To Compare the Efficacy of Betadine, Calcium Alginate and Recombinant Epidermal Growth Factor Dressing in Chronic Diabetic Ulcers

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Abstract: Diabetic ulcer is a common problem. No standard dressing is available. We have done this study to compare the efficacy of three types of dressings in chronic diabetic foot ulcers. Diabetic with non-healing for more than 3 months with saline dressing was randomized into 3 groups of 30 each. A thorough clinical examination was done to exclude ischemia and Xray to exclude osteomyelitis. Location of ulcer was noted. The wound size was measured by cutting a gauge piece to the size of the wound and placed over the graph paper. Group I received Betadine soaked gauge, II Calcium Alginate Fibers (Sorbalgon) and III Recombinant Epidermal Growth Factor gel (Eugraf 150 mcg gel) dressing minimum twice weekly, besides treatment of diabetes and co morbidities for 12 weeks. At the end of twelve weeks ulcers were assessed for healing. Calcium alginate is the significantly effective dressing in comparison to betadine and Eugraf. No significant difference in healing with Eugraf in comparison to betadine.

Keywords: Chronic diabetic ulcer, Dressing, Betadine, Calcium alginate, and Epidermal growth Factor

1. Introduction

The prevalence of diabetes mellitus is growing at epidemic proportions in the India and worldwide. India is known as Diabetic capital of the world. Foot disorders are a major source of morbidity and a leading cause of hospitalization for persons with diabetes. Ulceration, infection, gangrene, and amputation are significant complications of the disease, estimated to cost billions of dollars each year. Charcot foot due to diabetic neuropathy is another serious complication, in addition to diabetic foot ulcers, which is the leading precursor to lower extremity amputation in diabetic patients. Clinicians must determine how to more effectively prevent ulceration. Although not all diabetic foot disorders can be prevented, it is possible to effect dramatic reductions in their incidence and morbidity through appropriate evidence-based prevention and management protocols.

2. Aim, Objective & Methods

To compare the efficacy of Betadine, Calcium Alginate (Sorbalgon) and Recombinant Epidermal Growth Factor (Eugraf) dressing to treatment of chronic diabetic ulcers due to neuropathy, infection or both. Thirty patients were included in the study for each of the three dressings.

Inclusion criteria
1. Diabetic with ulcer not healing for three months.

Exclusion criteria
1) Patient presenting to hospital with frank gangrene of toes or foot.
2) Patients with vascular impairment leading to ulceration.
3) Doppler showing blocked or diminished flow in > 2 vessels.
4) Patients with radiologically proven osteomyelitis.

Diabetic with ulcer more than 3-month duration coming to our hospital were included in the study. After a thorough clinical examination, they were investigated. Besides the routine hematological, biochemical parameters for renal, liver function, USG Doppler for vascular evaluation and x-ray of the part were done to look for any evidence of osteomyelitis. Control of sugar was checked by blood sugar and glycoselated haemoglobin estimation periodically. The cases with gangrene of toes or foot indicating severe ischemia and osteomyelitis on plain X-ray were excluded from the study. Wound swab was taken for culture in all cases and antibiotics were given where necessary as per the sensitivity pattern. Good glycemic control was ensured by diabetic diet and adjusting the dosages of anti diabetic therapy used before by the patient, either insulin or oral hypoglycemic agent. Any cases having dead and devitalized tissue were taken up for wound debridement. And after the initial through debridement the dressings were started and subsequent debridement were done as and when requirement basis. The cases were randomized into 3 groups by sealed envelope method for different types of dressing Group I was given 5% Povidon iodine (Betadine from Lupin India) Group II – Calcium Alginate fiber (Sorbalgon 10 x 10 cm from Hartmann, Germany) and Group III – Recombinant Epidermal Growth Factor (rEGF) (Eugraf from Lupin India, 150mcg in 15 gm tube gel). At this stage the wound size was measured by cutting a gauge piece to the size of the wound and same was placed over the graph paper, which gives almost sq mm accuracy of total surface area of ulcer. In all the dressing the wound was cleaned initially with normal saline and the specific agent dressing were applied without any anaesthesia in the minor OT/ ward dressing room. Initially the dressing was done under the supervision by the guide and later after standardization by the author twice weekly on indoor/OPD basis. All the cases and their relatives were informed about the day and date of the next dressing and were told to come back as soon as the dressing become soaked till outer layer. In Group I (Betadine dressing) a betadine soaked gauge piece, in the II group Alginate fiber was in placed covering the wound and a dry gauge piece was applied over the wound. In the third group the rEGF gel was applied and saline moist gauge piece was
placed over the gel. All the three groups were then given loose bandage so as dressing medicament remain in place inside the covered wound. All the cases were advised to use covered foot-ware so as to avoid trauma and to keep the dressing in situ. Each case the same type of dressing was given for 12 weeks. All the wounds were measured twice 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 as done initially. The difference between the initial and final measurement was taken into account for analysis of results. The cost of twelve-week treatment was evaluated by including the cost of medicine, the sterile gauge piece and bandage. Manpower cost was not included.

