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Original Research Article

A comparative study of effect of epidermal growth factor on chronic leg ulcers with anti-septic dressing

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ABSTRACT

Background: Chronic wounds, particularly non-healing wounds, are one of the most prevalent surgical disorders that a surgeon may see. The characteristic of a chronic wound is that it does not heal despite daily dressings and costly local treatments. Aims of the study to investigate the healing effects of recombinant human epidermal growth factor (hEGF) on non-healing ulcers and to assess the effectiveness, acceptability, and safety of a new epidermal growth factor (EGF) wound dressing.
Methods: On 60 patients with chronic non-healing ulcers, a randomized, prospective, and comparative research was conducted in the department of general surgery, SVS medical college and hospital, Mahbubnagar. These 60 patients were separated into two groups, each with fifteen patients. The EGF was applied to group A, whereas normal saline was given to group B.
Results: The 60 patients who agreed to participate in the trial were separated into two groups (30 each) that were equal and comparable. Patients who received topical EGF 0.01% gel dressings were assigned to the trial, whereas those who received standard antiseptic wound dressing were assigned to the control group. Six of the fifteen patients in the test group were men, whereas eleven were males and four were females in the control group. When the two groups were compared, the test group had a substantial reduction in ulcer area compared to the control group ($p<0.001$)
Conclusions: EGF is a superior alternative for treating chronic non-healing ulcers because of its cost effectiveness, availability, reduced hospital stay, and simplicity of administration.

Keywords: EGF, Chronic leg ulcers, Wound dressing

INTRODUCTION

Chronic wounds, particularly non-healing wounds, are one of the most prevalent surgical disorders that a surgeon may see. The characteristic of a chronic wound is that it does not heal despite daily dressings and costly local treatments. Diabetic ulcers, venous ulcers, and pressure ulcers are all examples of this issue. As a result, the surgeon faces a continual difficulty in treating these wounds.

Although many surgeons still believe wounds should be kept dry, this belief is gradually fading. We now know that wounds that are treated with dressings that allow for moist wound healing generate granulation tissue.[1] A broad array of novel dressings have been launched throughout the previous two decades. People have attempted a variety of non-traditional wound healing topical treatments, such as normal saline, aloe vera, collagen, gentian violet, benzyl peroxide, impregnated gauze, insulin, mercurochrome, oxygen therapy, sugar and vinegar. Topical EGF has also been proven to be

superior in the therapy of decubitus ulcers, venous ulcers, pressure ulcers, and leprosy ulcers in studies.[2] The goal of this study was to evaluate the effectiveness of topical EGF dressing to traditional sterile wound dressing in the treatment of non-healing ulcers.

METHODS

This is a randomized, prospective, and comparative study of 60 patients with chronic non-healing ulcers conducted at the department of general surgery from May 2019 to April 2020 for a period of one year. These 60 patients were separated into two groups, each with 30 patients. The EGF was applied to group A, whereas normal saline was given to group B.

Inclusion criteria

Patients between the ages of 20 and 50, both sexes, were hospitalized with chronic non-healing diabetic ulcers, varicose veins, and any other non-malignant etiology. Despite standard therapy, size 4×4 cm and higher has shown no signs of healing in the last two months.

Exclusion criteria

Patients suffering from deep vein thrombosis, severe arterial insufficiency, severe neuropathy, renal insufficiency, malignant ulcers, and parasitic ulcers. The patients' informed permission is obtained. A thorough history of the patient's persistent non-healing leg ulcer is collected. The initial ulcer size is measured using a flexible measuring tape up to one decimal in cm at its greatest diameters. Cultures of wounds are taken. Debridement has been completed.

Random allocation software is created in Microsoft visual basic six, and it were used to allocate patients to one of the two study groups with an allocation ratio of 1:1. Patient randomization were done after enrollment in the study by us and random sequence will be generated and opened by the default viewer for the output file. Patients randomly assigned into two groups either group-A or group-B.

