EFFICACY OF TOPICAL HEPARIN ON DIABETIC ULCER- PROSPECTIVE STUDY

Submitted by

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P.G in General Surgery

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B.L.D.E. (DEEMED TO BE UNIVERSITY) SHRI B.M. PATIL MEDICAL COLLEGE HOSPITAL & RESEARCH CENTER, VIJAYAPURA, KARNATAKA - 586103.

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MASTER OF SURGERY

In

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UNDER THE GUIDANCE OF

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LIST OF ABBREVIATIONS USED

DM	Diabetes mellitus
HTN	Hypertension
FBS	Fasting blood glucose
PPBS	Post prandial blood glucose
HbA1c	Glycated haemoglobin
P value	Predictive value
INR	International normalized ratio
PT	Prothrombin time
ECG	Electrocardiogram
HIV	Human immunodeficiency virus
HbsAg	Hepatitis B Surface antigen

ABSTRACT

BACKGROUND: The complications of diabetes contribute to the delayed healing of diabetic foot ulcers[1]. The application of topical heparin on the wound has a beneficial effect on wound healing by several mechanisms.[2]

OBJECTIVES OF THE STUDY: To evaluate the efficacy of topical heparin in the treatment of Grade 1and Grade 2 diabetic ulcers in the form of analyzing and comparing wound area, granulation tissue, wound discharge, duration of hospital stay and culture sensitivity.

MATERIALS AND METHOD: All patients presenting to Shri B M Patil Medical College Hospital and Research Centre, Vijayapura and in whom the diagnosis of diabetic ulcer of Grade 1 and 2were made from NOVEMBER 2018 to JUNE 2020 were included in the study. A prospective interventional study was conducted with 80 patients alternatively assigned to two groups, i.e., 40 patients to topical heparin solution dressing group (Cases) and 40 patients to conventional dressing group (10% povidone iodine). Endpoint of study was a wound ready for either secondary suturing, skin grafting. All the data were analysed using the z-test, students T-test and the results were tabulated. A "p-value" of <0.05 was considered statistically significant.

RESULTS:

The reduction in the surface area of wound with time was more significant in Cases as compared to Controls. By day 14 , a significantly more number of Cases developed a healthy granulation tissue as compared to the Controls ($p< 0.005$).By 14 days, serous wound discharge was seen in 92.5% of case group and 70% in control group ($p< 0.001$).By the end of 3 weeks and 4 weeks, a significantly more number of Cases had achieved outcome as compared to Controls(72.5 % vs 32.5 %,$p= 0.006$ and 90.0 % vs 75.0 %,$p= 0.005$, respectively).The mean duration of hospital stay was significantly shorter for Cases as compared to Controls (21.3 days ± 6.2 days vs 26.7 days ± 6.4 days, $p< 0.001$).

CONCLUSION: Topical heparin dressing can be considered as a superior option in the management of diabetic ulcers. Nevertheless, we advocate further studies with a larger sample size to substantiate the findings we made.

KEYWORDS: diabetic ulcers, topical heparin solution

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INTRODUCTION

Diabetic foot ulcers have many pathogenic mechanisms, the most common aetiology being peripheral sensory neuropathy, trauma, deformity, high plantar pressures, and peripheral arterial disease. Due to the loss of sensation caused by peripheral neuropathy, injuries to the feet go unnoticed when they occur, and they are likely to get infected. If the blood supply is whole or partially blocked, tissue ischemia will occur, which can result in the development of painful ulcerations on the feet. For healing to take place, it is primarily essential to have intact microcirculation in the skin around the ulcer, and adequate arterial blood supply to the ulcer area. Hyperglycaemia can decrease fibrinolytic activity, which increases blood viscosity and induces a high coagulation state in people with diabetes mellitus. The high coagulation state can damage vessel walls and lead to vascular dysfunction, coagulation-anticoagulation disorders and hemorheological disturbances. This high coagulation state contributes to the slow healing of diabetic foot ulcers [(1)].

Wound healing in itself is a complex process. The complications of diabetes, like poor vascularity and uncontrolled infection, further increase its complexity. Diabetic foot ulcers are a significant cause of hospital admission and frequent cause of amputation resulting in economic loss and decreased quality of health [(1).] Treating diabetic ulcers are challenging to surgeons as they contribute to

morbidity, expenditure due to prolonged use of antibiotics and prolonged hospital stay[3].

The standard management of diabetic ulcers includes debridement, control of infection and local dressings. Newer modalities like off-loading technique, local phenytoin sodium application, use of growth factors, laser therapy have been tried with modest results.

The use of topical heparin on the wound has shown a beneficial effect on tissue microcirculation and oxygenation, proliferation of fibroblasts, promotion of migration of capillary endothelial cells and angiogenesis. It reduces bacterial translocation, thus minimizing the use of antibiotics. It also has a role in collagen I synthesis, thus producing stable, healthy granulation tissue contributing to the healing of the ulcer.[4]

In this prospective study, we are comparing a novel method of using topical heparin solution in the management of diabetic foot ulcer with conventional wound management using a 10 % povidone-iodine solution. The outcome of diabetic ulcer is compared between the two groups in terms of the wound area, granulation tissue, wound discharge, length of hospital stays and culture sensitivity.

AIMS AND OBJECTIVES

To evaluate the efficacy of topical heparin in the treatment of grade 1and grade 2 diabetic ulcers in the form of analyzing and comparing

1. Wound area
2. Granulation tissue
3. Wound discharge
4. Duration of hospital stay.
5. Culture sensitivity

REVIEW OF LITERATURE

Historical background of wound healing

• The treatment and healing of wounds are the oldest topics discussed in the medical literature and probably earliest problems of the human race[5].

• A lot has been written about wound care in early medical writings. In the Edwin Smith Papyrus (1700 BC) there are seven reports describing wounds and their management.

• More than 4000 years ago, the theory of the "three healing gestures" was recorded on a clay tablet from 2200 BC. The tablet describes the three gestures as:

- wound washing
- plasters over the wound
- application of bandage over the wound

• These gestures have evolved into varying forms of today's same basic themes. The Greek belief of dry healing came from Hippocrates, at a time when the only function of dressings was thought to be the protection of the wound from injury.

• In Egypt, Greece, India and Europe, the physicians nurtured ways of nursing wounds by removing foreign material, suturing, covering wounds with clean materials, and guarding damaged tissues from corrosive agents.

• During the fourteenth century, with the extensive use of gunpowder and the increasing frequency of bullet wounds, the surgeons had to play an important role, often not paying attention to aseptic precautions. For example, applying burning oil, scalding water, wine, turpentine, feathers, sugar, clay, bismuth, milk of magnesia to wounds. However, none of these uses was based on scientific study.

• The modern period of tender wound care started in the mid-sixteenth century, when Ambroise Pare, the great French army surgeon, applied milder agents like a digestive solution of egg yolk, rose oil, honey and turpentine to amputation stumps with remarkable results.

• Early surgeons like Ambrose Pare, John Hunter and Sir James Paget have given some scientific knowledge to their handling of wounds, particularly those resulting from the war.

• Halsted was intensely interested in the wound healing process.

• In the early 1900's Carrel and his associates made investigations with the scientific approach to wound healing. Later Carrel (1916) and Harvey &Howe's (1930) studied incised wounds and contributed to the knowledge of wound healing.

• Clinical biologists like John Hunter, William Stewart, Halsted, Alexis Carrel and others showed that minimizing tissue damage leads to quick and effective

healing paving the way for the concept of "minimal interference" in wound care. If the surgeon can remove all obstructions, the normal wound healing process will produce the best possible result.

• Joseph Lister promoted cleanliness in the hospital, the frequent use of soap and water on wounds and carbolic acid dressings of contaminated wounds. Later Semmelweis, Ehrlich, Fleming and Florey also realized that bacteria were pathogens. They advocated the control of bacteria by asepsis, antiseptics and antimicrobials, there by bringing in a new era in wound management.

• All the advances in wound care of the previous decades are only a run-up to the changes in wound care management that will ensue in the years to come.

DIABETES MELLITUS

Definition:

"Diabetes mellitus is characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat, and protein metabolism resulting from defects in insulin secretion, insulin action, or both"**.**

Hyperglycaemias may be due to the following etiological factors:

- Reduced insulin secretion
- Decreased glucose utilization
- Increased glucose production

Incidence

Estimates based on data from the World Health Organization (WHO) revealed that in 2011 approximately 366 million people worldwide had diabetes mellitus (DM); over 80% of DM is thought to occur in low- and middle-income countries. The International Working Group on the Diabetic Foot (IWGDF) defines a diabetic foot ulcer as a 'full-thickness' lesion of the skin. It occurs in 16% of people with DM and precedes 85% of foot-related amputations. The prevalence of diabetic foot ulcers varies from country to country. In the USA, the lifetime incidence of developing a diabetic foot ulcer may be as high as 25% for the 24 million people with DM, with 1% of this population requiring amputation. Every year in Germany 22,000 people with DM lose a leg as a result of diabetic foot ulcers. South Asians with DM are about 33% more likely to develop a foot ulcer than Europeans. The prevalence of diabetic foot ulcers is about 5.6% of those with DM in the Veterans Affairs Hospital of America Seattle, 10.2% in Britain, 10% in India and 14% in China[(1)].

Classification

TYPE I - due to complete or near-total insulin deficiency.

- Commonly develops before the age of 30 years

Type Pathology

I A: Autoimmune beta cell destruction _Insulin Deficiency

I B: Develop insulin deficiency by unknown mechanism causing the destructive process of beta cells

Type II- typically develops with increasing age

- Is characterized by:
    - Impaired insulin secretion
    - Insulin resistance
    - Excessive glucose formation

Type-2 DM is preceded by a period of abnormal glucose haemostasis classified as:

- Impaired glucose tolerance (IGT)
- Impaired fasting glucose (IFG)[6]

Diagnosis

The American Diabetes Association[7] has issued the following diagnostic criteria for Diabetes Mellitus:

- Random Blood Glucose concentration ≥200 mg / dL or ≥11.1 mmol / L with symptoms of DM (Polyuria, Polydipsia, Polyphagia, Weight

loss) where Random is defined as without regard to time since the last meal OR

- Fasting Plasma Glucose ≥126 mg/dL or ≥ 7.0 mmol / L where Fasting is defined as no caloric intake for at least 8 h OR
- 2-h Plasma Glucose (During an Oral Glucose Tolerance Test) ≥ 200 mg/ dL OR ≥11.1 mmol/L where the test should be performed using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water OR
- HbA1c ≥ 6.5%

Chronic Complications of DM.

Mortality and morbidity associated with Type 2DM are mainly due to the chronic complications of DM. The increased duration of the disease (hyperglycaemic state) is associated with an increase in the risk of chronic complications. During diagnosis, the patient may present with complications because of the long asymptomatic periods of hyperglycaemia.

The **macrovascular complications** of DM are:

- Coronary artery disease (CAD)/ Ischemic heart disease (IHD)
- Peripheral vascular disease (PVD)
- Cerebrovascular abnormality[8]

Macrovascular complications are related to dyslipidaemia and increased blood pressure. They have a more complex aetiology and occur even in those with careful glycaemic control.

The **microvascular complications** of DM are:

- Eye disease
  - Diabetic retinopathy
    -proliferative and non-proliferative
  - Macular oedema
- Diabetic nephropathy

- Diabetic neuropathy
  - sensory and motor
    -mono and polyneuropathy
  - autonomic[8,6]

The microvascular complications are seen in both type 1 and type 2 DM. Many clinical trials show that there is significant prevention/delay in retinopathy, neuropathy and nephropathy if the chronic hyperglycaemic phase is reduced. Microvascular complications are unarguably due to chronic hyperglycaemia and are less likely to be seen in those with excellent glycaemic control.[9]

Other complications of DM include:

- Gastro-intestinal (delayed/increased gastric emptying)
- Genitor-urinary (Uropathy / Sexual dysfunction)
- Dermatological
- Infections
- Ophthalmological (Cataracts and Glaucoma)

All the complications of DM have a positive correlation with FBS and PPBS glucose levels as well as with the HbA1C.

Pathogenesis of complications of DM.

Diabetes and related complications may gradually lead to long-term damage and failure of various organ systems. Chronic hyperglycaemia levels lead to a complex intersection between macrovascular and microvascular complications [(10)]. Several molecular mechanisms have been proposed to explain the adverse effect of hyperglycaemia on vascular tissues. These include increased polyol pathway (sorbitol pathway), activation of the diacylglycerol/protein kinase C pathway, increased oxidative stress, overproduction and action of advanced glycation end products, and increased hexosamine pathway. Besides, the alterations of signal transduction pathways induced by hyperglycaemia or toxic metabolites can also lead to cellular dysfunctions and damage vascular tissues by altering gene expression and protein function.

Hyperglycaemia might also inhibit the endogenous vascular protective factors such as insulin, vascular endothelial growth factor, platelet-derived growth factor and activated protein C, which plays essential roles in maintaining vascular homeostasis[11].

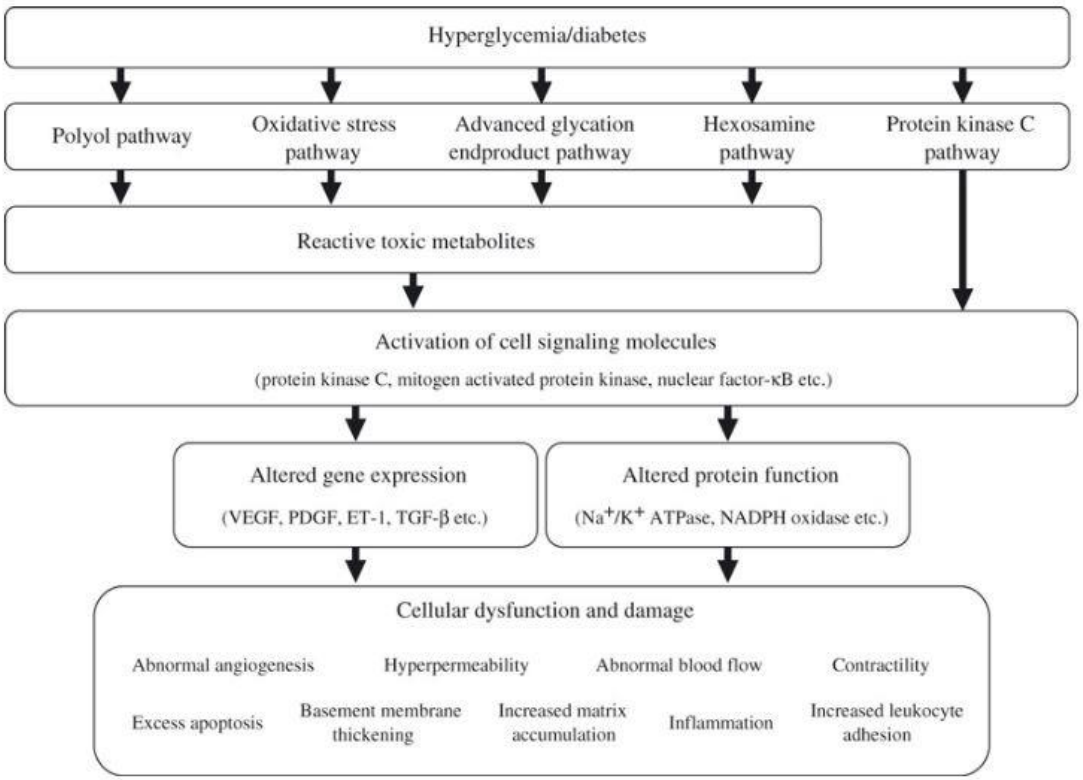

Fig1: Mechanisms by which hyperglycaemia induces diabetic vascular complications.

ET-1, endothelin-1; NADPH, nicotinamide adenine dinucleotide phosphate; PDGF, platelet-derived growth factor; TGF-β, transforming growth factor-β; VEGF, vascular endothelial growth factor.

Neuropathy and Diabetes Mellitus

-It is estimated that the prevalence of diabetic neuropathy in patients with type 2 diabetes is 32 percent overall and more than 50 percent in patients over 60 years of age.

- Diabetic neuropathy has a positive correlation with the disease duration and control of hyperglycaemia in type1 and 2 DM.

-It may manifest as Polyneuropathy/ Mono-neuropathy/Autonomic Neuropathy

- All the nerve fibres (including myelinated and nonmyelinated) are affected.

- Diabetic neuropathy have similar clinical features when comparing with other neuropathic diseases; therefore, all other likely aetiology should be excluded before making a diagnosis.

Poly-neuropathy / Mono-neuropathy:

-The most common form of diabetic neuropathy is distal symmetric polyneuropathy.

- It presents as:

- Distal sensory loss - most frequent presentation
- Hyperesthesia
- Paraesthesia
- Dysesthesia

-Symptoms includes a sensation of following, which begins in the feet and spreads proximally.

- Numbness
- Tingling
- Burning

Neuropathic pain typically involves the lower extremities and is usually present at rest, and worsens at night.

- With the progression of the disease, the intensity of the pain will decrease, and eventually, it disappears. However, in the extremities, a sensory loss may persist. Also, any of the following symptoms/signs may develop

- Loss of sensation
- Loss of Ankle deep-tendon reflexes
- Abnormal position sense(proprioception)[6]

Mononeuropathy

Mononeuropathy is the dysfunction of isolated cranial or peripheral nerves. It is less common as compared to polyneuropathy in DM and is observed as pain and motor weakness in the distribution of a single nerve. The third cranial nerve is most commonly involved. Physical examination reveals

- Diplopia
- Ptosis
- Ophthalmoplegia. [6]

Autonomic neuropathy

Persons with a long-standing type 1 or 2 DM may develop signs of autonomic dysfunction which involve the cholinergic, noradrenergic, and peptidergic (peptides such as a pancreatic polypeptide, substance P, etc.) systems. Autonomic neuropathy involves multiple systems:

- Cardiovascular system
  - Resting tachycardia
  - Orthostatic hypotension
- Gastrointestinal system

  -gastroparesis

-Hyperhidrosis of the upper extremities

-Anhidrosis of the lower extremities

-dry skin with cracking leading to increased foot ulcers

- metabolic systems
  - may reduce counter regulatory hormone release (especially catecholamines), leading to an inability to sense hypoglycaemia appropriately

Lower Extremity Complications

Foot ulcers and infections are a significant source of morbidity in individuals with DM. Many individuals with type 2 DM develop a foot ulcer (great toe or metatarsophalangeal areas are most common), and a significant subset who develop ulceration will ultimately undergo amputation (14–24% risk with that ulcer or subsequent ulceration)[6]. Increased occurrence of lower limb complications in DM is due to the interaction of many pathogenic factors which can be classified as Causative factors and Contributive factors.

Causative factors:

- **Peripheral neuropathy (sensory, motor, autonomic)**

  - It is the primary and most important causative factors.

  - Sensory neuropathy is usually quite deep (>50%). A loss of protective sensation is experienced, resulting in vulnerability to physical and

thermal trauma, thereby enhancing the risk of foot ulcers. The sensation of pain and pressure is lost, so are the proprioception of the sensation of foot position.

-Motor neuropathy affects all the muscles in the legs, leading to protrusion of abnormal bones, change in the standard architecture of the foot, distinctive deformity such as hammertoe and hallux rigidus.

- Autonomic neuropathy is characterized by dry skin, no sweating and increased secondary capillary refill thereby triggering fissures and skin crust, making the foot vulnerable to minimal trauma[(12)].

- **High foot plantar pressure**

  - It is the second most important causative factor.

  -It is related to two factors: limitations of joint mobility (ankle, subtalar and first metatarsophalangeal joints) and foot deformities.

  - In patients with peripheral neuropathy, 28% of patients with high plantar pressure, will have a foot ulcer within 2.5 years as compared with patients without high plantar pressure[(12)].

- **Trauma**

  - 21% individuals suffer from trauma due to friction from footwear, 11% due to foot injuries (mostly due to falling), 4% cellulitis due to tinea pedis complications and 4% due to fingernail cut errors.

