Efficacy of topical recombinant epidermal growth factor as compared to Povidone Iodine on chronic diabeic foot ulcers

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Abstract

Background: Diabetic foot ulcer is a common surgical complication in patient of diabetes mellitus. It is the most frequent reason for hospitalization for patients with diabetes. Still the ideal material for dressing is not known. This study has been conducted to compare the efficacy of topical application of Povidone- Iodine with recombinant epidermal growth factor in chronic diabetic foot ulcers of size 5 to 10 cm^2.**Methods:** Diabetic foot ulcers which were non-healing for more than 3 months were randomized into two groups of 30 each. Clinical examination of the ulcer and limb was done. Ischemic ulcers, ulcers with gangrene or associated osteomyelitis were excluded. One group had received Povidone iodine (Betadine 10% solution) soaked dressing while other group was dressed with Recombinant Epidermal Growth Factor gel (Eugraf 150 mcg gel) dressing twice weekly for 12 weeks. At the end of twelve weeks ulcers were assessed for healing. .**Results:**There were total 60 cases from Jan 2014 till Dec 2014. Age range from 45 to 70 yrs (mean age 55 yrs). There were 45 males and 15 females (M: F: 3:1). The ulcers were developed most commonly in foot in 48 patients (80%) followed by in lower leg around ankle in 06 patients (10%) and in 10 % of cases involved foot and leg both. Six (20%) patients on Povidone- Iodine dressing group showed complete wound healing while 23 (76%) patients on recombinant epidermal growth factor dressing group showed complete wound healing. Dressing with recombinant epidermal growth factor is the more effective than Povidone iodine dressing (P<. 001). Average healing time for complete healing for completely healed ulcers was 11 weeks in Povidone-Iodine Dressing and 8 weeks in Recombinant epidermal growth factor dressing group. **Conclusion:** Recombinant epidermal growth factor dressing is the significantly effective dressing in comparison to Povidone-Iodine in diabetic foot non healing ulcers of size 5 to 10 cm in size. Average time of complete healing of diabetic foot non healing ulcers is less with topical application of Recombinant epidermal growth factor soaked dressing as compared to Povidone – Iodine dressings.

Keywords: Diabetic foot ulcer, Dressing, Povidone-Iodine and recombinant epidermal growth factor.

Introduction

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Diabetic foot is defined as any inframalleolar wound in a person with diabetes mellitus. As different studies have showed that the up to 25 % of patient of diabetes needs hospitalization due to diabetic foot infections and it is the most frequent reason for hospitalization for patients with diabetes. Peripheral sensory neuropathy, trauma and foot deformity are the most commonly triad associated with this disease[1]. The prevalence of diabetes worldwide was estimated to be 2.8% in 2000 and 4.4% in 2030. The total number of patients with

diabetes increasing worldwide and estimated to rise from 171 million in 2000 to 366 million in 2030 and prevalence appears to be the increase in of people 65 years of age[2]. The prevalence of diabetic foot ulcer is 4-10% and the risk of developing diabetic foot infection during life-time in a diabetic is as high as 15% to 25%.[3].While 7% to 20% of patients with foot ulcers will subsequently require an amputation, foot ulceration is the precursor to approximately 85% of lower extremity of amputations in persons with diabetes. Diabetes continues to be the most common underlying cause of nontraumatic lower extremity amputations in the India[4]. Survival rates after amputation are generally lower for diabetic versus non diabetic patients[5] . Major factors responsible for DFU and amputation include com-promised blood supply due to peripheral micro vascular disease, with lack of sensation due to peripheral neuropathy and high blood sugar level. Both these factors in turn predispose to repetitive trauma and super imposed infection[6]. Almost 85% of the amputations are preceded by diabetic foot ulcers[7].In this modern era where we has started transplanting the body organs but still the management of of chronic wound remains a challenge for surgeons especially if associated with diabetes. Different types of dressing methods and material are available from decades but still the ideal method and material for non healing wounds is not known especially for diabetic foot infections. This study was conducted to compare the efficacy of Povidone iodine and Recombinant Epidermal Growth Factor (Eugraf) dressing in the treatment of chronic diabetic foot ulcers.

