

A STUDY ON THE EPIDERMAL GROWTH FACTOR IN DIABETIC ULCER MANAGEMENT

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ABSTRACT

BACKGROUND & OBJECTIVES

The wide reaching negative social impact of non-healing chronic diabetic ulcers is emphasised by the estimate that 70 million of the world population might be affected by diabetes by 2025 and these people will be physically and socially handicapped if they develop foot problems. A vital cog in the wheel of wound healing is Epidermal Growth Factor. Hence a novel approach for combating longstanding diabetic wounds is external application of growth factors. This study has been done with the view to evaluate the efficacy of Epidermal Growth Factor in accelerating the healing of diabetic foot ulcers and also to assess its tolerability. This study compares the Epidermal growth factor Versus the standard therapy of wound with antiseptic solution and moist saline dressing in healing of diabetic ulcer foot.

METHODS

Sixty cases of diabetic ulcers (Study group-30 and control group-30) were included in this study. Factors tabulated and analysed.

RESULTS & OBSERVATIONS

The overall rate of healing of ulcers in EGF group is 86.67% and in the control group is 66.67%.

CONCLUSION

The conclusion of this study is that recombinant Epidermal Growth Factor is effective in the healing of diabetic ulcers at a significantly higher rate.

KEYWORDS

Diabetes Mellitus, Diabetic Foot, Recombinant Epidermal Growth Factor.

HOW TO CITE THIS ARTICLE: Shanthini P, Selvi RRA, Sethuraman A et al. A study on the epidermal growth factor in diabetic ulcer management. J. Evid. Based Med. Healthc. 2016; 3(40), 1987-1994. DOI: 10.18410/jebmh/2016/442

INTRODUCTION: At present there are 25 million diabetic Indians. One of the most common problem for which diabetics are hospitalised is the diabetic foot disease, accounting for about 20-25% of all the hospital admissions.¹ The healing cycles in inflammation are extremely deranged in diabetic foot ulcers which lead to failure of epithelialisation and granulation tissue formation.^{2,3,4} These failures along with neuropathy and joint instability (Biomechanical) result in debilitating ulcer further exaggerated by arterial insufficiency (30-60%) and absence of strict glucose regulation. The topic of study, the growth factors or modulating factors, are peptides involved in signalling, which are increasingly produced during inflammation and target non-haematopoietic cells. They act locally on the target site without systemic side effects.

The Epidermal Growth Factor: It is a peptide with low molecular weight.^{5,6}

It lacks three amino acids namely-lysine, phenylalanine, alanine. It was first isolated from the submandibular gland of mouse. It acts by causing smooth muscle, epithelial cell and fibroblast proliferation thereby promoting wound healing in diabetic ulcer, venous ulcer and healing of burns wound. It also causes tissue repair and regeneration by stimulating formation of collagen and elastic fibres. Hence, this study has been done with the view to evaluate the efficacy of the Epidermal Growth Factor in accelerating the healing of diabetic foot ulcers. This study also compares the Epidermal Growth Factor vs the standard therapy of wash with antiseptic solution and moist saline dressing in healing of diabetic ulcer disease.⁷

AIM OF THE STUDY

- To evaluate the efficacy of the Recombinant Epidermal Growth Factor in the healing of diabetic ulcer.
- To assess the tolerability of the Recombinant Epidermal Growth Factor in the diabetic ulcer management.

Financial or Other, Competing Interest: None.
Submission 20-04-2016, Peer Review 05-05-2016,
Acceptance 14-05-2016, Published 18-05-2016.

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DOI: 10.18410/jebmh/2016/442

MATERIALS AND METHODS:

Study Design: Randomised, interventional, prospective comparative study.

Study Centre: Department of General Surgery and Department of Diabetology, KAPV Govt. Medical College, Trichy.

Duration of Study: 18 Months.

Sample Size: 60 (30+30); Study group A-30, Control group B-30.

Study Drug: Recombinant Epidermal Growth Factor.

