

Original Research Article

## **The Role of Epidermal Growth Factor Cream in Healing of Diabetic Foot Ulcer- Comparative Analytical Study in South India**

Thambi Durai David<sup>1</sup>, JA Jayalal<sup>2</sup>, Selwyn J Kumar<sup>3</sup>

<sup>1</sup>Asst Professor Department of Pediatric surgery KGMCH/Dr. MGR. Medical University India

<sup>2</sup>Professor Department of Surgery KGMCH/Dr. MGR. Medical University India

<sup>3</sup>Asst Professor Department of Surgery KGMCH/Dr. MGR. Medical University India,

Corresponding Author: JA Jayalal

### **ABSTRACT**

In spite of growing advances in medical technology and understanding of ulcer healing, no ideal method for treating the much dreaded Diabetic foot ulcer are defined. Numerous wound care methods, innovative natural healing processes, induced enhanced healing using innate and synthetic materials and simultaneous correction of comorbidity are postulated. This study is intended to evaluate one of the high technology modern advancements in wound care the use of epidermal growth factor for expected wound healing and to evaluate its role with a control group.

This prospective analytical case control comparative study is carried out in the Department of General Surgery Kanyakumari Government Medical College for the period of one year from 2017 January to 2017 December. The patients with diabetic foot coming for treatment are grouped into two groups under randomized control trial method with 25 patients in each group. The control group is treated with conventional methods and the experimental group with standardized Recombinant epidermal growth factor. (Regen-D 150) applications.

The data collected were tabulated and using SPSS software version 23.00 statistical analysis done. In our study we could observe statistically significant improvement in wound healing in the group receiving Recombinant epidermal growth factor cream. The pain score and the reduction in the size of ulcers are significant. The literature reviews also confirm this finding. Hence we conclude and propose it is worth using the Recombinant epidermal growth factor cream in diabetic foot ulcer to obtain early and complete wound healing.

**Key word:** Diabetic foot ulcer, Epidermal growth factor, wound healing, granulation tissue

### **INTRODUCTION**

Diabetes Mellitus, the metabolic disorder has percolated to the community across the world and become a global pandemic disease in the current century. The rise in the life expectancy, usage of junk food, sedentary life style and metabolic syndrome has paved the way for steady progression of the disease in the country. India has scored largest burden of Diabetic individual next to china. <sup>[1]</sup> With scientific advancement and based on research many innovative treatment modalities are

suggested. However due to lack of clear guidelines on treatment protocol and no uniform availability or affordability of treatment procedure, 15% of persons having diabetes proceed to Diabetic foot Ulcer and resulting in amputation. <sup>[2]</sup>

In 1962 Stanley Cohen, a renowned Biochemist in the Vanderbilt University Tennessee discovered and published the epidermal growth factor and its significant role in the process of wound healing. <sup>[3]</sup> In 1986 he got the Nobel Prize for his research on his success on isolation of this peptide

from a mouse and showing it had an impact on the eruption of incisor tooth and eyelid opening.

In 2002 Loot and Kenner et al had demonstrated the ability of haemopoietic cells to synthesize this epidermal growth factor. Epidermal growth factor acts by proliferation, mitigation and maturation of cells, by the mechanism of binding receptor kinase on target cells. [4]

EGF is a single chain polypeptide comprising 53 amino acid and having the molecular weight of 6200 Daltons. ECF stimulate cell proliferation, differentiation and maturation all important process in wound healing. [5]

Diabetic Ulcer are developing by the progression of neuropathy (sensory, automatic, motor) vasculopathy (micro and macro) and enhanced atmosphere for growth of microorganism by providing good culture media and imbibing the chemotactic properties of leukocyte and macrophages. [6] Early diagnosis of metabolic disorder of glucose, proper health education, life style modification and special focus on foot care can prevent the development of ulcer and complication. Appropriate usage of antibiotics, proper and adequate wound debridement, usage of tailor made dressing materials, off-loading the pressure and use of appropriate foot wears can prevent the ulcer resulting in amputation. 80% amputations happening today or due to Diabetic foot ulcer. [7]

Impact of various roles of EGF in ulcer pathogenesis and wound healing, recombinant human epidermal growth factor (rhEGF) progressed as a viable therapeutic option and as a most attractive growth factor for enhancing chronic wound healing. [8] EGF acts by stimulation, proliferation, and migration of keratinocyte; fibroblast stimulation and formation of granulation tissue; stimulation and proliferation of endothelial cells facilitating dermal regeneration and stimulator of fibroblast migration and wound contraction. [9]

### **Aims and objectives of the study**

The present study aims to study the efficacy of recombinant epidermal growth factor and its advantages over the conventional wound care methods.

