

Prospective Observational Study to Note the Clinical Outcomes and Explore Prognostic Factors Related to Ulcer Healing in Patients with Diabetic Foot

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ABSTRACT

The study nearly 415 million people globally have diabetes, with 75 % living in low and middle income countries. In India, about 70 million people have diabetes and the number is projected to rise to 125 million by 2040. The aim of this study is to analyse various factors affecting wound healing in diabetic foot patients like glycaemic control (HbA_{1c}), nutritional status and peripheral vascular disease. We also evaluated the disease load, the morbidity associated with diabetic foot in the form of amputations and also mortality. This study also examined the traditional and novel therapies like negative pressure wound therapy, hyperbaric oxygen therapy, various dressings to expedite wound healing. Our study was performed at a tertiary care hospital where 200 inpatients having infected diabetic foot were studied. The outcomes of traditional surgical techniques over recent modalities were studied. We found that apart from local factors, systemic factors like malnutrition, anaemia and presence of long - standing uncontrolled diabetes severely impacted prognosis. Amongst all the risk factors peripheral vascular disease was associated with the highest mortality. Significant number of patients benefitted with adjuvant therapy amongst which negative pressure wound therapy had significantly better outcomes, others like hyperbaric oxygen therapy and cadaveric skin graft were comparable.

KEYWORDS

Peripheral vascular disease, Cadaveric skin, Haemoglobin level, Blood sugar level, Glycosylated haemoglobin level

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INTRODUCTION

The aim of this study is to analyse various factors affecting wound healing in diabetic foot patients like glycemic control (HbA_{1c}), nutritional status and peripheral vascular disease. We also evaluated the disease load, the morbidity associated with diabetic foot in the form of amputations and also mortality. This study also examined the traditional and novel therapies like negative pressure wound therapy, hyperbaric oxygen therapy, and various dressings to expedite wound healing. Our study was performed at a tertiary care hospital where 200 inpatients having infected diabetic foot were studied. The outcomes of traditional surgical techniques over recent modalities were studied. We found that apart from local factors, systemic factors like malnutrition, anemia and presence of long - standing uncontrolled diabetes severely impacted prognosis. Amongst all the risk factors peripheral vascular disease was associated with the highest mortality. Significant number of patients benefitted with adjuvant therapy amongst which negative pressure wound therapy had significantly better outcomes, others like hyperbaric oxygen therapy and cadaveric skin graft were comparable. Since diabetes is on a rising trend and affects the patient and his family physically, psychosocially and financially the multifactorial nature of the disease should be acknowledged. Hence a careful assessment along with a multi - disciplinary approach can save the limb and the life of the patient.

MATERIAL AND METHODS

- Design – Prospective and observational
- Place of the study – Wards, intensive care units and operation theatres of the surgery department of a tertiary care hospital.
- Duration of the study – From March 2018 to June 2019, after obtaining Institutional Ethics Committee approval.
- Written informed consent was obtained from each and every patient by the investigator.
- Sample size – We have calculated our sample size depending upon previous studies. The sample size of a minimum of 200 patients in each set will be taken assuming alpha error of 0.05.
- Sampling method – Convenient, consecutive, consenting sample.

Inclusion Criteria

- Adult patients of any gender with diabetic foot ulcer.
- Patients with diabetes and having cellulitis, purulent discharge, blisters or wet gangrene involving foot.
- All patients with diabetic foot ulcer requiring hospital admission.
- Patients having peripheral vascular disease or associated complications of diabetic foot.
- Patients having any body mass index, haemoglobin level, blood sugar level or glycosylated haemoglobin level.

Exclusion Criteria

- Patients who do not continue treatment and leave the hospital mid - treatment.
- Patient who follow up with new ulcer.
- Patient who have healed diabetic foot.
- Patients who do not have infected diabetic foot

Parameters to be Studied

Nutrition: Nutrition is an essential factor affecting any kind of wound healing. In case of diabetic foot ulcer this becomes of utmost important due to the immunocompromised status of the patient. It was assessed by the following factors in the study group.

Body mass index: Body mass index denotes the general nutritional status of the patient. A low body mass index signifies undernourished status and a high body mass index suggests obesity along with its associated co - morbidities. Both the ends of the spectrum are deleterious to healing of diabetic foot ulcers (Table 1).²

BMI classification(kg/m ²)	
Normal	18.5 - 24.9
Overweight	25 - 29.9
Obese	30 - 34.9
Severely obese	> 35

Table 1. BMI classification (kg / m²).