Contributive factors

- **Atherosclerosis**:
  - Atherosclerosis of femoropopliteal and small blood vessels below the knee, is the primary contributing factor.
  - The risk of ulcers is twice as high in diabetic patients as compared to non-diabetic patients.
- **Diabetes**

- Diabetes leads to collagen cross-linking disorders, metricoproteinase matrix functional disorders and immunologic disorders, especially impaired polymorphonuclear leukocytes (PMN) function.
- Diabetic individuals have higher rates of onychomycosis and tinea infections, as the skin is easy to peel and catch infections.
- Sustained hyperglycaemia triggers an inflammatory response and leads to impaired cellular defence mechanisms.
- Sequential and self-limited inflammation and neovascularisation are essential in wound healing, but must be and closely controlled by the interaction of molecular cells. In DM, acute inflammatory responses are considered weak, and angiogenesis is disrupted, resulting in wound healing disorders[(12)].

The complex interactions among the various pathologies are aptly depicted in Figure 2.

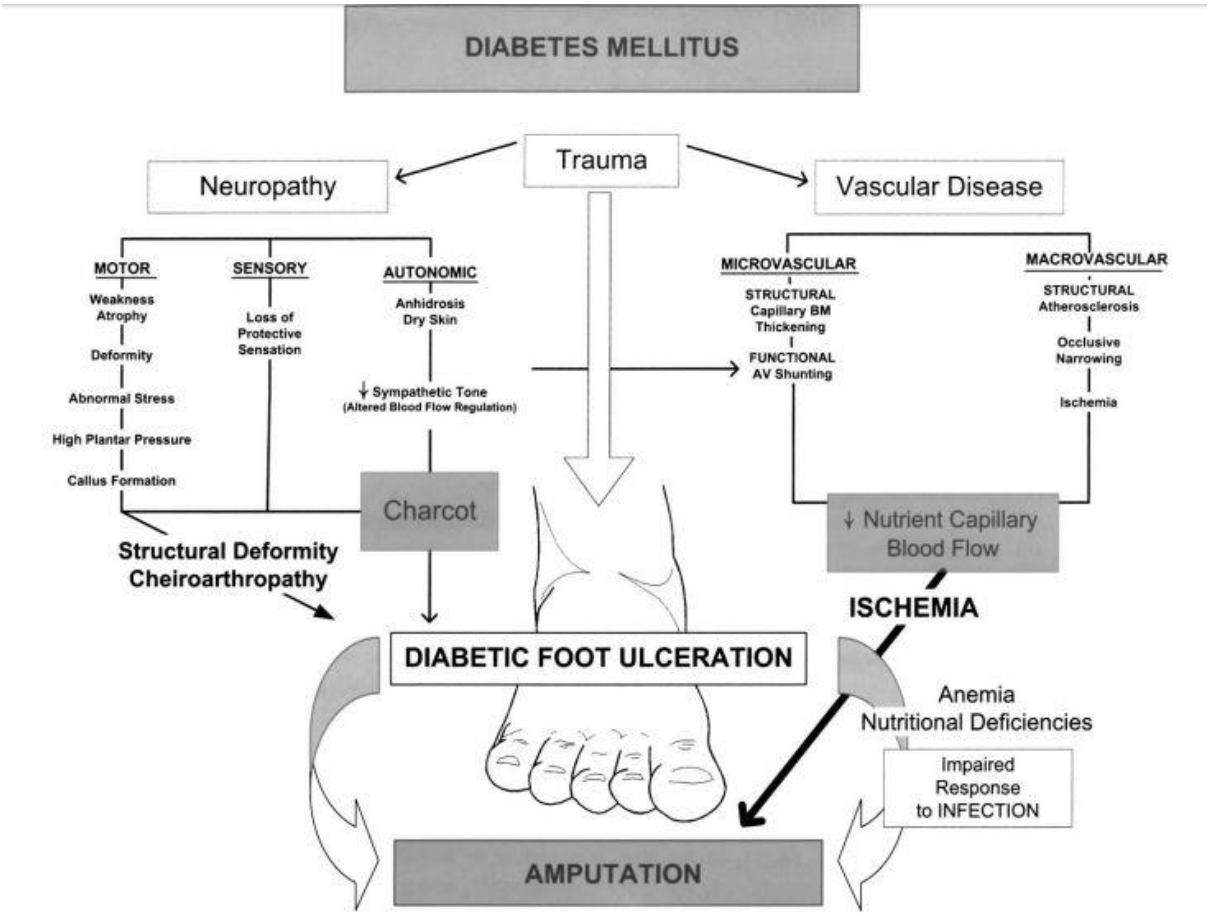

Figure 2: The multiple pathologies of ulceration in diabetes

Reproduced from: The guideline developed by the Clinical Practice Guideline Diabetes Panel of the American College of Foot and Ankle Surgeons [13](2006 revision)

PROCESS OF NORMAL WOUND HEALING:[14,15,16,17]

Wound healing is a mechanism wherein the body attempts to restore the integrity of the injured part. It is achieved through four highly integrated and overlapping bio-physiological phases, namely:

1. Haemostasis
2. Inflammation
3. Proliferation
4. Tissue remodelling/ resolution[15]

The series of events associated with wound healing begins at the moment of injury. For a wound to heal successfully, all four phases must occur in proper sequence and time frame and continue for a specific duration at an optimal intensity (that takes almost a year to complete).

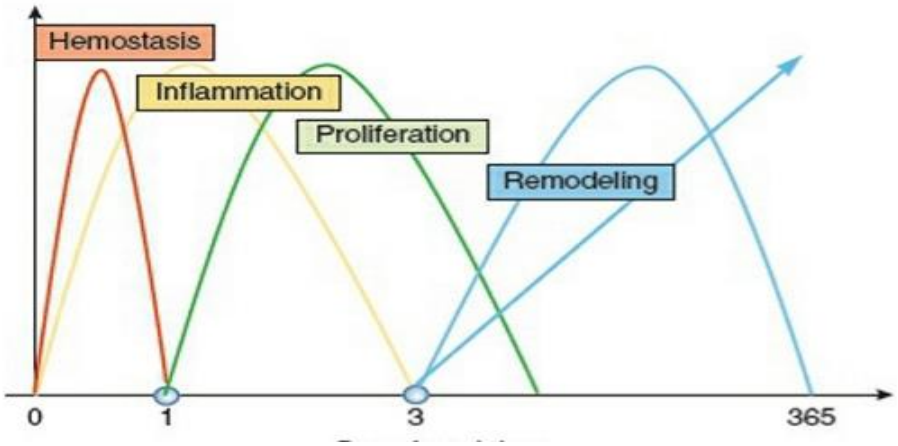

Figure 3: Four phases of wound healing plotted against "time" on X-axis.[15]

Table 1	Cellular and Biological Events that Frame the Normal Wound Healing Process
PHASE	**Cellular and Biophysiological Events**
Haemostasis	Vascular constriction Platelet aggregation, degranulation, and fibrin formation (thrombus)
Inflammation	Neutrophil infiltration Monocyte infiltration and differentiation to macrophage Lymphocyte infiltration
Proliferation	1. Re-epithelialization 2. Angiogenesis 3. Collagen synthesis 4. ECM (extracellular matrix) formation
Remodelling	1. Collagen remodelling 2. Vascular maturation and regression

Table 1: Components of normal wound healing[(15))]

A diabetic foot ulcer is a chronic wound. Diabetes is associated with large vessel occlusion and end-organ microangiopathy leading to tissue ischemia and infection.[(16)]Diabetic sensory neuropathy leads to repeated unnoticed trauma and constant pressure on the wound.[(16)]Tissue hypoxia is well demonstrated by reduced dorsal foot transcutaneous oxygen tension (TcO_2). [(16)] Also, the thickened basement membrane decreases perfusion of tissues.

VEGF upregulation in patients with diabetes is impaired.[(16)] Hyperglycaemia further increases pro-inflammatory mediators, i.e., TNF-α, IL-1.[(16)]There is also a loss of balance between metalloproteinases and MMP inhibitors (Muller et al., 2008) accelerating ischemia.[(18)]These alterations in the structure and functions of cells at the wound site lead to delayed healing in DFUs. Hence treatment of DFUs remains a challenge.

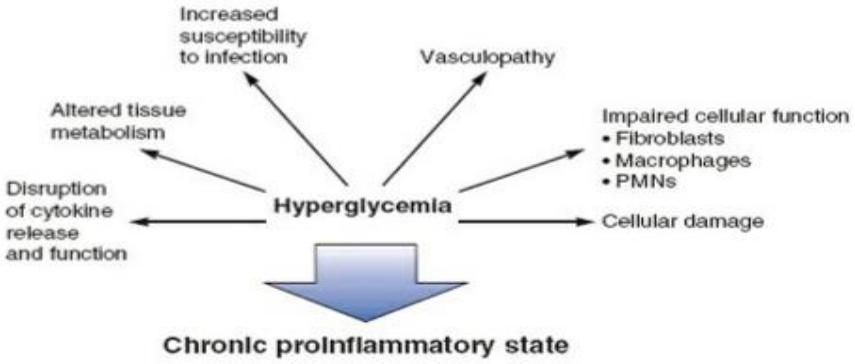

Figure 4: A cellular mechanism that impairs healing of a diabetic wound.[15]

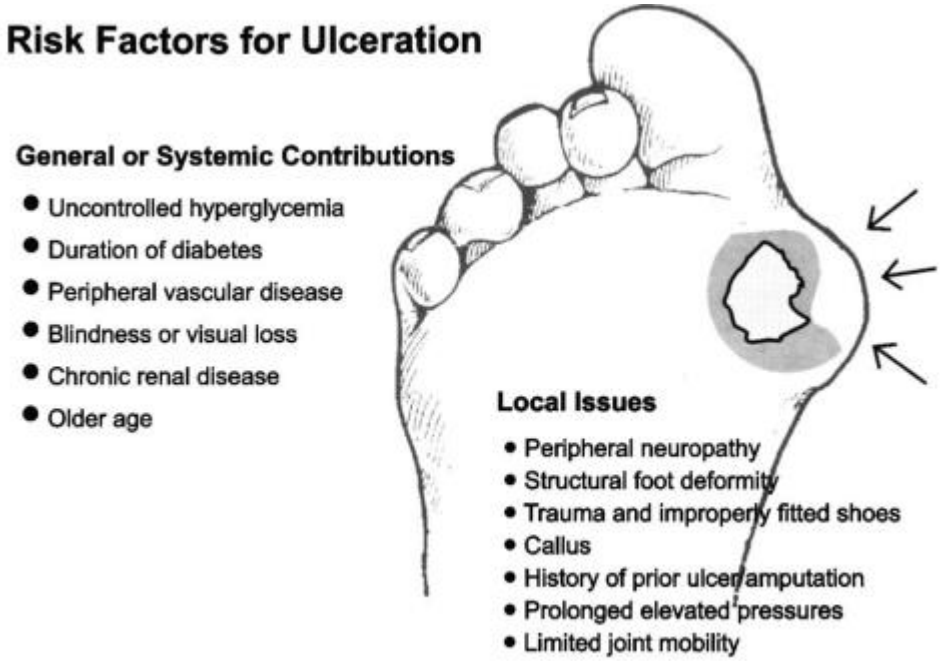

FIGURE 5 Adapted from: The guideline developed by the Clinical Practice Guideline Diabetes Panel of the American College of Foot and Ankle Surgeons (13)(2006 revision)

Additionally, male sex and smoking are also risk factors for ulceration[6].

Assessment of the diabetic foot

The assessment of the diabetic foot involves careful assimilation of the patient's history and physical findings with the results of necessary diagnostic procedures.

History: A thorough medical and foot history must be obtained from the patient. The history should address several specific diabetic foot issues as shown in Table 2

Global History	Foot Specific History	
	General	**Wound / Ulcer History**
• Diabetes - duration • Glycemic management/control • Cardiovascular, renal and opthalmic evaluations • Other comorbidities • Treating physicians • Nutritional status • Social habits: alcohol, tobacco, drugs • Current medications • Allergies • Previous hospitalizations/surgery	• Daily activities, including work • Footwear • Chemical exposures • Callus formation • Foot deformites • Previous foot infections, surgery • Neuropathic symptoms • Claudication or rest pain	• Location • Duration • Inciting event or trauma • Recurrence • Infection • Hospitalization • Wound care • Off-loading techniques • Wound response • Patient compliance • Interference with wound care (Family or social problems for patient) • Previous foot trauma or surgery • Presence of edema - unilateral vs bilateral • Charcot foot - previous or active • Charcot treatment

Table 2: Medical History

Physical Examination: All patients with diabetes require a general medical assessment (including vital sign measurements) before pedal inspection whenever they present to any health care practitioner. They should receive a thorough lower extremity examination at least once annually. Key components of the foot examination are presented in Table 3[13].

Table 3: Lower extremity diabetic foot exam

Vascular Examination

- Palpation of pulses
  - Common femoral, popliteal
  - Dorsalis pedis, posterior tibial
- Handheld Doppler examination
- Skin / limb color changes
  - Cyanosis, erythema
  - Elevation pallor, dependent rubor
- Presence of edema
- Temperature gradient
  (ipsilateral and contralateral extremity)
- Dermal thermometry
- Integementary changes
  - Skin atrophy - thin, smooth, parchment-like skin
  - Abnormal wrinkling
  - Absence of hair growth
  - Onychodystrophy
- Previous hospitalizations/surgery

Neurologic Examination

- Vibration perception
  Tuning fork 128 cps
  Measurement of vibration perception threshold (biothesiometer)
- Light pressure:
  Semmes-Weinstein 10 gram monofilament
- Light touch: cotton wool
- Two point discrimination
- Pain: pinprick (sterile needle)
- Temperature perception: hot and cold
- Deep tendon reflexes: patella, Achilles
- Clonus testing
- Babinski test
- Romberg test

Dermatologic Examination

- Skin appearance
  - Color, texture, turgor, quality
  - Dry skin
- Calluses
  - Discoloration / subcallus hemorrhage
- Fissures (especially posterior heels)
- Nail appearance
  - Onychomycosis, dystrophic, gryphotic
  - Atrophy or hypertrophy
  - Paronychia
- Hair growth
- Ulceration, gangrene, infection
  Note location, size, depth, infection status, etc.
- Interdigital lesions
- Tinea pedis
- Markers of diabetes
  - Shin spots - diabetic dermopathy
  - Necrobiosis lipoidica diabeticorum
  - Bullosum diabeticorum
  - Granuloma annulare
  - Acanthosis nigricans

Footwear Examination

- Type of shoe (athletic, oxford, comfort, etc.)
- Fit
- Depth of toe box
- Shoewear, patterns of wear
- Lining wear
- Foreign bodies
- Insoles, orthoses

Musculoskeletal Examination

- Biomechanical abnormalities
- Structural deformities
  - Hammertoe, bunion, tailor's bunion
  - Hallux limitus/rigidus
  - Flat or high-arched feet
  - Charcot deformities
  - Postsurgical deformities (amputations)
- Prior amputation
- Limited joint mobility
- Tendo-Achilles contractures / equinus
- Gait evaluation
- Muscle group strength testing
  - passive and active, non-weightbearing and weightbearing
  - Foot drop
  - Atrophy - intrinsic muscle atrophy
- Plantar pressure assessment
  - Computerized devices
  - Harris ink mat, pressure sensitive foot mat

Diagnostic procedures:

Diagnostic procedures indicated in the assessment and care of the diabetic foot include Laboratory tests, imaging studies, vascular evaluation, neurologic evaluation and Plantar foot pressure assessment.

Classification of ulcers:

Different systems are used to classify ulcers. The most commonly used classification system was described and popularised by Wagner. In the Wagner system (Table 4), foot lesions are divided into six grades depending on the depth of the wound and degree of tissue necrosis.

Grade	Lesion
0	No open lesions: may have deformity or cellulitis
1	Superficial ulcer
2	Deep ulcer to tendon or joint capsule
3	Deep ulcer with abscess, osteomyelitis, or joint sepis
4	Local gangrene - forefoot or heel
5	Gangrene of entire foot

Table 4: Wagner Classification system

Wagner's Grade 0 foot: They are the patients who are potentially "at-risk" to develop ulcer or infection due to varying degree of neuropathy and joint deformities. They need regular assessment annually for neuropathy and vascular status. The role of proper footwear and hygiene is prime. The diabetic patient and his family must establish a routine for daily foot and shoe inspection and hygiene. Washing the feet everyday with mild soap and rinsing and drying thoroughly, especially between the toes are advised.

The physician or health care provider must always set an example. Controlling blood glucose, weight, and blood pressure; eliminating smoking; encouraging

daily exercises are essential. Periodical neurological and vascular examinations are important. Early recognition and prompt reporting of a problem are encouraged.

Wagner Grade 1 foot: These are patients with superficial ulcers and cellulitis. Infection is controlled with appropriate antibiotics and debridement if required. Ulcers occur because of repetitive pressures. The pressure is relieved by complete bedrest, use of total contact cast, walker, braces etc. Associated vascular insufficiency has to be corrected by vascular reconstruction.

Wagner Grade 2 and Grade 3 feet: These are patients with deep ulcers, with or without complications like abscesses and osteomyelitis. Aggressive surgical debridement, excision of the infected bone and vascular reconstruction if necessary, is the mainstay of the treatment. To avoid recurrence education about foot care is essential.

Wagner Grade 4 and 5 feet: These are patients with localized or extensive gangrene. Management is by appropriate minor or major amputation followed by vascular reconstruction.

These grades do not consider the crucial roles of infection, ischemia, and other comorbid factors. Hence, subsequent authors have modified the classification system by including descriptors for these considerations. For example, the University of Texas-San Antonio (UTSA) system (Table 5) links lesion depth

with both ischemia and infection. This system has been validated and is generally predictive of outcome, as higher grade and stage of wounds are less likely to heal without revascularization or amputation. The UTSA system is now extensively used in many clinical trials and diabetic foot centres.

Table 5- UTSA system

Stage	Grade			
	O	I	II	III
A	Pre- or post-ulcerative lesions completely epithelized	Superficial wound not involving tendon, capsule, or bone	Wound penetrating to tendon or capsule	Wound penetrating to bone or joint
B	Infected	Infected	Infected	Infected
C	Ischemic	Ischemic	Ischemic	Ischemic
D	Infected and ischemic	Infected and ischemic	Infected and ischemic	Infected and ischemic

The Diabetic Foot- Medical and Surgical Management:

A. Baseline Approach in Managing the Acute Problem of the Diabetic Foot:

1. Appraise problem

- Careful inspection with emphasis on web spaces and back of heels.
- Record peripheral pulses, venous filling time, rubor
- Record sensation.

2. Describe lesion

3. Describe Necrotic tissue, probe sinuses with a sterile probe to determine the extent of disease.

4. Culture pus for aerobic and anaerobic organisms

5. Begin broad-spectrum antibiotic until appropriate antibiotics can be given according to culture and sensitivity.

6. Medical Management of Diabetes - Blood sugar monitoring, and anti-diabetic measures to achieve adequate glycaemic control, Doppler study of vessels.

7. X-ray both feet to exclude osteomyelitis.

8. No weight-bearing

9. Surgical Management of the Problem

- Antibiotics
- Medical management of diabetes
- Change of dressing at least once daily.
- Surgical debridement, frequently if necessary.
- If needed Consider for possible arterial reconstruction
- Drainage or open amputation.

10. Rehabilitation

- Podiatrist for patient education, preventive maintenance, orthotics, healing sandals and special shoes.
- Nutritionist to advice on diet needs.
- Surgeon to ensure proper wound healing and proper prosthetics
- The physician to make a final decision about diabetes management.
- Psychiatrist to return to regular activity.

B. Principles of Medical Management:

- Pus from ulcers sent for culture and sensitivity.
- Careful monitoring of the blood glucose levels.
- Appropriate antidiabetic measures, either insulin preparations or oral hypoglycaemic drugs.
- Broad-spectrum antibiotics to be started at the onset and change over toother antibiotics depending on the culture and sensitivity report.
- Patients with limb-threatening infections require hospitalization. It is most prudent, initially to administer antibiotics parenterally to ensure adequate serum levels.

C. Principles of Surgical Management:

- Early recognition and prompt intervention.
- Control of blood glucose

- Complete rest of injured area.
- Careful but complete debridement and drainage of all problematic areas.
- Appropriate antibiotic coverage
- Wound care and dressing
- Careful follow up, including podiatric appliances and modified footwear.