Selection Criteria:**Inclusion Criteria:**

- Age – 20-70 years.
- Both sexes.
- Fasting blood sugar <130 mg/dL and post-prandial blood sugar >130 mg/dL <180 mg/dL with treatment.
- Patients with grade 2 diabetic ulcer.
- Patients with diabetes along with other comorbidities like.
- Hypertension with BP <140/90 mmHg with antihypertensives, Anaemia with haemoglobin between 8-10 g%, Chronic renal failure stage 1 and 2, CAHD patients on drugs with no symptoms at present.
- Palpable peripheral pulses or Doppler showing flow in the peripheral vessels.
- Patients who give consent and are willing for regular follow-up.

Exclusion Criteria:

- Patient with extensive gangrenous changes.
- Patients with vascular occlusion (Absent peripheral pulses or no flow in peripheral vessels in the Doppler study.)
- Patients with diabetic ketoacidosis or with fasting blood sugar >130 mg/dL, post-prandial blood sugar >180 mg/dL in spite of treatment.
- Patients with diabetes with hypertension with BP >140/90 mmHg. Anaemia with haemoglobin <8 g%, chronic renal failure with stage III, IV, V, congestive heart failure and recent onset myocardial infarction.
- Pregnant or breastfeeding women.
- Not willing for the study or not willing for regular visits.

Baseline Investigations

- Haemoglobin.
- Red blood cell count.
- Total leukocyte count.
- Differential count.
- Urine sugar, albumin/Microalbuminuria.
- Fasting and postprandial blood sugar.
- HbA1c.
- Erythrocyte sedimentation rate.

- Renal function test including blood urea, serum creatinine, serum electrolytes.
- Liver function tests including bilirubin, SGOT, SGPT, alkaline phosphatase, serum proteins.
- Wound swab for culture and sensitivity.
- Electrocardiogram.
- Chest X-ray, X-ray of the affected limb.
- Doppler study of the affected limb.

Allocation in to Study and Control Groups:

The patients were divided into 2 groups.

Group 1 – Patients with diabetes alone.

Group 2 – Patients having diabetes together with hypertension with BP <140/90 mmHg or with asymptomatic CAHD patients on drugs, chronic renal failure stage 1 and 2. In these group, patients are subdivided into 2 groups, ulcer <5 cm in the greatest dimension and > 5 cm.

In each of the group, the patients were randomly allocated into the study group and the control group.

All the patients were enquired about their age, occupation, complaints and the history was enquired in detail. The duration of diabetes, the modality of treatment, associated comorbid conditions such as hypertension, ischaemic heart disease, list of drug intake were also enquired into. Their dietary habits, smoking or alcohol consumption were also recorded.

Examination of the patients was done in detail. General examination of the patient was done. Local examination of the ulcer was done. The size, site, extent, depth, base, floor, induration, surrounding tissues, the granulation tissue, slough, discharge were all noted. Photographs of the ulcer were taken.

The patients were also examined for the presence of any risk factors for ulceration. The sensation was tested with a help of Semmes-Weinstein 10 g monofilament. 10 sites in the foot were tested for sensation which includes the plantar aspect of the first, third and fifth digits, plantar aspect of the metatarsal heads of first, third and fifth metatarsal, medial and lateral aspect of the plantar midfoot, the heel on the plantar aspect. Peripheral pulses were examined.

The blood pressures in the ankle and also brachium were measured using a hand Doppler. Then, the ankle-brachial pressure index was calculated.

TREATMENT PLAN:**Group A (Study Group):**

- Glycaemic control.
- Wound debridement.
- Saline wash.
- Application of Epidermal Growth Factor.