Statistical Analysis – The end for the treatment was complete healing of the ulcer after twelve weeks of therapy. Sample size of 30 each was considered adequate. The non-healing group was divided as more than 50% healing and less than 50% healing. The 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 ChiSquare test and by calculation of odd ratio with 95% confidence interval. P value < .05 was considered significant

3. Results

Patients - Total 96 patients were recruited for the study. In one patient X-ray of foot was suggestive of osteomyelitis of first metatarsal and two had Doppler confirmed ischemia. These patients were excluded from the study. Two patients have to undergo amputation as they developed uncontrolled sepsis in Cal Alginate group. One patient lost follows up in Eugraf dressing group. Finally ninety patients were analyzed.

Age distribution - Youngest patient was 40 years old and eldest was 92 years old. Mean age was 62.22 years (SD 9.18 yrs).

Type of Diabetes mellitus - All were Type II Diabetes Mellitus.

Duration of diabetes – Duration varied from three years to thirty years. Mean duration of diabetes was 9.5 years (SD 5.07).

Sex distribution - Total Male patients were 57 and female patients were 33. M: F: 63:37(1.7:1).Incidence is more common in males as they are exposed to external environment more as compared to females. Trauma is also more common in males leading to diabetic foot ulcer. The main text for your paragraphs should be 10pt font. All body paragraphs (except the beginning of a section/sub-section) should have the first line indented about 3.6 mm (0.14”).

Addictions - Twenty-four patients out of ninety (26.6%) were active smokers/alcohol consumers during the presentation with ulcer. All the females were non-smoker.

Considering the males alone 42.1% were smokers. Any body that had stopped this habit six-month prior was not included.

Socioeconomic status -Nine (10%) patients belong to good socioeconomic strata(monthly income >20,000).

Location of ulcer - Most of the patients had ulcer on the foot (77/90 – 85%). Others had ankle, leg or sacral ulcer. Diabetic Ulcers are commonest on extremity as extremities are exposed to trauma. Shoe injuries also contribute to diabetic foot ulcer. Other contributing factors age microangiopathy, neuropathy, or combination of both. Studies have also proven these to be the etiological factors.

Ulcer size - Minimum ulcer size was 1 cm² and maximum was 35 cm². Mean ulcer size was 5.86 cm² (SD 5.62).

History of previous ulcer and amputation - Sixty-one patients out of ninety (67.7%) had history of previous healed ulceration and most of them had foot ulcer. Twenty-three (25.5%) patients had undergone amputation previously due to diabetic foot ulcer complication and all these patients had history of ulceration. Two of the alginate group requiring amputation during study was previous amputees.

Previous dressings - All patients were undergoing saline dressing prior to be included in study.

Duration of ulcer - Minimum duration of ulcer was three months and maximum was eight months. Mean ulcer duration was 4.2 months (SD 1.31).

