ORIGINAL RESEARCH PAPER

General Surgery

EFFICACY OF TOPICAL RECOMBINANT EPIDERMAL GROWTH FACTOR DRESSING IN MANAGEMENT OF CHRONIC NON-HEALING ULCERS.

KEY WORDS:

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ABSTRACT

The current study is to evaluate the efficacy of topical recombinant epidermal growth factor (rEGF) dressing in management of chronic diabetic ulcers. We compared the period of wound healing in recombinant epidermal growth factor dressing and with those conventional methods. The study was done on 120 patients at Katuri medical college and hospital, Guntur. We finally concluded that the recombinant human epidermal growth factor is a significantly effective dressing compared to betadine($p<.001$) and is efficient in reducing the size of ulcers to a significant extent. The Efficacy of rEGF doesn't seem to be lowered in diabetes or other systemic illness. The rEGF was found to lower the infection rate of ulcers. rEGF has an excellent safety profile and is easy to use by patients or caregivers outside the clinical setting.

INTRODUCTION:

An ulcer is defined as a break in the continuity of covering epithelium, involving skin or mucous membrane, and molecular death. The wound can be defined as a break in integrity of the skin or the tissues and is often associated with disruption of structure and function. By definition, chronic wounds are wounds that have failed to proceed through an orderly and timely reparative process to produce anatomic and functional integrity over a period of 3months (1).

Various factors have been implicated for an ulcer to develop in diabetic patients, of which important is peripheral vascular disease and decrease in sensation as a result of peripheral neuropathy(2).The successful treatment of ulcers in diabetic individuals is the key to reduce number of amputations that have been highlighted in the St Vincent Declaration (3). Venous ulcers have been thought to affect an average of 3.5%of general population(4).It has been observed that 15% of all diabetic patients are having ulcer foot at some time(5).Embarrassing dressings, restricted mobility, and disability are other issues that are often a great concern to patients(6).

TOPICAL RECOMBINANT EPIDERMAL GROWTH FACTOR DRESSING:

Recombinant Human Epidermal growth factor helps in the stimulation of cell growth resulting in faster wound healing. The Primary structure of recombinant human EGF is a single chain polypeptide chain with 54amino acids. It is identical to that of human natural EGF (urogastrone)composed of 53amino acids.

PROPERTIES & MODE OF ACTION:

- EGF has been shown to enhance wound healing. Besides growth factor, other extracellular signals, including disruption of cell-cell or cell-matrix contacts and provisional matrix, might contribute to initiation of migration re-epithelization, and activation of gene expression (7).
- EGF is a polypeptide involved in maturation of epithelia (8).
- It binds to EGF receptor (EGFR), which is also a receptor for EGF-related cytokines such as TGF alpha (9).
- In the normal adult epidermis, EGFR is predominantly expressed in basal keratinocytes, and signaling events elicited by it are known to affect their proliferation, differentiation, and migration (10).
- In healing skin wounds, EGFR expression is up-regulated in migrating and proliferating keratinocytes adjacent to wound (11).

MATERIALS AND METHODS:

Study type: Prospective comparative study

Study design: non-randomized control trial, nonconcurrent before &after comparative study between epidermal growth factor dressing and conventional dressing method.

Study setting:

The study will be conducted in hospitals belonging to Katuri Medical College & Hospital, Chinakondrupadu, Guntur.

INCLUSION CRITERIA:

1.Chronic non healing ulcers

EXCLUSION CRITERIA:

1. Presenting to hospital with frank gangrene
2. Patients with radiologically proven osteomyelitis.

Application and Methodology:

Ulcer more than 3month duration coming to our hospital included in the study. Control of sugar was checked by blood sugar and glycosylated hemoglobin estimation periodically. The cases were randomized into two groups by a sealed envelope method for different types of dressing. Group was given 5% Povidone-iodine, Group II–Recombinant Epidermal Growth Factor. At this stage, the wound size was measured by cutting a gauge piece to the size of the wound, and the same was placed over graph paper, which gives almost sq mm accuracy of the total surface area of Ulcer.All the cases and their relatives were informed about day and date of next dressing and were told to come Back as soon as dressing becomes soaked till the outer layer, in Group I(Betadine dressing),a betadine soaked gauge piece, in the II group, rEGF gel was applied,& saline moist gauge piece was placed over gel. In each case, same type of dressing was given for 12weeks.All the wounds were measured twice weekly during dressing time, and final measurement was done at end of 12weeks with variation of max 2days after exposing and cleaning wound as done initially. The difference between initial and final measurements was considered for analysis of results. A 12week treatment cost was evaluated by including cost of medicine, sterile gauge piece, and bandage. The frequency of application of rEGF can be done initially daily; subsequent dressings can be changed every 3 -4days and assessed.

STATISTICAL ANALYSIS:
The end of treatment was complete healing of the Ulcer after 12 weeks of therapy. The sample size of 60 each was considered adequate. The nonhealing Group was divided into more than 50% healing and less than 50% healing. Less than 50% were considered nonhealing while doing calculation. Calculation is done based on null hypothesis. Endpoints of comparable 2 groups at a time were done by chi square test &calculation of odds ratio with 95%confidence interval. P-value< .05was considered significant.

RESULTS:
Patients-A total of 120patients were recruited for study and finally, results of patients were analyzed.

Age distribution-Youngest Patient was 40years old, and eldest was84 years old. Mean age was 61.45years (SD 8.072 yrs).

All were Type II Diabetes Mellitus.
Duration of diabetes–Duration varied from 3years to 25years.Mean duration of diabetes was 9.47years (SD 4.733).