Group A: A topical EGF formulation is applied to the ulcer and coated with 4-5 gauze pieces and 5-6 sterile pads before being wrapped with bandages. This is done on a daily basis, and the results are compared.

Group B: Two layers of antiseptic-soaked gauze pieces are put over the cleansed ulcer, followed by two layers of dry gauze pieces. Two to three layers of sterile Gamjee pads are put over the gauze, and kerlix dressing is applied to keep it in place using bandages. This is done on a daily basis and compared.

Every day, the wound is examined and the healing progress is documented using digital photography at a magnification of 4× from a distance of 20 cm. The same procedure is repeated for another two weeks, and the results are compared using a visual analogue score for EGF and normal saline dressings. The proforma is used to plot the results.

Visual analog scale

This research used a ten-point scale. The grading system is based on a ten-point scale. The percentage of new skin tissue covering ranges from 0 to 10,10 to 20,20 to 30,30 to 40…90 to 100, and so on. The greater the proportion of skin covering, the higher the scale. The maximum amount of skin covering the whole wound is considered 100 percent and is awarded a score of ten. For example, on a scale of 10, 90 to 100 is provided, and 0 to 10 is supplied.

Statistical analysis

The graph pad prism software version 6.01 will be used to analyze the data. For continuous data, mean SD was used, median IQR (Inter quartile range) was used for score data, and percentages were used for categorical data. A repeated measures one way analysis of variance test was used to compare various days within the group, followed by a post hoc multiple comparison test for continuous data. For continuous data, the T test/Mann Whitney U test/was used to compare two groups. For categorical data, a Fischer's exact test/chi square test was used to determine the relationship between variables. We regarded all $p<0.05$ to be statistically significant.

RESULTS

The 60 patients who agreed to participate in the trial were separated into two groups that were equal and comparable. Patients who received topical EGF 0.01% gel dressings were assigned to the trial, whereas those who received standard antiseptic wound dressing were assigned to the control group.

Six of the fifteen patients in the test group were men, whereas eleven were males and four were females in the control group. A total of 60 individuals were observed in this chronic ulcer research. All of the patients were given a thorough history and a basic examination. Patients in the test group ranged in age from 31 to 51 years old, with a mean of 40.7±6.4 years. The average age in the control group was 46.9 years, with a standard deviation of 6.8 years and a range of 37 to 59 years. Because the p was not significant, there was no statistical significance when it came to age.

Table 1: Sex wise distribution of patients.

Groups	Male	Female	Total	P value
Control	22	8	30	0.2
Test	12	18	30	
Total	34	26	60	

Males made up 56.67% of the patients, while females made up 43.33%. Between the test and control groups, there was no significant effect of sex on treatment outcomes (p=0.2, non-significant)

Diabetic etiology was the most common, accounting for 11 of the 30 patients, or 36.7%, followed by traumatic (26.7%), post-burn (20%), and venous pathology (16.7%). With p=0.9 cause had no statistical significance.

The control group, on the other hand, received antiseptic dressings. The mean area was 20.00 cm^2 on day 0, with a standard deviation of 8.40 cm^2 and a range of 12.00 to 35.00 cm^2. The ulcer has shrunk to 13.10 cm^2 after two weeks, with a standard deviation of 5.20 cm^2 and a range of 6.00 to 20.00 cm^2.

The test group was given topical EGF over a two-week period. The ulcers had a mean area of 32.10 cm^2 on day 0, with a standard deviation of 16.60 cm^2. (Dimensions range from 10 to 60.00 cm^2). The ulcer area decreased to 8.80 cm^2 after two weeks, with a standard deviation of 3.70 cm^2 and a range of 4.00 to 18.00 cm^2.