Etiology of ulcer - Forty-two (46.6%) patients had ulcer of infective etiology started in inter-digital space and then spread proximally. Thirty-eight (42.2%) patients had ulcer of traumatic origin which patient did not noticed initially and get infected secondarily. Most of traumatic ulcers started at tip of the toe as patients were wearing proper footwear. Ten (11.1%) patients had pressure ulcers on the heel and on plantar aspect at the level of head of first metatarsal. These patients were either bed ridden or not using the proper footwear.

Systemic disease - 80 (88.9%) patients had associated systemic disease like Hypertension, Coronary Artery Disease or Chronic Kidney Disease. 21 (23.3%) patients had hypertension alone.40 (44.4%) patients had ulceration and most of them had foot ulcer. Twenty-three (25.5%) patients had undergone amputation previously due to diabetic foot ulcer complication and all these patients had history of ulceration. Two of the alginate group requiring amputation during study was previous amputees.

Doppler - In two patients clinical examination suggestive of critical limb ischemia, which was confirmed on Doppler. These patients were excluded from the study.

Wound Swab Cultures - In 58 patients (64.4%) wound swab culture was sterile. In 30(33.3%) cases wound swab culture grown Staphylococcus. In one patient each (2.2%) swab has grown Proteus and Citrobacter. Antibiotics were given only to the patients where culture was positive as per sensitivity.

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5 (17%) patients on betadine dressing shows complete wound healing. 24 (80%) patients on Cal Alginate dressing shows complete wound healing. 11 (36.6%) patients on Eugraf dressing shows complete wound healing. Calcium alginate is the significantly effective dressing in comparison to betadine and Eugraf (P<.001)(table No 2). No significant difference in healing with Eugraf in comparison to betadine (P>.05) (table No 2).

<table>
<thead>
<tr>
<th>Dressing</th>
<th>No of Patients</th>
<th>Complete healing</th>
<th>Reduction in sizes 50%</th>
<th>No healing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Betadine</td>
<td>30</td>
<td>5(17%)</td>
<td>7(23%)</td>
<td>18(60%)</td>
</tr>
<tr>
<td>Calcium Alginate</td>
<td>30</td>
<td>24(80%)</td>
<td>6(20%)</td>
<td>0</td>
</tr>
<tr>
<td>Eugraf</td>
<td>30</td>
<td>11(36.6%)</td>
<td>12(40%)</td>
<td>7(23.3%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Betadine</th>
<th>Eugraf</th>
<th>Cal Alginate</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non healing</td>
<td>25</td>
<td>19</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Complete healing</td>
<td>5</td>
<td>11</td>
<td>&gt;.05</td>
<td></td>
</tr>
<tr>
<td>Complete healing</td>
<td>5</td>
<td>24</td>
<td>&lt;.001</td>
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</table>

**Time for complete healing** – Betadine Dressing - Average healing time for complete healing for completely healed ulcers was 11.5 weeks (SD 1.00)

Eugraf Dressing - Average healing time for complete healing for completely healed ulcers was 10 weeks (SD 1.88)

Cal Alginate - Average healing time for complete healing for completely healed ulcers was 9.1 weeks (SD 2.42)

Cost of Dressing –

Average cost of Betadine dressing per patient over twelve weeks was Rs 787 (SD 57)

Average cost of Eugraf dressing per patient over twelve weeks was Rs 4886 (SD 1062)

Average cost of Cal Alginate dressing per patient over twelve weeks was Rs 1186 (SD226).

**Follow up** – Pts were followed up after 12 weeks of treatment with specific dressing type of dressing. In the patients where there was either sub optimal response or no response to the specific dressing had undergone skin grafting of Cal Alginate dressing. Patients later changed to Cal Alginate dressing where not included in study.

4. Discussion

**Patients** – India is the diabetic capital of the world. 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 62.5 years, which correlates with the other studies where they have reported the mean age around 65 years. Diabetic foot complications increase with the duration of diabetes. The study shows recurrent ulceration and multiple amputations common with long standing diabetes. 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. Repeated foot trauma due to ill-fitting shows my also be the contributing factor which was seen in other studies.