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Dressings:

In the management of diabetic foot, the central aspect is the dressing of the wound and wound management. For the limb to be salvaged, the proper scientific, cost-effective method should be used for dressing the wound. The various functions of the dressings are:

- wound isolation
- oedema limitation/reduction
- pain reduction.
- Inflammation should be limited
- exudates should be absorbed
- bacterial growth should not be promoted.
- contamination and desiccation should be prevented

Dressings can be classified as primary or secondary. The primary dressing is the one, which is in direct contact with the wound. Secondary dressing is of the

material, which holds the primary dressing in place. It has the function of compression, occlusion and additional protection.

The essential equipment necessary for bedside foot care is:

1. Sterile debridement set containing:

- Sharp scissors for debriding
- Blunt ended needle wound probe
- Smooth forceps

2. Sterile toenail clippers

3. Sterile gauze dressings

4. Tube gauge, paper tape, culture tubes

5. Medicines - Povidone-iodine - Bactericidal

- Dakin's solution (chlorazene 0.25%)
- Bacitracin ointment - antibacterial
- Vaseline gauze
- Normal saline

Dakin's solution: is a chlorine releasing agent that is both bactericidal and desloughing agent. Dakin's also helps to control fetid odours from severely infected wounds. Open wounds require packing using an unfilled gauze moistened with therapeutic solution. Changing pack two or three times a day is recommended for debridement of a necrotic wound. Allowing sufficient time between dressing changes gives the packing time to begin to dry and therefore provide gentle debridement as the packing is removed from the wound. Unfilled gauze is recommended for packing wounds. Care must be taken not to pack the wound too tightly as it tightly obstructs drainage. A properly applied dressing will not constrict the foot or leg or slip, possibly causing wound trauma or exposure. Spiralling or wrapping the roller gauze in a figure of eight fashion is the best way to prevent a tourniquet effect and will decrease the risk of compromising the circulation of the foot.

Routine Foot Dressings:

- Moisten gauze with the appropriate solution and pack the wound gently.
- Fashion a heel cup from a cut, folded and taped abdominal pad.
- Fluff two 4-inch gauze sponges over toes
- Apply paper tape to secure the roller gauze.

Casts / Splints:

A cast or splint may be applied to immobilize a limb after a skin graft or to protect the incision and reduce contractures after a below knee amputation. Applying a rigid plaster cast or splint to any neuropathic extremity can be hazardous and may cause pressure sores.

Non-Surgical Modalities to Enhance Healing:

1. Growth Factors

Growth factors originating from blood platelets, endothelium, or macrophages were thought to be potentially important treatment for diabetic foot ulcers. However, a Cochrane Database Systematic Review done in 2015 by Carvajal et al. [(19)]to assess the usefulness of growth factors for foot ulcers in patients with type 1 or type 2 diabetes mellitus included 28 randomized clinical trials involving 2365 participants in 10 countries concluded that growth factors may increase the possibility that people will have complete healing of foot ulcers in people with diabetes. However, this conclusion was based on randomized clinical trials with high risk of systematic errors (bias). Evaluation of the quality of the available evidence (GRADE) showed that further trials investigating the effect of growth factors were needed before firm conclusions could be drawn.

The safety profiles of the growth factors were unclear. The review recommended that future trials should be conducted according to SPIRIT statement and reported according to the CONSORT statement by independent investigators and using the Foundation of Patient-Centred Outcomes Research recommendations.

Greater understanding of the healing process at the cellular level has resulted in the use of growth factors like becaplermin, recombinant platelet derived growth factor which are produced through recombinant DNA technology.

2. Human Skin Equivalents

In the 1960s advances in tissue culture technologies led to the cultivation of human epidermal cells. Derma graft, a living, metabolically active, immunologically inert dermal tissue was developed. Derma graft contains normal dermal matrix proteins and cytokines, and is composed of cultural neonatal fibroblasts grown on a polyglycolic acid Bio-absorbable mesh. As the tissue grows it produces extracellular proteins and closely resembles human skin. In two studies by Gentzkow et al[(20)] and one by Pollak et al, patients were enrolled with full-thickness diabetic ulcers that had adequate perfusion. Pooled data showed that 51 percent of those who received a weekly application of Derma graft for 12 weeks achieved complete healing, vs31.7 percent in the control group.

Apligraf, another living tissue equivalent, was approved by the Food and Drug Administration in 1998 for venous leg ulcers. Apligraf consists of bovine collagen matrix containing fibroblasts and connected to a layer of stratified epithelium. The result is a sheet of tissue with both dermal and epidermal layers, metabolically and biochemically comparable to human skin.

In a study by Falanga[21], 293 patients with non-healing venous ulcers received either compression therapy or Apligraf. At six months, 63 percent of the patients receiving Apligraf healed vs. 49 percent in the control group and did so more quickly - than the control group - 61 vs. 181 days to closure**.**

3. Miscellaneous Topical Agent:

Collagen: Collagen is critical in the proliferative phase of wound healing. Exogenous sources of collagen, primarily purified bovine extracts, are available as gels, particles, and in an alginate dressing. Exogenous collagen provides additional protein for tissue repair. As a foreign agent it might also revert the chronic wound to an inflammatory phase, "jump-starting" the healing process.

Donaghue and coworkers[22] evaluated the collagen-alginate dressing (Fibracol, Johnson and Johnson, Arlington, Texas) in the treatment of diabetic foot ulcers. Seventy-five patients were randomly assigned to either a collagen-alginate dressing or gauze group. At the end of the study, the mean reduction in wound

size was 80.6 percent for the collagen-alginate group and 61.1 percent for the gauze group. Complete healing was achieved in 48 percent of the collagen-alginate group and 36 percent in the gauze group.

Hyaluronic Acid: Hyaluronic acid is involved in the structure and organization of the extracellular matrix and is associated with increased mitotic activity. It is a high molecular weight polysaccharide synthesized in the plasma membrane of fibroblasts and other cells. The ability of injured fetal tissues, which are high in Hyaluronic acid, to heal without scarring has prompted extensive research.

Beta Glucan: It is a major cell-wall carbohydrate extracted from such grains as oats and barley. The biological activity of beta glucan results from its ability to bind macrophage beta-glucan receptors and promote macrophage stimulation. Beta glucan products enhance the activities of not only macrophages but also neutrophils, natural killer cells, T cells and B cells. Beta glucan is thought to increase macrophage infiltration, speeding the onset of fibroplasia and fibrogenesis, stimulation of increased tissue granulation, and enhanced re-epithelialization. Beta glucan is available as either BCG matrix or Glucan II. Both are available in multifilament mesh dressings; BCG matrix is also impregnated with collagen.

Silver Arglaes: Silver compounds are powerful antimicrobials, useful in promoting healing. Arglaes is an inorganic phosphate similar to other compounds such as silver nitrate, silver oxide and silver chloride. It consists of

fused sodium and calcium phosphates with small amounts of silver in the presence of water, these materials release free silver ions.

Oxandrolone: Oxandrolone is an anabolic steroid with a high anabolic and low androgenic ratio, and has anticatabolic, protein-sparing properties. Exogenous anabolic agents clubbed with nutritional intervention can result in a three-fold to four-fold higher rate of protein synthesis than with nutritional interventions alone. Demling and De Santi [(23)]studied eight patients with non-healing wounds and a 10percent or greater loss of body weight. Nutrition was optimized over four weeks, without significant effect on weight gain or healing. Adding Oxandrolone resulted in gains of approximately 4 pounds per week across 12 weeks. During this time, five wounds closed completely and three others were 75 percent closed.

5. Devices

Vacuum Assisted Closure (VAC): Argenta and Morykwas[(24)] determined that controlled negative pressure at 125 mmHg promoted wound healing by improving blood flow, granulation tissue growth rates and nutrient flow and reduced bacterial levels. Based on these findings, Kinetic Concepts (San Antonio, Texas) developed the VAC system. Three hundred wounds were treated: 175 chronic wounds, 94 subacute wounds, and 31 acute wounds. Two hundred ninety-six wounds responded favourably to sub-atmospheric pressure

treatment, with an increased rate of granulation tissue formation. Wounds were treated until completely closed, were covered with a split-thickness skin graft, or a flap was rotated into the healthy granulating wound bed. The technique removes chronic oedema, leading to increased localized blood flow, and the applied forces result in the enhanced formation of granulation tissue. Vacuum-assisted closure is an extremely efficacious modality for treating chronic and difficult wounds.

Radiant Heat Bandage: Heat therapy has been employed for a long time for musculoskeletal conditions, but it has not been widely used as a wound healing modality. Heat increases local blood flow, subcutaneous oxygen tension which improves healing mechanisms. In clinical studies by Santilli and Robinson[(25)] on patients with venous leg ulcers, those who used radiant heat bandage devices reported significant decreases in both wound size and pain across two weeks with no adverse effects.

Topical Hyperbaric Oxygen Therapy:

The therapy is based on achieving an atmospheric pressure of 1.02 to 1.03atmosphere, which is thought to stimulate fibroblast growth, collagen formation and neoangiogenesis. This provides a lethal environment for anaerobes. It is achieved by putting a sealed polyethylene bag over the affected area and administering 100 percent oxygen to a pressure between 20 and 30 mmHg. Treatments last 2 to 2 .5 hours.

In a study conducted by Landau and Schattner[26], 50 patients with diabetic ulcers were treated with topical hyperbaric therapy, alone or with a low-energy laser. On average, 25 treatments were performed over three months. Forty-three of the 50 patients experienced resolution of their ulcers.

The outcome of diabetic foot ulcers management is poor, and there is continuing uncertainty regarding the ideal approach to management. It was for these reasons that the International Working Group of the Diabetic Foot (IWGDF) working group on wound healing undertook a systematic review of the evidence to inform protocols for routine care and to highlight areas which should be considered for further study in 2006, 2010, 2012 and 2018. All the systematic reviews did not find any evidence to justify the use of newer therapies, except for negative pressure wound therapy in post-surgical wounds. The review of 2018 found additional evidence to support some interventions including a sucrose-octasulfate dressing, the combined leucocyte, fibrin and platelet patch as well as topical application of some placental membrane products, all when used in addition to usual best care[27].

In the present study, we are adopting a novel method of using topical heparin in the management of diabetic ulcer to investigate the effect of heparin on outcome of diabetic ulcer.

Topical Heparin

Heparin is a natural anticoagulant which is produced in the body. Commercial heparin is obtained from the mucous membranes of pig intestine and ox lungs. Heparin is a mixture of natural sulphated mucopolysaccharides (glycosaminoglycans (GAGs)), which are generally found in granules of mast cells[28] . Anticoagulant properties of heparin are based on the amount of sulfation of the saccharide units. The mean molecular weight of heparin is about 12000 D consisting of repeating units of trisulphated disaccharides. It has an additional number of disaccharide structures, which makes heparin structure complex. It is acidic in nature. The biological activity of heparin is determined by the degree of sulfation and the chain size of heparin[29].

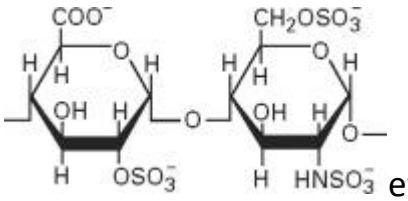

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Figure 6

It has potent anticoagulant properties that are used to treat and prevent clotting disorders where there is excessive or undesirable clotting, including, thrombophlebitis, acute myocardial infarction, stroke, and pulmonary embolism.

Heparins can be separated into two groups:

i. **unfractionated heparin (UFH)** (heparin in a range of molecular sizes)

UFH is a naturally-occurring polysaccharide that acts as an anticoagulant by inhibiting the activity of several blood coagulation factors. Laboratory work has shown that heparin-induced precipitation of low-density lipoprotein in the blood causes a reduction in the levels of fibrinogen, a clotting agent. This could lead to the confining of necrotic tissue and a reduction in the amputation rate in people with severe diabetic foot syndrome [(30)]. A study by Li et al. [(31)] in 2002 and another by Bonnie et al. [(32)] in 2011 claimed that heparin can improve hemorheological parameters, increase arterial blood supply and enhance healing in patients with diabetic foot ulcers [(1)].

ii. **low-molecular-weight heparin (LMWH)** (smaller heparin molecules).

LMWHs consist of short chains of polysaccharide, obtained from various methods of fractionation (separation) or enzymatic depolymerization (cutting) of UFH(33).

Mechanism of action

Heparin and related substances are GAGs that exist naturally inside the cell and in the extracellular matrix. They act by binding selectively to varieties of proteins and pathogens and are important to many disease processes [34,35].Researchers have proposed their mechanism of action to be as follows:

1. They have beneficial effects on local tissue microcirculation and oxygenation through the inhibition of thrombin generation and increase in plasma fibrin gel porosity, which may promote vascular perfusion in the ischaemic foot significantly and lead to improvements in its blood supply.[36]

2. They can promote healing of chronic ulcers by stimulating production of basic fibroblast growth factor and transforming growth factor-beta 1 [37].

3. Laboratory work has also shown that they have positive effects in vitro, including promotion of the synthesis of heparin sulphate in endothelial cell cultures[38], and the proliferation of fibroblasts obtained from diabetic ulcers [39].

4. Heparin can promote neo vascularisation in ischaemic limbs by improving the structure and number of capillaries [40,41].

5. Heparin promotes migration of capillary endothelial cell[42,43] and produces angiogenesis[44] and thus formation of healthy granulation tissue.

6. It also reduces bacterial translocation[45] and necessity for antibiotics is minimized.

7. Heparin also enhances Type 1 collagen synthesis[46,47]and hence the stable granulation tissue causes better healing.

All these properties mean that heparin and related substances might act as a scaffold to enhance the activity of growth factors and reduce the inflammatory response in the ulcer bed[1].

Clinical experience

A study by Jorneskog et al. [48] reported that subcutaneous injection of dalteparin, a type of LMWH, could improve the capillary circulation in the ulcer margin, which positively influenced the healing process of chronic foot ulcers in diabetic patients[48] .Ten diabetic patients with peripheral arterial occlusive disease, peripheral polyneuropathy and chronic foot ulcers were given 2500 U low molecular weight heparin (Fragmin, Kabi-Pharmacia AB, Sweden) subcutaneously once a day during 8 weeks. The mean age was 63 (47-80) years and the mean duration of foot ulcers 8 (4-12) months. All patients had previously received conventional treatment during 12 weeks, without any noticeable improvement on ulcer healing. The ulcer area was measured, and the skin microcirculation of the forefoot and around the ulcers was investigated before, during and after treatment with Fragmin. The total skin microcirculation

was measured by laser Doppler fluxmetry, the nutritional skin microcirculation by vital capillaroscopy and the macrocirculation by determination of the ankle/arm pressure ratio. The ulcer area decreased significantly in eight patients of which four healed the ulcers completely. Of the remaining two patients one worsened, whereas one showed a decrease of the ulcer area during treatment, but an increase when treatment was stopped. The macro- and total microcirculation were unchanged in all patients, whereas the nutritional capillary circulation improved in seven out of nine patients, concomitantly with clinical improvement. The biological zero value (a flow-independent part of the LD signal) was high in 4 patients before treatment, but decreased during treatment and remained low even after treatment with Fragmin. The results indicated that Fragmin positively influenced the healing process of chronic foot ulcers in diabetic patients, possibly by improving the capillary circulation in the ulcer margin, in spite of an unchanged arterial and total skin microcirculation of the region.

In 2003, Kalani et al.(49)studied the effect of dalteparin on curative properties on chronic foot ulcers in diabetics with peripheral arterial occlusive disease in a prospective, randomized, double-blind, placebo-controlled study. A total of 87 patients were investigated. Participants (n=44) were randomized to treatment with subcutaneous injection of 5000 units dalteparin (Fragmin, Pharmacia Corporation) or an equivalent volume of physiological saline (n = 43) once

daily until the ulcer healed or for a maximum of 6 months. Ulcer outcome was analysed by evaluating the number of patients 1) who healed with intact skin; 2) in whom the study ulcer was improved, unchanged, or impaired; or 3) who were amputated above or below the ankle level, as compared with control subjects. Two patients, one on dalteparin and one on placebo, dropped out of the study. Ulcer outcome was significantly better (P = 0.042, two-sided chi (2) test for trend) in the dalteparin group (n = 43) compared with the placebo group (n = 42). A total of 29 patients healed with intact skin (n = 14) or decreased the ulcer area >or=50% (n = 15) in the dalteparin group compared with 20 (n = 9 and 11, respectively) in the placebo group. Five patients in each group showed impaired ulcer healing, i.e., the ulcer area increased >or=50%. Two patients in the dalteparin group were amputated compared with eight in the placebo group. Time to healing with intact skin was 17 +/- 8 weeks in the dalteparin group compared with 16 +/- 7 weeks in placebo group (NS). The study concluded that dalteparin improved the outcome of chronic foot ulcers in diabetic patients with peripheral arterial occlusive disease.

In another study in 2007, Kalani et al.(50) reported the favourable effects of dalteparin on haemostatic function and local tissue oxygenation in patients with diabetes, severe vascular disease and foot ulcers. 87 patients with the above indications were studied in a prospective, randomized, double-blind and placebo-controlled study. They were randomized to either administration of

subcutaneous injections of 5000 U dalteparin (n=44) or placebo (n=43), once daily till the ulcer healed or for a maximum of six months. Plasma fibrinogen, fibrin gel structure [permeability coefficient (Ks) and fiber mass/length ratio (mu)], prothrombin fragment 1+2 (F1+2) antigen, plasminogen activator inhibitor-1 (PAI-1) activity and tissue plasminogen activator (tPA) antigen were analysed before randomization (baseline value), and at the end of the treatment period. The skin microcirculation of the foot was studied by transcutaneous oxygen tension ($TcPO_2$) and laser Doppler fluxmetry (LDF). The changes in Delta-values of Ks, mu, tPA and $TcPO_2$ were more ($p<0.05$) when treated with dalteparin, as compared to the changes during treatment with placebo. At baseline, plasma fibrinogen and Ks were significantly correlated to $TcPO_2$.The study concluded that local skin oxygenation improved and a less thrombogenic fibrin gel structure was formed in patients treated with dalteparin. Beneficial effects on haemostatic function were likely to contribute to the improved skin oxygenation observed during treatment with dalteparin.

In a Spanish study by Rullan et al.(51), diabetic foot ulcers treated with bemiparin, another LMWH preparation, administered once daily by subcutaneous injection were observed to have better ulcer improvement rates, complete healing rates and few adverse reactions. A triple-blind, parallel, randomized, placebo-controlled trial in patients aged > 18 years, [corrected] having diabetes for a minimum of 3 years, and with a foot ulcer persisting for >

3 months, Bemiparin 3500 IU/day was administered sub cutaneous for 10 days, followed by 2500 IU/day for up to 3 months plus standard care for ulcers and was compared with placebo along with standard care for ulcers for 3 months. The primary efficacy end-point was an objective decrease in ulcer area of >or= 50%, measured by digital photography and ImageJ software, and/or any decrease in Wagner's ulcer grade at 3 months. It was observed that **Ulcer** improvement rates were 70.3% (26 of 37 patients) in the bemiparin group and 45.5% (15 of 33 patients) in the placebo group [absolute difference 24.8; 95% confidence interval (CI) 2.3, 47.3; P = 0.035] (number needed to treat 4; 95% CI 2, 43). Complete healing rates at 3 months were similar in both groups (35.1% vs. 33.3%; P = 0.874), as were the number of adverse events. The researchers concluded that Bemiparin was more effective than placebo in the management of diabetic foot ulcers and had few side-effects.

Topical heparins are extensively used in Europe for the prevention and treatment of local symptoms associated with peripheral vascular disorders. A comprehensive review of the literature by Vecchio & Frisinghelli[52] gauged the safety and efficacy of topically smeared heparins for the treatment of vascular diseases in 20 studies (n=1055). The studies compared topical heparin formulations with either placebo, no treatment, heparin administered subcutaneously or with each other in the cure of superficial thrombophlebitis or

venous insufficiency. The list of comparative studies used in the review for patients with superficial thrombophlebitis is given in the Table 6.