### **MATERIALS AND METHODS**

**Study design:** It is a prospective randomized (1:1) double blind, case controlled analytical comparative study to evaluate the efficiency of human epidermal growth factor cream (Regen-D 150G) used in the wound care of diabetic foot ulcer.

**Duration:** one year 2017 January to 2017 December

The study was done with 50 patients and they were randomized into two group

1. Control group - 25 patients
2. Experimental group – 25 patients

#### **Inclusion Criteria**

- Patient with diagnosis of Diabetic Foot Ulcer with Wagner grade 1 – 2
- Age 25-75 both sex
- Blood sugar is on control with medication
- Ulcer size 2-10 cm.

#### **Exclusion Criteria**

- Patient with active systematic infection or comorbidities
- Ulcer size more than 10 cm
- Immuno compromised individuals
- Patient having diabetic foot ulcer of Wagner grade more than 3
- Patient not willing to give consent
- Pregnancy
- Malignancy
- Chronic alcoholic and smokers

**Procedure:** The demographic data of all participants collected. Diabetic status assessed. Adequate surgical debridement of the ulcer was done. The ulcer is washed using normal saline and complete hemostasis secured. Swab culture done. Measurement of wound was done on day 1, 15, 30. After randomization and obtaining consent, for the control group dressing was done with Povidone ointment and for the experimental group with adequate application of Recombinant Human

epidermal growth factors available in standardized preparation Regan-D 150 g.

collected. Participants were given the option to withdraw from the study at any time.

**Ethical consideration**

This proposed study ethical clearance obtained from the college ethical board. Both written and oral information in local language given to the participants of the study and then signature obtained. Demography data and study data were

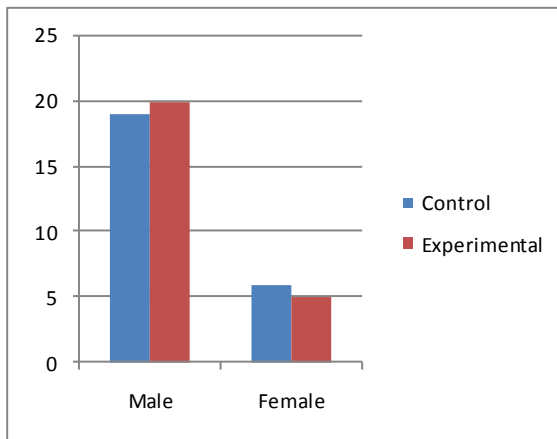
**OBSERVATION**

**1. Gender Distribution**

Male predomination (78%) observed. However there was no statistical significance between two genders between the experimental and control groups.

**Table 1: Gender Distribution within group**

	Male		Female		Total	
	Number	Percentage	Number	Percentage	Number	Percentage
Control	19	6	6	24	25	100
Experimental	20	80	5	20	25	100
Total	39	78	11	22	50	100



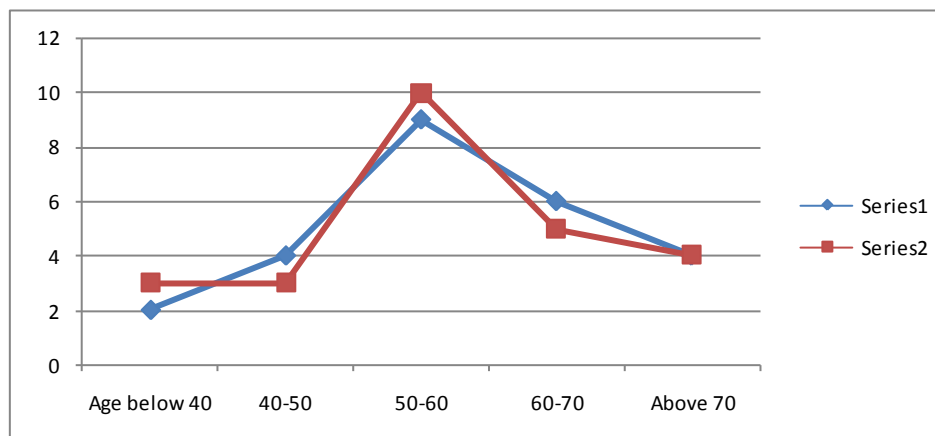
**Fig:1: Gender Distribution in both the groups .**

**2. Age distribution**

In our study mean age in the experimental group was 56 years and control group 57 years and not statistically significant.