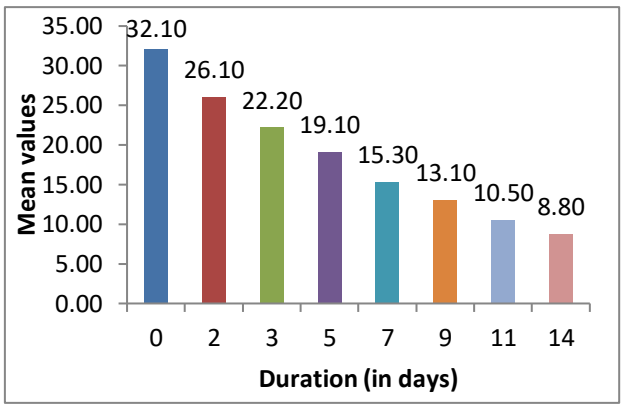

Figure 1: Mean distribution of ulcer area when treated with EGF over two weeks.

Table 2: Cause wise distribution of ulcer.

Groups	Diabetic	Post burn	Traumatic	Venous	Total	P
Control	12	6	6	6	30	0.9
Test	10	6	10	4	30	
Total	22	12	16	10	60	

Table 3: Mean distribution of ulcer area when treated with antiseptic (control) over two weeks.

Duration (days)	Minimum	Maximum	Mean	SD	P value
0	12.00	35.00	20.00	8.40	<0.0001
2	11.20	33.80	19.20	7.90	
3	11.00	32.50	18.60	7.70	
5	9.60	30.00	17.50	7.40	
7	8.80	27.50	16.50	6.80	
9	8.30	25.00	15.40	6.10	
11	7.50	22.40	13.90	5.40	
14	6.00	20.00	13.10	5.20	

Table 4: Comparison between two groups.

Duration (days)	Groups	Minimum	Maximum	Mean	SD	P value
0	Test	10.00	60.00	32.10	16.60	0.02
	Control	12.00	35.00	20.00	8.40	
2	Test	9.80	45.00	26.10	11.00	0.06
	Control	11.20	33.80	19.20	7.90	
3	Test	9.40	40.00	22.20	8.90	0.3
	Control	11.00	32.50	18.60	7.70	
5	Test	8.00	29.30	19.10	7.30	0.5
	Control	9.60	30.00	17.50	7.40	
7	Test	7.00	24.50	15.30	5.20	0.6
	Control	8.80	27.50	16.50	6.80	
9	Test	6.00	24.10	13.10	4.80	0.3
	Control	8.30	25.00	15.40	6.10	
11	Test	5.00	20.50	10.50	4.20	0.06
	Control	7.50	22.40	13.90	5.40	
14	Test	4.00	18.00	8.80	3.70	0.01
	Control	6.00	20.00	13.10	5.20	

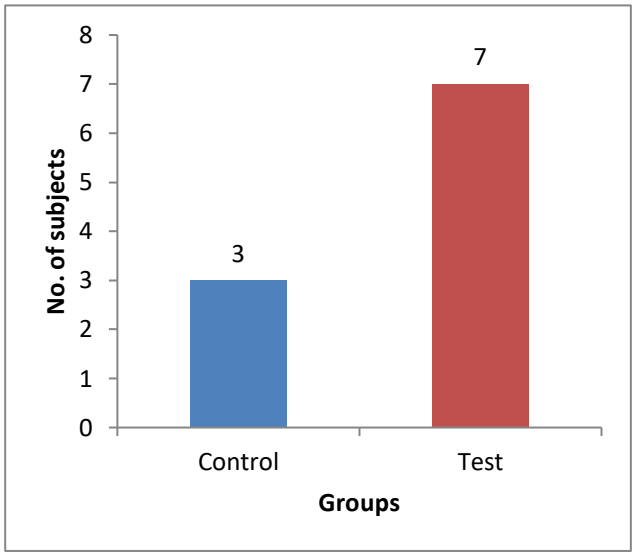

Figure 2: Comparison between two groups (point scale).