Table 6

Table II. Comparative studies in patients with superficial thrombophlebitis

Heparin	Comparator	Patients (n)	Aetiology of thrombophlebitis	Duration of treatment	Endpoints	Study design	Reference
Treatment							
Heparin gel 1000 IU/g	Placebo	126	Infusion-related	7 days	Time to healing Signs and symptoms	Double-blind Treatment allocation concealed	15
Heparinoid mucopolysaccharide cream	Placebo	100	Infusion-related	5 days	Time to local sign/ symptom relief ^{125}I-fibrinogen uptake	Double-blind Treatment allocation concealed	16
Heparinoid mucopolysaccharide cream	Placebo	40	Infusion-related	Unclear	Local sign/symptom relief ^{125}I-fibrinogen uptake	Double-blind Treatment allocation unclear	17
Heparinoid mucopolysaccharide cream	Placebo	50	Sclerotherapy in patients with varicose veins	1 or 2 weeks	Pain Signs and symptoms Investigator-assessed improvements	Double-blind One leg was exposed to mucopolysaccharide cream and the other to placebo (randomized allocation)	18
Heparinoid mucopolysaccharide cream	Placebo, piroxicam	68	Spontaneous or infusion-related	2 weeks	Thrombophlebitic status Thrombophlebitic area Pain	Single-blind for mucopolysaccharide cream Allocation concealment unclear	19
Heparin gel 1000 IU/g	Heparinoid mucopoly-saccharide cream	44	Various vascular disorders (seven patients with superficial thrombophlebitis or post-phlebitis syndrome)	4-6 weeks	Symptom score	Blinding unclear Randomization unclear	20
Heparin gel 1000 IU/g	Heparin/ aescinate/ phospholipid	30	Various vascular disorders (six patients with superficial thrombophlebitis or post-phlebitis syndrome)	20 days	Symptom score	Blinding unclear Randomization unclear	21

Table II. Contd

Heparin	Comparator	Patients (n)	Aetiology of thrombophlebitis	Duration of treatment	Endpoints	Study design
Heparin gel 1000 IU/g	Heparin/ aescinate/ phospholipid	40	Various vascular disorders (32 with superficial thrombo-phlebitis or post-phlebitis syndrome)	Mean 57.5 days	Improvement or no improvement	Blinding unclear Randomization unclear
Liposomal heparin spray gel 2400 IU/g	Enoxaparin sodium	46	Superficial venous thrombosis	14 days	Symptom score Duplex ultrasound	Open-label Randomized
Prevention						
Heparin ointment	Untreated controls, fluocinolone acetonide	110	Prevention of infusion-related thrombophlebitis	Duration of infusion	Incidence of superficial thrombophlebitis	No blinding Unclear if treatment was randomized
Organoheparinoid 0.2%, adrenocortical extract, salicylic acid (Movelat®)	Placebo	97	Prevention of infusion-related thrombophlebitis	Duration of infusion	Incidence of superficial thrombophlebitis. Time to development of superficial thrombophlebitis	Blinding unclear Concealment of treatment allocation unclear

Source: Topical Heparins in Vascular Disorders [52]

The list of comparative studies used in the review for patients with venous insufficiency is given in table 7.

Table 7

Table III. Comparative studies in patients with venous insufficiency

Heparin	Comparator	Patients (n)	Aetiology of venous insufficiency	Duration of treatment	Endpoints	Study design	Reference
Heparin/aescinate/ phospholipid gel	Placebo	22	Varicose veins	Single dose	Microcirculation	Double-blind Treatment allocation concealed	29
Heparin/aescinate/ phospholipid gel	Placebo	10	Venous ulceration	Single dose	Microcirculation	Double-blind Treatment allocation concealed	30
Heparin/aescinate/ phospholipid gel	Placebo	28	Venous ulceration	3 days	Microcirculation	Double-blind Treatment allocation concealed	31
Heparin/aescinate/ phospholipid gel	Placebo	30	Venous ulceration	4 weeks	Pain and oedema Microcirculation Ulcer healing	Double-blind Treatment allocation concealed	32
Heparin/aescinate/ phospholipid gel	Placebo	30	Diabetic neuropathies	Single dose	Microcirculation	Double-blind Treatment allocation concealed	33
Heparin/aescinate/ phospholipid gel	Placebo	15	Diabetic neuropathies	4 weeks	Microcirculation	Double-blind Treatment allocation concealed	34
Heparin/aescinate/ phospholipid gel	Placebo	35	Diabetic neuropathies	2 weeks	Microcirculation	Double-blind Treatment allocation concealed	35
Heparin gel 1000 IU/g	Heparinoid mucopoly-saccharide cream	44	Various vascular disorders (31 patients with chronic venous insufficiency)	4–6 weeks	Symptom score	Blinding unclear Randomization unclear	20
Heparin gel 1000 IU/g	Heparin/ aescinate/ phospholipid	30	Various vascular disorders (24 patients with chronic venous insufficiency)	20 days	Symptom score	Blinding unclear Randomization unclear	21
Heparin gel 1000 IU/g	Heparin/ aescinate/ phospholipid	40	Various vascular disorders (eight patients with varicose ulcers)	Mean 57.5 days	Improvement or no improvement	Blinding unclear Randomization unclear	22

Source: Topical Heparins in Vascular Disorders [52]

The review showed that Heparin gel 1000 IU/g (LiotonR 1000 gel, MenavenR 1000gel) was superior as compared to placebo in alleviating the signs and symptoms of superficial thrombophlebitis. Liposomal heparin gel 2400 IU/g (LipoHepForteR)was equivalent in efficacy to subcutaneously administered low-molecular-weight heparin at alleviating local symptoms of superficial venous thrombosis. In studies comparing different formulations of topical heparin, all preparations appeared effective. Still, heparin gel 1000 IU/g was superior to a heparinoid mucopolysaccharide cream (HirudoidR) in patients

with vascular disorders in respect of reducing spontaneous pain, induced pain, oedema and heaviness in the foot. Another study showed that heparin gel 1000 IU/g was superior as compared with a gel formulation containing heparin 100 IU/g, aescinate and essential phospholipids (EssavenR), for resolving the symptoms. All treatments were generally well-tolerated, with a relatively low incidence of local skin events. In summary, topical heparin preparations may be useful for relieving the signs and symptoms of vascular disorders while improving microcirculation. There was some evidence to suggest that heparin gel 1000 IU/g may be more effective than other topical preparations in treating these conditions, possibly because of the relatively high heparin levels in this formulation. That remained to be tested in well-controlled, adequately powered clinical trials.

A prospective comparative study of Conventional and Topical Heparin Dressing in Lower Limb Diabetic Ulcers by Srinivasan and Muralidharan[(4)]in a teaching hospital in Coimbatore, divided diabetic ulcer foot patients into two groups: one was treated with conventional saline dressing (n=32)and the other using topical aqueous heparin (n=32). The wound healing was assessed using Bates-Jensen wound assessment tool and the hospital stay, antibiotic and analgesic requirement were recorded in both groups. On statistical analysis, the hospital stay was found to be lower in the heparin group as compared to conventional dressing group (16.4 days vs. 13.6 day). The antibiotic requirement was also

low for the heparin dressing group. The analgesic requirement was almost similar for both the groups (2.1 mean doses per day for conventional group vs. 2.0 mean doses per day for heparin group). The mean Bates-Jansen wound healing score was lower for the heparin group at the end of 1, 2 and 3 weeks. Wound healing was better and earlier in heparin group. 2 patients from the conventional dressing group required amputation as compared to nil from the heparin group. The study concluded that topical heparin dressing of lower limb diabetic ulcers showed significant improvement in healing, reduction in hospital stay and antibiotic requirement.

MATERIALS AND METHODS

- **SOURCE OF DATA:** This study was carried out in the Department of General Surgery, Shri B.M Patil Medical College, Hospital and Research centre, Vijayapura.
- **STUDY PERIOD**: from November 2018 to June 2020.
- **STUDY DESIGN**: Prospective, comparative study of efficacy of topical heparin solution dressing versus conventional dressing with 10% povidone- iodine solution in wound healing.
- **STUDY SAMPLE**: Total of 80 patients with 40 in each group i.e., 40 patients in study group and 40 patients in control group.
- **APPROVAL**: Study was approved by the Institutional Medical Ethics Committee and written informed consent was obtained from all patients participating in the study.
- **STUDY POPULATION:** Patients with diabetic ulcers of Wagner's grade 1 and 2 during the study period were diagnosed on the basis of thorough clinical examination, appropriate laboratory and radiological investigations. They were included in the study based on the inclusion and exclusion criteria. A Proforma was used to collect all the relevant data from the patients. Detailed history was taken; thorough clinical examination and investigations were performed on all the patients included in the study. All the cases were followed up to discharge and subsequently for a follow up

till wound healing. Data was entered on master chart for analysis. It was analyzed by using student t- test.

Inclusion criteria

All the patients presenting with grade 1 and grade 2 diabetic ulcers admitted in the Dept of Surgery, Shri B M Patil Medical College Hospital and Research Centre.

Exclusion criteria

- Wagner's classification of diabetic ulcer grade 3 and above.
- With low platelet count or altered APTT/INR/sepsis
- Allergy to heparin
- Albumin <2gm/dl of blood
- Patient with personal or familial history of bleeding disorders.
- Marjolijn's ulcer/ Skin malignancies

METHOD OF PREPARATION OF HEPARIN SOLUTION FOR TOPICAL USE

- Unfractioned heparin available in 5ml vials of 5000IU/ml strength was used. One vial was mixed with 100ml ml of normal saline and stirred to make heparinized sodium solution fit for topical application. The medication was applied to the ulcer drop by drop with 10ml syringe, once daily.

- Clotting time was done during the course of heparin treatment to monitor the dose of heparin. APTT and INR was done every 7 days. This was done to look into the systemic absorption of topically applied and its effects on bleeding profile of patient

- From infected wounds swabs were taken for culture and sensitivity every week, to monitor infection status of the wound.

- Patients were thoroughly examined and ulcer size (length, breath, depth) was measured.

- Every week the ulcer area was calculated by placing sterile gauze over the ulcer and two maximal perpendicular diameters were taken and multiplied.

- The wound area in cm^2 and pre dressing status of wound in terms of presence of granulation tissue, presence of discharge, duration of hospital stay, culture sensitivity was compared between two groups.
- End point of the study includes presence of healthy granulation tissue, culture negative wound and wound ready for grafting.

RESEARCH HYPOTHESIS:

Heparin promotes the healing of diabetic ulcers without any adverse events.

SAMPLE SIZE CALCULATION

- 80 patients are required (40 per group) to have an 80% chance of detecting, as significant at the 5% level, a decrease in the primary outcome measure from 10% in the control group to 35% in the experimental group.
- Calculation based on the formula:
- $n = f(\alpha/2, \beta) \times [p_1 \times (100 - p_1) + p_2 \times (100 - p_2)] / (p_2 - p_1)^2$
- where p_1 and p_2 are the percent 'success' in the control and experimental group respectively

- Hence the sample size is 80, patients are selected on systematic random sampling method, 40 in control group and 40 in study group (3)

STATISTICAL ANALYSIS

- All characteristics were summarized descriptively. For continuous variables, the summary statistics of N, mean, standard deviation (SD) were used. For categorical data, the number and percentage were used in the data summaries and data was analyzed by Chi square test for association, comparison of means using t test, ANOVA and diagrammatic presentation.

RESULTS

Table 8: Distribution of Age between Cases and Controls

Parameters	Case		Control		p value
	Mean	SD	Mean	SD	
Age(yrs)	57.1	11.6	54.0	11.7	0.245

Figure 7: Distribution of Age between Cases and Controls

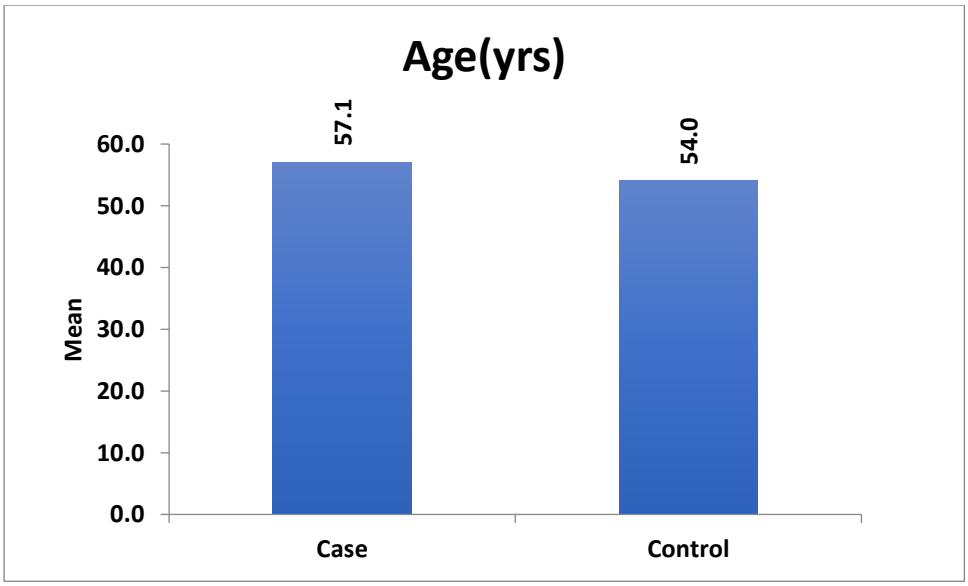


Table 8 and Figure 7 shows that mean age of patients in the case group was 57.1 years while it was 54.0 years in the control group. The mean age

of the case group was not statistically different from that of the control group.

Table 9: Distribution of Sex between Cases and Controls

Sex	Case		Control		p value
	N	%	N	%	
Male	34	85.0%	30	75.0%	0.264
Female	6	15.0%	10	25.0%	
Total	40	100.0%	40	100.0%	

Figure 8: Distribution of Sex between Cases and Controls

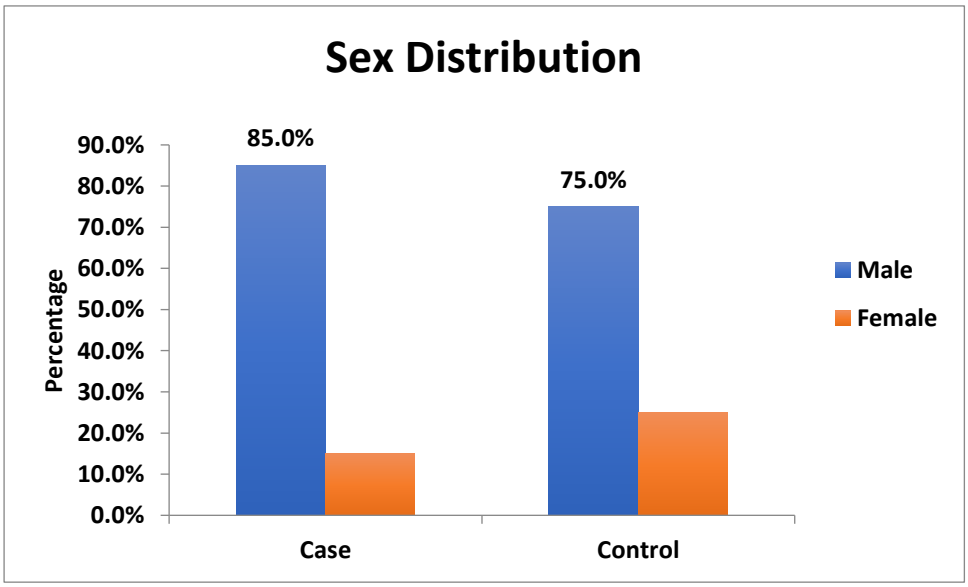


Table 9 and Figure 8 shows the sex distribution among cases and controls. Males predominated both the groups. The male: female ratio in the cases group was 5.7:1 whereas it was 3: 1 in the control group. The difference in sex distribution among cases and controls was not statistically significant.

Table 10: Background parameters between Cases and Controls

Parameters	Case		Control		p value
	N	%	N	%	
Diabetic	40	100.0%	40	100.0%	-
Hypertensive and diabetic	10	25.0%	11	27.5%	0.799

Figure 9: Background parameters between Cases and Controls

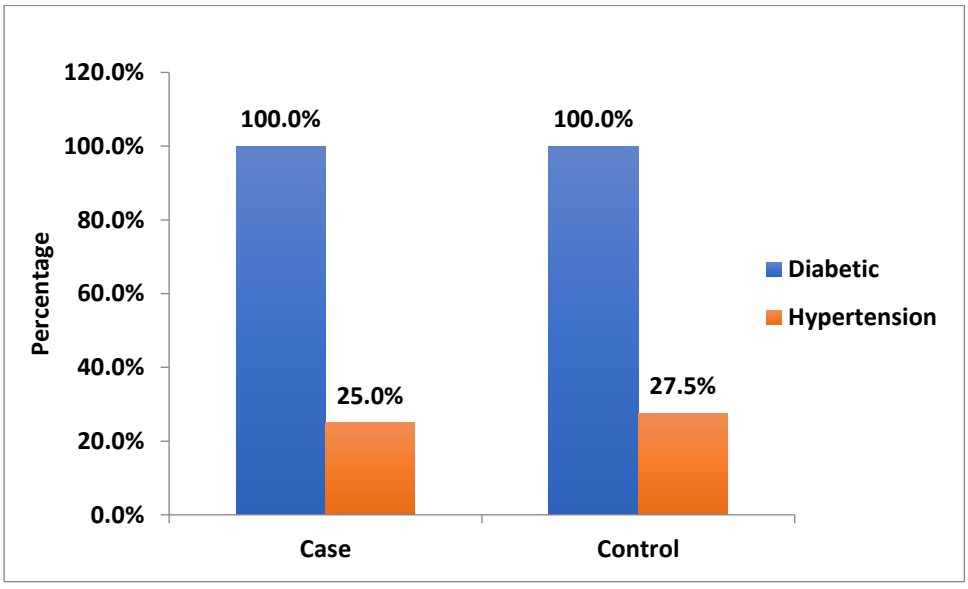


Table 10 and Figure 9 show the comorbid conditions between cases and controls. There was no significant difference in the number of cases presenting with hypertension among cases and controls.

Table 11: Distribution of HbA1c between Cases and Controls

Parameters	Case		Control		p value
	Mean	SD	Mean	SD	
HbA1c	8.51	1.2	8.48	1.0	0.904

Figure 10: Distribution of HbA1c between Cases and Controls

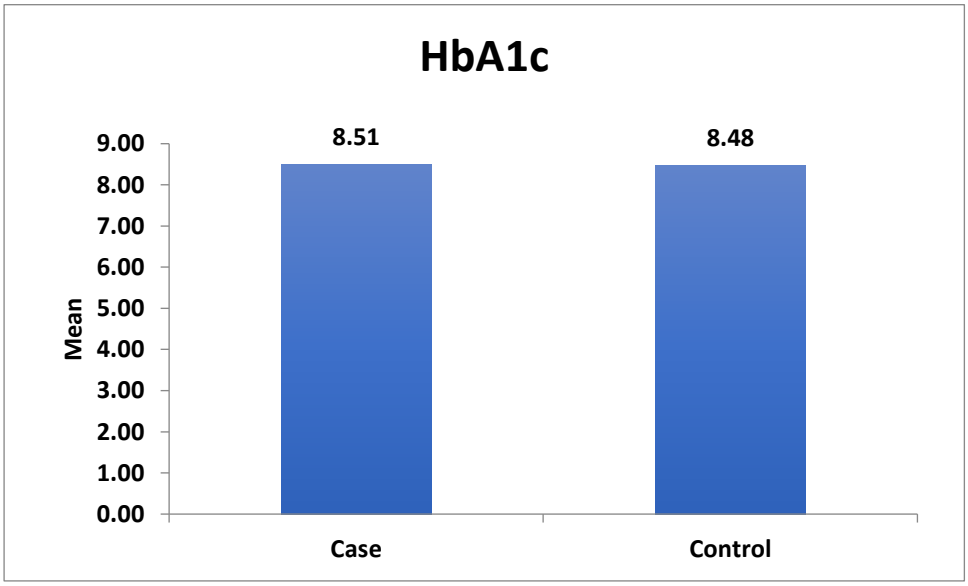


Table 11 and Figure 10 show the mean glycated haemoglobin levels of cases and controls. There was no statistically significant difference in the mean glycated haemoglobin levels among the cases and controls.