**Table 2: Age Distribution within group**

	Control		Experimental		Total	
Age below 40	2	8	3	12	5	10
40-50	4	16	3	12	7	14
50-60	9	36	10	40	19	38
60-70	6	24	5	20	11	22
Above 70	4	16	4	16	8	16
Total	25	100	25	100	50	100



**Fig: 2 Distribution of age in both the groups.**

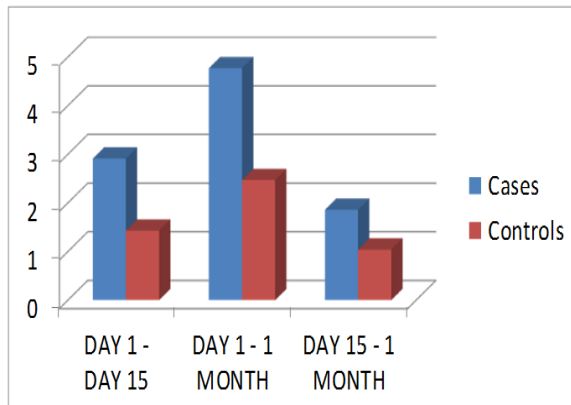
**3. Comparison of change in size of the Ulcer due to healing**

In our study as ulcer size are measured on day 1, 15<sup>th</sup> and 30<sup>th</sup> the results are observed and there is statistical significant between ulcer size reduction between control group and experimental group.

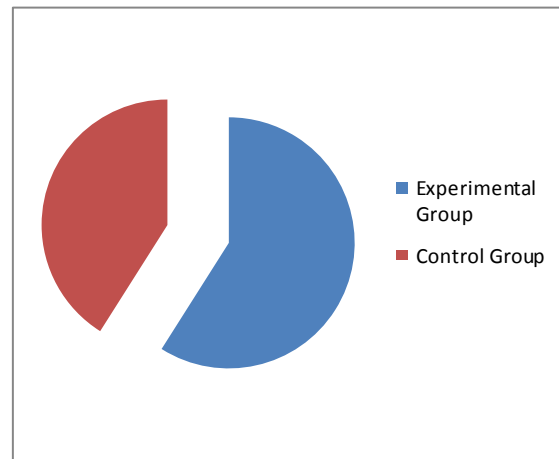
On the 30<sup>th</sup> day the ulcer healing in terms of size ranged from 54-81.5% in the EGF group as compared to the conventional group in which the decrease in size ranged from 34-47%

**Table: 3 Comparison wound size reduction in both groups.**

	Mean	Std. deviation	95% confidence interval of difference		Bonferroni "P" Value	
			Lower	Upper		
Experimental						
Day 1-15 <sup>th</sup>	2.90970	1.95287	1.99573	3.82367	.000	HS
Day 1-30 <sup>th</sup>	4.7692	2.05014	3.5985	5.09388	.000	HS
Day 15 <sup>th</sup> – 30 <sup>th</sup>	1.8594	1.58945	1.11556	2.60334	.000	HS
Control Group						
Day 1-15 <sup>th</sup>	1.43050	1.47412	0.74059	2.12041	.000	HS
Day 1-30 <sup>th</sup>	2.4690	2.2078	1.4357	3.5023	.000	HS
Day 15 <sup>th</sup> – 30 <sup>th</sup>	1.01421	1.01421	.056384	1.51316	.000	HS



**Fig 3: Comparison between changes in ulcer size in two groups**



**Fig :4: Percentage of wound healed in both the groups**

#### 4. Comparison between healed ulcers in two groups

The number of ulcers healed in experimental group is statistically significant P value 0.014

**Table 4: Healed Ulcers in Experimental (n=25) and Control group (n=25)**

	Completely healed Ulcer	D-Value
Experimental Group	23(92%)	0.014
Control Group	16(60%)	

#### 5. Reduction in wound size comparison

The reduction in wound size is significantly high in the experimental group with Recombinant Epidermal growth factor cream application .It is also noted the significant reduction in the size was most apparent and prominent in the first 15 days than the second 15 days.