Materials and methods

Study design & duration
This prospective study was conducted in patients with diabetic foot ulcers presenting in OPD or admitted in the surgical ward in Rohilkhand Medical College and Hospital, Bareilly, U.P. during Jan 2014 to Dec 2014
Inclusion criteria
Diabetic foot ulcer (infra malleolar foot ulcers) not healing from past three months and size 5 cm to 10 cm. Only patients with type 2 diabetic mellitus were included.
Exclusion criteria
Patient presenting to hospital with gangrene of the toes or foot. Patients with vascular compromise of lower limb vessels documented by Colour Doppler study. Patients with osteomyelitis or associated fracture of bone on x ray. All patients with septic shock, diabetes keto-acidosis or associated serious co-morbidities needs emergency care were excluded.

Assessment and monitoring
 All the cases included in this study were investigated. Complete blood count, random blood sugar, post prandial blood sugar, HbA1c, renal function test, Colour Doppler of the lower limb for vascular evaluation and x-ray of the involved part were done to look for any evidence of osteomyelitis or fracture. Glycemic control was done by repeated blood sugar estimation and HbA1c estimation periodically. Culture of all the wounds were done at time of enrollment in the study and repeated if required and antibiotics were as per culture and sensitivity reports. Ulcers associated with dead and necrosed tissue or having pus flakes were taken up for wound debridement and wound was subsequent debridement was done if necessary as per clinical evaluation of the ulcer. The cases were randomized into two groups. Group I was given 10 % Povidone iodine solution (Betadine 10 % solution from Win medicare India) and Group II– Recombinant Epidermal Growth Factor (rEGF) (Eugraf from Lupin India, 150 mcg in 15 gm tube gel). In the beginning of the study, the wound size was measured with the help of gauge piece by cutting it approximately to the size of the wound and then placed over the graph paper. In all the patients, the wound was washed with normal saline and the specific agent dressing were applied without applying any local anaesthesia in the minor OT/ ward dressing room. Dressing was done twice weekly on indoor/OPD basis. In Group I (Povidone iodine dressing) a povidone- iodine soaked gauge piece, in the II group the rEGF gel was applied and left for 5 minutes and then saline moist gauge piece was placed over the gel and bandage was applied. In each group dressing was continued for 12 weeks. All the wounds were measured once weekly during the dressing time and final measurement done at the end of twelve weeks with the variation of max two days after exposing and cleaning wound. The difference between the initial and final measurement was taken into account for analysis of results.
Observations
Age distribution
Youngest patient was 45years old and eldest was 70 years old. Mean age was 55 years.
Duration of diabetes
 Duration of type 2 diabetes mellitus varied from one year to twenty five years. Mean duration of diabetes was 7 years. Five patients were diagnosed diabetes mellitus when they developed ulcers.
Sex distribution
 Total Male patients were 45 and female patients were 15. M: F: 3:1 Incidence was more common in males as

most of patients were from rural area and prone to trauma and secondary infections leading to diabetic foot ulcers as compared to females. Trauma is also more common in males leading to diabetic foot ulcer.

Location of ulcer

In this study, the lesions developed most commonly in foot in 48 patients (80%) followed by in lower leg around ankle in 06 patients (10%) and in 10 % of cases involved foot and leg both . This might be due to prevalence of rural populations working in agriculture fields, walk barefoot and neglect the early inflammation leads to secondary infection.

Ulcer size

Minimum ulcer size was 5 cm^2 and maximum was 10cm^2. Mean ulcer size was 7.2 cm^2. History of previous ulcer and amputation - forty five patients out of 60 (75%) had history of previous healed

ulceration and most of them had foot ulcer especially at the tip of toe. 10 (16.6%) patients had undergone amputation previously due to diabetic foot leading to gangrene either in the same limb or opposite limb. Three of the patients included in the study had amputated stump with surrounding ulcer not healing from few month.

