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Role of Epidermal Growth Factors (EGF) in healing of chronic leg ulcers.

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I. Introduction

Chronic leg ulcers is ubiquitous problem of varied etiology. Chronic venous ulcer account for 70-90%. Ulcer healing rates can be poor with upto 50% of venous ulcers turning into nonhealing with one third recurrences. Several growth factors have been explored as wound healing agents. EGF plays a essential role in wound healing by stimulation , proliferation and migration of keratinocytes , endothelial cells and fibroblast – epidermal and dermal regeneration .

Aim of The Study

- To analyse the efficacy of rhEGF in healing of chronic ulcers by serially recording the reduction in size of ulcer on weekly basis , mean healing time and percentage of ulcers healed in the given study period
- To evaluate the safety profile of rhEGF in healing of chronic leg ulcers by analysing the adverse effects in the form of local or general events including some of the serious events

II. Materials and Methods

Study design - prospective randomized ,double blind , comparative (rhEGF and placebo) study to evaluate the safety and efficacy of recombinant human epidermal growth factor
Study centre – Osmania general hospital
Study duration – the maximum and expected duration of exposure to the study drug or placebo for an individual subject in treatment and follow up for upto 12 weeks or complete wound closure which ever is earlier
Number of subjects – 25
Informed consent – informed consent is obtained from the patient with signature and date. Subject information sheets are provided to patients which will be available in three languages

Inclusion criteria:

- Pt able to understand and has signed the informed consent form
- A diagnosed case of venous insufficiency
- Target ulcer between 2sq.cm to 50sq.cm
- Pt expected to available for 12 weeks study period and are able to adhere to the treatment regimen
- Pt age 18 to 75
- Ulcers which remained open without healing for more than 2-3weeks

Exclusion criteria:

- Life threatening or serious cardiac failure (NYHA grades III- IV) , gastrointestinal , hepatic , renal , endocrine , haematological or immunological disorders
- Uncontrolled hypertension grade III
- Squamous cell carcinoma and basal cell carcinoma of wound
- Known case of hypersensitivity to incipient
- Uncontrolled diabetes , diabetic ketoacidosis or coma
- Pregnant and nursing mothers
- Past history of acute or chronic autoimmune disease

- Chronic alcohol abuse

Pt received within one month prior to visit 1 any treatment known to impair wound healing

- use of any marketed or investigational or herbal medicine or nonregistered drugs for wounds in past six months
- Clinically relevant abnormal haematological or biochemical
- Presence of systemic or deep infection or nonviable tissue that cannot be removed by debridement
- Treatment with dressing containing any other growth factors or other biological dressings within 30 days prior to screening visit

Discontinuation criteria:

- Request by patient
- Pt requires any treatment or therapy that would compromise the evaluation of test product
- Lack of adherence to study protocol
- Adverse reaction which precludes continued treatment
- Female patient who becomes pregnant
- Non compliance of patient

Classification of ulcers into groups :

- Group 1 - <5 sq.cm.
- Group 2 - 5 to 10 sq.cm.
- Group 3 - >10 sq.cm.

Screening of patients

Initially wound swab test for estimation of microbial load is done every 3-4 days , after which the weekly schedule is followed

Initially progress of ulcer is observed daily for 2 weeks and the duration of observation is changed depending on further progress of ulcer

- Patients meeting all the inclusion criteria and none of the exclusion criteria are randomised to one of the treatment groups and for each patient a subject id is given after screening

Double blinding :

This study uses double blinding method . The study drug and its look alike placebo are similar in size of tube , colour, smell , consistency and appearance.

All supplies are pre labled with subject numbers

Identity of test drug and placebo:

Study drug

Generic name – rhEGF

Dosage – gel base

Strength – 150 mcg/gm

Manufacturer – bharath biotech international limited

Ingredients – active – rhEGF

Inactive – propyl paraben , methyl paraben , carbopolultrez , glycerol , mannitol , lysine HCL

Placebo

Dosage – gel base

Manufacterer - bharath biotech international limited

Active – none

Inactive - propyl paraben , methyl paraben , carbopolultrez , glycerol , mannitol , lysine HCL

Dosage and administration –

Topical application using sterile swab twice daily till wound heals or till end of 12 week

Compliance – checked at each visit, acceptable percentage is 85 %

Efficacy evaluation – the wound was debrided and once the wound was free of necrotic tissue and slough , study medication was applied . After application of medication wound was dressed with saline soaked gauze .

