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Effect of Topical Recombinant Human Epidermal Growth Factor on Wound Healing in Diabetic Foot Ulcers – A Randomized Controlled Trial

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KEYWORDS
Diabetic foot ulcer, Recombinant human epidermal growth factor (hEGF), Wound healing, Randomized controlled trial, Glycemic control, Wound debridement

ABSTRACT:

Background: Diabetic foot ulcers (DFUs) are a serious complication of diabetes mellitus, often resulting in significant morbidity, amputations, and increased healthcare expenditures. Chronic hyperglycemia impairs the wound healing process by inhibiting cellular proliferation, growth factor responses, and angiogenesis. Topical recombinant human epidermal growth factor (hEGF) is a promising therapeutic agent that mimics the body's natural healing mechanisms by promoting epithelial cell proliferation, migration, granulation tissue formation, and re-epithelialization. **Objective:** To evaluate the effectiveness of topical recombinant hEGF in comparison to conventional saline dressings for the treatment of diabetic foot ulcers. **Methods:** This randomized controlled trial involved 80 inpatients with diabetic foot ulcers treated at the General Surgery Department of Aarupadai Veedu Medical College between November 2022 and April 2024. Patients aged between 30 and 80 years were included in the study, with exclusions for those presenting with gangrenous lesions, uncontrolled diabetes, or hypersensitivity to hEGF. Participants were divided into two groups: Group A (n=40) received normal saline dressings along with topical hEGF, while Group B (n=40) received normal saline dressings only. Ulcer sizes were measured on days 1, 7, 14, and 21, and data on granulation, wound size reduction, pus culture results, and length of hospital stay were recorded. **Results:** Patients in Group A demonstrated significantly smaller final wound sizes, greater reductions in wound area, and shorter hospital stays compared to Group B ($p<0.05$). No significant differences were observed between the two groups in terms of mean age, gender distribution, or duration of diabetes. Staphylococcus aureus was the most commonly isolated organism, followed by E. coli (26%). **Conclusion:** The use of topical recombinant hEGF in conjunction with normal saline dressings significantly improves wound healing in diabetic foot ulcers. This treatment approach reduces wound size, accelerates healing, and shortens hospital stays, indicating enhanced treatment efficacy and the potential for reduced healthcare costs. Incorporating hEGF into standard wound care protocols for diabetic foot ulcers could lead to better patient outcomes and increased healthcare efficiency.

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Introduction

Diabetes mellitus is a metabolic disorder marked by high blood sugar levels due to either defective insulin secretion or increased resistance to insulin.(1) This condition is linked with various microvascular and macrovascular changes that can lead to numerous complications.(2) When a person with type 1 or type 2 diabetes sustains an injury, the healing process is often complicated and prolonged, leading to what is known as a diabetic wound.(3) A diabetic foot ulcer which is characterised by ischemia, osteoarthropathy, neuropathy, microbial infection, and ulceration, poses a significant burden on both the community and the patients.(4) Chronic diabetic foot ulcers are a major cause of amputations in people with diabetes and are one of the most severe complications of the disease. Effective management of diabetic foot ulcers requires a multidisciplinary approach to wound care.(5) Studies suggest that glycaemic control, wound debridement, advanced dressings, hyperbaric oxygen therapy, growth factors, negative pressure wound therapy, and bioengineered skin can be used as adjunct therapies to promote rapid healing.(6–8)

Wound repair involves a complex series of cellular and molecular events. Growth factors such as epidermal growth factor (EGF), TGF-beta, fibroblast growth factor, platelet-derived growth factor, and amphiregulin play crucial roles in wound healing by restoring cellular integrity.(9) EGF, in particular, promotes cellular proliferation through its receptor, which has a tyrosine kinase cytoplasmic domain, a single transmembrane domain, and an extracellular domain involved in EGF binding and receptor dimerization.(10) EGF stimulates fibroblast proliferation leading to epithelial regeneration, angiogenesis, and increased collagen production. It enhances the formation of granulation tissue and accelerates wound healing.(11)

Research has shown that a decrease in growth factors and their cell-surface receptors is a primary cause of refractory diabetic foot ulcers. EGF is involved in various phases of wound healing, including cell migration, proliferation, and differentiation.(12–14) This study aims to provide high-quality evidence to distinguish the true therapeutic effects and to observe the healing rate of diabetic foot ulcers. It compares the efficacy of saline-only dressings with topical recombinant human EGF (hEGF) application in promoting earlier wound healing and reducing the duration of hospital stays.

Materials and Methods

This randomized controlled study was conducted in the Department of General Surgery at Aarupadai Veedu Medical College and Hospital (AVMCH), Puducherry, between November 2022 and April 2024. The study received approval from the Institutional Human Ethics Committee (Approval No. AV/IHEC/2022/105) and was registered in the Clinical Trials Registry of India (CTRI Reg. No. 068922). The study included patients aged 30 to 80 years with diabetic foot ulcers, excluding those with gangrenous lesions, uncontrolled diabetes, hypersensitivity to hEGF, or ulcers resulting from other aetiologies.

