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# **Original Research Article**

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# A comparative study on topical recombinant human epidermal growth factor vs conventional betadine dressing in management of diabetic wounds

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# **ABSTRACT**

**Background:** Major complications of diabetes mellitus include cardio vascular disease, chronic kidney disease, diabetic foot ulcers and non-healing wounds. Lack of knowledge and awareness has led to worsening of wounds which can involve deeper tissues and bones also. If treated on time majority of patients can be prevented from undergoing major debilitating surgical procedures such as amputation of toes, foot etc.

**Methods:** In this proposed study, 60 cases of diabetic wounds were studied for healing who were randomly allocated into two groups of 30 patients each. Group A included topical recombinant epidermal growth factor (EGF) application and group B included conventional Betadine dressing for wound healing.

**Results**: Anaemia had a significant role in delaying wound healing in group B patients. Blood sugars had no significant role in delaying wound healing in this study as patients in group A had mean FBS more than group B and still the wound healing was observed better in group A patients. Topical recombinant EGF resulted in faster wound healing than conventional dressings in diabetic wounds. 90% wound healing rates were seen with topical EGF dressings in comparison to 36.67% in conventional betadine dressings. Signs of wound healing i.e., early granulation, decreased discharge, early wound closure were seen faster in group A. Moreover, all patients in group A showed healthy granulation tissue by the end of our study.

**Conclusions**: We concluded that topical recombinant EGF resulted in faster and better wound healing than conventional betadine dressing.

Keywords: EGF, Betadine, Diabetic wounds, Human recombinant EGF, Granulation, Wound discharge

# INTRODUCTION

Wound is called any tissue, soft tissue, bone or any internal organs disruption.

An ulcer is an epithelial lining continuity disturbance or split, which may be skin, mucous membrane or others. An ulcer is one of the types of wounds. The treatment of the wound has been ideal since ancient times. Speedy recovery with minimal scarring and best function is ultimate aim of wound healing. Wound healing is a

multifaceted approach and has been the topic of focused study for a long time.

The main pathology is often in trauma, roadside injuries, stab wounds, battle wounds, bites and burn wounds. In humans, tissue regeneration is restricted and only the liver and epithelium can regenerate. Most of the other tissues grow by repair, which results in a scar. Wounds expose patients to multiple risks, such as infection, tissue damage, scar disfigurement and disability. Wound and their management are fundamental in the practices of

surgery and it is the surgeon's task is to minimize the adverse effects of injuries, remove or repair the damaged structure and hasten the process of wound healing to restore the function.

# Wound healing

It is a dynamic technique in which the functional & anatomical integrity of the tissue is achieved. Various elements, such as macrophages, lymphocytes, fibroblasts, collagen, are involved in the healing process in a coordinated manner.

Haemostasis  $\rightarrow$  inflammation  $\rightarrow$  proliferation  $\rightarrow$  matrix synthesis (collagen and proteoglycan ground substance)  $\rightarrow$  maturation  $\rightarrow$  remodelling  $\rightarrow$  epithelialisation  $\rightarrow$  wound contraction (by myofibroblasts).

# Factors affecting wound healing

#### 1. Patient specific\endogenous factors

*Age:* Healing is better in children and young adults, slows down in geriatric age group.

*Nutrition:* Healing is prolonged in anaemic, malnourished and weak patients having hypoproteinaemia.

*Diabetes:* Poor glycemic control results in lessened inflammatory response, neovascularization and collagen synthesis therefore delaying healing.

Obesity: Has an adversative effect on wound healing.

*Chronic diseases:* Cause wasting thereby leading to poor wound healing.

Jaundice and uremia: Badly affect wound healing.

Malignancy: Is expected to delay wound healing.

*Immunosuppression:* Patients on immunosuppressive agents have delayed wound healing.

# 2. General factors

There are numerous factors like time/duration of surgery, emergency procedures, contamination, poor tissue perfusion, microbial infection etc. affecting the wound healing.

# 3. Local factors

*Blood circulation:* Wound heals well in areas with rich tissue vascularity while in areas with low vascularity it is delayed.

*Tension and oedema:* Undue tension during suturing and oedema hampers wound healing.

*Infection:* Decreased synthesis of collagen is the most important causative agent for wound dehiscence in local infection.