At each visit , area of ulcer measured , photographs were taken once every week

Efficacy endpoints – observe reduction in wound size

Safety evaluation – monitoring adverse effects , serious adverse affects , deaths , discontinuation

Routine blood investigations, liver function tests , urine examination , blood sugar , serum creatinine , were done at beginning and end of the study .

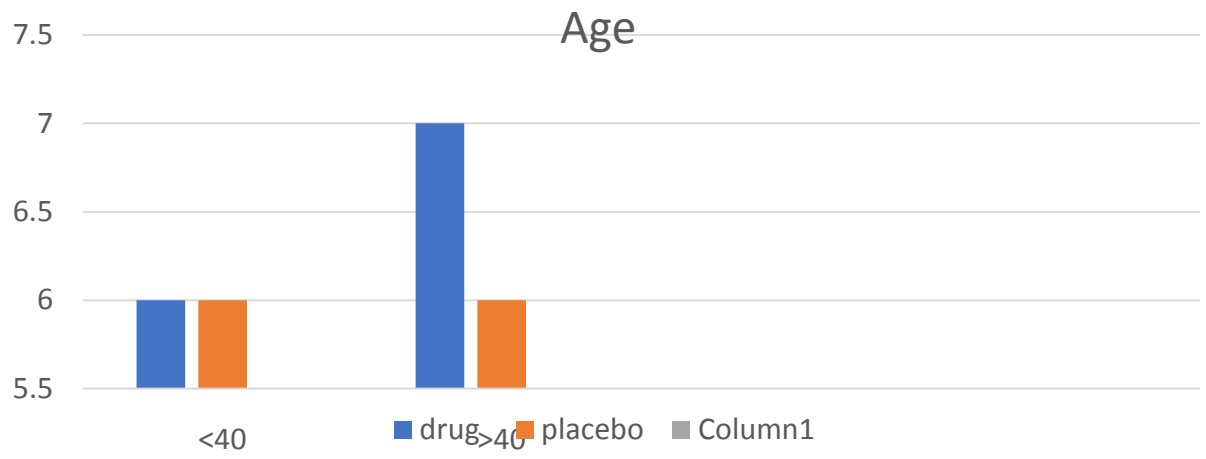
Concomitant therapy –
Any medication that the subject takes other than the study drugs specified is considered
Discontinuation from study – reasons evaluated and recorded , withdrwal due to adverse event is distinguished

Age	Number (drug + placebo)	Percentage
<40	12 (6+6)	48
>40	13(7+6)	52

Statistical analysis –

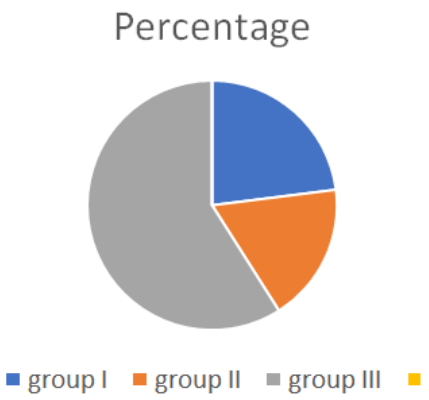
The results were analysed by comparing the mean time to heal between the drug and placebo groups and by perentage of completely healed ulcers . Results were analysed for all grades together and individually . Adverse events considered related and those uncertain cause are included in the safety analysis . The saftey profile of drug are compared by comparing the percentage discontinued from therapy due to adverse events .

III. Results and analysis



Ulcer category before unblinding:

Group	Size	Number	Percentage
I	<5	5	23%
II	5 -10	4	18%
III	>10	13	59 %
		TOTAL = 22	



Healing of ulcers (group wise before unblinding):

Group I n = 5	**Group II n=4**	**Group III n=13**
21 days	71 days	13 days
80	67	33%decrease
29	58	25%decrease
26	21	79
24		36
		83.4%decrease
		38
		80% decrease
		50%decrease
		58.4decrease
		25%decrease
		80% decrease
		70% decrease
		Not healed =9
Healed =5	Healed =4	Healed = 4

Healing of ulcers (group wise after unblinding):

