Role of Epidermal Growth Factor in Healing of Diabetic Foot Ulcers

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Abstract Diabetes mellitus may lead to amputation in 3 % of population. Risk for amputation is 15 folds in diabetics compared with nondiabetics. The aim of the study is to compare the outcome of dressing a diabetic foot ulcer with epidermal growth factor with that of conventional dressing with normal saline. The patients with diabetic foot were divided into study and control groups of 20 each. In the study group, epidermal growth factor (EGF) gel was used as dressing; in control group, dressing was done with normal saline. Treatment was given for 8 weeks or until ulcer healed, whichever occurred first. Evaluation of healing response was recorded on 1, 3, 5, and 8 weeks. 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. After the eighth week of dressing in the study group, 80 % of the patients showed complete response to EGF application. Whereas in control group only 35 % of the

patients showed complete response. Duration of hospital stay in the study group was lower as compared with the control group. EGF dressing causes early healing up to first 5 weeks as compared with conventional dressing. The results in healing were not significantly different in two study groups after 8-week duration. Hospital stay was lower in the study group as compared with the control group.

Keywords Diabetic foot · Ulcers · EGF · Healing

Introduction

Diabetes mellitus is a metabolic disorder associated with long-term vascular and neurological complications. Diabetic foot is one of the common complications of diabetes affecting the quality of life of the patients. Around 20 % of the total diabetic population has foot problems, while 5–10 % have foot ulcers, up to 3 % have amputations during their lifetime.

The treatment of diabetic foot ulcer is complex. Even when properly managed, the wounds may not heal as expected, when they do heal, the closure is often temporary and difficult to maintain. The fundamentals of caring for diabetic foot ulcers are off-loading, frequent debridement, and moist wound healing. New advanced topical dressings such as polyurethane foams, capillary dressings, Kerraboot, vacuum-assisted closure, alginates, cellular composites, nonadherent dressings, and film dressings are emerging that may improve wound care. Such dressings are designed to modulate levels of biological molecules such as growth factors that may promote wound healing [1].

Growth factors are a special subgroup of cytokines whose main activity is induction of mitosis [2]. Role of such factors in wound healing has been suggested, and this study was conducted to compare the outcome of dressing diabetic foot

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Wound after 1st week EGF dressing Wound after 3rd week EGF dressing Wound after 5th week EGF dressing

with one such novel agent—epidermal growth factor with that of conventional dressing with normal saline in terms of rate of healing and hospital stay.

Material and Methods

This prospective study was conducted in the Department of Surgery, IGMC Shimla and included cases of diabetic foot either admitted or attending Surgical OPD over 12 months period with effect from 1 March 2007 to 1 March 2008.

Diabetes Mellitus was confirmed in all these patients by estimating the fasting blood glucose levels.

Inclusion Criteria

Patients older than 18 years with fasting blood glucose levels >126 mg % with ulcer grade 1–2 according to Wagner's classification were included in this study.

Exclusion Criteria

Patients suffering from carcinoma, vasculitis, connective tissue disease, immune system disorder, and those on treatment with corticosteroids, immunosuppressive agents, radiation therapy, and chemotherapy were excluded from the study.

After explaining the procedure and purpose of study, written informed consent was taken from all the patients. All the patients were subjected to complete hemogram, complete biochemistry, urine R/E, pus C/S, X-ray foot,

and color Doppler study of lower limb to see for involvement of large vessels.

Methods

The wound area was determined by means of planimetry (greatest width $\times$ greatest length). Eligible patients were categorized into two groups: study group and control group of 20 each.

In the study group, epidermal growth factor (EGF) gel was applied as primary dressing and then covered with gauze, bandage, and tape. No other chemical was used. Dressing was changed daily.

In the control group, isotonic NaCl solution moistened gauze was applied as primary dressing over the wound area and covered with bandage and tapes.

Patients were put on diabetic diet, OHA, and plain insulin (if not controlled with OHA). After control of infection and healing of wound, patients were switched to long-acting insulin or OHA. Treatment was given for eight consecutive weeks or until ulcer healed, whichever occurred first.