The sample size was calculated based on a similar study by Kundal et al., which focused on the percentage reduction in wound size at six weeks. The study reported a reduction of 20.28±17.39% in the hEGF dressing group (Group A) and 31.7±17.06% in the normal saline dressing group (Group B). Using these values, a sample size of 72 was determined. Allowing for a 10% attrition rate, the final sample size was adjusted to 80, with 40 participants in each group. All participants provided informed consent and underwent clinical examination, routine investigations, glycaemic control, and wound debridement. Ulcer sizes were measured on the 1st, 7th, 14th, and 21st days. Data on granulation, wound size reduction, pus culture results, and duration of hospital stay were documented.

Statistical Analysis: Data were analysed using SPSS version 26. Continuous variables were expressed as mean and standard deviation and analysed using independent t-tests or Mann-Whitney U tests, as appropriate. Categorical variables were analysed using chi-square or Fisher's exact tests. A p-value of less than 0.05 was considered statistically significant.

Results

The present study included 80 patients who met the inclusion criteria, randomly assigned into two groups: Group A (n=40) received normal saline dressings with topical recombinant hEGF, while Group B (n=40) received normal saline dressings alone. Patients in Group A demonstrated significantly smaller final wound sizes, greater reductions in wound area, and shorter hospital stays compared to those in Group B.

There were no significant differences between the groups in terms of mean age, gender distribution, or mean duration of diabetes mellitus, although the duration of diabetes was slightly shorter in Group A.

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The mode of onset, limb involvement, and ulcer site were similar across both groups. Staphylococcus aureus was the most commonly isolated organism, followed by E. coli (26%). Group A showed notably better outcomes in wound healing, including smaller final wound sizes, more substantial reductions in wound area, and shorter hospital stays compared to Group B.

Discussion

Diabetic foot ulcers (DFUs) are a significant complication of diabetes mellitus, affecting millions globally and often leading to severe morbidity, lower limb amputations, and increased healthcare costs. The complex pathology highlights the need for advanced therapeutic strategies to enhance wound repair and regeneration. Topical recombinant human epidermal growth factor (hEGF) has emerged as a promising agent, promoting epithelial cell proliferation and migration, accelerating granulation tissue formation, and enhancing re-epithelialisation by mimicking the natural wound healing process.(15–17) Investigating hEGF's efficacy in DFU treatment could provide critical insights into optimising diabetic ulcer management and establishing new care standards.

The present study included 80 patients who met the inclusion criteria, divided into two groups: Group A received normal saline dressing with topical recombinant hEGF, and Group B received normal saline dressing alone. There were no significant differences in mean age, gender distribution, or mean duration of diabetes mellitus between the groups, although the duration of diabetes was slightly shorter in Group A. The mode of onset, limb involvement, and ulcer site were comparable between the groups. Staphylococcus aureus was the most commonly isolated organism, followed by E. coli (26%). Group A patients exhibited significantly smaller final wound sizes, greater reductions in wound area, and shorter hospital stays compared to Group B patients.

In line with the present study, Kundal et al. found similar age and physical characteristics between the groups.(3) The duration of diabetes was comparable across groups, with no significant differences. Tuyet et al., observed that EGF has positive effects on rapid granulation and better wound closure rates in DFUs. EGF binds to its receptor on epidermal and fibroblast cells, building collagenous tissue and facilitating wound granulation and epithelization, thus accelerating wound healing.(18) Studies by Zhao et al.(6) and Yang et al.,(19) also support the efficacy and safety of topical hEGF, with fewer adverse effects compared to intralesional administration. Kundal et al. found that topical recombinant EGF resulted in faster wound healing than conventional betadine dressings in diabetic wounds, with 90% wound healing rates with hEGF compared to 36.67% with betadine.(3) These findings indicate that topical recombinant hEGF, when used with normal saline dressing, significantly enhances wound healing in DFUs. Patients treated with hEGF experienced notable improvements, including reduced wound size and area, as well as shorter hospital stays. These benefits suggest that hEGF accelerates the wound healing process and enhances overall treatment efficacy. The observed reduction in wound size and area is crucial, as larger or non-healing wounds carry a higher risk of complications such as infections and surgical interventions. By accelerating wound closure, hEGF treatment potentially minimises these risks and promotes faster recovery. The decreased hospital stay for patients treated with hEGF highlights its efficiency in expediting the healing process, leading to quicker patient discharge and lessening the burden on healthcare resources.

From a clinical perspective, these findings support incorporating topical recombinant hEGF into standard wound care protocols for DFUs. Incorporating hEGF into treatment regimens could enhance healing outcomes, reduce complication rates, and improve the overall quality of care for diabetic patients.(20) The potential reduction in healthcare costs is significant, as quicker healing translates to fewer hospital visits, lower need for prolonged medical interventions, and reduced incidence of severe complications requiring intensive care or surgical procedures. Overall, this study underscores the therapeutic value of topical recombinant hEGF in managing DFUs, advocating for its broader use in clinical practice to achieve better patient outcomes and enhance healthcare efficiency.