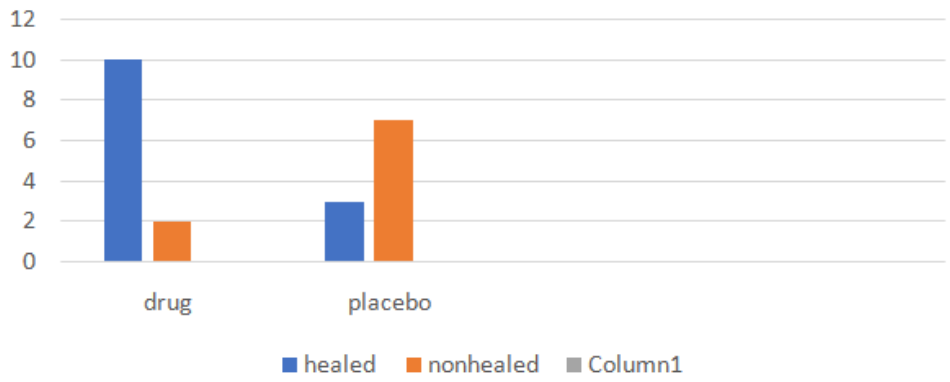
Drug	**Placebo**
Group I	
21 days	26 days
80 days	24 days
29 days	
Group II	
71 days	67 days
58 days	
21 days	
Group III	
21 days	50 % decrease
33% decrease	80 % decrease
25 % decrease	83.4 % decrease
79 days	80 % decrease
38 days	58.4 % decrease
36 days	25% decrease
	70% decrease

Comparison of drug and placebo in ulcers that healed completely :

	Drug	Placebo
Completely healed	10	3
Incompletely healed	2	7
	Total = 12	Total = 10

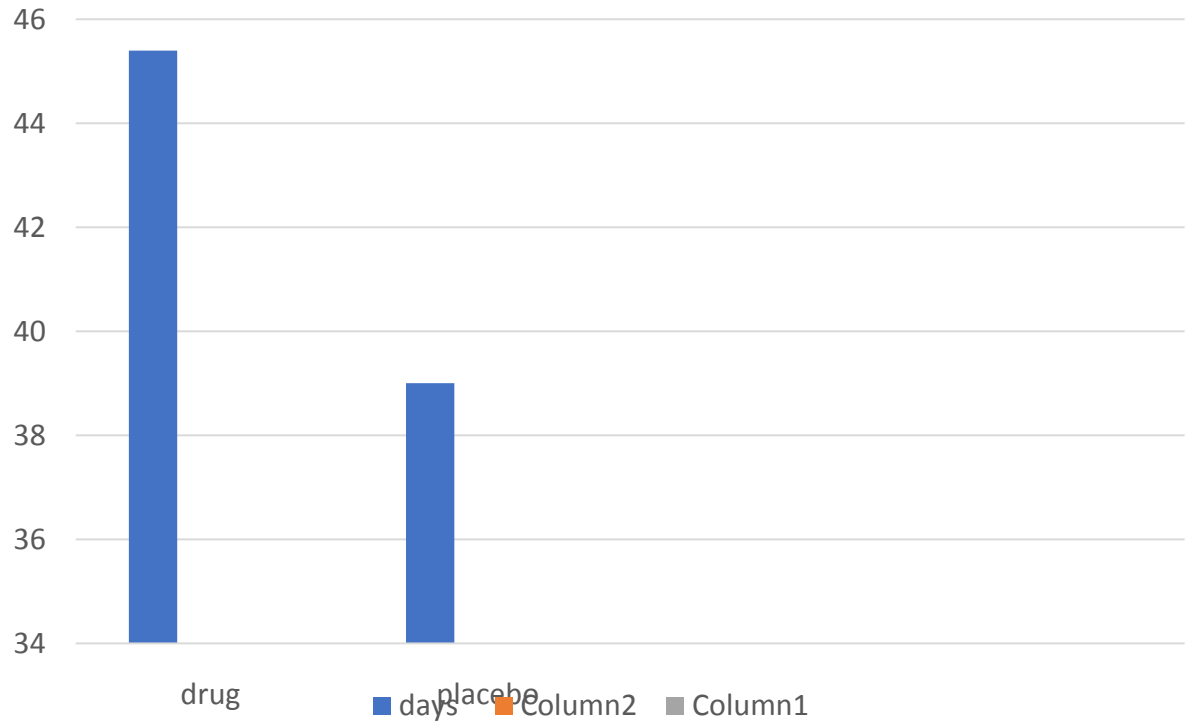
	Drug	Placebo
Sample proportion	0.83	0.3
Sample size	12	10
Significance level	0.05	
1 or 2 tailed test	1 tailed	