Table12: Mean Duration of DM between Cases and Controls

Parameters	Case		Control		p value
	Mean	SD	Mean	SD	
Duration of DM(Yrs)	8.2	6.4	7.3	6.4	0.521

Figure 11: Mean Duration of DM between Cases and Controls

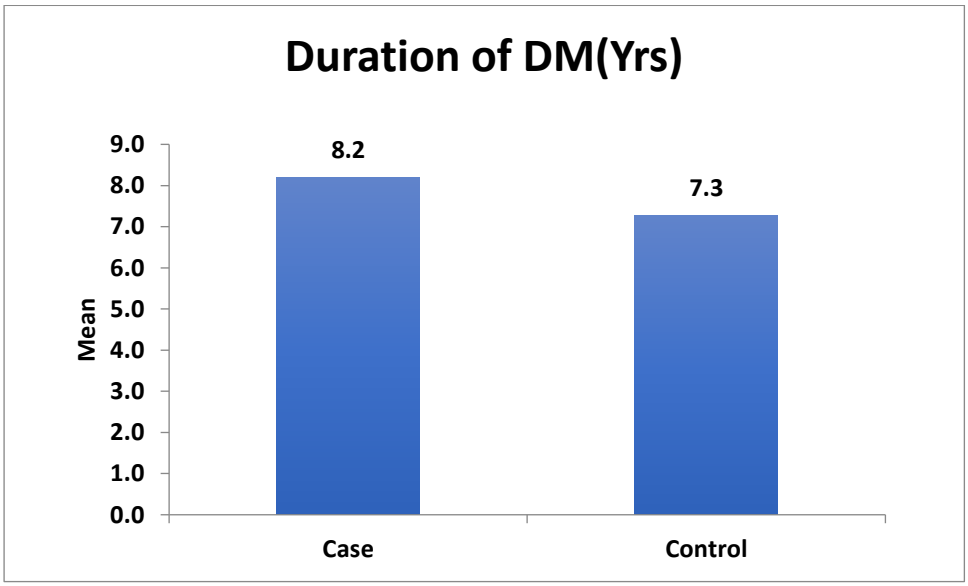


Table 12 and Figure 11 shows the mean duration of diabetes mellitus among cases and control. There is no statistically significant difference among the two groups with regards to the mean duration of DM.

Table 13: Mean Surface Area of Ulcer between Cases and Controls

Surface Area of Ulcer(cm2)	Case		Control	
	Mean	SD	Mean	SD
At Day 0	25.6	7.2	26.2	6.8
By 7 Days	24.5	7.1	25.5	6.8
By 14 Days	23.0	6.9	24.7	6.8
By 21 Days	15.6	3.3	20.6	4.7
By 28Days	12.1	9.6	14.7	3.7

Figure 12: Mean Surface Area of Ulcer between Cases and Controls

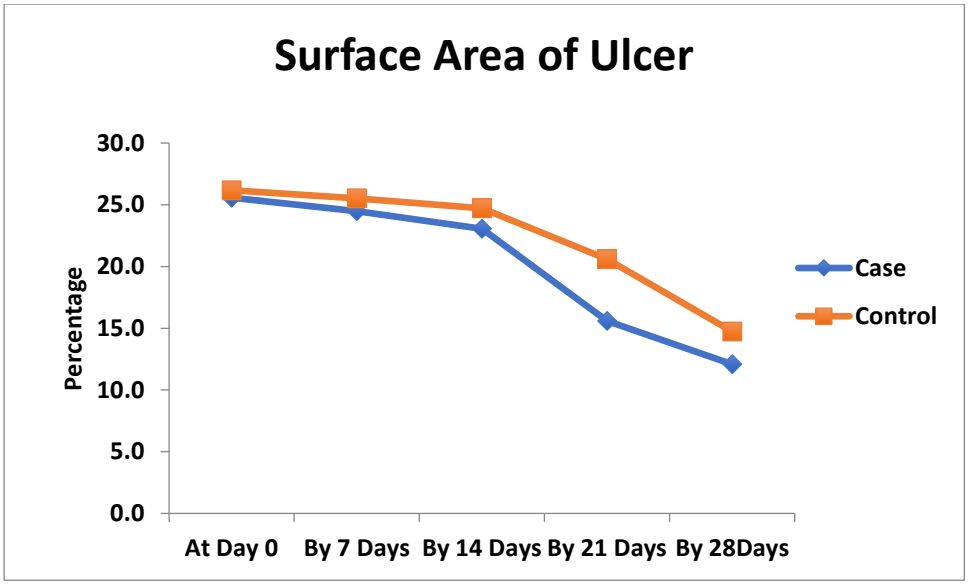


Table 13 and Figure 12 shows the mean surface area of ulcer in Cases and Controls from day 0 to day 28. From the figure it is clear that the rate of

reduction in the surface area of ulcer in Cases is greater and faster as compared to Controls.

Table 14: Reduction in mean Surface Area of Ulcer between Cases and Controls

Groups	Reduction in Surface Area of Ulcer (cm^2)			
	Day 0 to Day 7	p value	Day 0 to Day 14	p value
Case	4%	<0.001*	10%	<0.001*
Control	3%	<0.001*	6%	<0.001*

Note: * significant at 5% level of significance (p<0.05)

Figure 13: Reduction in mean Surface Area of Ulcer between Cases and Controls

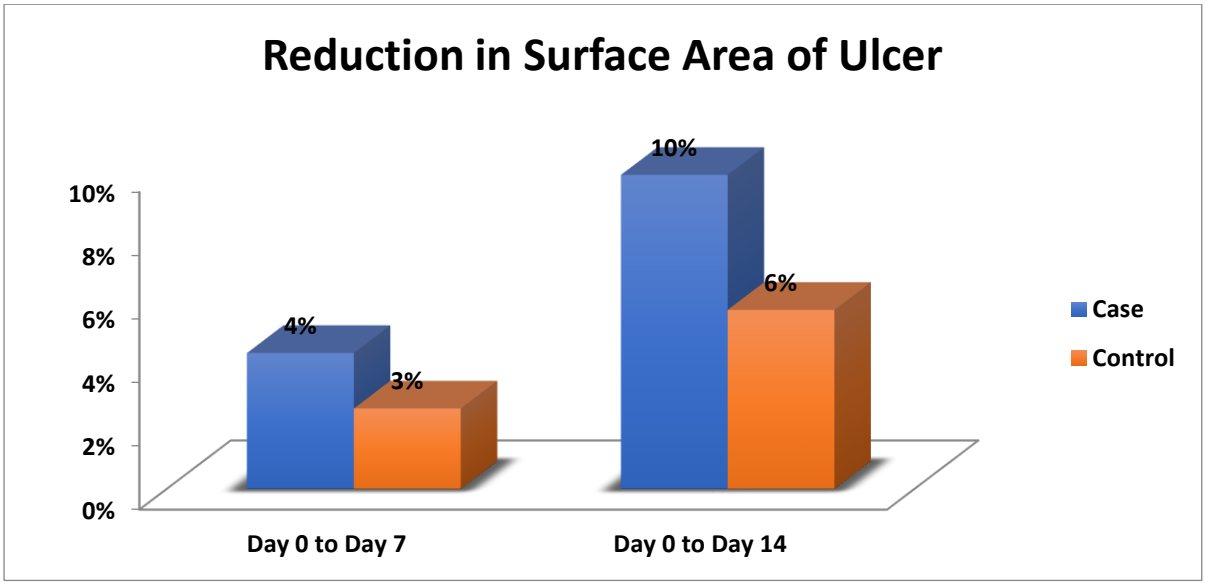


Table 14 and Figure13 show the reduction in mean surface area of ulcer between Cases and Controls at the end of 1 week, 2 weeks, 3 weeks and 4 weeks. The reduction in surface area at the end of each week is statistically

significant in both Cases as well as Controls but the % reduction is more in Cases as compared to Controls.

Table 15: Reduction in mean Surface Area of Ulcer Per Day

Groups	Change in Mean Surface Area of Ulcer (cm^2) per day				
	Day 0 to Day 7	Day 0 to Day 14	Day 0 to Day 21	Day 0 to Day 28	Overall
Case	0.2	0.4	0.7	1.1	0.6
Control	0.1	0.2	0.3	0.4	0.3

Figure 14: Reduction in mean Surface Area of Ulcer Per Day

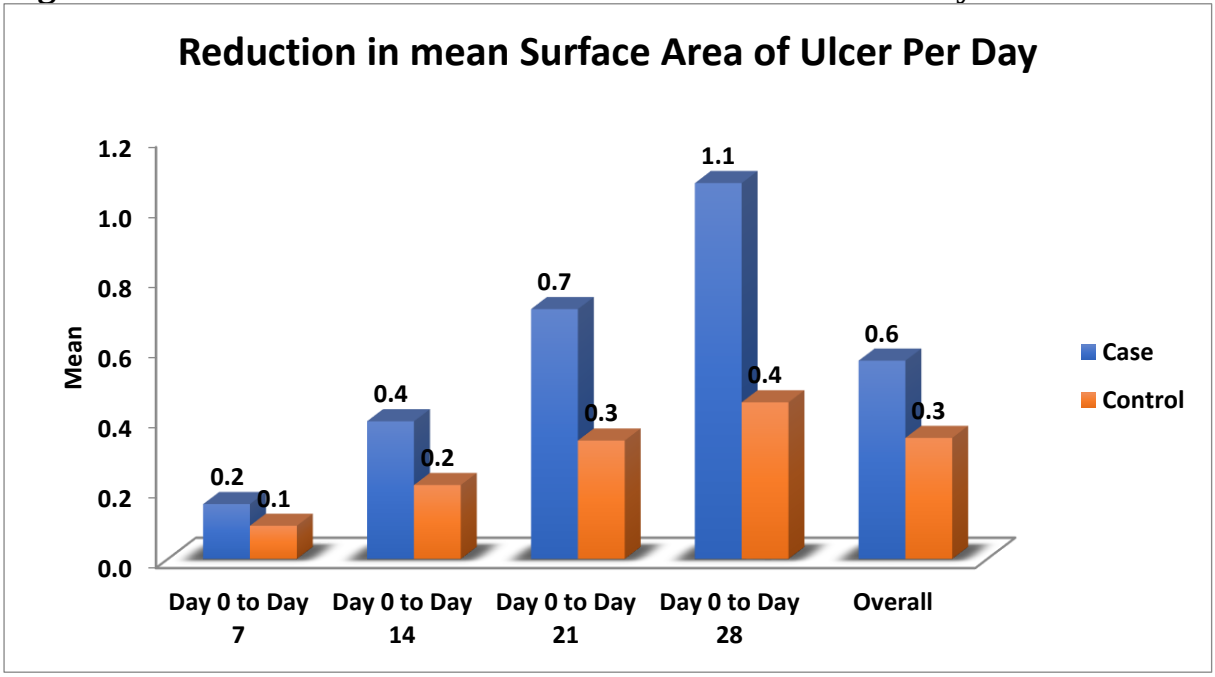


Table 15 and Figure 14 show the reduction in surface area of ulcer per day. The reduction in surface area of the wound is more in Cases as compared to Controls.

Table 16: Healthy Granulation Tissue between Cases and Controls

Healthy Granulation Tissue	Case		Control		p value
	N	%	N	%	
0 DAYS	0	0.0%	0	0.0%	-
BY 7 DAYS	20	50.0%	11	27.5%	0.041*
BY 14 DAYS	37	92.5%	27	67.5%	0.005*
BY 21 DAYS	40	100.0%	40	100.0%	-
BY 28DAYS	40	100.0%	40	100.0%	-

Note: * significant at 5% level of significance (p<0.05)

Figure 15: Healthy Granulation Tissue between Cases and Controls

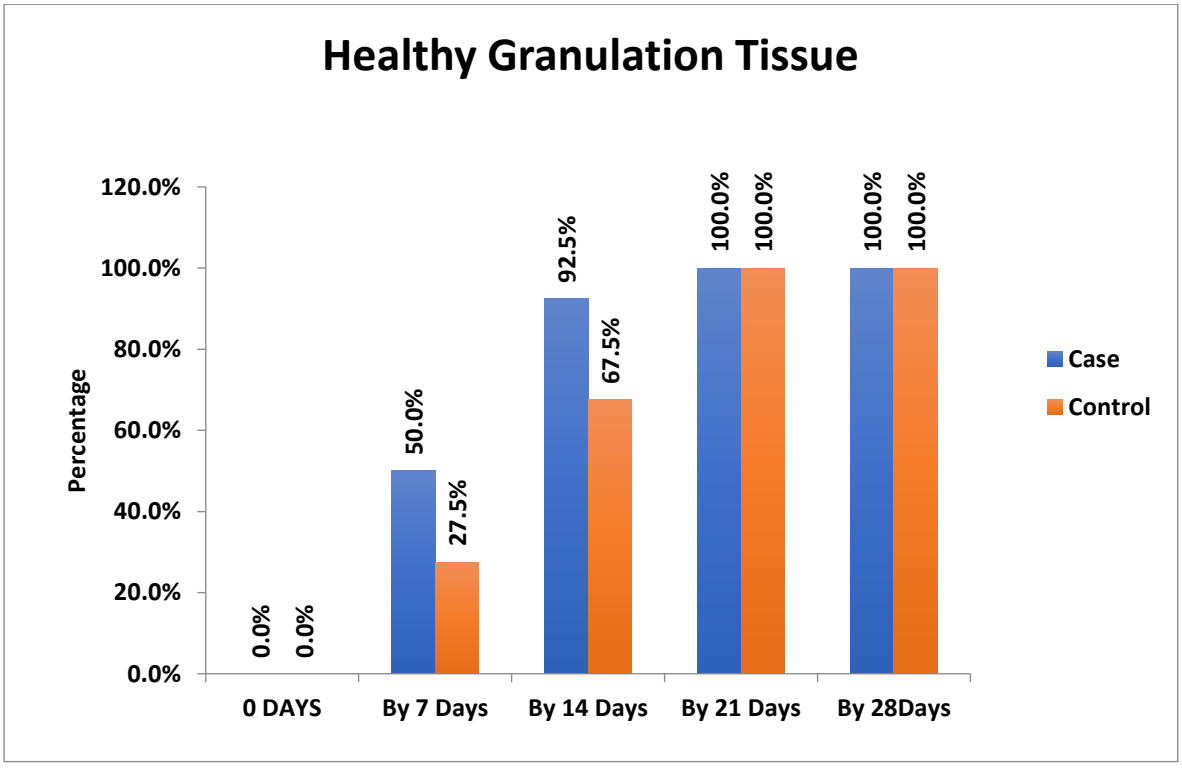


Table 16 and Figure 15 show the growth of healthy granulation tissue in Cases and Controls from day 0 to day 28. By day 7, 50% of Cases had developed a healthy granulation tissue which was significantly more than that developed in Controls (p 0.048). By day 14, 92.5 % Cases had a healthy granulation tissue as compared to 67.5% Controls who had developed a healthy granulation tissue. This difference was statistically significant (p< 0.05).

Table 17: Wound Discharge between Cases and Controls

Serous Discharge	Case		Control		p value
	N	%	N	%	
BY 7 DAYS	20	50.0%	10	25.0%	0.048*
BY 14 DAYS	37	92.5%	28	70.0%	0.010*
BY 21 DAYS	40	100.0%	40	100.0%	-
BY 28DAYS	40	100.0%	40	100.0%	-

Note: * significant at 5% level of significance (p<0.05)

Figure 16: Discharge between Cases and Controls

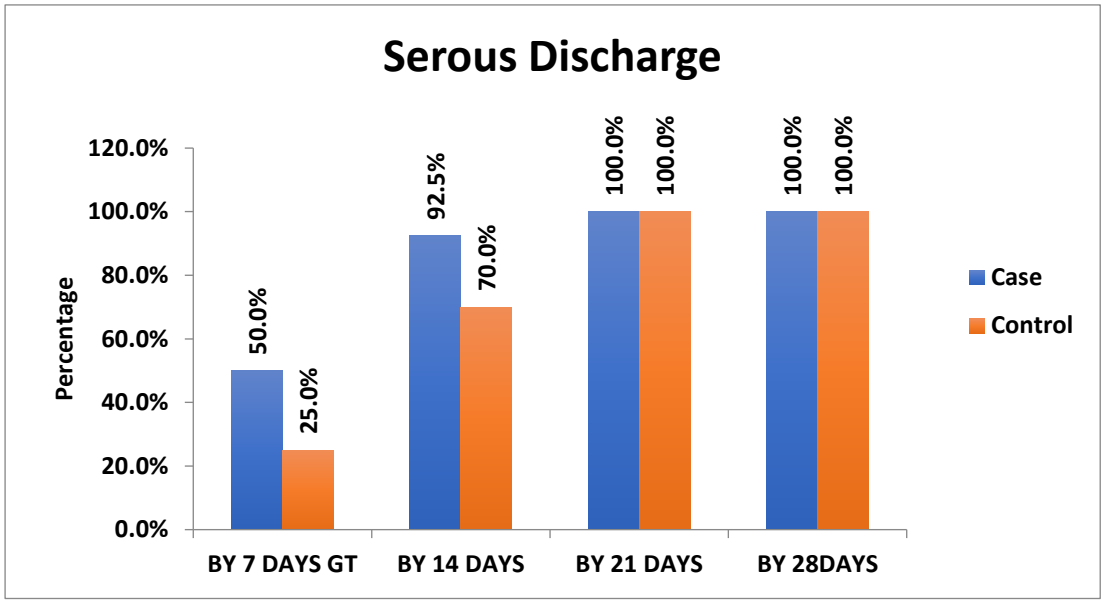


Table 17 and Figure 16 shows the serous wound discharge between Cases and Controls at the end of each week. By 7 days, serous discharge was seen in more number of patients in Case group as compared to Control group (50 % vs 25 %). By 14 days also, serous discharge was seen in more number of patients in Cases group as compared to Control group (92.5 % vs 70.0 %, $p< 0.010$).

Table 18: Culture between Cases and Controls at day 14

Organism	Case		Control		p value
	N	%	N	%	
Citrobacter	5	12.5%	9	22.5%	0.332
E. Coli	5	12.5%	5	12.5%	
Klebsiella	7	17.5%	8	20.0%	
Pseudomonas	4	10.0%	4	10.0%	
Aureus	7	17.5%	10	25.0%	
Sterile	12	30.0%	4	10.0%	
Total	40	100.0%	40	100.0%	

Figure 17: Culture between Cases and Controls at day14

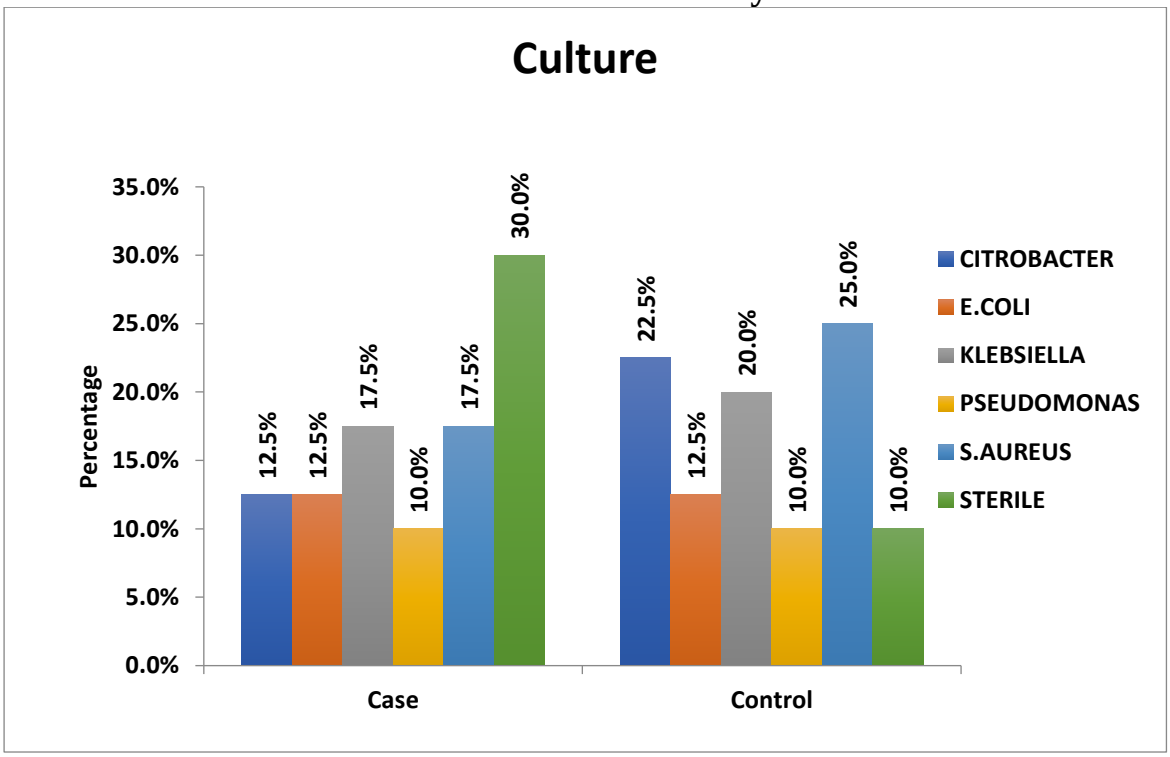


Table 18 and Figure 17 shows the culture of Cases and Controls. There was significant difference among the two groups with regards to the distribution of microorganisms.