Duration of ulcer

Minimum duration of ulcer was three months and maximum was two years. The mean duration of ulcer was 4.5 months. Precipitating factors of ulcer - The majority (50%) of foot lesions developed after trauma followed by infection in this study. In 40 % cases ulcers developed spontaneously without any apparent cause noticed by the person and in 10% cases, infected nail bed, fissures or cracks in foot was found to be precipitating factor.(table no 1)

Table 1 :showing precipitating factors of ulcers

Precipitating factors	Number of cases	Percentage
Spontaneous	24	40
Infected nail bed/Fissure	06	10
Trauma	30	50
Total	60	100

Culture and sensitivity report of the wound- In this study out of 60 patients, culture and sensitivity report was sterile in 36 patients (60%).. In 14 patients (23.3%) culture report was Staphylococcus, pseudomonas in5 patient (8.3%), proteus in 3(5%) patients and klebsiella in 2(3.3%). Two culture and sensitivity report came to be MRSA and one VRSA. (Table No 2)

Table 2: shows culture and sensitivity report

Culture report	Cases
Sterile	36
Staphylococcus	14
Pseudomonas	5
Proteus	3
Klebsiella	2

Healing with dressing: Six (20%) patients on Povidone iodine dressing group showed complete wound healing. Twenty three (76%) patients on rEGF dressing group showed complete wound healing. Dressing with recombinant epidermal growth factor is the more effective than Povidone iodine dressing (P<. 001)(Table No 3).

Table 3 : shows healing with specific dressing

	Povidine iodine group	Recombinant Epidermal Growth Factor (Eugraf)	P Value
Complete Healing	6	23	>.05
Complete Healing	6	23	<. 001
reduction in ulcer size > 50%	8	6	
non healing	16	1	

Time for complete healing – In Povidone Iodine Dressing - Average healing time for complete healing for completely healed ulcers was 11 weeks (SD 1.25). In rEGF Dressing - Average healing time for complete healing for completely healed ulcers was 8 weeks (SD 1.50)

Table 4: showing time of complete healing

Average healing time	Weeks
Povidone iodine group	11
Recombinant epidermal growth factor group	8

Results

Total 60 patients were included in this study. They were grouped randomly in two. In one group dressing was done by application of Povidone- Iodine solution over wound and in other with recombinant epidermal growth factor twice daily. Debridement of the wound done prior to the application of dressing material if needed and repeated if required. All the patients with diabetes mellitus type 2 with inframalleolar ulcer were included as per inclusion and exclusion criteria. The dressing was continued for 12 weeks and changes in the size of ulcer was noted. All the patients who underwent amputation during the study were excluded. Eight patients did not come regularly for dressing were also excluded.

Statistical analysis
The success of the treatment was determined by complete healing of the ulcer in twelve weeks of therapy. All the cases which do not achieve complete healing were categorized in two groups depending on their wound healing status. One group with more than 50% healing and other with less than 50% healing of the ulcer in 12 weeks therapy. The cases with less than 50% were considered non-healing while doing the calculation. The calculation done based upon null hypothesis. The endpoints of the comparable two groups at a time were done by Chi Square test and by calculation of odd ratio with 95 % confidence interval. P value < .05 was considered significant.