	Drug	Placebo	Difference
Sample proportion	0.83	0.3	0.53
95%CI	0.6516- 1.0084	0.0616-0.5384	0.1835-0.8765
Z value	2.5		
P value	0.0059		
Intrepretation	Statistically significant		
Fisher test – p = 0.027421			



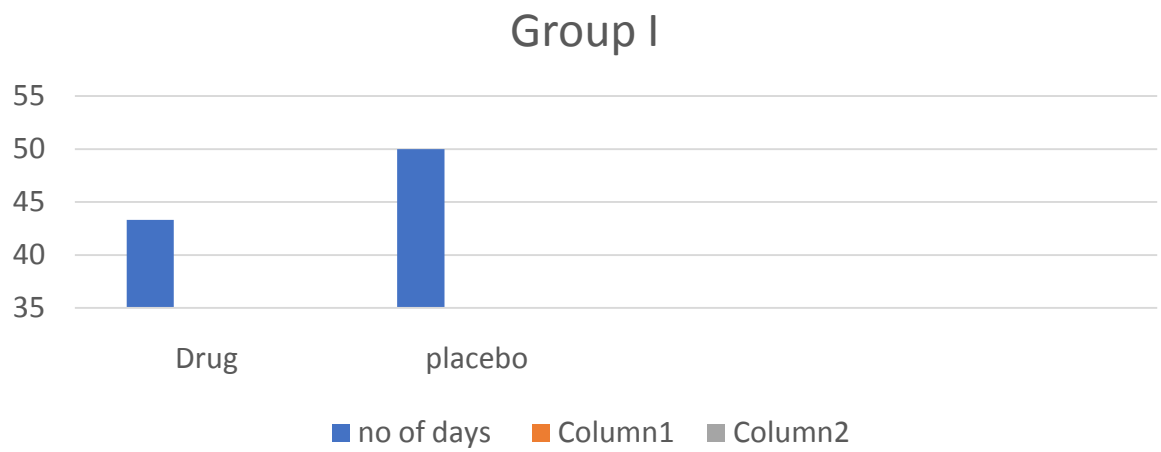
Mean healing time in completely healed ulcers (without dividing into groups):

Drug	**45.4 days**
Placebo	39 days



Healing time of ulcers that healed completely
Group I

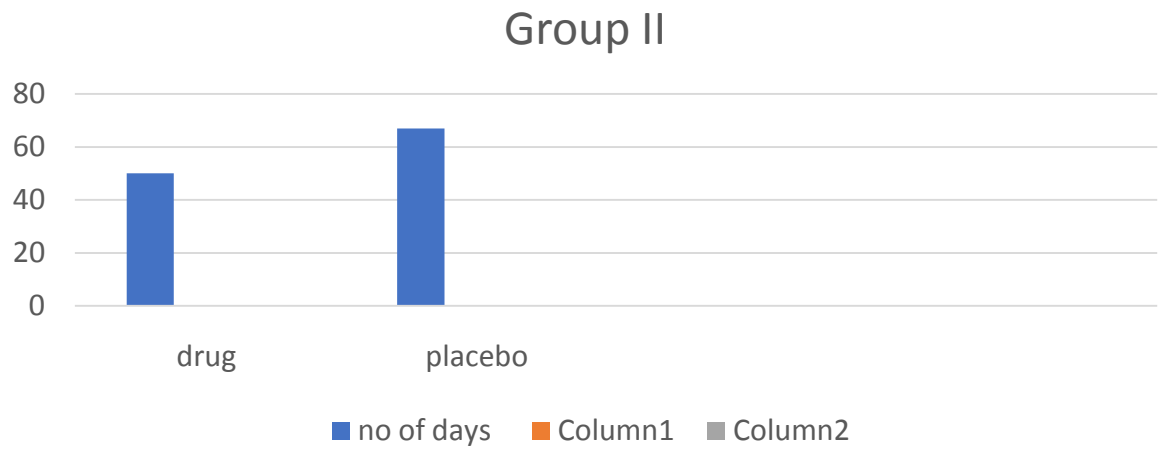
Drug	Placebo
80	24
29	26
21	
Mean =43.3	Mean =50