Haemoglobin: Haemoglobin levels are markers of the oxygen carrying capacity of blood. Anaemia can cause impaired healing of any ulcer. Anaemia can be divided in 3 groups based on its severity (Table 2).³

Severity of anaemia	Haemoglobin in gm /dl
Mild	10 – 10.9
Moderate	7 – 9.9
Severe	< 7

Table 2. Severity of anaemia.

Glycaemic Control

Glycosylated haemoglobin: For diabetic foot ulcer to develop, many risk factors are identified, out of which chronic sugar control is important. Since it is a chronic factor, a chronic marker for diabetes should be used. It is also observed that patients who have longer duration of poor sugar control have more chances of neuropathy indirectly leading to ulcer. It is best assessed by three monthly sugar controls by glycosylated haemoglobin (Table 3).

HBA_{1c} levels 4

HBA _{1c} levels (in %)	
Normal	< 5.7
Pre - diabetic	5.7 - 6.4
Diabetic	> 6.5

Table 3. HBA_{1c} Levels (in %).

Fasting and post - prandial blood sugar levels: For assessing the current sugar levels and also quick assessment of glycemic index 12 hours fasting and a 2 hours post prandial blood sugar level was obtained. It shows the associated comorbid conditions and diabetic ketoacidosis. Also it is the basis for changing insulin dose according to sliding scale (Table 4).⁵

Blood sugar levels	Fasting blood sugar(mg /dl)	Post - prandial blood sugar (mg / dl)
Normal	70 – 100	70 – 140
Pre - diabetics	101 – 125	141 – 200
Diabetics	> 125	> 200

Table 4. The Pre - Treatment and Post Treatment Sugar were Controlled, and it was Ensured that Patients have Better Glycemic Control at Discharge.

End Organ Damage

These assess the severity of the disease and indicate amount of uncontrolled sugar levels complicating healing of ulcer. Also, while treating the patients, these must be kept in mind as our treatment should not further complicate their general status.

Medical renal disease: These patients had decreased urine output. Serum creatinine levels, urine protein levels and ultrasound of kidney were done. The grades of medical renal disease are three and are decided by ultrasound examination, based on the remnant of renal parenchyma.

Diabetic retinopathy: It was assessed in patients with deranged blood sugar levels and who complained of decreased vision. The assessment was done by fundus examination.

Diabetic neuropathy: The patients having loss of sensation have increased chances of developing ulcer due to repeated trauma. This was assessed by testing superficial and deep sensations. The superficial sensation was tested by pin prick and cotton wisp (monofilament suture), also temperature sensation was looked for by

using test tube containing warm and cold water. The deep

sensation was tested by tuning fork of 128 Hz, deep pinch, reflex testing.

Peripheral vascular disease: This was assessed by doing lower limb Doppler to look for the blood flow and the underlying vessel condition. It was seen that patients having peripheral vascular disease also had claudication and tingling sensation over limbs. It caused severe impairment of wound healing. It is based on the Doppler principle in which ultrasound beam is used to measure the velocity and direction of the blood flow in the vessels and the blood pressure at ankle or wrist. Ratio of ankle – bacterial pressure is known as pressure is known as pressure index.⁶

- 1 – Normal
- 0.5 – Arterial reconstruction is not necessary.
- < / = 0.25 – Amputation is inevitable unless reconstruction performed.

To assess for extent and reversibility of lesion of PVD a digital subtraction angiography can be done and intervention accordingly planned.

Comorbidities: Some patients may have associated cardiac and other vascularity related comorbidities, evaluation of the above is necessary as it collectively affects the outcome of patient. When needed cardiac echocardiography, assessment for the need for dose moderation of certain drugs, the need for dialysis, angiography was done.

Wound swab: For all patients at initial admission, a wound swab was taken before giving antibiotics after washing the wound with normal saline. It was then sent for culture sensitivity and gram staining.

Blood culture: Blood cultures to rule out bacteraemia and systemic infection were sent. They also guided further antibiotic therapy.

SIRS or septicemia shock: If patients presented with features of systemic illness or shock then serial blood cultures were sent. Monitoring of total white blood cells was done. The swabs were also repeated. Such patients were given appropriate supportive care in the intensive care units.

PEDIS score: PEDIS score may be used to assess the wound and compare one wound to other, depth of infection and the morbidity associated with procedure.