**History of previous ulcer and amputation** – History of healed ulceration and amputation are important risk factor for diabetic foot ulceration. In our study 67% patients had history of previous healed foot ulcers and 25% had amputation. This may be due to increase life expectancy with diabetes. Risk of amputation in patients with diabetic ulcer in our study group was 2.3%. Other studies has shown amputation rate varying from 2% to 16%.

**Duration of ulcer** – Long duration ulcers can lead to extensive tissue necrosis and gangrene, requiring amputation to prevent more proximal limb loss. This includes soft tissue infection with severe tissue destruction, deep space abscess, or osteomyelitis. The mean Duration of ulcer in the present study was 4.2 months. We had excluded the osteomyelitis cases. In spite of this we had 2 amputations (2.3%) during study period.

**Etiology of ulcer** - Risk factors include peripheral neuropathy, micro and macro angiopathy, limited joint mobility, foot deformities, abnormal foot pressures, minor trauma, a history of ulceration or amputation, and impaired visual acuity. This study had almost same risk factors except the macroangiopathy, which was excluded from the study by using Doppler. 46.6% patients had ulcer of infective etiology started in inter-digital space and then spread proximally. Nonhealing wounds can become stuck in the inflammatory phase of healing, increasing cytokine response with subsequent elevatedprotease levels and impaired growth factor activity. Present study has not done any evaluation of growth factors. 42.2% patients had ulcer of traumatic origin which patient did not noticed initially and get infected secondarily. Most of traumatic ulcers started at tip of the toe as patients were wearing improper footwear. Ten (11.1%) patients had pressure ulcers on the heel and on planter aspect at the level of head of first metatarsal. These patients were either bed ridden or not using the proper footwear. Combination of Similar factors leading to ulcer formation are reported

**Systemic disease** - Cardiovascular complications are the most common cause of premature death among patients with diabetes. Other common co morbidities are hyperglycemia and vascular diseases such as cerebral vascular accidents, transient ischemic attacks, myocardial infarctions, angina, valvular heart disease, atrial fibrillation, aneurysms, renal dysfunction, hypertension, hypercholesterolemia, and hyperlipidemia. In present study 88.9% patients had associated systemic disease like Hypertension; Coronary Artery Disease (CAD) or Chronic Kidney Disease (CKD). 23.3% patients had hypertension alone. 44.4% patients had hypertension with CAD. 21.1% patients had HTN, CAD and CKD. Because diabetes is a multi-organ systemic disease, all co morbidities that affect wound healing must be assessed and managed by a multidisciplinary team for optimal...
outcomes in the diabetic foot ulcer. That is why we had treated all our cases with co morbidities in consultation with vascular surgeon, cardiologist and nephrologists.

**Imaging** - Imaging play an important role in the assessment and evaluation of the diabetic foot ulcer. Plain x-rays are indicated based on the extent, nature of the ulcer, and clinical change in the appearance of the ulcer or failure to heal. In our study we had done imaging in form of x-ray, Doppler. In two patients X-ray was suggestive of osteomyelitis. Persons with diabetes have an increased risk for developing an infection of any kind and a several-fold risk for developing osteomyelitis. Most of our cases that were having sepsis were due to uncontrolled hyperglycemia. Two had osteomyelitis and two patients without osteomyelitis-required amputation because of fulminant sepsis.

Peripheral Arterial Disease (PAD) rarely leads to foot ulcerations directly. However, once ulceration develops, arterial insufficiency will result in prolonged healing, imparting an elevated risk of amputation and infection. In two patients with suspicion of ischemia, Doppler was confirmatory. Attempts to resolve any infection will be impaired due to lack of oxygenation and difficulty in delivering antibiotics to the infection site. Therefore, early recognition and aggressive treatment of lower extremity ischemia are vital to lower limb salvage.