Evaluation of response was recorded on weeks 1–3, 5, and 8. At the end of the study period of 8 weeks, the patients were categorized subjectively as follows:

1. Complete responder—complete healing
2. Partial responder—50 % or greater reduction in the product of two longest perpendicular diameters from baseline.
3. Noncomplete responder— <50 % reduction.
4. Nonresponder—no reduction.

Follow-up Evaluation

Was completed on weekly basis at each visit in the following manner.

1. Condition of the dressing and wound
2. Compliance with dressing use and change
3. Change in medication
4. Presence or absence of any adverse effects
5. Number of dressings changes since previous visit

Final evaluation was done at the eighth week or sooner if wound had healed.

Observations

Forty patients with diabetic foot were subjected to clinical examination and investigations. These patients were divided into two groups, study group and control group. Twenty patients who received EGF-based dressing were labelled as study group and 20 patients who received conventional dressing were labelled as control group.

In the study group, 60 % were male and 40 % were female. In the control group 70 % were males and 30 % were females. In the study group, 18 (90 %) of patients were known diabetics, whereas in the control group, 19 (95 %) of patients were known diabetics. In the study group, 16 (80 %) patients presented with single ulcer, whereas 4 (20 %) patients presented with multiple ulcers. In the control group, 18 (90 %) patients presented with single ulcer, whereas 2 (10 %) patients presented with multiple ulcers. All the patients with multiple ulcer had two ulcers each. Therefore, the study group had 24 ulcers and the control group had 22 ulcers. According to Wagner's classification in the study group, of the 24 ulcers, 10 were grade I and 14 were grade II ulcers. In the control group, 8 ulcers were grade I and 12 ulcers were grade II.

In aerobic cultures, pus culture positivity was seen in 19 (79 %) ulcers in the study group and was sterile in 5 (21 %). The culture was positive in 18 (82 %) ulcers in the control group and was sterile in 4 (18 %). The main organism isolated was *Escherichia coli* in 10 (42 %) and *Staphylococcus aureus* in 9 (38 %) ulcers.

In anaerobic cultures, growth was obtained in 11 (46 %) ulcers in the study group patients and 9 (41 %) ulcers in the control group patients, and no growth was obtained in 13 (54 %) ulcers in the study group patients and 13 (59 %) ulcers in the control group patients. The main organisms isolated were *Peptostreptococcus* followed by *Bacteroides* and anaerobic streptococci.

X-ray Foot

X-ray foot showed changes in 7 (35 %) study group patients and 11 (55 %) control group patients. Of these, 4 (20 %)

study and 5 (25 %) control group patients had loss of foot arch, 3 (15 %) study and 6 (30 %) control group patients showed demineralization of bones.

Ankle Brachial Pressure Index

In the study group, 11 (15 %) and in control group 12 (60 %) patients were found to have decreased ankle brachial index (ABPI) in the right lower limb, whereas 13 (65 %) study group and 14 (70 %) control group patients were found to have decreased ABPI in the left lower limb.

Healing Response in the Study and Control Groups After 1 Week

After 1 week of dressing, in the study group, 12 were partial responders and 6 noncomplete responders, whereas 2 were nonresponders. In the control group, 4 patients were partial responders and 8 patients were noncomplete responders, and 8 were nonresponders.

Healing Response in the Study and Control Groups After 3 Weeks

After the third week of dressing, in the study group, complete responders were 7, partial responders were 10, noncomplete responders being just 1 along with 2 nonresponders. In the control group, 1 patient was complete responder, 7 were partial responders, 5 were noncomplete responders with 7 nonresponders.

Healing Response in the Study and Control Groups After 5 Weeks

After the fifth week of dressing, in the study group, complete responders were 15 and partial responders were 3. There was 1 noncomplete responder and 1 nonresponder. In the control group, 5 patients were complete responders, 9 were partial responders. There were 2 noncomplete responders and 2 nonresponders.

Healing Response in the Study and Control Group After 8 Weeks

After the eighth week of dressing, in the study group, complete responders were 16 and partial responders were 3 with 1 noncomplete responder. In the control group, 7 patients were complete responders, 9 were partial responders. There were 2 noncomplete responders and 2 nonresponders.