Table 19: Outcome between Cases and Controls

Outcome	Case		Control		p value
	N	%	N	%	
SEC Suturing	8	20.0%	8	20.0%	0.840
SI	2	5.0%	1	2.5%	
STSG	30	75.0%	31	77.5%	
Total	40	100.0%	40	100.0%	

Figure 18: Outcome between Cases and Controls

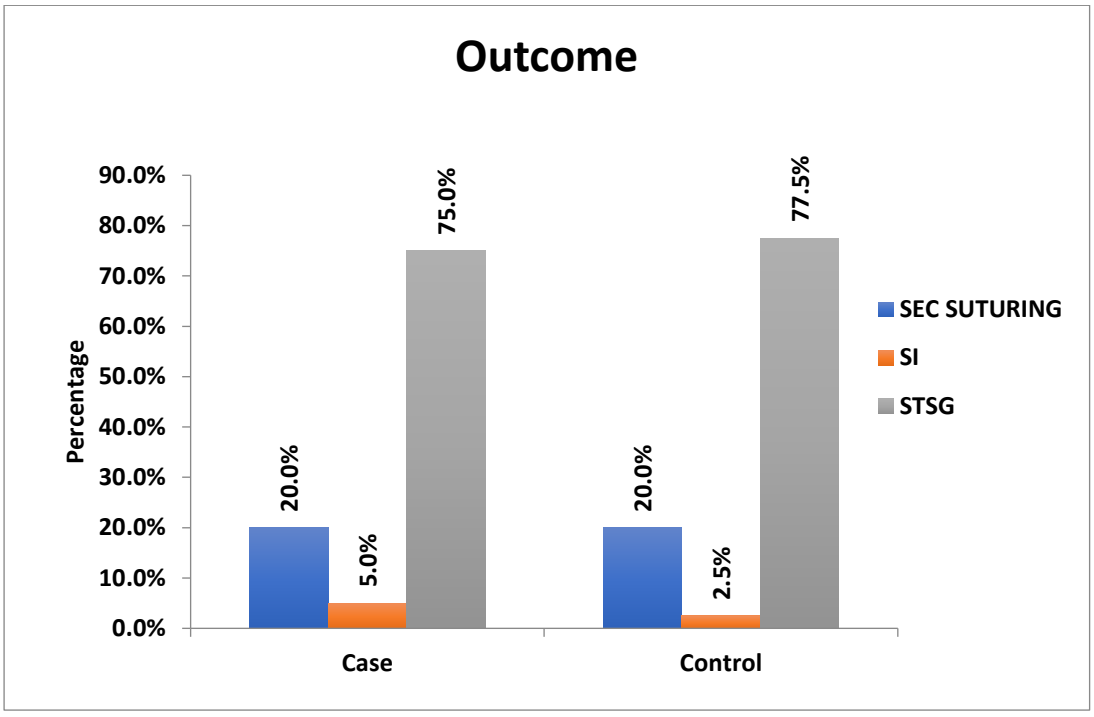


Table 19 and Figure 18 shows the outcome of Cases and Controls. There was no significant difference among the groups with respect to the outcome of secondary suturing, SI or skin grafting (p=0.840).

Table 20: Mean Duration of Outcome between Cases and Controls

Parameters	Case		Control		p- value
	Mean	SD	Mean	SD	
Duration of Outcome (Days)	18.2	5.6	23.5	5.7	<0.001*

Note: * significant at 5% level of significance (p<0.05)

Figure 19: Mean Duration of Outcome between Cases and Controls

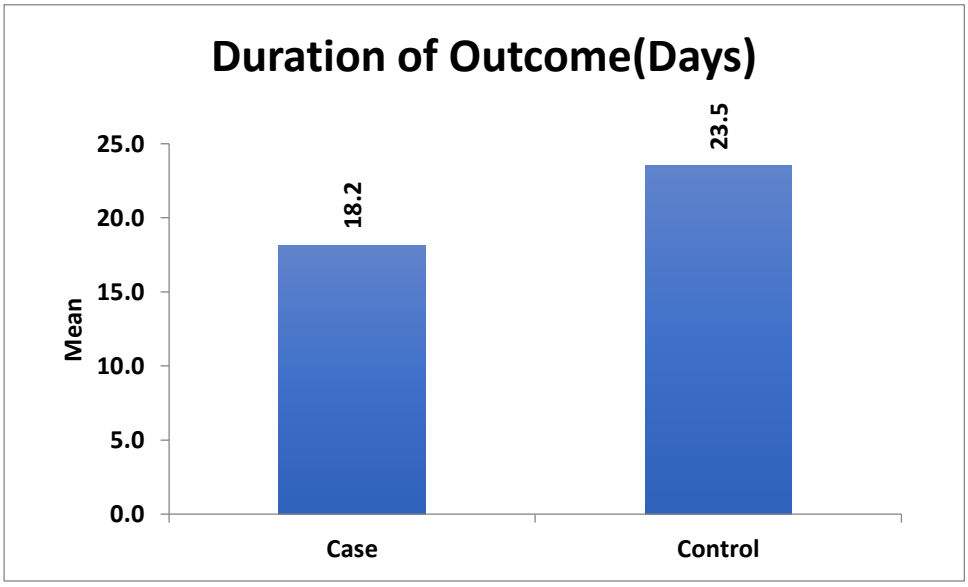


Table 20 and Figure 19 show the mean time required to reach the outcome for Cases and Controls. The mean time required to reach outcome is significantly lower for Cases as compared to Controls ($p<0.001$).

Table 21: Mean Duration of Hospital Stay between Cases and Controls

Parameters	Case		Control		p value
	Mean	SD	Mean	SD	
Hospital Stay (Days)	21.3	6.2	26.7	6.4	<0.001*

Note: * significant at 5% level of significance ($p<0.05$)

Figure 20: Mean Duration of Hospital Stay between Cases and Controls

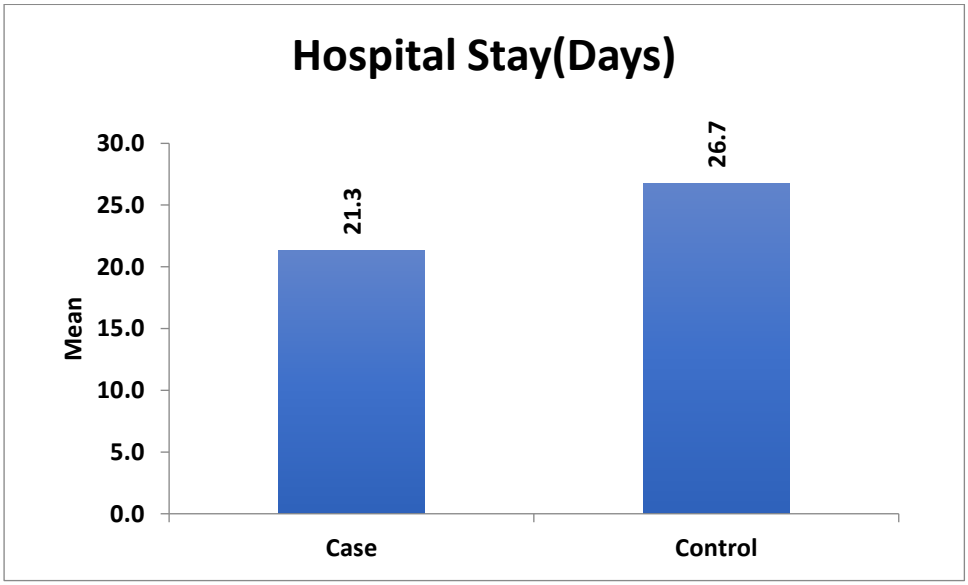


Table 21 and Figure 20 show the comparison of mean duration of hospital stay between Cases and Controls. The mean duration of hospital stay was significantly shorter for Cases as compared to Controls (p< 0.001).

Table 22: Time for Outcome

Time for Outcome	Case		Control		p value
	N (no of cases operated)	%	N (no of cases operated)	%	
Within 1week	1	2.5%	0	0.0%	0.006 *
1- 2weeks	12	30.0 %	5	12.5 %	
2-3weeks	16	40.0 %	8	20.0 %	
3-4weeks	9	22.5 %	17	42.5 %	
>4weeks	2	5.0%	10	25.0 %	
Total	40	100.0 %	40	100.0 %	

Note: * significant at 5% level of significance (p<0.05)

Figure 21: Time for Outcome

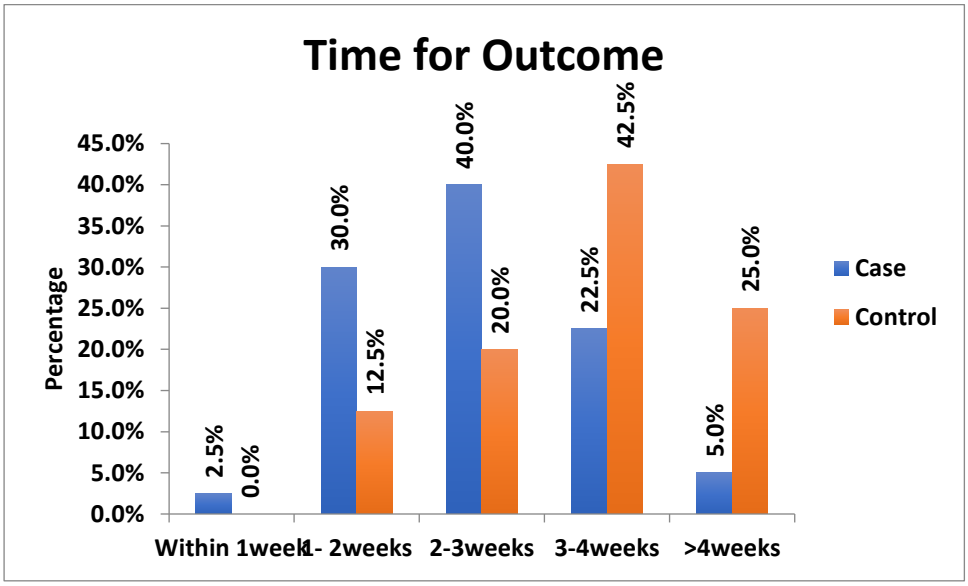


Table 15 and Figure 15 show the time for outcome between Cases and Controls. By the end of 3 weeks, 72.5 % Cases had achieved outcome as compared to 32.5% Controls who had achieved outcome. This was statistically significant (p= 0.006).

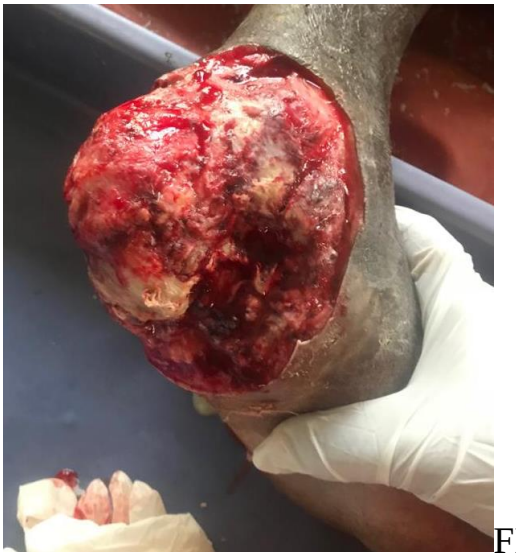


FIG 22(day 0)

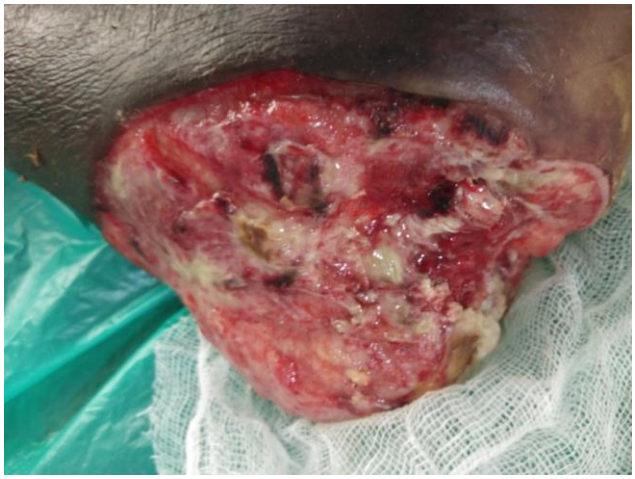


FIG 23(day 7)

FIG 24(day 14)

Figure 22,23,24 showing healing progress with topical heparin dressing.

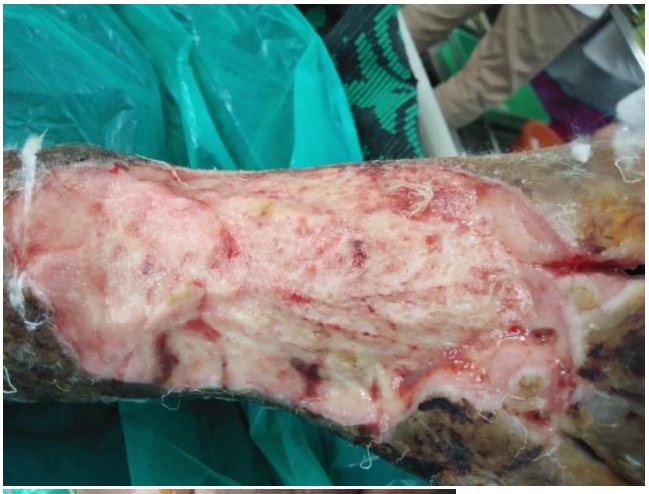


FIG 25(day 0)

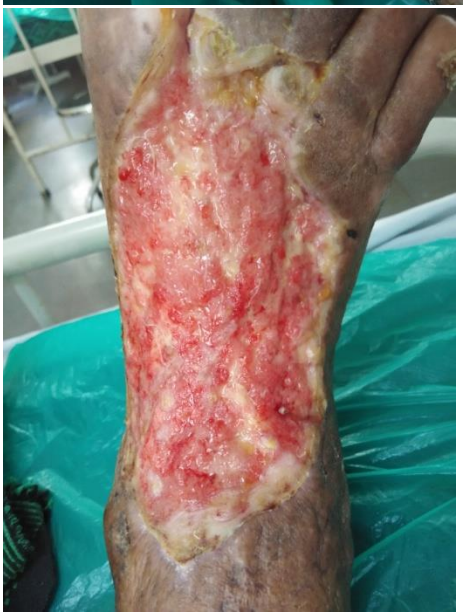


FIG 26(day 7)

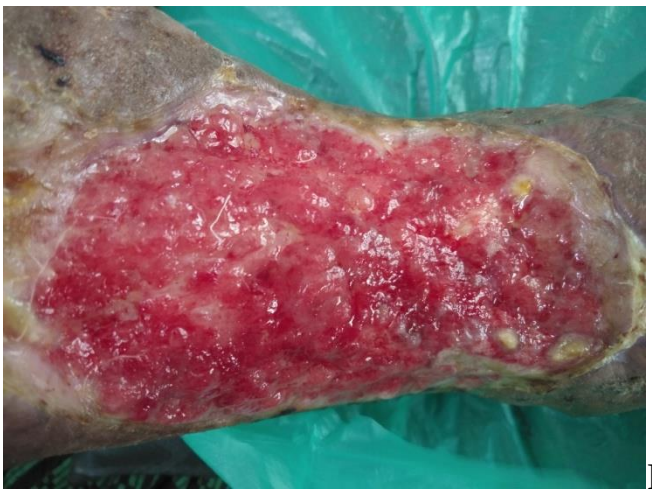


FIG 27(day 14)

Figure 25,26,27 showing healing progress with topical heparin dressing.

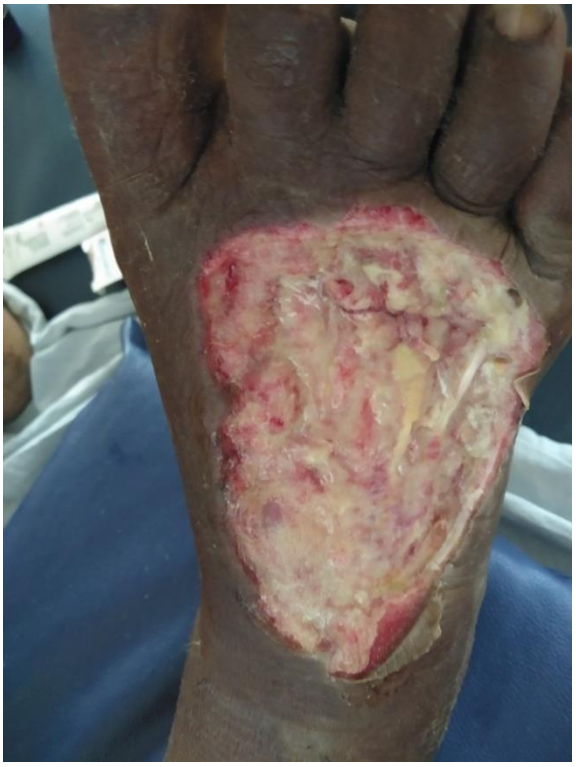


FIG 28(day 0)

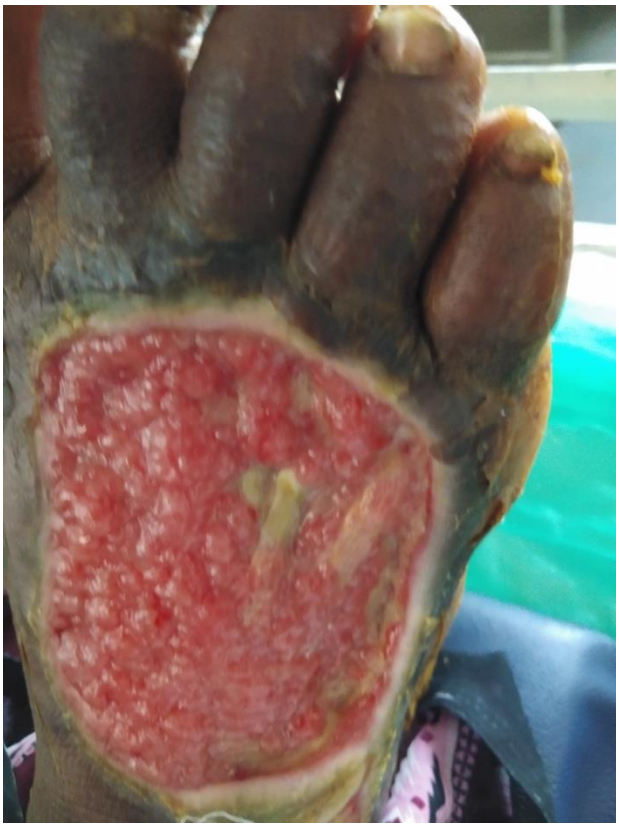


FIG 29(day 7)

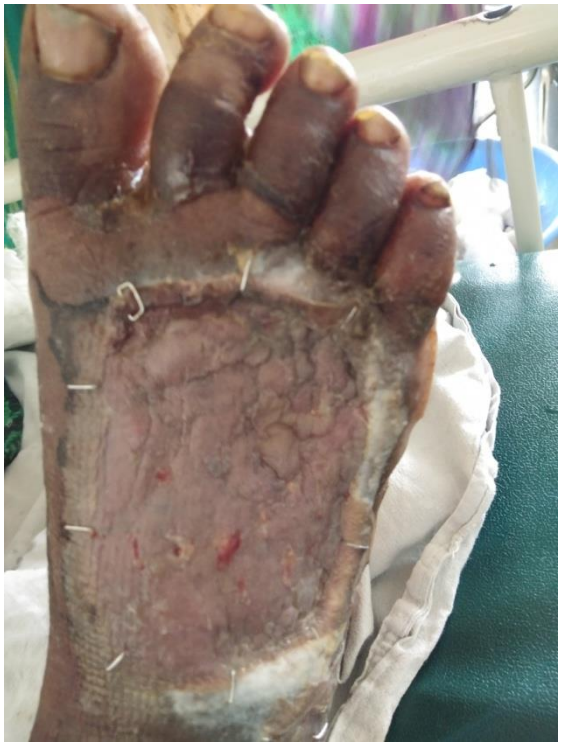


FIG 30 (skin graft done on day15)

Figure 28,29,30 showing healing progress with topical heparin dressing.