Sex distribution-
Total Male patients were 74, female patients were 46.

M: F ratio was 74:46. Incidence is more common in males as they are exposed to external environment more than females.

Addictions- 24 patients out of 90(26.6%) were active smokers/alcoholic during presentation with Ulcer. All the females were non-smokers. Considering males alone,42.1% were smokers. Anybody that had stopped smoking 6 months prior was not included.

Location of Ulcer-Most of the patients had Ulcer on foot (100/120–83.3%). Others had ankle, leg, or sacral ulcer.

Table 1 : Ulcer size variation in study groups:

	ULCER SIZE cm2
MEAN	6.33
MEDIAN	4.00
STD.DEVIATION	6.473
MINIMUM	1
MAXIMUM	35

History of previous Ulcer and amputation-
82 out of 120 patients (68.3%) had history of previously healed ulceration, & most of them had foot ulcers.34(28.3%) patients had undergone amputation previously due to diabetic foot ulcer complications, all these patients had history of ulceration.

Duration of Ulcer-Minimum duration of Ulcer was 3months, &maximum was 8months.Mean ulcer duration was 4.35months (SD 1.358).

Etiology of Ulcer-56(46.7%)patients had Ulcer of infective etiology started in inter-digital space and then spread proximally.48(40.0%)patients had Ulcer of traumatic origin.16(13.3%)patients had pressure ulcers on heel &plantar aspect at level of head of first metatarsal.

Systemic disease-24(20.0%) patients had hypertension alone.54(45.0%) patients had HTN with CAD.28(23.3%) patients had HTN, CAD, CKD.

Wound Swab Cultures-In 74 patients (61.7%), wound swab culture was sterile. In 42 (35%) cases, wound swab culture grown Staphylococcus. In 2 patients, each (1.7%) swab has grown Proteus, Citrobacter.

Healing with dressing:
10(16.7%) patients on betadine dressing show complete wound healing.

48(80%) patients on rEGF dressing show complete wound healing

rEGF dressing is a significantly effective dressing compared to betadine(P<0.001).

FIG.1A and 1B Shows ulcer size on recruitment and after ten weeks of dressings with rEGF.

FIG.1A - Ulcer size on recruitment.

FIG.1B - Ulcer size after 10 weeks.

Time for complete healing:
Betadine dressing- Average healing time for complete healing for completely healed ulcers-11.5weeks (SD 1.00).

rEGF-Average healing time for complete healing for completely healed ulcers-9.1weeks (SD 2.42).

Follow up: Pts were followed up after 12weeks of treatment with specific type of dressings.

DISCUSSION:
The study included all such patients with large or nonhealing ulcers.

AGE AND SEX DISTRIBUTION –Our study's mean age was 61.45years, which correlates with other studies where they have reported the mean age around 65 years (11,12). The study shows recurrent ulceration and multiple amputations common with long-standing diabetes (13-16). Present study also had a similar finding.

HISTORY OF PREVIOUS ULCER AND AMPUTATION– In our study,68.3% of patients had a history of previously healed foot ulcers, and 28.3% had an amputation.

DURATION OF ULCER- Mean Duration of Ulcer in present study was 4.35months.

ETIOLOGY OF ULCER- 56%of patients had Ulcer of infective etiology started in inter-digital space and then spread proximally.13%of patients had pressure ulcers on heel and plantar aspect at level of head of first metatarsal. A combination of Similar factors leading to ulcer formation is reported(17,18)

SYSTEMIC DISEASE- Cardiovascular complications are most common cause of premature death among patients with diabetes (8). In present study, patients associated with systemic disease like Hypertension, Coronary Artery Disease (CAD) or chronic kidney disease (CKD).20% of patients had hypertension alone.45%of patients had hypertension with CAD.23.3%of patients had HTN, CAD, CKD.

WOUND SWAB CULTURES-The diabetic foot infections are frequently polymicrobial (19). Here, the majority,74%, reported as sterile possibly. we recruited previously treated cases even with antibiotics and in 42% wound swab culture grown Staphylococcus. In 1 Patient, each (2%) swab has

grown Proteus and Citrobacter.

HEALING –

Viswanathan V et al. (20) evaluated Efficacy and safety of rEGF 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 rEGF as compared to control. Similar observations were noted here Singla S et al. (21) stated that after first week of dressing,90% of study group and 30% of control group patients showed a decrease in wound soakage, size, and increase in proliferation of healthy granulation tissue. Similar observations of effectiveness of rEGF in wound healing observed here.

Afshari M et al. (22) observed in their study that after 4weeks, average wound closure in the EGF group was significantly greater than in placebo (71.2vs.48.9%, p= 0.03).

Singla S et al. 13(2014), among 50 patients in Ludhiana compared effects of rEGF gel as a topical application in diabetic foot ulcer management and concluded that application of rEGF shortens wound healing time significantly. Identical findings were seen here also. In our study, healing with rEGF dressing was significantly better(p<.001) than betadine dressing. Studies have proved faster and better wound healing with rEGF as compared to conventional dressing.

CONCLUSION:

1. Diabetes is the commonest cause for chronic non healing ulcers.
2. The recombinant human epidermal growth factor is a significantly effective dressing compared to betadine (p<.001).
3. The recombinant human epidermal growth factor is efficient in reducing size of ulcers to a significant extent.
4. The Efficacy of rEGF does not seem to be lowered in diabetes or other systemic illness.
5. The rEGF found to lower infection rate of ulcers.
6. rEGF has an excellent safety profile and is easy to use by patients or caregivers outside clinical setting.

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