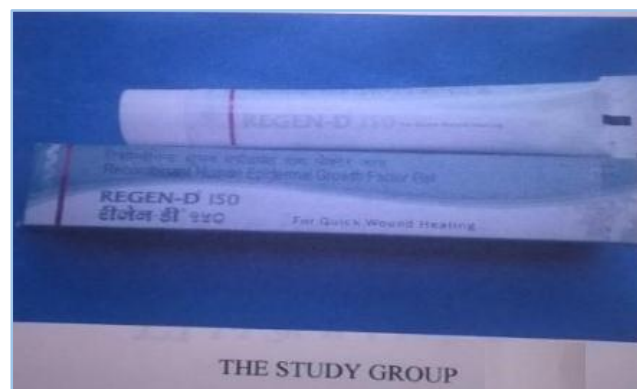
Group B (Control Group)

- Glycaemic control.
- Wound debridement.
- Wash with antiseptic solution.

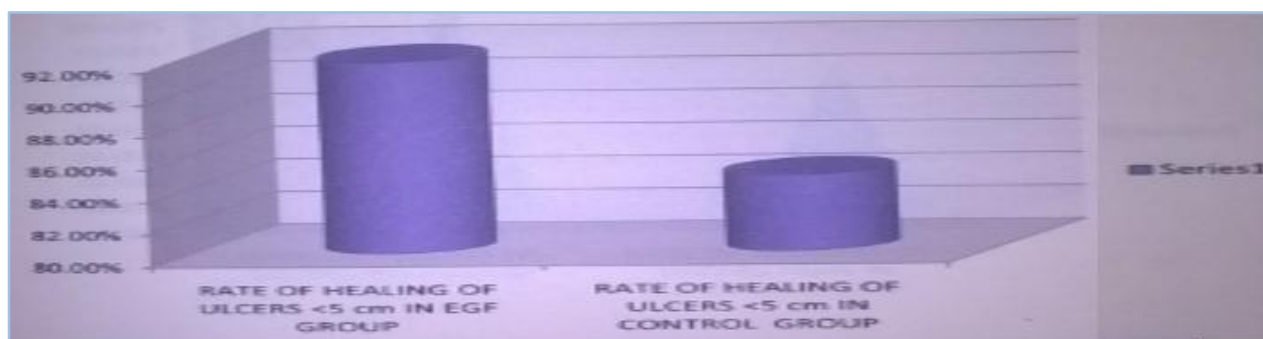
Instructions for Topical Application of the EGF:

- Epidermal Growth Factor gel must be stored at 2-8°C.
- The wound must be debrided first before applying the gel.
- Before applying the Epidermal Growth Factor gel, hands must be washed thoroughly.
- Before each application, the ulcer must be cleaned either with water or normal saline.
- Each tube of EGF should be used for only one patient.
- The tip of the tube should not be in contact with the ulcer.
- After applying the gel, the wound is covered with sterile gauze and dressing is done.
- Dressing is done twice a day with EGF.
- Follow-up is done once in a week for a maximum up to 15 weeks.

Ulcers which do not heal after 15 weeks are considered non-healing.



The Patients for whom Skin grafting was done after the appearance of granulation tissue are also not taken into consideration in calculating the rate of healing & duration of healing.