RESULTS

The results of PEDIS before and after treatment may be compared (Table 5).⁷

Grade	Perfusion	Extent	Depth	Infection	Sensation	Score
1	No pad	Skin Intact	Skin Intact	None	No loss	0
2	PAD, No, CLI	< 1CM	Superficial	Surface	loss	1
3	CLI	1 - 3cm ²	Fascia, Muscle, Tendon	Abscess, Fasciitis, Septic arthritis		2
4		> 3cm	Bone or Joint	SIRS		3

Table 5. PEDIS Classification System.

	Grade	Symptoms
Perfusion	p1	No symptoms / Size of pad
	p2	symptoms / Size of pad, but not of CLI
	p3	CLI
Extended / Size	E	Wound size (measured in square centimeters)
	D1	Superficial full thickness ulcer, not penetrating any structure deeper than the dermis
Depth/tissue lost	D2	Deeper ulcer, penetrating below the dermis to subcutaneous structures, involving fascia, muscle, or tendon
	D3	All subsequent layers of the foot involved, including bone and / or joint (exposed bone, probing to bone)
	11	No symptoms or signs of infection
Infection	12	Infection involving the skin and the subcutaneous tissue only (without involvement of deeper tissues and without systemic signs); at least 2 of the following items are present: Local swelling or induration - erythema > 0.5 to 2 cm surrounding the ulcer - Local tenderness or pain - local warmth - purulent discharge
	13	Erythema > 2 cm plus one at the sites described above or infection involving structures deeper than skin and subcutaneous tissues (abscess, osteomyelitis, septic arthritis, fasciitis) without systemic inflammatory response signs
	14	Any foot infection with the following signs of SIRS manifested by two or more of the following conditions: - Temperature >38 or <36 Celsius Heart rate > 90 beats / Min Respiratory rate \geq 20 breaths / min PaCO ₂ <32 mm Hg White blood cell count >12,000 or < 4,000 / cu mm 10% immature (band) forms No loss of protective sensation
Sensation	S1	No loss of protective sensation
	S2	Loss of protective sensation with absent pressure sensation on 2 of 3 sites on the plantar side of the foot or absent vibration sensation or vibration threshold > 25 on the hallux

Table 6. Grade and Symptoms.

Wound Healing

The endpoint of study was a healed wound, healing in this aspect includes

- Preparation of adequate wound bed for both grafting and which is devoid of Infection.
- The presence of healthy granulation tissue post - surgery.
- Presence of healthy granulated wound post - amputations of the forefoot.
- Amputations proximal to Trans metatarsal amputations were considered in the wound not healed category or treatment failure category. This was irrespective of the wound status post amputation.
- Epithelialisation necessarily was not needed to consider wound healing.

Treatment of Wound

Patients requiring admission for diabetic foot ulcers were offered primary treatment in the form of surgery. Surgery in the context of this study included and was limited to debridement of diabetic foot ulcers with or without amputations distal to and including Trans metatarsal amputation. Patients were then given daily dressing along with treatment of other co - morbidities as mentioned above. Certain categories of patients requiring adjuncts

were offered suitable options to promote wound healing. These included:

- Negative pressure wound therapy – This treatment was offered to patient with exudative wounds. It was an option considered for large surface wounds to promote contraction and early granulation. Patients who did not tolerate the pain associated with daily dressing benefitted from it.
- Hyperbaric oxygen therapy – Infected wounds, especially those with anaerobic species and clostridium species were given HBOT. Excessive slough and purulent discharge from the wound were criteria for patients to receive HBOT. It led to a reduction in the necrotic load of the wound and helped wounds heal faster.
- Special dressing containing silver releasing molecules, cadexomer iodine, Colloid dressing, and autolytic enzymes were administered as per wound status.
 - Cadaveric skin grafts were used to provide natural cover to wounds. They promoted healthy granulation and early epithelialization.

Skin Grafting: Healthy granulated wounds, especially large surface area wounds were operated for skin grafting. It reduced the time required for wound healing and promoted early rehabilitation of the patient. Days of **Hospitalization:** Patients were quantified as requiring less than 10 or more than 10 days of indoor hospital treatment. It signified the morbidity and increased healthcare costs associated with diabetic foot ulcers.

Statistical Analysis

- Statistical analysis data were statistically described in terms of mean (\pm SD), frequencies (number of cases) and percentage when appropriate.
- *Chi square* and Fischer Exact Probability tests were used to compare Percentages between 2 or more groups.
- Students unpaired t test were used to compare means between 2 groups if the data follows normal distribution.
- All statistical tests were 2 tailed
- Probability value (p value) less than 0.05 was considered statistically significant.
- Computer programs Microsoft Excel 365 and SPSS (statistical package for social science) version 17 were used for statistical analysis.
- ANOVA test for comparing pre 0 - treatment and post treatment in the same group.