Fig 30- end point

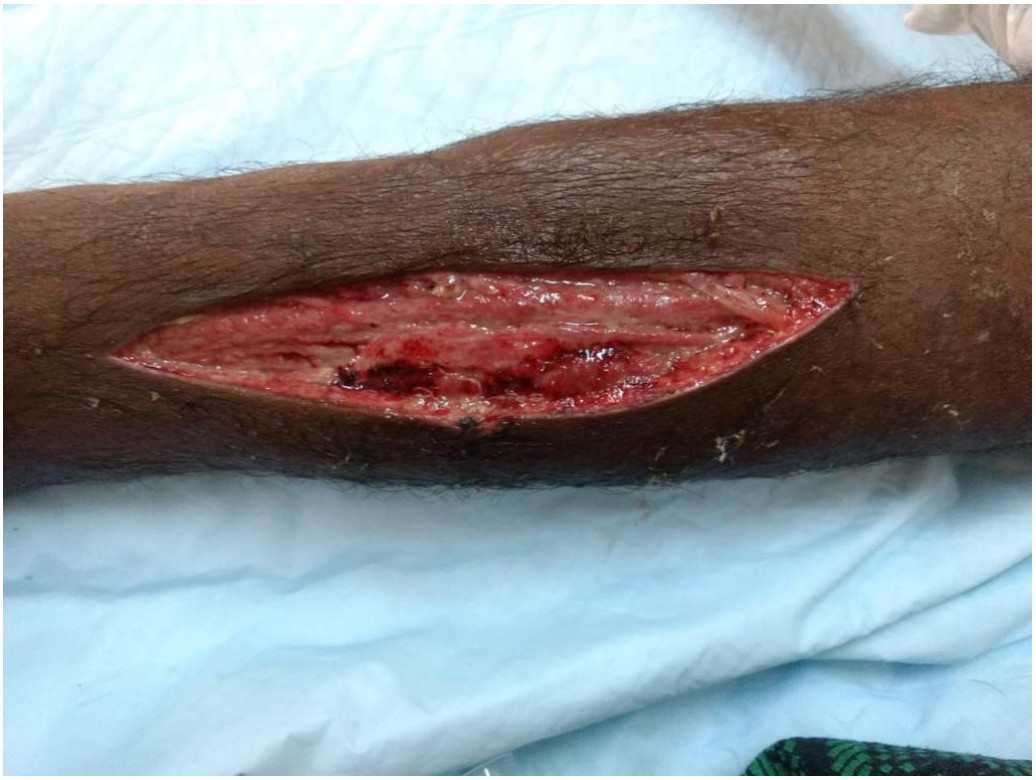


FIG 31(day 0)

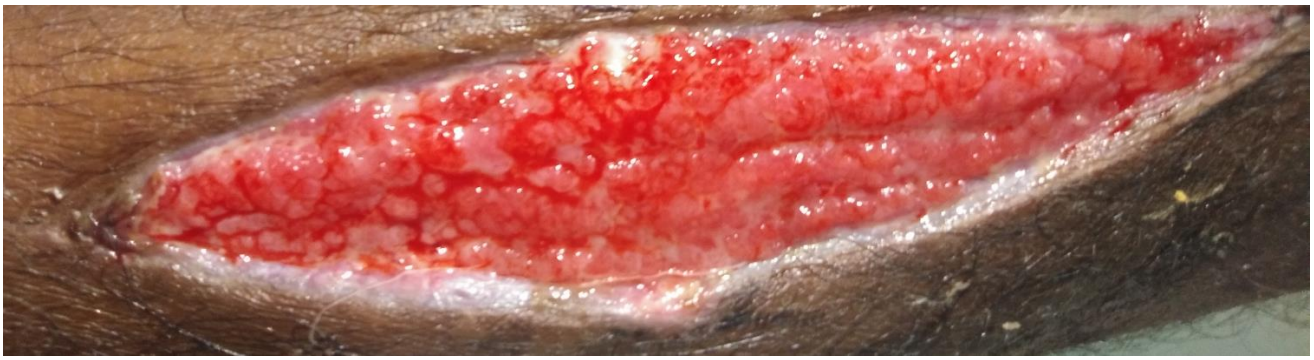


FIG 32(day 7)

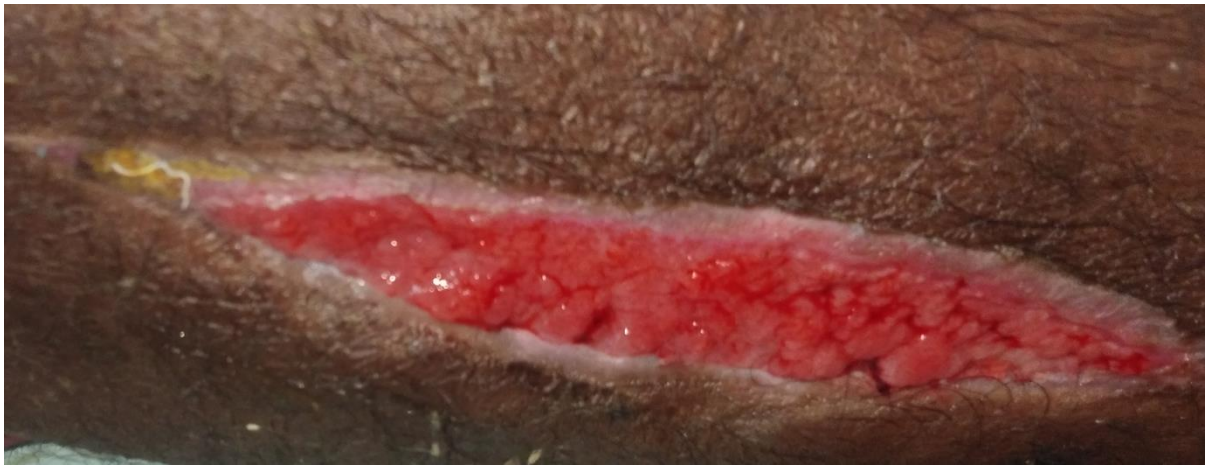


FIG 33(day 14)

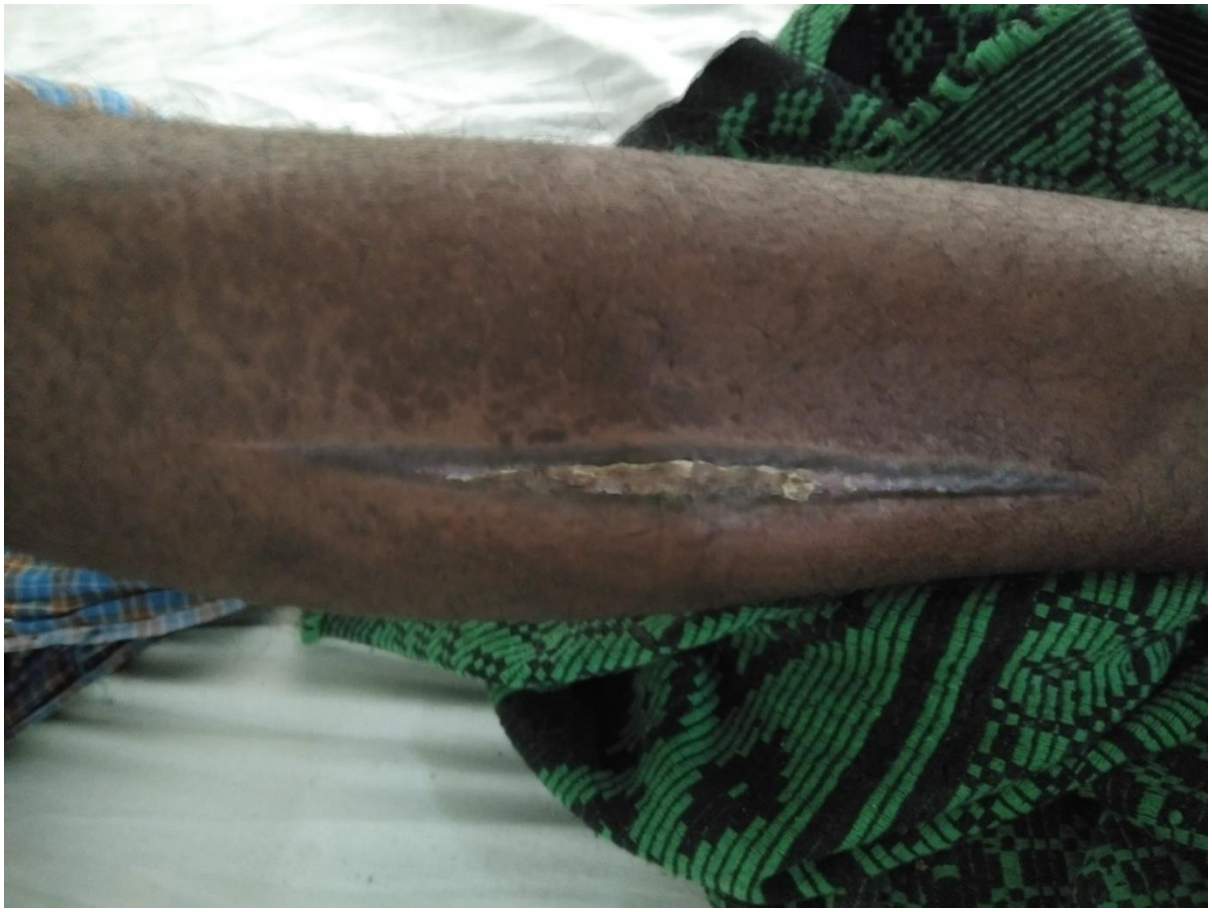


FIG 34 (day 26)

Figure 31,32,33,34showing healing progress with topical heparin dressing.

Fig 34- end point- healed by secondary intention

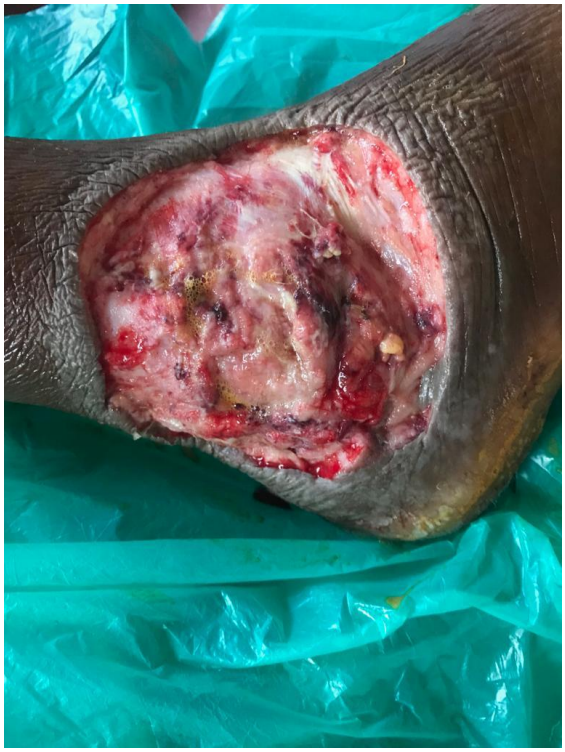


Figure 35(day 0)

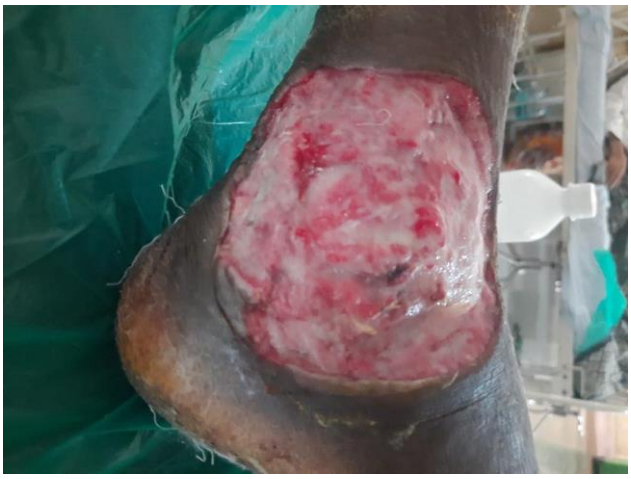


Figure 36(day 7)

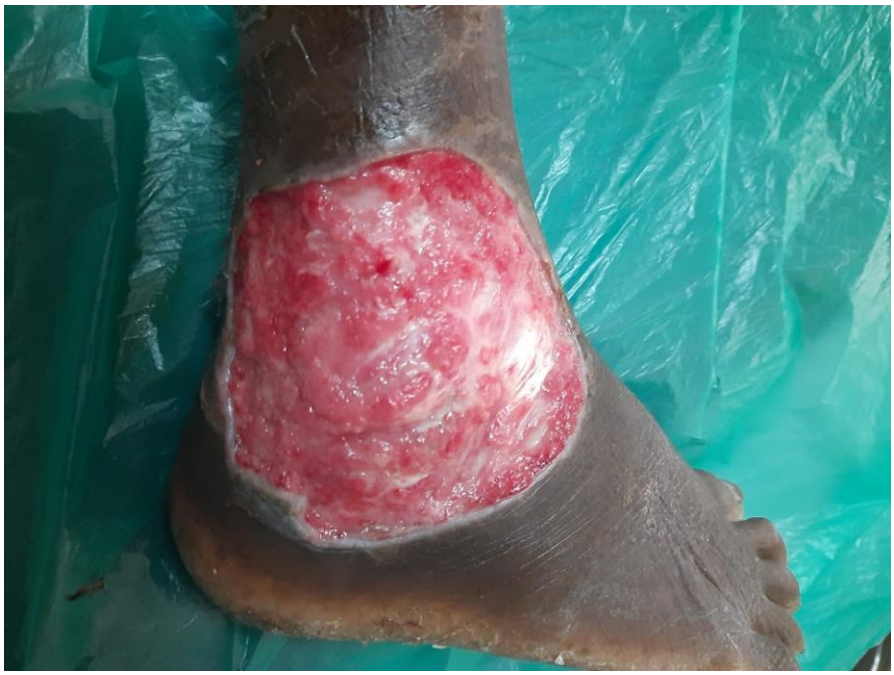
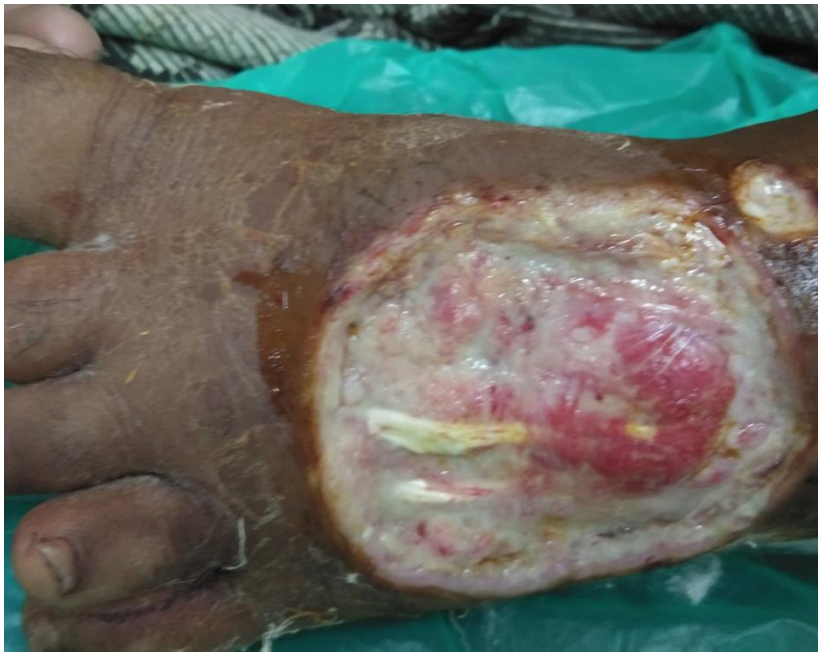


Figure 37 (day 14)

Figure35,36,37 showing healing progress with topical heparin dressing

Fig 38 

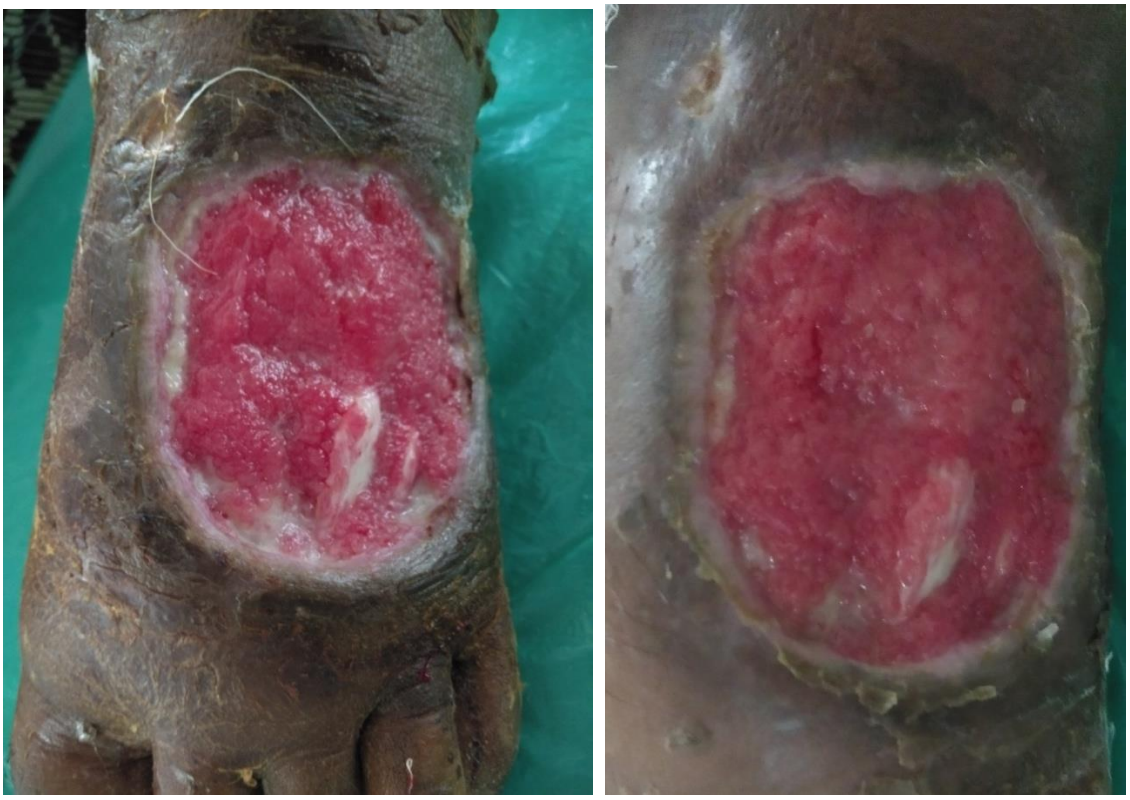


Fig 39(day 7)&40(day 14)(respectively)

Figure 38,39,40 showing healing progress with topical heparin dressing.

DISCUSSION

Diabetic ulcers are chronic wounds, stuck in inflammation phase and show a cessation of epidermal growth. An ideal dressing is one that promotes chronic ulcer healing without any complications. Successful wound dressing should keep the wound devoid of any adverse reactions such as infection, maceration and allergy.

The present study was conducted to compare the efficacy of heparin dressings (Cases) with conventional dressings (Controls) on diabetic ulcer healing dynamics.

