Original Research Article

A comprehensive study on effect of recombinant human epidermal growth factor gel in diabetic foot ulcer

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Abstract

Background: Ulcer healing in the diabetic patients is challenging due to a prolonged inflammatory response, extracellular matrix degradation irregularities, and increased bacteria presence. Recombinant human epidermal growth factor (REGEN-D 150), which was cloned and over expressed in E. coli, has shown enhanced healing of chronic diabetic foot ulcers (DFU) by significantly reducing the duration of healing in addition to providing excellent quality of wound healing and re-epithelization.
Aim: To compare the efficacy and safety of collagen granule dressings and conventional dressing in deep wounds in terms of reduced healing time, number of dressing, healing quality and complications.
Materials and methods: Thirty patients with foot ulcer were evaluated. A recombinant human Epidermal growth factor gel or conventional dressings were applied, and the patients were followed as per standard post-application treatment protocol. Patients underwent dressing changes every day until wound healing or for maximum period of 12 weeks. Changes in wound size were recorded when the dressing was removed; and at 4 and 12 weeks.
Results: Common age groups were 41-50 and 51-60 years of age. Complete healing was present in 12 cases.
Conclusion: There was statistically significant difference between the results of Recombinant human epidermal growth factor gel and saline dressings as collagen dressings had better healing response rate as compared to placebo when given along with standard treatment of diabetic foot ulcer.

Key words

Diabetic foot ulcer, Recombinant human epidermal growth factor gel, Effect.

Introduction

Physiologically, wound healing can be divided into three stages: inflammation, proliferation, and remodeling. Wound repair is characterized by a series of complex cellular and molecular events. Numerous growth factors are involved in these processes and act by stimulating chemotaxis, cellular proliferation, extracellular matrix formation, and angiogenesis, with contraction and reestablishment of cellular integrity. Both in vivo and in vitro data have demonstrated the efficacy of growth factors in enhancing wound healing. The most studied growth factors are PDGF, fibroblast growth factor (FGF), transforming growth factor-β1, and epidermal growth factor (EGF). Early experimental studies have shown the potential of EGF in promoting wound healing. EGF clearly stimulates epidermal repair in animal excisional and thermal injury models and may also stimulate dermal repair. Nanney, using a pig partial thickness wound model, reported a dose-dependent increase in the thickness of granulation tissue and epithelization with EGF. By means of Northern hybridization specific for the content of mRNA of type I and III procollagens, Laato, et al. confirmed that EGF is a potent dose-dependent mitogen for the granulation fibroblast. However, early clinical studies provided mixed data on the utility of exogenous growth factors in chronic wound healing. In a small study published in 1993, Lev-Ran and Hwang reported an elevation of PDGF and EGF in the plasma of diabetic subjects compared with control subjects. However, Cooper, et al. showed that a number of growth factors were markedly reduced in wound fluid from chronic wounds compared with acute wounds. Bennett and Schultz postulated increased destruction or inhibition of growth factors by elevated levels of proinflammatory cytokines and metallomatrix protein following repeated trauma and infection. In the current study, we postulated that there was a relative deficiency of growth factors in chronic wounds such as diabetic foot ulcers and aimed to determine whether local application of a high concentration of human EGF (hEGF) might be effective in promoting wound healing of diabetic foot ulcers.

Materials and methods

Thirty patients with foot ulcer were evaluated. A recombinant human Epidermal growth factor gel or conventional dressings were applied, and the patients were followed as per standard post-application treatment protocol. Patients underwent dressing changes every day until wound healing or for maximum period of 12 weeks. Changes in wound size were recorded when the dressing was removed; and at 4 and 12 weeks.

Primary Endpoints

Ulcer healing time: Time required to completely heal ulcer after the initiation of the therapy with Collagen/Conventional dressings in patients with chronic foot ulcer.

Secondary Endpoints

Duration of antibiotic therapy: Duration for which antibiotic therapy was continued to completely heal ulcer after the initiation of the therapy with Collagen/ Conventional dressings in patients with chronic foot ulcer. Follow up period: Duration of follow up after the initiation of the therapy with Collagen/Conventional dressings in patients with chronic foot ulcer. Adverse events reported with Collagen/ Conventional dressings in patients with chronic foot ulcer.

Eligibility criteria

The following eligibility (inclusion/ exclusion) criteria were used for recruitment of patients in the study.

Inclusion criteria

- Patients with chronic foot ulcer (diabetic/burn patients).
- Patient willing to give informed consent
- In case of diabetic patients- diabetes mellitus is defined as per World Health Organization (WHO) criteria of age and duration of therapy (Age ≥35 years and absence of insulin requirement in the first 5 years after diagnosis).