The present study is not without limitations. It includes single centre study design, short-term follow up, and lack of blinding.

Conclusion

These findings demonstrate that using topical recombinant hEGF alongside normal saline dressing markedly improves the healing of diabetic foot ulcers. The observed decrease in wound size and area, coupled with reduced hospital stay durations, points to enhanced treatment effectiveness and the potential for reduced healthcare expenses for diabetic foot ulcer

patients. This study advocates for the integration of topical recombinant hEGF into conventional wound care protocols to enhance patient outcomes.

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Conflict of interest: Nil

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Table 1: Showing the mean difference between the variables

	Group A		Group B		p-value
	Mean	SD	Mean	SD	
Age (in years)	53.8	10.5	55.9	10.3	0.32
Duration of DM (in years)	8.3	5.1	9.2	4.6	0.32
Initial wound size (in sq.mm)	2957.2	867.2	3323.3	634.0	0.15
Final wound size (sq.mm)	2329.3	741.9	3028.6	571.3	0.01*
Area reduced	22.4	4.7	8.8	1.9	0.01*
Duration of hospital stay	14.6	4.9	16.5	4.5	0.01*

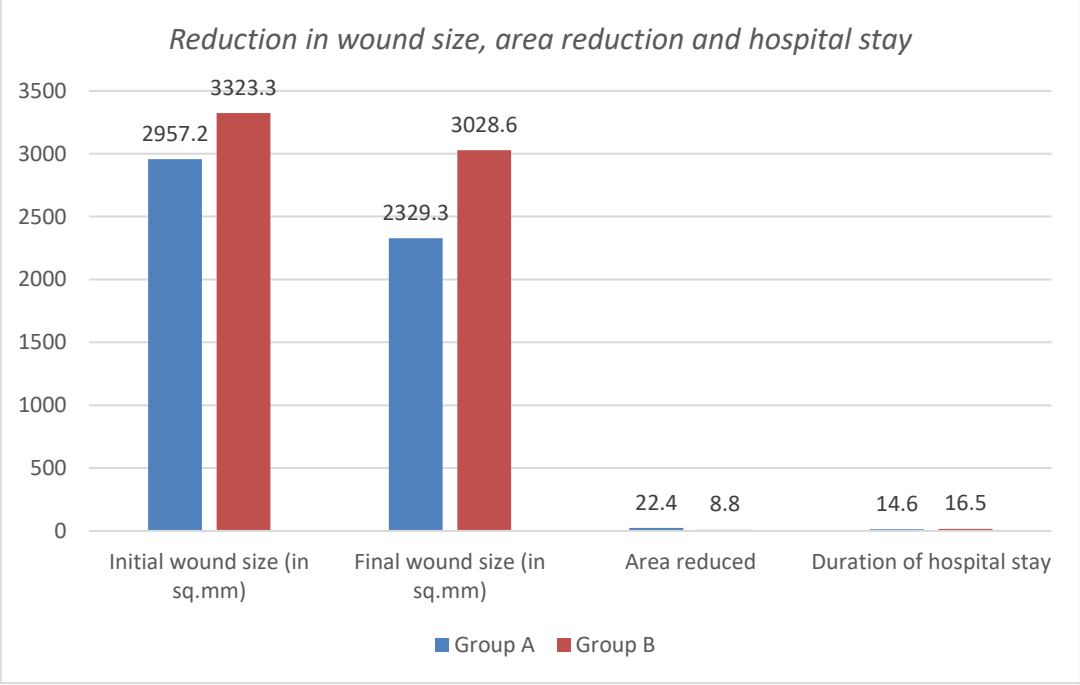

Figure 1: Showing the reduction in wound size, area reduction and hospital stay

Table 2: Showing distribution of variables between the groups

		Group A		Group B		Chi-square (p-value)
		Count	N %	Count	N %	
Gender	Female	16	40.0%	17	42.5%	1.21 (0051)
	Male	24	60.0%	23	57.5%	
Mode of onset	Spontaneous	20	50.0%	18	45.0%	0.201 (0.654)
	Traumatic	20	50.0%	22	55.0%	
Limb	Left	19	47.5%	20	50.0%	0.05 (0.823)
	Right	21	52.5%	20	50.0%	
Site	Dorsum	20	50.0%	20	50.0%	-

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	Plantar	20	50.0%	20	50.0%	
Pus C/S	EC	8	20.0%	10	25.0%	7.71 (0.260)
	KP	5	12.5%	7	17.5%	
	MRSA	0	0.0%	1	2.5%	
	PA	6	15.0%	11	27.5%	
	PM	5	12.5%	3	7.5%	
	SA	13	32.5%	8	20.0%	
	SP	3	7.5%	0	0.0%	

Initial wound **Final Wound**

Figure 2: Clinical photographs - Diabetic foot ulcer treated with hEGF