### 4. Microbes associated factors

Dirtier the wound, the greater the risk of being infected.

The foot is the most common site for complications in patients with diabetes associated with limb-threatening ischemia. The main causes of hospitalization are tissue necrosis in the feet, leading to ulceration and inflammation in patients with diabetes. Signs of infection are less likely to be seen in these lesions since people with diabetes do not have a typical inflammatory response to infection.

Awareness of the microbial aetiologies of DFIs is essential to the successful management and treatment of DFIs, including antibiotic therapy, and to the study of resistance in DFIs<sup>1</sup>. A number of species, such as aerobic and anaerobic bacteria, maybe colonized with DFIs. However, antimicrobial treatment is not recommended unless a suspected or established infection can occur. <sup>2</sup>

In patients with early stages of superficial infections, gram-positive cocci like staphylococcus aureus and streptococci are the most common isolated organisms. Patients with long-standing infected wounds, necrosis, gangrene and continuous use of antibiotics have mixed microbial causes. Several microorganisms might be isolated from these patients at the same time such as Gram-positive cocci (e.g., *Peptostreptococcus spp.*), Gram-negative rods (e.g., *Escherichia, Proteus and Klebsiella sp.*), non-fermenting gram-negative bacteria (*Pseudomonas aeruginosa*) and anaerobes (*Bacteroides*), Methicillin-resistant *staphylococcus aureus* (MRSA) was the most resistant pathogen.<sup>3,4</sup>

DFIs caused by MRSA are associated with worse outcomes than DFIs caused by *Staphylococcus aureus* (MSSA) or other pathogens that are susceptible to methicillin.<sup>5</sup>

Involvement of the foot affects superficial and deep tissues which can, later on, involve bones also resulting in gangrene of toes or fingers, ultimately leading to amputation. More than 15% of foot ulcers result in lower limb or foot amputation.<sup>6</sup> With a prevalence of 65.1 million, India holds second place in the world. In India, around 2.4% of the rural and 12-17% of the urban population have diabetes. 15-20% is the estimated risk of developing diabetic foot ulcers in a patient's life span. The rate of amputation can be reduced to 49-85% by a combination of approaches. Diabetes is the leading cause of non-traumatic lower limb amputations which is often preceded by a non-healing ulcer.<sup>7</sup>

Dressing form an essential part of ulcer treatments among different wound-healing management procedures.<sup>8</sup> It is

generally assumed that an ideal wound dressing should: to promote the proliferation and migration of keratinocytes and fibroblasts and to boost collagen synthesis, to give a humidified and wet wound-healing environment. Have the capacity to provide gas exchange and thermal insulation. Be biocompatible, nontoxic and non-allergenic. Should be able to protect the wound from other secondary infections. Be easily removed without producing any further trauma. 11,12

## Topical epidermal growth factors

EGF is a 53 amino acid polypeptide that was first isolated from mouse salivary gland by Stanley Cohen in 1962 as part of his Nobel prize winning work with growth factors.<sup>13</sup>

The growth factor family comprises of 4 proteinsepidermal growth factors, TGF-alpha, heparin binding epidermal growth factors (EGF) and amphiregulin

Epidermal regeneration is a process in which residual epithelial cells proliferate in an integrated manner to regenerate the intact epidermis. These factors stimulate RNA, DNA and protein formation in many cell types. It first binds with high affinity to specific cell surface receptors and then induces their dimerization, which is essential for tyrosine kinase in the receptor cytoplasmic domain, starting signal transduction that leads to DNA formation and cellular division. It also stimulates keratinocyte division and epidermal regeneration. It also helps by acting on mesenchymal cells by producing a marked proliferation of the dermis. They also stimulate fibroblast motility. 14,15 EGF has mitogenic effects on the epithelial, endothelial, and mesothelial cells and has the following effects: Hastens re-epithelialization, boosts the proliferation and tensile strength, and upgrades the longterm effects on wound healing.

# Effects of EGF

Acts as a mitogen for the epithelial cells, endothelial cells and the macrophages, helps in epithelialization. Promotes angiogenesis, Up-regulates the secretion of collagen, Stimulates the proliferation of fibroblasts. Aids in scarless wounds healing and Encourages the rate of formation of the granulation tissue and enhances the healing of wounds.