When the two groups were compared, the test group had a substantial reduction in ulcer area compared to the control group ($p<0.001$)

DISCUSSION

The patients were separated into two equal groups of 30, one for the control group and the other for the test group. On the basis of inclusion and exclusion criteria, patients were chosen at random. The study comprised ulcers of various kinds, including infectious, traumatic, non-healing diabetic, and post-burn ulcers. Patients in the test group were given 0.01% topical EGF, while those in the control group were given antiseptic dressings.

The 60 subjects with chronic non-healing ulcers aged 30 to 50 years were chosen using a systemic random sampling technique and divided into 2 groups: test (EGF dressing) and control (antiseptic dressing), each with 30 patients. A pre-made questionnaire was used to collect data from both groups of patients with chronic non-healing ulcers. Before intervention, the duration of sickness linked to medical history was evaluated in both groups. The experimental group received EGF treatment, while the control group received standard saline dressing. The effectiveness of wound healing was measured after the intervention using a 10-point visual analog scale. The data was collected with the approval of the institutional ethics committee.

Wound healing necessitates the coordinated integration of complicated biological processes such as cell migration, cell proliferation, extracellular matrix deposition, revascularization, and tissue integrity restoration.[3] EGF, PDGF, FGF, transforming growth factor-b (TGF-b), granulocyte colony stimulating factor (G-CSF), and keratinocyte growth factor (KGF) are some of the growth factors involved in these processes.[4,5] Cohen first identified EGF in 1962.[6]

EGF therapy, in particular, has been linked to increased collagen and glycosaminoglycan content in experimental tissue granulation models in a number of prior investigations.[7] For fibroblasts and epithelial cells, EGF is recognized to be a powerful mitogenic factor.[8] EGF has been found to have stimulatory effects on wound healing by increasing the proliferation of collagen-producing fibroblasts, according to Laato et al.[9] Brown et al found that applying an EGF-containing ointment to a wound helps it recover faster. They also showed that using cream as a medication delivery medium decreases the risk of bacterial infection and avoids wound desiccation.[10]

EGF interacts with the EGF receptor on epidermal cells and fibroblasts, according to Nanney.[11] EGF promotes epithelial cell proliferation over the wound surface, improves epidermal regeneration, and speeds epithelialization, according to numerous additional investigations. Despite the fact that clinical outcomes for diabetic foot ulcers treated with EGF have been published in only a few trials, the results are promising.[12]

In their observational study, Hong et al found that topical rhEGF applied with an advanced dressing resulted in complete healing in 76% (52/68) of chronic diabetic foot ulcer patients.[13] In a single-center trial, Tsang et al discovered that rhEGF cream reduced the median time to complete healing of DFUs.[14]

The best concentration and dosage of rhEGF for improving diabetic foot ulcer healing is still up for debate. Tsang et al colleagues reported that 20 of 21 diabetic foot ulcers healed completely after therapy with 0.04% rhEGF cream administered locally.[14] They did, however, claim that 0.02% rhEGF cream did not provide substantial advantages above standard ulcer treatment.

Hong et al on the other hand, observed full healing of diabetic foot ulcers in 52 of 68 patients who received topical wound therapy with low-concentration rhEGF (0.005%).[13]

According to Park et al 63, 60 of 82 diabetic foot ulcers patients obtained complete ulcer healing within 12 weeks of commencing treatment with twice daily application of 0.005% rhEGF with multimodal wound care.