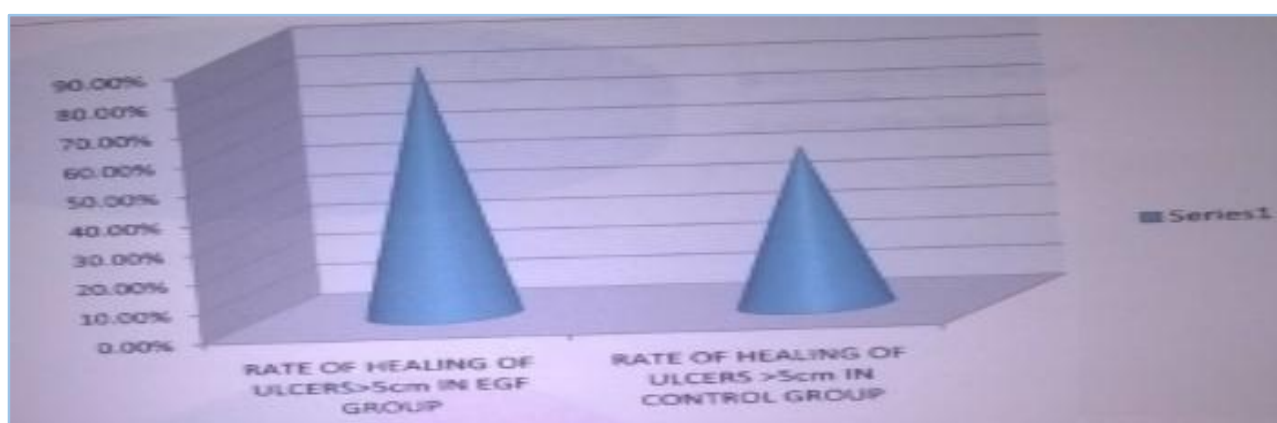
RESULTS & DISCUSSIONS:**RESULTS:**

The Rate of Healing of Ulcers <5 cm are Compared between the EGF & the Control Groups

The Rate of Healing of Ulcers <5 cm

In EGF Group → 91.67%

In the Control Group → 84.62%



The Rate of Healing of Ulcers >5 cm are Compared between the two Groups

The Rate of Healing of Ulcers >5 cm

In EGF Group → 83.33%

In the Control Group → 52.94%



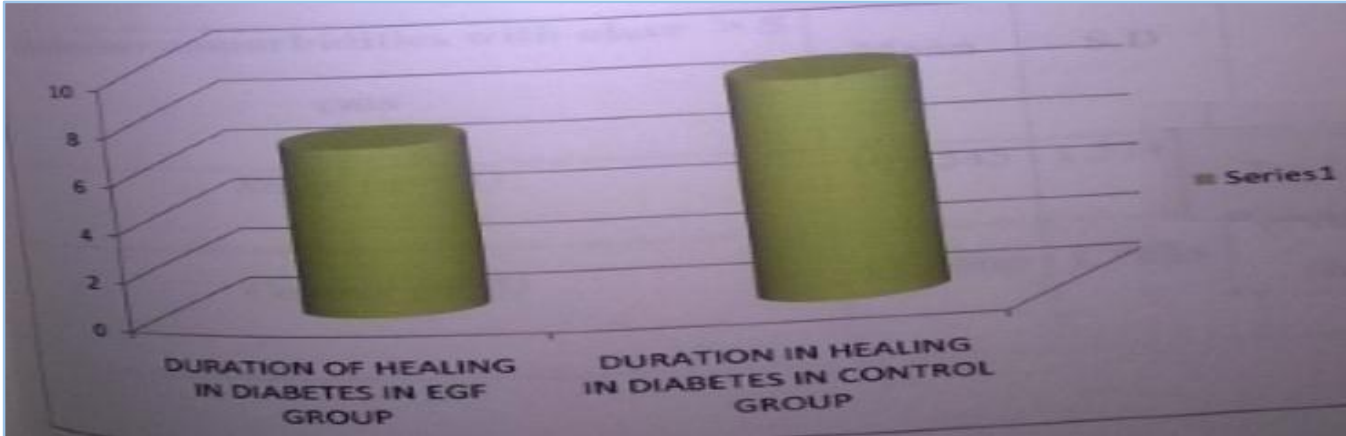
Overall the Rate of Healing of Ulcers in the EGF Group compared with the Control Group

Rate of Healing in EGF Group - 86.67%. Control Group - 66.67%

Next, the duration of healing of the Ulcers are compared between the two Groups. Those Ulcers which are not healed by 15 weeks & those that are treated by skin grafting are considered as non-healing and are not considered in the T test.