Exclusion criteria

- Critically ill patients
- Patient refusal
- Any evidence of underlying bone osteomyelitis
- Malignancy

The study was conducted on total thirty patients with diabetic ulcer patients who reported at Villupuram Medical College. All diabetic ulcer patients attending the Surgery Department were invited to participate in the study and written informed consent was taken. All patients underwent a standard clinical and laboratory evaluation. Briefly, information about age, known DM duration, smoking habits, arterial blood pressure, and anthropometric measurements was collected. Patients with diabetic ulcer who were willing to give informed consent were considered. Critically ill patients and patients who refused were excluded. In case of Type II diabetic patients, WHO criteria of age and duration of therapy (Age ≥35 years and absence of insulin requirement in the first 5 years after diagnosis) were used.

In all patients, wound size was noted before treatment initiation. A recombinant human epidermal growth factor gel or conventional dressings were applied to wound, and all patients were followed as per standard post-application treatment protocol. Patients underwent dressing changes every day until wound healing or for maximum period of 12 weeks. Changes in wound size were recorded when the dressing was removed; and at 4 and 12 weeks. Healing time, duration of antibiotic therapy, follow up period were noted. All patients were also followed up for adverse events.

Results

Table - 1 documents the age distribution of the patients taken for the study. **Table – 2** shows effect of healing.

Table - 1: Age distribution.

Age group (Years)	Case	Control
<20	0	0
21-30	0	0
31-40	3	2
41-50	4	6
51-60	6	5
61-70	1	1
>71	1	1

Table – 2: Effect of healing.

	Case	Control
Complete healing	12	5
Partial healing	3	10

Discussion

Foot problems are the most common indication for hospital admission in diabetes. They account for approximately 20% of all hospital admissions in diabetics [1]. Approximately 50% of all non-traumatic amputations are in diabetics. Most hospital beds are occupied with diabetic patients with foot problems than all other causes associated with the disease.

Of the many complications of diabetes, those involving the foot lead not only to pain and suffering, but take months to heal. It leads to loss of working hours, hospitalization and great expense both to the patient and the community.

Different modalities of treatment have been used time to time to treat the diabetic foot ulcers such as debridement, different anti- infective wound dressing, antibiotics according to culture sensitivity, skin grafting etc. [2-4].

Even after various modes of treatment, treatment failure rate is very high. Hence we planned to use the recombinant human epidermal growth factor gel for the treatment of diabetic foot ulcer. we postulated that there was a relative deficiency of growth factors in chronic wounds such as diabetic foot ulcers and aimed to determine whether local application of a high concentration of human EGF (hEGF) might be effective in promoting wound healing of diabetic foot ulcers [5-7].

As a biomaterial, recombinant human epidermal growth factor gel offers several advantages over traditional dressings, growth hormones and biological coverings. For this purpose, we selected 30 diabetic foot ulcer patients.

We included only chronic ulcers of at least 30 days duration. We excluded those patients who were having neoplastic disease, pre-existing cardiovascular, pulmonary or immunological disease.

We did collagen dressing in 15 patients, in remaining patients standard dressing was used. We also followed standard treatment of diabetic foot that includes good glycemic control, control of infection by appropriate antibiotics according to culture sensitivity and debridement if needed in all patients.

After 12 weeks of collagen treatment, there were 12 patients who achieved complete healing and 3 patients achieved partial healing, while in control group, only 5 patients achieved complete healing and 10 patients had partial healing [8].

In our study complete response at 1st and 2nd weeks in both study as well as control groups were statistically at par but after 2 weeks complete response was significantly higher in study group. Partial response was significantly higher in study group except at 3rd week as compared to control group.

Duration of ulcer also have effect on healing response, if ulcer was of prolonged duration, healing was delayed in both groups, but healing was better in study group as compared to control group.

In conclusion, our data support the contention that hEGF application, in addition to good foot care with a multidisciplinary team approach, enhances diabetic ulcer wound healing and significantly reduces the healing time. Further study is required to define the optimal hEGF dose, the optimal frequency of application, and potential interaction of hEGF with other growth factors, such as PDGF, in promoting wound healing [9].

Conclusion

Our study is a hospital based case control prospective study done in 30 patients of chronic diabetic foot ulcers. There was statistically significant difference between the results of Recombinant human epidermal growth factor gel and saline dressings as collagen dressings had better healing response rate as compared to placebo when given along with standard treatment of diabetic foot ulcer.

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