Discussion

India is the diabetic capital of the world[5]. We have significant number of the patients with diabetic foot ulcer reported to our hospital in last two years. Study included only patients with neuropathy, infection and both.
Age and Sex Distribution
Diabetes is the disease of old age. Mean age in our study was 55 years, which correlates with the studies done in India[8] but in western countries they have reported the mean age around 65 years[9,10].. Diabetic foot complications increase with the duration of diabetes. The study shows recurrent ulceration and multiple amputations common with long standing diabetes[11,12]. Present study also had similar

finding.In our study diabetic foot ulcers were seen more commonly in males as compared to females. Increase Incidence in males may be because they are exposed to external environment more as compared to females, which is prevalent in Indian society. Trauma is also more common in males leading to diabetic foot ulcer[13]. Repeated foot trauma may be due low socioeconomic state and barefoot especially in rural population as in this study, ill-fitting shoes, thorn prick may also be the contributing factor which was seen in other studies[14].The majority (50%) of foot lesions developed after trauma followed by infection in this study. In 40 % cases ulcers developed spontaneously without any apparent cause noticed by the person and in 10% cases, infected nail bed, fissures or cracks in foot was found to be precipitating factor. In study done by Khan et al, 68.33 % had history of trauma by thorn prick, shoe bite, nail prick, wood piece prick etc. which is similar to our study[15].A study done in Nigeria by Andrew et al showed that spontaneous blisters (32%) is most common precipitating factor followed by puncture injury (10 %) and trauma is causative factor only in 7% of cases of diabetic foot ulcers in their locality which may be due to different cultural and personal habits[14].. Reiber et al in their study in 1999 from among 92 study patients from Manchester and 56 from Seattle, found that neuropathy, minor foot trauma and foot deformity was present in more than 63% of patient's causal pathways to foot ulcers[15].Incidence of Involvement of the Parts of the Body : In this study, the lesions developed most commonly in foot (80%) followed by in lower leg around ankle (10%) and in 10 % of cases involved foot and leg both . This might be due to prevalence of rural populations working in agriculture fields and walk barefoot and neglect the early inflammation. Khan et al in 2016 in their study over diabetic foot ulcer found similar results. The most common site of lesion was toes found in 23 patients (38.33%) followed by dorsum of foot involved in 18 patients (30%) and whole foot involvement found only in 1 patient (1.67%)[13].
History of previous ulcer and amputation
 History of healed ulceration and amputation are important risk factor for diabetic foot ulceration[16]. In our study 45 patients had history of previous healed foot ulcers and 10 patients had amputation. In the study done by Madar Jk et al over diabetic foot also found

the incidence of recurrent ulcers and amputation was high in diabetes patients 71% and 32.9% respectively[17]. Duration of ulcer – Chronic wound in diabetic patients a common challenging problem as these ulcers often display suboptimal wound healing due to association with neuropathy and poor blood supply. These wounds will never heal unless the underlying disease and cause will be addressed properly. The early recognition of the high-risk patients and timely treatment may prevent foot ulcers, save limbs, potentially save lives, and improve patient QOL[18].These individuals often have a history of previous foot ulcer or lower limb minor or major amputation. The mean duration of ulcer in the present study was 4.5 months.

Etiology of ulcer

In this study, the lesions developed most commonly in foot in 48 patients (80%) followed by in lower leg around ankle in 06 patients (10%) and in 10 % of cases involved foot and leg both. Peripheral neuropathy was present in 60% of the patients with diabetic foot ulcers in all patients who had previous amputation. The pathological process was started in the inter digital spaces of toes in 06 patients in this study(10%). Traumatic ulcers most commonly started at tip of the toe due to mino injuries occurred during agriculture work and spread proximally due to inadequate treatment and infection control. Fifteen patients (25%) patients had deep ulcers on the heel and on plantar aspect at the level of head of first metatarsal and were associated with sensory loss in the foot. Risk factors for development of chronic wound in diabetic patients include peripheral neuropathy, peripheral vascular disease, limited joint mobility, foot deformities leading to abnormal foot pressures, minor trauma and history of previous ulceration or amputation[14].Many studies have also reported the combination of similar factors in patients with diabetic foot ulcers[16,19,20].