DISCUSSION

Study Procedure

Pre operatively patients detailed history was taken and the parameters like BMI, haemoglobin, age, glycosylated haemoglobin, random blood sugar, PEDIS score was evaluated. All other relevant blood investigations were sent. If the blood sugars were deranged then bringing them back to normal acceptable levels was done. All patients of diabetic foot were put on subcutaneous insulin as per sliding scale, to promote adequate control. History regarding any comorbidity was obtained and treatment change if any was done. If patient presented with normal sugar and gangrenous changes of the limb, or had claudication pain then Doppler of lower limb was arranged.

For evaluation of foot lesions

- Inspection of ulcer - site, size, edge, shape and base of ulcer, looking for amount of slough, discharge or exposure of bone, tendon, surrounding structure, colour of the foot, gangrenous discoloration.
- Palpation of local warmth, pulsation, tenderness, crepitus.
- To evaluate any severe form of disease by looking for neuropathy (sensorimotor):
Touch and pressure - by using monofilament, cotton.
Vibration perception - 128 Hz tuning fork on malleoli.
Thermal sensation – sensation of hot and cold, heat pain and cold pain. Pain control was achieved, swabs were collected by cleaning the wound with normal saline and intravenous antibiotics were started. On the basis of PEDIS score and condition of wound, patient was taken for surgery. Surgery with respect to this study is considered as debridement of the diabetic foot ulcer along with amputations distal to and including the Trans - metatarsal amputation. Wounds were reassessed regularly after surgery and depending on the type of wound appropriate adjuvant wound therapy was given. If on reassessment if any wound was found unhealthy then debridement or amputation was taken into consideration, to aid wound healing. Wounds were reassessed post adjuvant therapy and if found healing then patients was considered for split skin grafting or discharge. If the wound was found unhealthy then other factors hampering healing were reassessed and identified. The following were also

provided improved nutrition, vitamin supplement, and correction of anemia by iron therapy and blood transfusion. Failure of treatment was considered as those who presented with unhealed ulcer and requiring more proximal amputation hampering their day to day life.⁸ The disease like peripheral vascular disease if associated with diabetic foot was treated by conservative medical management including vasoactive agents and anti - platelet drugs. Certain cases as per the angiography report required invasive procedures like stenting, embolectomy or any bypass procedure. Once wound healing was achieved patients were given occupational therapy and physiotherapy, including orthotic footwear.

CONCLUSION

Diabetic foot ulcer was most commonly seen in the mean age distribution of 54.03 years. The minimum age affected by diabetic foot was 29 years and maximum age affected was 89 years. Overall there was no difference in the distribution of diabetic foot in male or female. The male and female ratio of diabetic foot in the age group of 51 - 60 years was 1.4:1. 125 patients having diabetic foot ulcer had normal body mass index, 8 were obese with no mortality in the obese patients. Body Mass Index was shown not to affect wound healing. The patients with uncontrolled diabetes had more risk of developing ulcer and subsequently a non - healing ulcer than the others who are well controlled or pre - diabetic. The study shows that 109 patients of diabetic foot had moderate anaemia. Anaemia was shown to not significantly affect wound healing. 53 patients with diabetic foot had associated end organ damage. As the age increases the rate of mortality post any procedure for diabetic foot is high. Highest mortality being recorded in patients > 70 years of age – about 35.7 % Patients with type 3 medical renal disease had higher chances of mortality, in this study out of 4 patients having type 3 end organ damage 3 patients died leading to 75 % mortality. 22 having peripheral vascular disease with diabetic foot 77.37 % had poor wound healing and 63.6 % died. Peripheral vascular disease had high significance on healing, morbidity and mortality of diabetic ulcer. After undergoing primary surgery, negative pressure wound therapy was found the best among the other adjuncts, 92.7 % showed healing, which was highly significant in terms of early wound healing, less duration of hospital stay and less need for eventual split skin grafting. Most common organism affecting diabetic foot was klebsiella with about 37 % patients showed wound swab positive for klebsiella. Apart from the glycaemia control several other factors influence healing of ulcer in diabetic foot disease. Assessment and treatment of these factors in essential in management of diabetic foot ulcers. Multiple adjunctive treatments exist and should be utilized to promote healing and reduction of hospital stay. Multiple systemic diseases co - exists with diabetic foot disease and is a cause of added morbidity and mortality. Thus, a multi - disciplinary approach is needed to improve outcome in patients suffering from diabetic foot disease.

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