### Mechanism of action

Phosphate which helps in the communication of the signal is denoted as "P". EGF binds with EGFR. Phosphate activates the MAPK pathway which enters the cell nucleus leading to DNA transcription and is finally expressed as protein.

On the surface of the cell, the epidermal growth factor receptor (EGFR) has an intrinsic cytoplasmic protein tyrosine kinase domain, a transmembrane domain, and an

extracellular domain that when bound by the EGF, leads to dimerization and auto-phosphorylation of the EGFR, which in turn activates the pathway of microtubule-associated protein kinase (MAPK), currently known as the' mitogen-activated protein kinase. <sup>16</sup> The transcription factors are phosphorylated and the activation of signal transduction contributes to a wide range of biochemical changes, including an increase in intracellular calcium due to the activation of protein kinase C, protein synthesis, and increased glycolysis, which eventually leads to DNA synthesis and cell proliferation.

# Betadine/povidone iodine

Povidone-iodine is a stable chemical complex of polyvinyl-pyrrolidone.

It is an iodinated polyvinyl polymer used as topical antiseptic in surgery and for skin and mucous membrane infections. This unique complex was discovered in 1955 at the industrial toxicology laboratories in Philadelphia by H. A. Shelanski and M. V. Shelanski. It may be used both to disinfect the skin of the patient and the hands of the healthcare providers. It may also be used for minor wounds. It may be applied to the skin as a liquid or a powder.<sup>17</sup>

#### Uses

Used as first aid for minor wounds and abrasions. As a cleansing material pre- and post-surgery. Various gynecological infections like trichomonas, candidiasis and bacterial vaginosis in form of 7-10% spray. A buffered solution of 2.5% concentration is used for treatment of neonatal conjunctivitis caused by Neisseria or Chlamydia. Used as a gargling agent for sore-throat when mixed with water

# Mechanism of action

The biocidal effect of iodine is due to its ability to react with various functional groups e.g. -OH, -NH2, -SH and carbon-carbon double bonds of unsaturated fatty acids. These reactive groups have essential functions in the metabolic processes of the target organisms such as bacteria and yeasts. These metabolic processes are interrupted by the binding of iodine and the microorganisms are thus inactivated.

The microbicidal properties are because of the release of elemental iodine. The determining factor for the microbicidal effect is not only the free iodine concentration in the solution but more importantly the free iodine concentration at the cell wall (the site of action) of the target organisms. The povidone binds rapidly and firmly to the cell walls and ensures that the free iodine is transported to the site of action.

The present study was performed to compare the effects of recombinant epidermal growth factors vs conventional betadine dressing in the treatment of diabetic wounds. The final results of this study are based on the appearance of wounds and other signs of wound healing like granulation tissue, discharge on the wound surface and swab culture sensitivity on every regular follow-up study after every two weeks till the end of the eighth week.

# **Objectives**

To study the effect of recombinant epidermal growth factor in the management of diabetic wounds. To study the effect of conventional betadine dressings in the management of diabetic wounds. To study the comparative effects of epidermal growth factor over conventional betadine dressings in management of diabetic wounds.

#### **METHODS**

The randomised single blind study was done on consecutive 60 patients of DFU admitted in Sri Guru Ram Das institute of medical sciences and research, Vallah, Amritsar from April 2019 to August 2020. Patients were divided into two groups of 30 each. In both groups, debridement was done first. One group was treated with conventional betadine dressings. The other group was treated with recombinant topical growth factors. Wounds were cleaned with normal saline first followed by local application of growth factors at wound margins. The wound was examined for decrease in size, granulation tissue appearance and discharge on wound surfaces. Follow up was done every 2 weeks till the 8th week and results will be compared in both the groups. Randomization was done by doing betadine dressing to first five patients and the next five patients were treated with recombinant epidermal growth factor topically. Thus, batches of five were given drugs alternatively till the target count of 30 patients each is met in both groups.

Statistical method and data collected was analysed using SPSS 23.0 and unpaired T test.

#### Inclusion criteria

Inclusion criteria included all the patients more than eighteen years and patients of both sexes, patients admitted in the department of general surgery, medicine and orthopaedics in SGRDIMSR and patients with diabetic wounds and foot ulcer conditions, wound size up to 10x10 cm.