**Table 5: Showing the paired difference in wound size reduction**

	Group	Paired Differences				t value	p value	
		Mean	Std. Deviation	95% Confidence Interval of the Difference				
				Lower	Upper			
Pair 1	Experimental	2.90970	1.95287	1.99573	3.82367	2.698	.010	sig
DAY 1 - DAY 15	Control	1.43050	1.47412	.74059	2.12041			
Pair 2	Experimental	4.7692	2.5014	3.5985	5.9398	3.053	.004	HS
DAY 1 - 1 MONTH	Control	2.4690	2.2078	1.4357	3.5023			
Pair 3	Experimental	1.85945	1.58945	1.11556	2.60334	2.051	.046	sig
DAY 15 - 1 MONTH	Control	1.03850	1.01421	.56384	1.51316			

## DISCUSSION

In 1991 through a study conducted by Brown et al in people with chronic diabetic foot ulcer 90% of them were healed with application of Epidermal growth factor. [10] VK. Mohan et al in 2007 through a phase three clinical trial using Regen =D 150 ,stated Epidermal Growth factor result in healthy granulation and stimulate epithelialization, thus leading to final wound

closure. [11] Tsang and colleagues in their study involving 61 diabetic patients with foot ulcer with Wagner score 1 or 2 and normal ABPI state treatment with 0.04% EGF accomplished much better healing. [12] Larijani et al. also found that after four weeks of treatment ,mean closure was significantly higher in patients treated with epidermal growth factors comparing with the control group with the conventional

treatment methods (71.2% vs 48.9%,  $p < 0.03$ ).<sup>[13]</sup>

In our study, we found that rhEGF improved the percentage of complete ulcer healing and in the size of the ulcer significantly. The decrease in ulcer size was more evident in the first 15 days when compared to the next 15 days. There was 50% reduction in the size of the ulcer as compared to the conventional group in which the decrease in size was less than 25%.

In our study we also noted that as compared to the first day, on the 30th day the ulcer healing in terms of size ranged from 54-81.5% in the EGF group as compared to the conventional group in which the decrease in size ranged from 34-47%. The patient satisfaction and co-operation was much better in the EGF group as compared to the conventional group in most ulcers. The possible reason attributed to this is the lesser need of surgical debridement due to lesser slough.

The amount of pain experienced was lesser in the study group as compared to the conventional group in most ulcers.

In accordance with the study results published by Hoon et al, Yera- Alos IB et al, Fernández-Montequín, Tuyet HL et al, Man Wo Tsang et al, Ramakrishna et al, Huo Qiu et al, Dogan, Demirer et al, Yang s et al, Afshari M et al, Richard et al, Doerler et al, and Khanbanha et al.<sup>[14-18]</sup> our study showed a positive effect on wound healing and granulation issue formation.

Fernández-Montequín et al had postulated the intralesional injections of epidermal growth factor had yielded more and quicker results as the wound milieu may destroy the growth factors. However in our study we have not used the injection but only the topical application of cream.<sup>[19]</sup>

## CONCLUSION

Epidermal Growth Factor plays a major role in wound healing with better and faster results than conventional dressings in the healing of diabetic ulcers. The dreaded complication of amputation can be

prevented by the appropriate use of epidermal growth factor in chronic diabetic foot ulcers.