Duration of Hospital Stay

Nine (45 %) patients of the study group were discharged within 1–2 weeks, whereas in the control group 7 (35 %) were discharged in 3–4 weeks while 5 were discharged after 4 weeks.

Discussion

This study was conducted to compare the outcome of dressings of diabetic foot ulcer with EGF with that of conventional dressing with normal saline.

Ulcers and Their Causes

The incidence of multiple ulcers was 20 % in the study group and 10 % in the control group patients. This is similar to the incidence as reported by Reiber et al [3].

In the present study, history of trauma to foot before the development of ulcer was present in 15 (75 %) patients of the 20 in the study group and in 16 (80 %) patients of the control group of 20. According to Pecoraro et al [4], minor footwear-related trauma has been reported as the most frequent cause leading to the development of lower extremity ulcer. Ellenberg [5] found that 90 % of diabetic ulcers occurred under the pressure bearing areas of the foot with punched out edges. The same findings were observed in the present study, where of the 24 ulcers in the study group, 19 (79 %) ulcers had punched out edges, whereas of the 22 ulcers in the control group, 17 (77 %) had punched out edges while remaining 5 (21 %) ulcers in the study group and 5 (23 %) ulcers in the control group had sloping edges.

Radiographic Findings

Hardy et al [6] and Clouse et al [7] reported that skeletal changes in diabetic feet may be manifested by several findings including generalized demineralization, focal osteolysis, Charcot's joint and infection. All foot bones may be diffusely demineralized. All these findings were similar to those found in the diabetic feet of our study.

Healing Response in the Study and Control Groups

Ulcers in the study group were clean and covered with healthy granulation and with minimal soakage, whereas control group ulcers were slower to heal. After the eighth week, there was only 1 nonresponder in the study group, rest of the patients responded well to EGF application. In the control group, patients' wounds had improved, soakage had decreased, and granulation tissue's proliferation was evident.

Tsang, and Wong [8] in their study on application of EGF on diabetic foot ulcers concluded that EGF significantly enhances diabetic foot ulcer wound healing.

Henemyre–Harris and Adkins [1] in their study on addition of epidermal growth factor in an in vitro model reported improved healing of skin injuries following addition of EGF as compared with control. Wounds treated with EGF show increased number of fibroblasts. It is postulated that EGF promotes healing by stimulating migration and division of epithelial cells by increasing protein synthesis, such as fibronectin, which aids in cell attachment and migration. EGF has also been reported to increase tensile strength of wound incision promoting rapid closure. Although EGF does not induce synthesis of mRNA for extracellular matrix proteins such as collagen, EGF presumably increases the number of fibroblasts in wound through chemotaxis and mitosis, resulting in more collagen production.

Duration of Hospital Stay

It was lower in the study group patients as compared with those in the control group, as their wound heals early. Average duration of hospital stay in another study was reported to be 29.6 ± 20.95 days⁹

Result

The EGF dressing resulted in early healing of ulcers up to first 5 weeks as compared with conventional dressing (*P* value 0.012, 0.015, 0.025, and 0.049 in first, second, third, and fifth week). The results in healing were not significantly different in the two groups after 8-week duration, *P* value being 0.574 in the eighth week (results compared with chi square test statistically). The mean duration of stay in the study group was 19.3 days and 29.5 days in the control group (*P*=0.011).

Conclusion

Despite many major advances in health care delivery to patients with diabetes, foot problems continue to extract a heavy toll on the quality of life of diabetic patients. The high morbidity and mortality, loss of working hours, and expenditure associated with diabetic foot problems necessitate the need for a prompt and proper approach to foot ulcer management. The treatment of diabetic foot ulcer is complex. Even when properly managed, wounds may not heal as expected; when they do heal, the closure is often temporary and difficult to maintain. The fundamentals of caring for diabetic foot ulcers are off-loading, frequent debridement and moist wound healing. New advanced topical dressing with EGF leads to early healing with less complication rate as compared with conventional dressing. Therefore, it is

concluded that EGF dressing is safe, convenient and cost effective in early healing of diabetic foot ulcer and reduced hospital stay.

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