Diabetic ulcer < than 5 cm	Mean	S.D	Statistical inference
Study (n=5)	5.2000	.83666	T = -4.017 Df=8 P value = .004<0.05 Significant
Control (n=5)	7.4000	.89443	
Table 1: Duration of Healing of Ulcers <5 cm are Compared between EGF Group and Control Group in Patients with Diabetes alone Without Comorbidities			

Diabetic ulcer > than 5 cm	Mean	S.D	Statistical inference
Study (n=4)	8.7500	.95743	T = -2.954 Df=6 P value = .025< .05 Significant
Control (n=4)	10.7500	.95743	
Table 2: Duration of Healing of Ulcers >5 cm are Compared between 2 groups in Patients with Diabetes alone Without comorbidities			



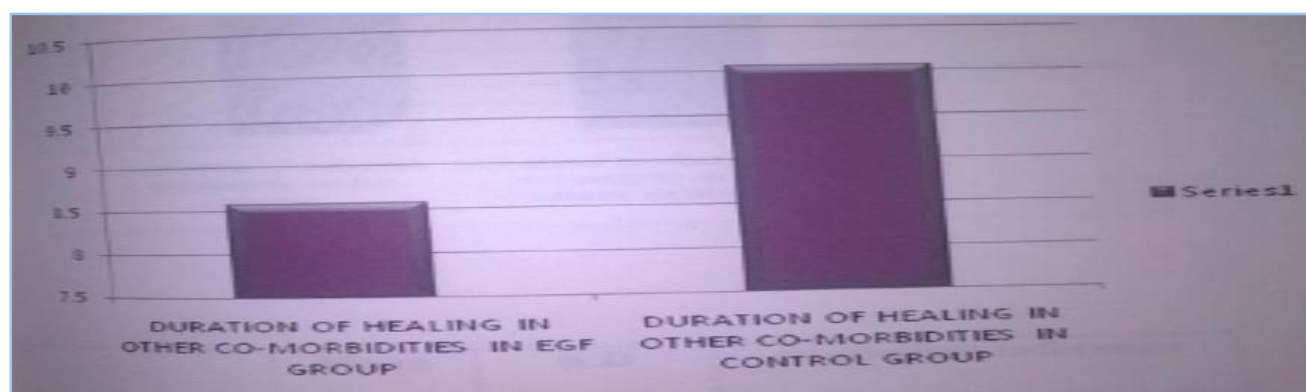
Duration of Healing of Ulcers in Patients with Diabetes alone are Compared

Diabetes + added comorbidities ulcer < 5 cm	Mean	S.D	Statistical inference
Study (n=6)	6.6667	1.03280	T = -2.565 Df=10 P value = .028<0.05 Significant
Control (n=6)	8.3333	1.21106	

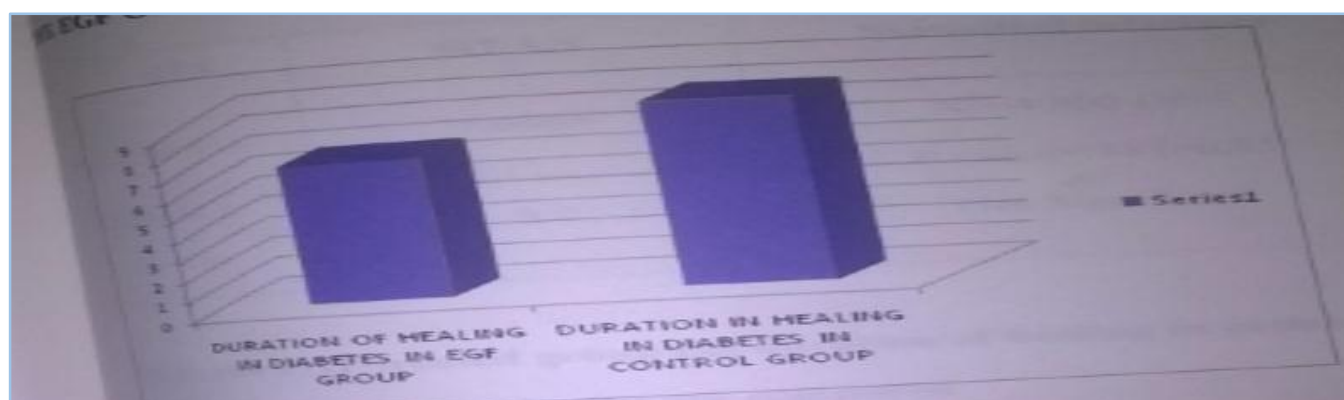
Table 3: Duration of Healing in Patients with Diabetes and added Comorbid Conditions in ulcers < 5 cm are Compared