# Exclusion criteria

Exclusion criteria excluded patients less than 18 years, patients with significant co morbidities like liver cirrhosis, patients with malignancies etc, patients positive for HBsAg, HCV and HIV, patients on steroids, immunosuppressive agents, radiation, or chemotherapy and patients who cannot report for the regular follow up.

Bias would be removed by single blinding of the study. Patients would be unaware of the dressing being done on them and results would be collected by the interviewer.

# Ethical approval

Ethical approval was taken from the institutional ethical committee.

#### **RESULTS**

Out of 30 patients in group A, 4 patients were of the 30-40-year age group, 8 patients were in 41-50 years, 6 patients were in 51-60 years, 9 patients were in 61-70 years and 3 were >70 years. In group B, only 1 patient was 30-40 years, 7 patients were in between 41-50 years, 7 patients were in 51-60 years group, 9 patients were in 61-70 years and 6 were >70 years old. The mean age is lower (55.03±11.42) in group A than in B (60.53±12.18). The data is not statistically significant as p>0.076.

Table 1: Age distribution.

Age group	EGF (A)		Beta (B)	dine	Total	
(years)	No.	%	No.	%	No.	<b>%</b>
30-40	4	13.33	1	3.33	5	8.33
41-50	8	26.67	7	23.33	15	25.00
51-60	6	20.00	7	23.33	13	21.67
61-70	9	30.00	9	30.00	18	30.00
>70	3	10.00	6	20.00	9	15.00
Total	30	100.00	30	100.00	60	100.00
Mean age	55.03±11.42		60.53±12.18		57.78±12.03	

P value=0.347

The study showed that mean FBS is higher in group A as compared to group B. The data is statistically insignificant asp >0.05.

Table 2: FBS levels.

Cwarm	FBS			
Group	Mean	SD		
EGF (group A)	206.33	68.49		
Betadine (group B)	182.57	55.07		
Total	194.45	62.77		

P value=0.114

Table 3: Haemoglobin levels.

Chann	Haemoglobi	n	
Group	Mean	SD	
EGF	10.57	1.80	
Betadine	9.38	1.57	
Total	9.98	1.78	

In Table 3, mean Hb levels in group A was 10.57 as compared to 9.38 in group B. The data showed statistical significance as p<0.005.

In Table 4, group A, the initial wound size was  $22.49\pm21.06$ . In group B, the initial wound size was  $49.52\pm25.32$ . After 8 weeks, the wound size was  $5.07\pm1.62$  and in group B, the wound size was  $10.47\pm7.71$ .

At 2 weeks, size reduction in group A was 41.35 and 17.22% in group B. At 8 weeks, 97.77% reduction in wound size and 86.61% in group B. This showed that wound size reduction is insignificant in the first 2 weeks of follow up and at week 4, 6 and 8, mean wound size reduction is significant in group A as compared to group B in the same time period.

In Table 6, At the end of study (week 8), 27 wounds had healed in group A as compared to 11 in group B. 90% wounds healed in group A as compared to 36% group B.

At presentation, 23 out 30 in group A have discharge present on the wound as compared to 29 in group B. After 8 weeks, group A have 27 patients with healed wounds and no discharge was present on the wounds of remaining 3 patients. In group B, 11 wounds healed and 3 patients out of remaining 19 still have discharge present.

At presentation, 14 out of 30 patients in group A and 5 out of 30 patients in group B had granulation tissue

present on the wound surface. After 2 weeks, group A only had 1 wound healed completely and 27 patients out of the remaining 29 presenting with granulation tissue. In group B, only 10 out of 30 patients presented with granulation tissue. After 4 weeks, group A patients had 10 wounds healed and the remaining all 20 patients showed granulation tissue. In group B, only 1 wound had healed and 23 out of the remaining 29 patients presented with granulation tissue.

After 8 weeks, 27 patients in group A had completely healed wounds and the remaining 3 patients also showed granulation. Similarly, in group B, 11 wounds healed completely and the remaining 19 patients showed granulation tissue.

Micro-organisms isolated from all the wound surfaces of the patients showed different results. Based on culture reports, suitable antibiotics can be administered to the patients to facilitate wound healing. In study, we found swab cultures were sent from the wound site at every two weeks follow up. Most common pathogens isolated were *E. coli* (26.27%), *Staphylococcus aureus* (13.33%) and *Acinetobacter species* (11%). Out of 30, no growth was seen in 10% of patients in group A being treated with EGF dressings as compared to 0% in group B.