Park et al randomized 167 adult patients at six medical facilities to receive normal wound care with either topical rhEGF (n=82) or an equivalent amount of saline spray (n=85) twice a day until ulcer healing or for up to 12 weeks. In comparison to the placebo group, more patients in the rhEGF group had complete wound healing (73.2% versus 50.6% respectively; p=0.001). Regardless of HbA1c levels, wound healing was quicker in the rhEGF group (p=0.029). The rhEGF group had a faster time to 50% ulcer size reduction (21 vs 35 days; hazard

ratio=3.13, p=0.001) and full ulcer healing (56 versus 84 days; hazard ratio=2.13, p=0.001).[15]

Adverse effects associated with rhEGF therapy have been reported to be minor to severe and fairly managed in the past. Skin irritation was the most prevalent adverse event following topical application of EGF, according to Tiaka et al with greater dosages of EGF causing more adverse events than lower doses.[16]

Fernandez-Montequı´n et al reported that 8 (7.9%) of 101 patients receiving EGF treatments experienced SAEs, including severe infection, cellulitis, renal failure, myocardial infarction, and pneumonia, although these SAEs were not thought to be connected to the EGF therapy.[17]

Tuyet et al discovered mild over-granulation in one of 28 patients (3.7%) in another early trial utilizing spray-applied 0.005% rhEGF for the treatment of diabetic foot ulcers, but no cutaneous adverse responses.[18]

Six cases (7.3%) of significant adverse events (SAEs) were recorded in the EGF treatment group by Park et al however these SAEs were not judged to be EGF treatment-related and were equivalent to seven cases (8.2%) of SAEs in the placebo group. These findings back up rhEGF's safety in the treatment of diabetic foot ulcers.[15]

HbA1c was found to be substantially related with wound healing rate by Christman et al.[19] According to Vella et al HbAlc is a significant biomarker for predicting wound healing time.[20]

HbA1c, on the other hand, had no relationship with wound healing, according to Park et al. Healing velocity, time to reach a 50% decrease in ulcer size, and time to complete ulcer healing were all substantially quicker in the rhEGF group than in the placebo group, regardless of HbA1c level.[15]

Several studies have already shown that quicker diabetic wound healing reduces the severe consequences of diabetic foot ulcers. In a randomized 12-week trial of 208 patients with diabetic foot ulcers, Veves et al found that cell treatment dramatically reduced the rates of osteomyelitis and major/minor amputation.[21]

During the research period, neither group had any cases of osteomyelitis or amputation, according to Park et al. However, in the rhEGF group, the rate of superficial wound infection at the investigated ulcer was reduced.[15]

Despite the fact that our trial was not designed to look at diabetic foot ulcers consequences as a main or secondary endpoint, the results are promising and suggest that spray-applied rhEGF can help avoid superficial and deep wound infection, which can lead to lower limb amputation.

The rate of healing of ulcers shorter than 5 cm in the EGF treated group was substantially higher than in the control group, according to Prabakar et al. The rate of healing of ulcers larger than 5 cm was also substantially higher in the EGF-treated group than in the control group. Overall, the EGF group outperformed the control group in terms of ulcer healing. Healing was 86.67% in the EGF group and 66.67% in the control group.[22]

The reduction in ulcer size was more noticeable in the first 15 days compared to the next 15 days, according to Ramachandran et al. In comparison to the traditional group, where most ulcers shrank by less than 25% over this period, the ulcer size shrank by more than 50%. In our research, we discovered that, compared to the first day, ulcer healing in terms of size varied from 54-81.5 percent in the EGF group on the 30th day, whereas the conventional group's drop in size ranged from 34-47%.[23]

Limitations

Our study is the small sample size, with the surgical strategy being dependent on the usual practice of a single centre. it was specialized hospital-based study so its results cannot be generalized with the population.

CONCLUSION

There were 56% males and 54% females in this research of 60 individuals with non-healing ulcers. The majority of the patients were between the ages of 41 and 60. With the most clustering occurring between the ages of 41 and 50. A 0.01% EGF dressing was given to the research group. When compared to traditional (antiseptic) ulcer treatment, it demonstrated a good response toward full healing of chronic non-healing ulcers. The only disadvantage is the expensive cost of dressing, which is measured in thousands of rupees when purchased commercially. This research is based on those ideas, although with restricted resources and setup. Because non-healing ulcers are caused by a variety of factors, a multidisciplinary approach with a holistic perspective is essential for their treatment.

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