## REFERENCES

1. Diabetes facts and figures -International Diabetes Federation IDF Diabetes Atlas, Eighth Edition, International Diabetes Federation publication, 2017. [www.diabetesatlas.org](http://www.diabetesatlas.org)
2. Hardwick J Sch Maljohan D et al Epidermal growth factor therapy and wound healing - Past future perspective the surgeon 2008 Jan 30;6(3) 172.7
3. Carpenter G. Cohen S. Epidermal growth factor. Annual review of Biochemistry 1979 Jul. 48 (1): 193-216
4. Loots MA, Kenter SB et al Fibroblasts derived from Chronic Diabetic Ulcers differ in their response to stimulation with EGF, 1 GF – 1 bFGF and PDGF – AB compared to controls. European journal of Cell Biology 2002 Mar 31; 81 (3) 153-60
5. Tsang MW<sup>1</sup>, Wong WK, Hung CS et al Human epidermal growth factor enhances healing of diabetic foot ulcers. Diabetes Care. 2003 Jun;26(6):1856-61
6. Matthew J. Young, Aristidis Veves et al The diabetic foot: Aetiopathogenesis and management- Diabetes metabolism Research and review July 1993 <https://doi.org/10.1002/dmr.5610090204>
7. Sampath Kumar K.P, Diabetes epidemic in India, A comprehensive review of clinical features, management and remedies, The Pharma Innovation publication, Vol. 1 No. 2 2012, page no 16
8. B. Ananda Rama Rao. Recombinant Human Epidermal Growth Factor in Healing of Pressure Ulcers. International Journal of Health Sciences & Research ([www.ijhsr.org](http://www.ijhsr.org)). Vol.7; Issue: 11; November 2017
9. Vimal Ramachandran et al Epidermal Growth Factor Versus Conventional Wound Dressings In Treatment Of Diabetic Ulcers- A Comparative Study. IOSR Journal of Dental and Medical Sciences (IOSR-JDMS). Volume 16, Issue 3 Ver. V (March. 2017), PP 09-15. DOI: 10.9790/0853-1603050915
10. Brown GL, Garisinger L, Jarkiewicz MY. Stimulation of healing of chronic wound by epidermal growth factor. Plastic. Reconstr.

- Surg. 88, 189–194 (1991)
11. Mohan VK Recombinant human epidermal growth factor (REGEN-D 150): effect on healing of diabetic foot ulcers. *Diabetes Res Clin Pract.* 2007 Dec;78(3):405-11. Epub 2007 Jul 25. PMID: 17655964
  12. Tsang MW, Wong WK, Hung CS et al (2003) Human epidermal growth factor enhances healing for diabetic foot ulcers. *Diabetes Care* 23:1856–1861
  13. Larijani B et al(2003) Iran J Effect of local epidermal growth factor in healing diabetic foot *Endocrinol Metab* 2003; 5:2 121-125 (SN 18)
  14. Hoon, JoonPio, Jung, Heun Don, Kim, Yun Wha. Recombinant human epidermal growth factor to enhance diabetic foot ulcers. *Annals Of Plastic Surgery*: 2006; 56(4):394-398
  15. Isis B Yera-Alos, Liuba Alonso-Carbonell, Carmen M Valenzuela-Silva Angela D Tuero-Iglesias, Martha Moreira-Martínez, Ivonne Marrero-Rodríguez et al. Active post-marketing surveillance of the intralesional administration of human recombinant epidermal growth factor in diabetic foot ulcers. *BMC Pharmacol Toxicol.*2013; 14: 44.
  16. Valenzuela-Silva CM1, Tuero-Iglesias AD, García-Iglesias E, González-Díaz O, Del Río-Martín A, YeraAlos IB, Fernández-Montequín JI, López-Saura PA. Granulation response and partial wound closure predict healing in clinical trials on advanced diabetes foot ulcers treated with recombinant human epidermal growth factor. *Diabetes Care.* 2013;36(2):210-5
  17. Fernández-Montequín JI, Valenzuela-Silva CM, Díaz OG, Savigne W, Sancho-Soutelo N, Rivero-Fernández F, Sánchez-Penton P, et al. Intra-lesional injections of recombinant human epidermal growth factor promote granulation and healing in advanced diabetic foot ulcers: multicenter, randomised, placebo-controlled, double-blind study. *Int Wound J.* 2009 Dec;6(6): 432-43 .
  18. Tuyet HL, Nguyen Quynh TT, Vo Hoang Minh H, ThiBich DN, Do Dinh T, Le Tan D, Van HL, Le Huy T, Doan Huu H, Tran Trong TN. The efficacy and safety of epidermal growth factor in treatment of diabetic foot ulcers: the preliminary results. *Int Wound J.* 2009 Apr;6(2):159-66
  19. Fernández-Montequín JI, Betancourt BY, Leyva-Gonzalez G, Mola EL, Galán-Naranjo K, Ramírez-Navas M et al. Intralesional administration of epidermal growth factor-based formulation (Heberprot-P) in chronic diabetic foot ulcer: treatment up to complete wound closure. *Int Wound J.* 2009 Feb;6(1):67-72

How to cite this article: David TD, Jayalal JA, Kumar SJ. The role of epidermal growth factor cream in healing of diabetic foot ulcer- comparative analytical study in south India. *Int J Health Sci Res.* 2018; 8(6):1-6.

\*\*\*\*\*