EGF (group A) Betadine (group B) Wound size at P value Mean SD Mean SD 0 week 22.49 21.06 49.52 25.32 0.001 2<sup>nd</sup> week 16.65 15.86 41.99 23.20 0.001 4th week 9.54 10.85 29.76 20.30 0.001 6th week 6.05 5.45 21.29 14.31 0.001 8th week 5.07 10.47 0.001 1.62 7.71

Table 4: Wound size.

Table 5: Percentage reduction in wound size difference.

Wound size difference	EGF (A)			Betadine	Davolaro		
would size difference	Mean	SD	% reduction	Mean	SD	% reduction	P value
Initial-2 <sup>nd</sup> week)	9.30	6.98	41.35	8.53	4.84	17.22	0.620
Initial-4 <sup>th</sup> week)	16.13	12.27	71.20	20.76	12.24	41.92	0.150
Initial-6 <sup>th</sup> week)	20.28	17.39	90.17	31.78	17.06	64.17	0.012
Initial-8 <sup>th</sup> week)	21.99	20.10	97.77	42.89	23.09	86.61	0.001

Table 6: Number of wounds healed.

Wound hooling	EGF (A)		Betadine	e (B)	Total	Total	
Wound healing	No.	%	No.	%	No.	%	
0 week	0	0.00	0	0.00	0	0.00	
2 <sup>nd</sup> week	1	3.33	0	0.00	1	1.67	
4 <sup>th</sup> week	10	33.33	1	3.33	11	18.33	
6 <sup>th</sup> week	19	63.33	5	16.67	24	40.00	
8 <sup>th</sup> week	27	90.00	11	36.67	38	63.33	

Table 7: Discharge status.

Dischause of	EGF		Betadine		Total		Danilar
Discharge at	No.	%	No.	%	No.	%	P value
0 week							
No	7	23.33	1	3.33	8	13.33	<b>V</b> 2. <b>5</b> 102.
Yes	23	76.67	29	96.67	52	86.67	X <sup>2</sup> : 5.192;
Healed	0	0.00	0	0.00	0	0.00	df: 2; p=0.023
2 <sup>nd</sup> week							
No	17	56.67	3	10.00	20	33.33	<b>V</b> 2. 16 56.
Yes	12	40.00	27	90.00	39	65.00	X <sup>2</sup> : 16.56;
Healed	1	3.33	0	0.00	1	1.67	df: 2; p=0.001
4 <sup>th</sup> week							
No	17	56.67	6	20.00	23	38.33	<b>v</b> 2. 20.00.
Yes	3	10.00	23	76.67	26	43.33	$X^2$ : 28.00;
Healed	10	33.33	1	3.33	11	18.33	df: 2; p=0.001
6 <sup>th</sup> week							
No	11	36.67	13	43.33	24	40.00	X2. 22.00.
Yes	0	0.00	12	40.00	12	20.00	$X^2$ : 23.00;
Healed	19	63.33	5	16.67	24	40.00	df: 2; p=0.001
8 <sup>th</sup> week							
No	3	10.00	16	53.33	19	31.67	<b>v</b> 2. 10.62.
Yes	0	0.00	3	10.00	3	5.00	X <sup>2</sup> : 18.63;
Healed	27	90.00	11	36.67	38	63.33	df: 2; p=0.001

