
<tr>
<td>Female</td>
<td>8(50)</td>
<td>8(50)</td>
<td>16(26.7)</td>
</tr>
<tr>
<td>Total</td>
<td>30(50)</td>
<td>30(50)</td>
<td>60(100)</td>
</tr>
</tbody>
</table>

**Table 2. Distribution of Study Groups Based on Total Area of Ulcer on Day 0**

<table>
<thead>
<tr>
<th>Gender</th>
<th>rhEGF Group Mean (in cm²)</th>
<th>Saline Group Mean (in cm²)</th>
<th>Difference in Mean (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>38.1</td>
<td>26.4</td>
<td>11.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female</td>
<td>34.3</td>
<td>20.0</td>
<td>14.3</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Table 3. Distribution of Study Groups Based on Percentage of Reduction in Ulcer Size after 6 Days**

<table>
<thead>
<tr>
<th>Gender</th>
<th>rhEGF Group Mean Percentage Red. (n = 30)</th>
<th>Saline Group Mean Percentage Red. (n = 30)</th>
<th>Difference in Mean (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>25.82</td>
<td>15.26</td>
<td>10.56</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female</td>
<td>31.25</td>
<td>19.57</td>
<td>11.68</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Table 4. Distribution of Study Groups Based on Percentage of Reduction in Ulcer Size after 14 Days**

**DISCUSSION**

The present study was an attempt to evaluate the effectiveness of recombinant epidermal growth factor (rhEGF) dressing over conventional saline dressing method. The mean area of ulcer in rhEGF group of patients was 38.1 cm² and in saline group the mean of ulcer area was 26.4 cm². Rate of reduction in ulcer size is faster in rhEGF group as compared to that of saline group of patients. At the
time of inclusion in the study none of the patients had granulation in their foot ulcers in either groups. With treatment patients in rhEGF group developed granulation much earlier as compared to saline group at various different time intervals. Among the patients who were treated with rhEGF the rate of epithelialization was much faster as compared to the patients who were treated with conventional saline dressings. Proportion of patients with discharge in the wounds reduced significantly with time in the rhEGF group when compared to those patients who are treated with saline dressings, at various different time intervals.

Viswanathan V et al10 evaluated the efficacy and safety of rhEGF gel applied topically in patients with Grade I or II (Wagner’s classification) diabetic foot ulcers and it was found that healing was faster in patients treated with rhEGF as compared to control. Similar observations were noted in the present study also. Singla S, et al11 stated that after the first week of dressing 90% of the study group and 30% of the control group patients showed decrease in wound soakage, size, and increase in proliferation of healthy granulation tissue. Similar observations with respect to effectiveness of rhEGF in wound healing was observed in the present study. Afshari M, et al12 observed in their study that after four weeks, average wound closure in the EGF group was significantly greater than in placebo (71.2 vs. 48.9%, p= 0.03). In another study by Singla S, et al13 (2014) among 50 patients in Ludhiana compared the effects of rhEGF gel as topical application in the management of diabetic foot ulcers and concluded that the application of rhEGF shortens the wound healing time significantly. Identical findings were seen in the present study also.

Also, Gomez-Villa R et al14 determined the efficacy and safety of rhEGF in patients with diabetic foot ulcers. The study observations showed that compared to the placebo group, more ulcers achieved complete healing in the rhEGF group and ulcers in the rhEGF group decreased in area size (12.5 cm² (rhEGF) vs. 5.2 cm² (placebo); p= 0.049). Identical conclusion was drawn in a study by Tsang MW et al15 that application of hEGF-containing cream, in addition to good foot care from a multidisciplinary team, significantly enhances diabetic foot ulcer wound healing and reduces the healing time. Falanga V et al16 used human recombinant epidermal growth factor (h-EGF) to treat 44 patients with venous ulceration of the lower extremities. The results of the study showed that 35% of h-EGF treated patients and 11% in the placebo group had healed completely (p= .10) and median ulcer size reduction was 7% for h-EGF versus 3% for placebo per week (p= .29), and 73% versus 33% at study end (p= .32). Similar effectiveness of rhEGF was noted in the current study also in healing diabetic foot ulcers as compared to conventional saline dressings. Buchberger B et al17 in a review stated that add-on therapy with growth factors and active skin substitutes for treating uncomplicated diabetic foot ulcers could be an alternative to standard wound care alone, this was in turn explained by the efficacy of rhEGF in healing diabetic foot ulcers as demonstrated by the present study reports.

With regard to the effects on epithelialisation be rhEGF, Hong JP et al18 in their study showed that the wounds treated with EGF concentrations of 1 and 5 ug/g achieved the fastest re-epithelialisation. Likewise, it was observed in the present study that epithelialization was faster in patients treated with rhEGF as compared to conventional saline dressing. Similarly, Gomez-Villa R et al14 also reported that rate epithelialization was present at a higher rate (28% vs. 3%; p= 0.025) among the patients treated with rhEGF. With regard to granulation in the wound, Valenzuela-Silva CM et al19 in their study on healing effects of rhEGF showed that by the end of 2 weeks of treatment >50% granulation was noted. Whereas in the present study it was noted that all the patients treated with rhEGF developed granulation by the end of two weeks, which in much high.

**CONCLUSIONS**

The effectiveness of recombinant epidermal growth factor (rhEGF) dressing over conventional saline dressing method was evaluated in the present study. The findings of the study suggest that rhEGF had significantly better effects on wound healing of diabetic foot ulcers in terms of faster rate of development of granulation, epithelialisation and reduction of the amount of wound discharge.

**REFERENCES**


Wong WK. Effective Treatment of an unhealed incision of a diabetic patient with recombinant human epidermal growth factor. Modern Chemistry & Applications 2015;3(4).