**Wound Swab Cultures** - The diabetic foot infections are frequently polymicrobial. In this study majority 64.4% reported as sterile possibly we recruited previously treated cases even with antibiotics and in 33.3% wound swab culture grown Staphylococcus. In one patient each (2.2%) swab has grown Proteus and Citrobacter. Surprisingly we could not isolate mixed organism from our culture study. We cannot explain this variation. Possibly we have taken the culture in the phase of callus ulcer. We have taken very few tissue specimen cultures, which might have given mixed bacteriology. Tissue specimens collected by curettage or biopsy are preferred, because they provide more accurate results than superficial swabs.

**Healing** – In our study healing with Cal Alginate dressing was significantly better (p < .001) than betadine and Eugraf Dressing. Statistically there was no significant difference in healing with Eugraf Dressing as compared to betadine dressing. Studies has proved faster and better wound healing with calcium alginate as compared to saline dressing. Recently one report found hypercalcemia with use of large quantity of calcium alginate dressing on a large surface area burnt wound. We have not had similar experience, possibly because of small ulcer size. Calcium alginites can create the ideal environment for wound healing and reduce healing times. Alginate dressings facilitate an optimum environment for healing and are useful in the management of exudate. The literature suggests that alginites are not painful at dressing change. We have noticed same, less painful dressing change in our alginate group. Alginate can reduce healing times compared with other types of dressing like collagen and saline. When used appropriately, alginites facilitate trauma-free dressing removal and are conformable and easy to use, with high levels of absorbency. The gelling action of alginate dressings creates warm moist environment that is ideal for wound healing. Pressure ulcers treated with alginate dressings showed favorable results when compared with those treated with dextranomer paste dressings. Alginites have been shown to be of benefit in moderate to highly exuding wounds because of following reasons:

1. The haemostatic properties of alginate dressings high in calcium may be useful for podiatrists in arresting small bleeding points during the sharp debridement of neuropathic ulcers.
2. Alginate dressings high in mannnuronic acid, which consequently form only a weak gel on contact with exudate, may have a place in managing wounds with a sinus as they are less likely to plug and can be flushed easily with saline.
3. Alginate dressings are conformable and flexible, and because they come in small sizes, they are easily used on areas of the foot that are difficult to dress.

Even betadine is the long standing dressing chemical no literature available on rate of wound healing. We have found no benefit of betadine dressing. The non-healing and partial healing was maximum. This corroborates with lack of literature on this context as negative findings are neither reported nor get published.

Recombinant human epidermal growth factor (EGF) stimulates the proliferation and migration of epithelial cells in human culture systems. EGF has been shown to enhance wound healing. Besides growth factor, other extracellular signals, including disruption of cell –cell or cell matrix contact and the provisional matrix might contribute to the initiation of migration re-epithelization, and activation of gene expression. There is no study available, which has compared EGEF with other dressing. Our results show it is significantly inferior to alginate (p < .001). However, we have got better healing rate with EGF dressing than betadine, which is not statistically significant (p > .05). The cost of 12 weeks dressing per patient with Betadine, Alginate and Eugraf has come to Rs 787, Rs 1186 and Rs 4886 respectively. Most likely the cost of EGF is prohibitive for routine dressing.

It is clear that dressings are only one element in the holistic management of this patient group. Diabetic foot ulceration is a recognized complication of diabetes and can never be managed in isolation. In addition to dressing selection, emphasis must be placed on good glycaemic control, pressure reduction, appropriate antibiotic therapy and skilled debridement.

5. Conclusion

1. Foot ulcer is seen minimum 3 years after initiation of diabetes.
2. Calcium alginate is the significantly effective dressing in comparison to betadine and Eugraf (p < .001).
3. No significant difference in healing with Eugraf in comparison to betadine (p > .05).
4. Eugraf is costliest and betadine is least costly but both are less effective in ulcer healing.
5. Dressing change least painful and less frequent with
Alginate.

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