**Table 8: Granulation tissue.** 

Granulation at	EGF	EGF		Betadine			P value
Granulation at	No.	%	No.	%	No.	%	- r value
0 week							
No	16	53.33	25	83.33	41	68.33	X <sup>2</sup> : 6.239;
Yes	14	46.67	5	16.67	19	31.67	df: 2; p=0.012
Healed	0	0.00	0	0.00	0	0.00	u1. 2, p=0.012
2 <sup>nd</sup> week							
No	1	3.33	20	66.67	21	35.00	— X/2 22 141
Yes	28	93.33	10	33.33	38	63.33	$X^2$ : 33.141;
Healed	1	3.33	0	0.00	1	1.67	df: 2; p=0.001
4 <sup>th</sup> week							
No	0	0.00	6	20.00	6	10.00	— X <sup>2</sup> : 13.573;
Yes	20	66.67	23	76.67	43	71.67	df: 2; p=0.001
Healed	10	33.33	1	3.33	11	18.33	— u1. 2, p=0.001
6 <sup>th</sup> week							
No	0	0.00	0	0.00	0	0.00	V2. 12.611.
Yes	11	36.67	25	83.33	36	60.00	$-X^2$ : 13.611;
Healed	19	63.33	5	16.67	24	40.00	df: 1; p=0.001
8th week							
No	0	0.00	0	0.00	0	0.00	X <sup>2</sup> : 18.373;
Yes	3	10.00	19	63.33	22	36.67	df: 1; p=0.001
Healed	27	90.00	11	36.67	38	63.33	ur. 1, p=0.001

# **DISCUSSION**

The commonest causes of foot ulcers in people with diabetes are peripheral neuropathy (nerve damage), foot deformity, external trauma, peripheral vascular disease, and peripheral oedema. Other significant risk factors include being over 75 years of age, use of insulin, poor

psychosocial status, hyperkeratosis (thickening of the outermost layer of skin), macrovascular and microvascular complications, and duration of diabetes. <sup>19</sup> Uncontrolled diabetes with foot lesions are most common cause for lower limb amputations in India. Around 90,000 lower limb amputations are done yearly as a result of non-traumatic diabetic foot lesions.

In our study, patients of different age groups were included in both groups. Group A had most patients in the 61-70 years age group. In group B, maximum numbers of patients were also in the 61-70 years age group. Mean age group in group A was 55.03±11.42 and in group B mean age is 60.53±12.18 so age distribution is almost comparable in both groups.

Mendoza et al studied that with regard to age, a linear increase in the frequency of disruption with age was found. No linear correlation was seen till the age of seventy.<sup>20</sup>

Holt et al studied the effect of wound healing on old and young volunteers. They noted that there was a significant delay in epithelisation by 1.9 days in volunteers who are of 70 years or more age as compared to young healthy volunteers.<sup>21</sup>

Reed reported that people of elder group are at a greater risk of developing foot ulcers and more susceptible to abscess and osteomyelitis. <sup>22,23</sup>

In our study, in group A, 16.67% were females and 83.33% were males whereas in group B, 26.67% were females and 73.33% were males. Male sex predisposition is more as males are more involved in outdoor activity and workplace traumas. The incidence of smoking and alcohol intake is more in males as compared to females. This can also be a factor for males having more associated co-morbidities which can further lead to poor epithelial circulation, damage and decreased wound healing rates.

Despite mean FBS being more in group A as compared to group B, the response to treatment was better seen in group A in terms of wound healing, granulation tissue and discharge from the wound.

Park et al performed a study in chronic diabetic wounds to assess the safety and effectiveness of a recombinant human epidermal growth factor spray (0.005% rhEGF) in comparison with saline spray. The previous group was noted to have substantially full wound healing irrespective of blood sugar levels and Hba1c status.

The data shows that the reduction in wound size in group A is significantly more as compared to group B only after 2 weeks of treatment. In our study, by the end of 8th week, 90% patients in group A had completely healed wounds in comparison to 36.67% patients in group B.

In a study conducted by Hong et al, patients with chronic diabetic wounds were treated with hydrocolloid dressings and 68 patients were crossed over with EGF dressings. Patients who were crossed over showed improved healing rates as compared to patients receiving hydrocolloid therapy alone.<sup>24</sup>

In our study, the mean reduction in size of the wound by  $8^{th}$  week is  $5.07\pm1.62$  in group A and in group B, wound size was  $10.47\pm7.71$  (p value<0.005).

Singla et al did a study where EGF treatment showed decreased discharge, decreased wound soakage and early granulation tissue production. After 8 weeks, 80 % of the patients showed complete response to EGF application. Whereas in control group only 35% of the patients showed complete response. <sup>25</sup>

#### Limitations

Further studies with large sample size are needed. Only diabetic foot ulcer patients were studied.

#### **CONCLUSION**

We conclude from our observations that topical recombinant human EGF dressing is a better, faster tool in comparison to conventional betadine for the healing of diabetic wounds. We highly recommend topical EGF treatment over conventional betadine dressings in patients with diabetic wounds.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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