Bacteriology of diabetic foot

Diabetic foot is a frequent complication in patients with diabetes mellitus and the risk of this complication increases with duration of diabetes mellitus. Diabetic polyneuropathy is one of the commonly associated risk factor for development of diabetic foot which later on complicated by superadded bacterial and fungal infection and if not treated promptly may lead to amputation of the limb(Shankar et al). These infections are frequently polymicrobial[21]. On culture in this study most of the culture reports are sterile(60 %) which might be due to the cases treated previously by multiple antibiotics for longer duration. Forty percent of wound culture had grown micro organism out of which 50 % are polymicrobial.

Staphylococcus was the most commonly grown micro organism in 14 cases (58%) followed by pseudomonas in 5 patients(20.88%), proteus in 3 patient and klebsiella in 2 cases. Md Shakeel and Arshiya Taranum in their study over 50 cases also found Staph.aureus was the most common organism isolated from diabetic foot infections[22] Shankar et al in 2005 in their study also found that diabetic foot infections are polymicrobial in 68 % of cases. But in their study they found gram-negative bacteria (57.6%) were more commonly isolated than gram positive organism (42.3%), [23] The most frequent bacterial isolates were *Pseudomonasaeruginosa*, *Staphylococcus aureus*, coagulase-negative staphylococci (CONS), and Enterobacteriaceaes. About 44% of *P. aeruginosa* were multi-drug-resistant, and MRSA was recovered on eight occasions (10.3%). Ramakant et al in their study found that the most common pathogens in the first culture were Pseudomonas aeruginosa (20.1%), Staphylococcus aureus (17.2%) and Escherichia coli (16.3%)[24].Seesdharan et al[21] in their study, out of the total samples, 44.3% were monomicrobial and 55.7% were polymicrobial. Gram negative pathogens were predominant (58.5%). Seven of the total isolates were fungal; 0.7% showed pure fungal growth and 1.7% was mixed, grown along with some bacteria. The most frequently isolated bacteria were Staphylococcus aureus (26.9%), followed by Pseudomonas aeruginosa (20.9%)Dressings of diabetic foot ulcers are one important factor in the management of this patient group but in addition to dressing, good glycemic control, pressure reduction, appropriate antibiotic therapy and surgical debridement of the wound debridement is very important in healing of the wound and prevention of amputation of the limb. The use of anti microbial dressing may enhances the wound healing in diabetic foot ulcers as compared to non anti microbial dressings[25]. In this study 6 (20%) patients on Povdone- Iodine dressing shows complete wound healing and 23 (6.6%) patients on rEGF dressing shows complete wound healing. Dressing with recombinant human epidermal growth factor in chronic diabetic foot ulcers is the significantly effective in wound healing as comparison to Povidone- Iodine dressings (P<. 001). Singla et al in their study[26] on 25 patients found that the application of recombinant EGF shortens the wound healing time significantly and the mean closure was significantly higher in the EGF group as compared with placebo. The treatment with rEGF had an advantage concerning complete wound closure and the time to complete wound healing in many RCT, cost effective analysis and meta analysis included in the study done by Buchberger et al[27]. In 2012 study

done by Singla et al also reported better results with recombinant epidermal factor.

Conclusion

 In conclusion, this study supports the application of recombinant EGF application over chronic diabetic foot ulcers of size 5 to 10 cm^2 which is adequately debrided surgically, in addition to good foot care with a multidisciplinary team approach, enhances diabetic ulcer wound healing and significantly reduces the wound healing time as compared to Povidone- Iodine dressing. Further study is required to define the optimal dose and frequency of application of recombinant EGF over diabetic foot wound.

What this study add to existing knowledge
 After the eighth week of dressing, 80 % of the patients showed complete response to EGF application whereas in control group only 35 % of the patients showed complete response.EGF binds to its corresponding receptor on epidermal cell and fibroblast cell surface membranes in order to build collagenous tissue, and accelerate the generation of wound granulation and epithelial tissues, which accelerate the wound healing process[28]. It also stimulates wound matrix transformation, granulation tissue cell repopulation and angiogenesis evidenced on histological examination of the wound. Epidermal growth factor intralesional infiltrations can prevent amputation in patients with advanced diabetic foot wounds.[29]

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