Diabetes + comorbidities with ulcer > 5 cm	Mean	S.D	Statistical inference
Study (n=11)	10.4545	1.57249	T = -1.524 Df=14 P value = .150>0.05 Not Significant
Control (n=5)	11.8000	1.78885	

Table 4: Duration of Healing in Patients with Diabetes and Added Comorbid Conditions In Ulcers > 5 cm are Compared



In Patients with Diabetes and Added Comorbidities, the Duration of Healing of Ulcers is Compared between the 2 Groups



Overall the Duration of Healing of Ulcers in the EGF Group is Compared with the Control Group

	Mean	S.D	Statistical inference
Study (n=26)	8.3077	2.46202	T = -1.643 Df=44 P value = .108 >0.05 Not Significant
Control (n=20)	9.4500	2.16370	

Sex	Mean	Statistical inference
Male (n=11)	7.0909	X2= 4.800 Df=3 P value = .108>0.05 Not Significant
Female (n=11)	9.2	

Table 5: In the EGF Treated Group, the Duration of Healing between the Males and Females are Compared

EGF	Mean	S.D	Statistical inference
Less than 40 yrs. (n=12)	7.0909		T=1.177 Df=24 P value = .251>0.05 Not Significant
More than 40 yrs. (n=14)			

Table 6: In the EGF treated Group, the Duration of Healing in Patients Aged <40 Years and >40 Years are Compared

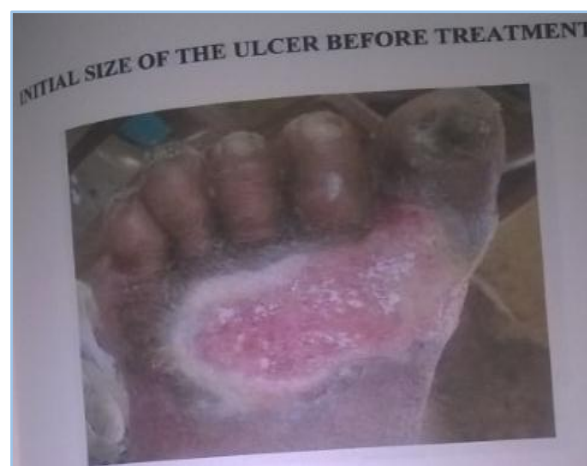
DISCUSSION:

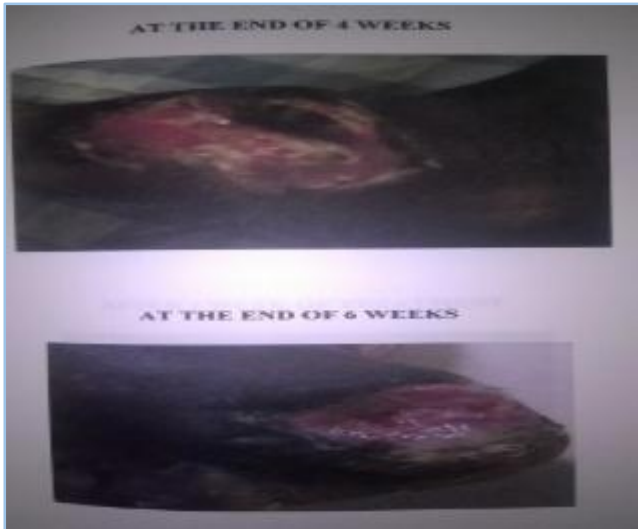
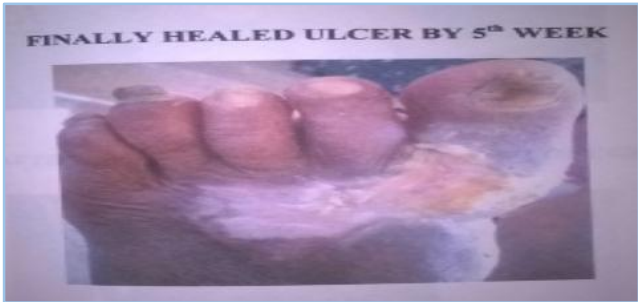
- The rate of healing of ulcers <5 cm in the EGF treated group is significantly greater than in the control group.
- The rate of healing of ulcers >5 cm in the EGF treated group is significantly greater than in the control group.
- Overall the rate of healing of ulcers in the EGF treated group is significantly greater than in the control group.
- The duration of healing of ulcers in the patients with diabetes alone with ulcer size <5 cm is significantly shorter in the EGF group than in the control group.
- The duration of healing of ulcers in the patients with diabetes alone with ulcer size >5 cm is significantly shorter in the EGF group than in the control group.
- Overall the duration of healing of ulcers in the patients with diabetes alone is significantly shorter in the EGF group than in the control group.
- The duration of healing of ulcers in the patients with diabetes and added comorbidities with ulcer size <5 cm is significantly shorter in the EGF group than in the control group.
- The duration of healing of ulcers in the patients with diabetes and added comorbidities with ulcer size >5 cm is shorter in the EGF group than in the control group, but there is no statistical significance in the duration of healing between the 2 groups.
- Even though the duration of healing of ulcers in patients with diabetes and added comorbidities in the EGF group is shorter than in the control group, it is not statistically significant.
- As a whole, there is no statistical difference in the duration of healing of ulcers in EGF group and the control group. This is due to the fact that
 - a) Number of patients with non-healing ulcers are greater in the control group.
 - b) Only smaller ulcers have healed in the control group in patients with diabetes and added comorbidities whereas both small and large ulcers have healed in the EGF group.
 - c) The sample size is small.
- In the patients treated with topical EGF, there is no statistical difference in the duration of healing between male and female.

Also, there is no difference in the duration of healing between those <40 years and those >40 years.

CONCLUSION: The conclusion of this study is that Recombinant Epidermal Growth Factor is effective in the healing of diabetic ulcers at a significantly higher rate. The duration of healing is significantly shorter in the group with diabetic patients alone and marginally shorter in the group with diabetes and added comorbidities.

No adverse reactions are encountered. It is tolerated well by all the patients.







REFERENCES

1. John M Giurini, Frank W Logerfo. The diabetic foot, the medical and surgical management. Springer 2012;3rd edn.
2. McCartney-Francis NL, Wahl SM. TGF-beta and macrophages in the rise and fall of inflammation, in TGF-beta and related cytokines in inflammation. Breit SN, Wahl SM, ed. Birkhauser, Basel 2001;65-90.
3. Iesler CU, Ferguson MWJ. TGF-beta superfamily cytokines in wound healing, in TGF-beta and Related Cytokines in Inflammation. Breit SN, Wahl SM, ed, Birkhauser, Basel 2001;173-198.
4. Wahl SM. Transforming growth factor beta. In inflammation: basic principles and clinical correlates. Gallin J, Snyderman R, eds, Lippincott-Raven Publishers, Philadelphia 1999;3rd edn:883-892.
5. Tsang MW, Wong WK, Hung CS, et al. Human epidermal growth factor enhances healing of diabetic foot ulcers. Diabetes Care 2003;26(6):1856-1861.
6. Taylor JM, Mitchell WM, Cohen S. Epidermal growth factor, the physical and chemical properties. J Biol Chem 1972;247(18):5928-5934.
7. Sharon Baranoski, Elizabeth A Ayello. Wound care essentials and practical principles. Lippincott Williams & Wilkins 2008;2nd edn.