Healed time of ulcers that healed completely
Group II

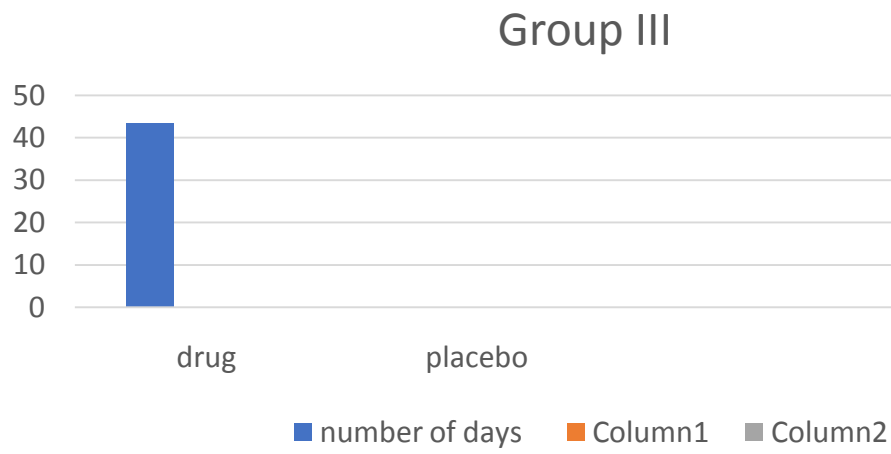
Drug	Placebo
71 days	67 days

58 days	
21 days	
Mean = 50 days	Mean = 67 days



Healing time of ulcers that healed completely
group III

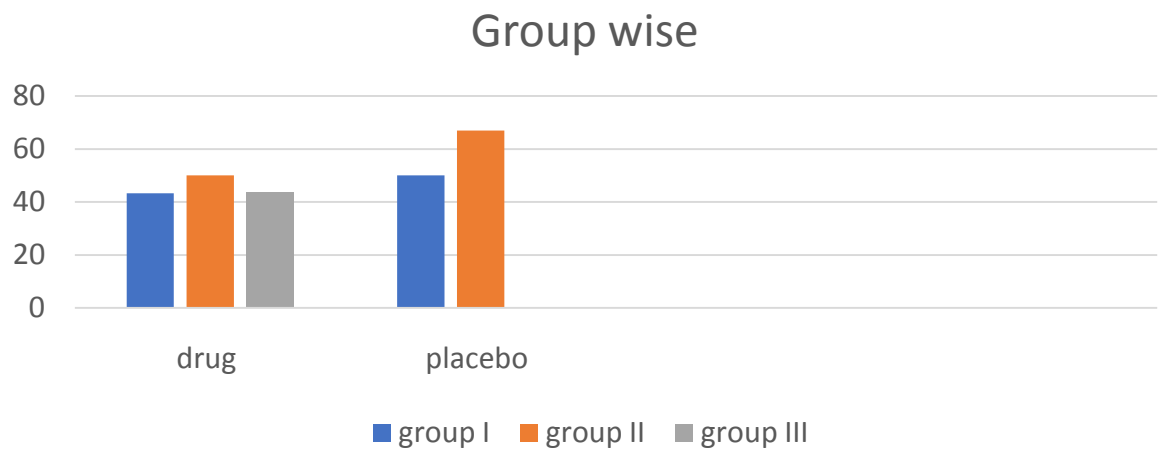
Drug	Placebo
21 days	--
79 days	
36 days	
38 days	
Mean = 43.5	Mean = 0
Completely healed ulcers = 50 %	Completely healed ulcers = 0%



Mean healing time for drug and placebo (group wise):

Group	Drug	Placebo
Group I	**43.3 days**	**50 days**

Group II	**50 days**	**67 days**
Group III	**43.5 days**	**0**



Safety evaluation and reasons for discontinuation from study

	Drug	Placebo
AE	**0**	**0**
SAE	**0**	**0**
Protocol violation	**0**	**0**
Missed two consecutive visits	**0**	**0**
Pregnancy	**0**	**0**
Non compliance	**0**	**0**
Patient request	**1**	**2**

Adverse events:

	Drug	Placebo
Local		
Pain	**0**	**0**
Redness	**0**	**0**
Itching	**3**	**0**
Skin necrosis	**0**	**0**
Wound discharge	**0**	**0**
Blisters	**0**	**0**
Vascular changes	**0**	**0**
Systemic	**0**	**0**
Fever	**0**	**0**

Headache	**0**	**0**
Sweating	**0**	**0**
Vomiting	**0**	**0**

IV. Discussion

- This is only a pilot study , only few similar studies on the role the rhEGF in healing of venous ulcers are published in literature so far .
- Falanga et.al , studied rhEGF on venous ulcer in 44 patients out of which 9 patients were excluded from the study due to protocol violation . Efficacy analysis was done in 35 patients . percentage of ulcers that healed completely

	Falanga et.al	**Present study**
Drug	**35%**	**83%**
Placebo	**11%**	**30%**

- Though the overall percentage of completely healed ulcers was higher in both studies , sample size is too small for definite conclusions to be made on the efficacy of the drug
- Another drawback in falanga et.al study is that ulcers were not divided into groups as per the size of ulcers as had been done in the present study
- Larijani et.al studied effect of EGF in 40 patients with diabetic ulcer as a single placebo controlled trial . After 4 weeks mean healing time was significantly faster in EGF group than placebo
- In linux et.al studies , it was found that rhEGF speeded up wound healing on second degree burns , chronic burn wounds , donor site of split skin grafting. Wound closure time was shorter than placebo in deep partial thickness burns wound
- In the present study with the use of rhEGF , a good number of venous ulcers healed completely (10 out of 12) with a reduction in mean healing time by 26 % in group II
- As regards the safety concerns and adverse reactions none of the patients in the study developed any serious adverse events. Only 3 patients in the drug group developed mild itching which subsided without any treatment .

Chronic wound:

- Chronic wound is that a wound failing to heal even after 4 weeks
- Decrease in wound size of at least 0.7mm per week is 80 % sensitive and specific for ultimate wound closure
- Less than 10% decrease in wound surface per month may empirically be a predictor of poor healing , although reliability and predictive values are missing

Rationale of use of growth factors :

- Growth factors are known to play significant roles in all phases of wound healing
- They bind to specific receptors in plasma membrane of target cells activating signal transduction mechanisms .
- Chronic wounds show deficient expression of growth factors

Mechanism of action of EGF:

- EGF is a single chain polypeptide consisting of 53 amino acids with molecular weight 6200 Daltons
- Six cysteine residues in sequence of EGF form three disulphide bonds which are required for EGF to be biologically active
- EGF trigger cell proliferation via signal transduction pathways invoving EGF-R , adapter proteins , Ras , Raf ,MAP kinases
- A number of in vivo models have extensively documented that EGF is involved in embryonic, fetal and neonatal development , differentiation .
- Other evidences clearly show that EGF is fundamental growth factor in maintaining tissue morphology and physiology in adult organisms
- It participates in cyto protection , cellular population renewal and epithelial healing

Clinical studies:

- Falangaetal (1992)
- Thomas DR (2001)
- Pastor JC (1992)
- Vajpayee etal (2003) – use of autologous serum eye drops to treat persistent defects in cornea with outstanding results confirming that EGF , which is present in serum ,plays an important role in healing of the defect .
- Tsubota and Kaniele (1992)- neuro paralytic keratopathy

V. Conclusions:

- Chronic venous ulcers is a ubiquitous problems of varied etiology . Chronic venous ulcers account for nearly 70 -90 % of them .
- Ulcer healing rates can be poor with up to 50 % of venous ulcer turning into non healing ulcers .
- Ulcer recurrence rates are also common in 1/3 patients
- Although several growth factors have been currently explored as potential wound healing agents – rhEGF , PDGF , TGF- b are widely used growth factors in healing of various ulcers .PDGF is the only FDA approved growth factor .
- Present study is a double blind randomized controlled study done on 25 patients with chronic venous ulcers of lower limb extremities and observed for a maximum period of 12 weeks for any appreciable results . Results of the study suggest that rhEGF increases the percentage of complete healing of ulcers and reduces the time for complete healing mainly in ulcer groups II & III . Moreover rhEGF had excellent safety profile and easy to apply
- The role of rhEGF in healing of other chronic leg ulcers was also explored , its role in healing of venous ulcers is a field of future research . Further , issues such as role of rhEGF on health care resources utilization and improvement in patients quality of life need to be addressed

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