The mean age of the patients in the Cases group was 57.1 years, which was not significantly different from the mean age of patients (54.0 years) in the Control group (Table 8 and Figure7).

In the present study, it was seen that the incidence of diabetic ulcers was more among the males in the Cases as well as Controls (85.0% and 75.0 % respectively). The difference in the distribution of sex among the groups was not statistically significant (p= 0.264) (Table 9 and Figure 8)

A study by Srinivas and Muralidharan[(2)] in Tamilnadu, India, also reported a higher incidence of diabetic ulcers among males in the Cases as well as Controls (84.4% and 75.0%).

The National Hospital Discharge Survey of the Centre for Disease Control in the US documented higher hospital rates in males suffering from diabetic ulcers.

In the present study, there was no statistically significant difference in the comorbidity of hypertension between the Cases and Controls (p=0.799). Among the cases, 25% of patients had hypertension, while among the Controls, 27.5 % of patients reported hypertension (Table 10 and Figure 9).

Glycated haemoglobin (HbA1c) is the gold standard for monitoring glycaemic control in patients with diabetes mellitus. The HbA1c assay provides an accurate, precise measure of chronic glycaemic levels and correlates with the risk of diabetes complications. In 2010, the International Expert Committee and the American Diabetes Association proposed diagnostic criteria for diabetes and prediabetes based on HbA1c levels. These are HbA1c ≥6.5% (≥48 mmol/mol) to diagnose diabetes mellitus and between 5.7–6.4% (39–46 mmol/mol) for prediabetes.[53]

In the present study, the difference in mean glycated haemoglobin between Cases and Controls was not statistically significant (8.51 mg/dL ± 1.2 mg/dL vs. 8.48 mg/dL ± 1.0 mg/dL, p=0.904) (Table 11 and Figure 10).

Also, the mean duration of diabetes mellitus between Cases and Controls was not significantly different (8.2 years ± 6.4 years vs 7.3 years ± 6.4 years, p=0.521) (Table 12 and Figure 11).

Thus, the Cases and Controls were matched correctly for age, sex, comorbid condition, glycated haemoglobin values and duration of DM in the present study, thereby justifying comparisons of study parameters between the two groups.

The rate of reduction of surface area of the ulcer was more among the Cases as compared to Controls, as seen in Table 13 and Figure 12 in the present study. By day 7, the surface area of ulcer in the Cases, as well as Controls, had reduced significantly ($p<0.001$). By day 14, a reduction of 10% was observed in the surface area of ulcer in Cases as compared to a decrease of 6% in Controls. Both these decreases were found to be statistically significant ($p<0.001$) (Table 14 and Figure 13). The reduction in mean surface area of ulcer per day was more in Cases as compared to Controls (0.6 cm^2 vs 0.3 cm^2 overall) **s**uggesting that topical application of heparin enhances wound healing in diabetic ulcers (Table 15 and Figure 14).

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In a similar Case-Control study, Srinivasan and Muralidharan[2] have also reported a lower Bates -Jensen wound healing score for Cases as compared to Controls at the end of week three and week 4.

The proliferative phase of wound healing is typified initially by the formation of granulation tissue, followed by re-epithelialization, and neovascularisation. *Healthy granulation tissue* is an indicator of recovery. Once granulation tissue fills the wound to the level of the original epithelium; the epithelia can proliferate and regenerate.

In the present study, by the end of 7 days, healthy granulation tissue was seen in 50% Cases as compared to just 27.5% in Controls. This difference was statistically significant. Similarly, by the end of day 14, healthy granulation tissue had developed in 92.5% Cases as compared to 67.5 % Controls who had developed a healthy granulation tissue. This difference between the two groups was statistically significant ($p<0.005$) (Table 16 and Figure 15).

Heparin enhances Type 1 collagen synthesis, and hence the stable granulation tissue causes better healing. Heparin also promotes migration of capillary endothelial cell[42,43] and produces angiogenesis[44] and thus the formation of healthy granulation tissue.

Serous drainage is expected during the inflammatory stage of wound healing, and smaller amounts are considered normal wound drainage. The serous fluid

contains sugars, white cells, proteins, and other chemicals that are vital in the healing process to move across the wound site. Seropurulent wound drainage is a sign that the wound is becoming colonized and treatment changes are needed. In the present study, by the end of 7 days, 50% Cases had serous wound discharge as compared to 25 % Controls who had a serous wound discharge. The rate at which the Cases group had serous wound discharge was significantly faster as compared to the Control group ($p<0.001$). By the end of 14 days, 92.5 % Cases had serous wound discharge as compared to 70.0 % Controls who had serous wound discharge. This difference among the groups was statistically significant ($p = 0.010$). By 21 days, all the Cases, as well as Controls, had serous discharge (Table 17 and Figure 16).

When skin is broken, its protective defence mechanisms are impaired, and the environment becomes more conducive for bacteria, which increase in number. These bacteria come from two primary sources; the environment (e.g. dust, foreign bodies, bacteria on hands, clothing and equipment), the surrounding skin (commensals). In the present study, by the end of 14 days, the culture sensitivity of the wound was done for both Cases as well as Controls. It was observed that in the Cases, a sterile culture was obtained in 30.0 % patients by the end of 14 days, while in Controls only 10% patients showed sterile culture by the end of 14 days. The microorganisms colonizing the wounds were not significantly different among the Cases and Controls (Table 18 and Figure 17)

Srinivasan and Muralidharan[2] have reported lower requirement of antibiotic and fewer changes in antibiotics in the Cases as compared to Controls as the sterile culture was obtained earlier in Cases as compared to Controls, similar to our study.

Heparin reduces bacterial translocation[45], thereby promoting a sterile culture early in the healing process and minimizing the need for antibiotics.

In the present study, there was no statistically significant difference between the number of Cases and Controls undergoing secondary suturing, secondary intention and skin grafting (p=0.840) (Table 19 and Figure 18).

In the present study, the mean duration for achieving the outcome, i.e. wound ready for either secondary suturing, secondary intention or skin grafting, was significantly lower in Cases as compared to Controls (18.2 days ± 5.6 days vs 23.5 days ± 5.7 days, p< 0.001) (Table 20 and Figure 19).

The mean duration of hospital stay was significantly lower for the Cases as compared to Controls (21.3 days ± 6.2 days vs 26.4 days ± 6.4 days, p<0.001) (Table 21 and Figure 20).

A similar study by Srinivasan and Muralidharan reported a lower mean hospital stay for Cases as compared to Controls (13.6 days vs 16.4 days, n=32 in each group). However, the statistical significance was not reported for the study.

Thus, in the present study, the group having the application of heparin dressing showed significantly better granulation tissue development, faster reduction of ulcer area, the earlier achievement of outcome and shorter duration of hospital stay, as compared to conventional dressing using normal saline. The topical application of heparin results in faster healing.

A comprehensive review of 20 studies with 1055 participants by Vecchio & Frisinghelli[52]concluded that topical heparin preparations might be useful for relieving the signs and symptoms of the vascular disorders by improving microcirculation. Heparin may show beneficial effects in diabetic foot ulcers by the same mechanisms.

Several studies [49,50,48,51]have been reported in literature where LMWH preparations have been administered subcutaneously for diabetic foot ulcers with reasonable healing rates. Our study reinforces the hypothesis that topical heparin dressings are equally effective in the treatment of diabetic ulcers, thereby presenting a more straightforward route of administration.

CONCLUSION

40 patients with diabetic ulcers of Grade 1 and 2 were managed with topical dressing of heparin solution and were compared to the ulcer management in 40 patients with conventional dressing i.e. 10% povidone iodine solution. Serial examination of ulcers has shown significant reduction in the ulcer surface area with appearance of healthy granulation tissue, decreased length of hospital stays in patients treated with topical heparin solution as compared to conventional dressing.

However, additional successful clinical evidence is required with validated laboratory findings to establish topical application of heparin solution as one of the most effective alternative topical agents in treatment of diabetic ulcers.

SUMMARY

This study was performed in Shri B.M Patil Medical College in the department of General Surgery during the study period of November 2018 to June 2020. The aim was to evaluate efficacy of topical heparin in treatment of Grade 1 and Grade 2 diabetic ulcers in the form of analyzing and comparing the wound area, granulation tissue, wound discharge, duration of hospital stays and culture sensitivity.

Total of 80 patients with diabetic ulcers of Grade 1 and 2 were enrolled into the study and randomly divided into topical heparin dressing group (Cases, n=40) and conventional dressing group (Controls, n=40). In the Cases group, heparinized sodium solution was prepared and applied to the ulcer drop by drop with 10ml syringe, once daily. In the Control group, regular dressing was done with 10% povidone iodine solution, once daily.

In our study, the Cases and Controls were appropriately matched with respect to the background parameters of mean age (57.1 years ± 11.6 years vs 54.0 years ± 11.7 years), distribution of sex (p=0.264), comorbid condition of hypertension (25 % vs 27.5%, p=0.799), glycated haemoglobin levels (8.51 ± 1.2 vs 8.48 ± 1.0, p= 0.904) and mean duration of diabetes (8.2 years ± 6.4 years vs 7.3 years ± 6.4 years, p= 0.521), thereby justifying further comparisons between the treatment groups.

The reduction in the surface area of wound in both Cases as well as Controls was significantly greater at the end of day 7 and day 14 ($p<0.001$). However, this reduction was more in the Cases as compared to Controls.

The reduction in the surface area of wound with time was greater and faster in Cases as compared to Controls.

The reduction in mean surface area of ulcer per day was higher in Cases as compared to Controls.

By day 7, 50 % of Cases had developed a healthy granulation tissue which was significantly more than that developed in Controls (27.5 %) ($p <0.041$). By day 14, 92.5 % Cases had a healthy granulation tissue as compared to 67.5% Controls who had developed a healthy granulation tissue. This difference was statistically significant ($p< 0.005$).

By 7 days, serous discharge was seen in more number of patients in Case group as compared to Control group (50 % vs 25 %). By 14 days also, serous discharge was seen in more number of patients in Cases group as compared to Control group (92.5 % vs 70.0 %, $p< 0.010$).

There was no significant difference among the two groups with regards to the distribution of microorganisms.

There was no significant difference among the groups with respect to the type of outcome of secondary suturing, skin grafting or healed by secondary intention(p=0.840).

By the end of 3 weeks, 72.5 % Cases had achieved outcome as compared to 32.5% Controls who had achieved outcome. This was statistically significant (p= 0.006). By the end of 4 weeks 95.0 % Cases had achieved outcome as compared to 75.0 % Controls who had achieved outcome. This was statistically significant.

The mean time required to reach outcome is significantly lower for Cases as compared to Controls (18.2 days ± 5.6 vs 23.5 days ± 5.7 days, p<0.001).
The mean duration of hospital stay was significantly shorter for Cases as compared to Controls (21.3 days ± 6.2 days vs 26.7 days ± 6.4 days, p< 0.001).

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ANNEXURE I CERTIFICATE OF ETHICAL CLEARENCE

B.L.D.E (Deemed to be University)
SHRI.B.M.PATIL MEDICAL COLLEGE HOSPITAL & RESEARCH CENTRE
VIJAYAPUR – 586103

IEC/NO:286/2018
17-11-2018

INSTITUTIONAL ETHICAL COMMITTEE

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this college met on 13-11-2018 at 03-15 PM scrutinize the Synopsis of Postgraduate Students of this college from Ethical Clearance point of view. After scrutiny the following original/corrected and revised version synopsis of the Thesis has accorded Ethical Clearance.

Title : To study the efficacy of heparin on Diabetic ulcers : A Prospective Study.

Name of P.G. Student : Dr Abhishek.
Department of General Surgery

Name of Guide/Co-investigator: Dr Vijaya L Patil, Professor of Surgery

DR RAGHAVENDRA KULKARNI
CHAIRMAN
Institutional Ethical Committee
BLDE(Dt. Shri B.M. Patil
Medical College,BIJAPUR-586103.

Following documents were placed before E.C. for Scrutinization:

1) Copy of Synopsis/Research Project
2) Copy of informed consent form.
3) Any other relevant documents.

INFORMED CONSENT FORM

B.L.D.E (DEEMED TO BE UNIVERSITY) SHRI B.M. PATIL MEDICAL COLLEGE, HOSPITAL AND RESEARCH CENTRE, VIJAYAPURA – 586103, KARNATAKA.

TITLE OF THE PROJECT:

EFFICACY OF TOPICAL HEPARIN ON DIABETIC ULCER- PROSPECTIVE STUDY

PRINCIPAL INVESTEGATOR: **DR ABHISHEK**
Department of General Surgery

PG GUIDE: **DR. VIJAYA L PATIL$_{MS}$**
Professor of Surgery
BLDE (DEEMED TO BE UNIVERSITY)
Shri B.M. Patil Medical College & Hospital

PURPOSE OF RESEARCH:

I have been informed that this study will analyze the usefulness of topical heparin on diabetic ulcers.

I have been explained about the reason for doing this study and selecting me/my ward as a subject for this study. I have also been given free choice for either being included or not in the study

PROCEDURE:

I understand that relevant history will be taken. I will undergo detailed clinical examination after which necessary investigations will be done whenever required, which would help the investigator for appropriate management.

RISKS AND DISCOMFORTS:

I understand that I/my ward may experience some pain and discomfort during the examination or during my treatment. This is mainly the result of my condition and the procedure of this study is not expected to exaggerate these feelings which are associated with the usual course of treatment.

BENEFITS:

I understand that I/my wards participation in this study will help to analyze the effectiveness of topical heparin in healing of diabetic ulcers.

CONFIDENTIALITY:

I understand that medical information produced by this study will become a part of this Hospital records and will be subjected to the confidentiality and privacy regulation of this hospital. Information of a sensitive, personal nature will not be a part of the medical records, but will be stored in the investigator's research file and identified only by a code number. The code key connecting name to numbers will be kept in a separate secure location.

If the data are used for publication in the medical literature or for teaching purpose, no names will be used and other identifiers such as photographs and audio or video tapes will be used only with my special written permission. I understand that I may see the photograph and videotapes and hear audiotapes before giving this permission.

REQUEST FOR MORE INFORMATION:

I understand that I may ask more questions about the study at any time. DR. ABHISHEK is available to answer my questions or concerns. I understand that I will be informed of any significant new findings discovered during the course of this study, which might influence my continued participation.

If during this study, or later, I wish to discuss my participation in or concerns regarding this study with a person not directly involved, I am aware that the social worker of the hospital is available to talk with me and that a copy of this consent form will be given to me for careful reading.

REFUSAL OR WITHDRAWL OF PARTICIPATION:

I understand that my participation is voluntary and I may refuse to participate or may withdraw consent and discontinue participation in the study at any time without prejudice to my present or future care at this hospital.

I also understand that DR ABHISHEK will terminate my participation in this study at any time after he has explained the reasons for doing so and has helped arrange for my continued care by my own physician or therapist, if this is appropriate.

INJURY STATEMENT:

I understand that in the unlikely event of injury to me/my ward, resulting directly to my participation in this study, if such injury were reported promptly, then medical treatment would be available to me, but no further compensation will be provided.

I understand that by my agreement to participate in this study, I am not waiving any of my legal rights.

I have explained to _____ the purpose of this research, the procedures required and the possible risks and benefits, to the best of my ability in patient's own language.

Dr. VIJAYA L PATIL
(Guide)

Dr. ABHISHEK
(Investigator)

PROFORMA

CASE NO:

- Name: IP No:
- Age/sex: DOA:
- Occupation:
- Address:

- CHIEF COMPLAINTS:

WOUND:

- Mode of Onset
- Duration
- Number
- Site
- Size and Extent
- Associated Pain
- Discharge
- Others
- Any Associated Disease
- Past History of Similar Wound
- Personal History

PAST HISTORY:

- Diabetes Mellitus

- Hypertension

- Peripheral vascular disease

PERSONAL HISTORY:

- Diet
- Sleep
- Appetite
- Bowel & bladder

7. GENERAL PHYSICAL EXAMINATION:

- Mental Status Weight:
- Built Height:
- Nourishment BMI:
- Hydration status
- Pallor
- Pulse
- Blood Pressure
- Any Obvious Deformity

A. <u>LOCAL EXAMINATION:</u>

INSPECTION-

- NUMBER
- SITE
- SIZE
- SHAPE
- EXTENT
- MARGIN
- EDGE OF THE ULCER
- FLOOR OF THE ULCER
- DISCHARGE:
    - Amount
    - Character
    - Odor
- ADJACENT AREA:
    - Any Swelling

- Any Skin Change
- Any Secondary Changes

PALPATION:

- TEMPERATURE
- TENDERNESS
- SIZE
- MARGIN
- EDGE
- MOBILITY
- DEPTH
- BLEEDING

B. EXAMINATION OF LYMPH NODES

C. EXAMINATION OF VASCULAR SYSTEM

D. EXAMINATION OF NERVE SUPPLY OF THE LIMB

SYSTEMIC EXAMINATION

PER ABDOMEN:

Inspection:

Palpation:

Percussion:

Auscultation:

R*ERSPRATORY SYSTEM*:

Inspection

Palpation

Percussion

Auscultation

CARDIO-VASCULAR SYSTEM:

Inspection

Palpation

Percussion

Auscultation

CENTRAL NERVOUS SYSTEM:

Higher Mental functions

Diagnosis

INVESTIGATIONS:

- Hemoglobin
- Total Count
- Differential Count
- Blood Urea
- Serum Creatinine
- PT/INR
- Serum albumin
- BLOOD SUGAR RBS, FBS, PPBS
- Urine for Ketone Bodies
- HbA_1C
- Urine Routine
- Culture Sensitivity of Discharge
- X-Ray of bone Or Joint Involved
- Arterial doppler
- HIV, HBSAG, HCV

COMMENTS:

PRE-TREATEMENT MEASUREMENTS:

SERIAL MEASUREMENTS DURING THE TREATEMENT:

FINAL MEASUREMENTS:

INFERENCE:

KEY TO MASTER CHART

A	AGE
S	SEX
DIAB	DIABETES
HTN	HYPERTENSION
C/S	CULTURE
OUTC	OUTCOME
DUR	DURATION FOR OUTCOME
HO	HOSPITAL STAY

SI.N	NAME	A	G	IPNO	DIABE	HTN	HBA1C	DURATIO	ACE AREA OF ULCER IN				GRANULATION TISSUE				DISCHARGE				C/S	OUTCO	DUR	HO
									DAY0	7DAY	4 DAY	21 D	28D	7 DAYS	14 DAYS	21 DAYS	28DAYS	7 DAYS	14 DAYS	21 DAYS	28 DAYS				
1	SHIVARUD	48	M	1395	YES	YES	7.3	5	24	23	21.5	19		HEALTHY	HEALTHY	HEALTHY		SEROUS	SEROUS	SEROUS		KLEBSIELLA	STSG	21	24
2	ANLAGAPP	44	M	4096	YES	NO	7.5	3	35	34	32	30		HEALTHY	HEALTHY	HEALTHY		SEROUS	SEROUS	SEROUS		S.AUREUS	STSG	19	22
3	UDAYKUM	43	M	3327	YES	NO	8	3	30	29	27	25		HEALTHY	HEALTHY			SEROUS	SEROUS			CITROBACTER	STSG	21	25
4	PRABHU	42	M	6500	YES	NO	7.4	2	30.5	29	27	25		HEALTHY	HEALTHY			SEROUS	SEROUS			E.COLI	STSG	22	26
5	SHAMRAYA	63	M	7896	YES	NO	11.3	18	40	38.5	36	35		UNHEALTH	HEALTHY	HEALTHY		SEROPURU	SEROUS	SEROUS		E.COLI	STSG	24	27
6	KALESAB	50	M	5558	YES	NO	12.6	8	24	23	21	20		HEALTHY	HEALTHY	HEALTHY		SEROUS	SEROUS	SEROUS		KLEBSIELLA	STSG	21	24
7	SOMANING	50	M	14162	YES	YES	9	6	28	26.5	25			HEALTHY	HEALTHY			SEROUS	SEROUS			STERILE	STSG	15	19
8	UDAY	60	M	18765	YES	NO	9.6	10	35	34	32.5	31	24	UNHEALTH	HEALTHY	HEALTHY		SEROPURU	SEROUS	SEROUS		PSEUDOMONAS	STSG	28	32
9	MALLAMM	65	F	19475	YES	YES	8.3	20	18	17	15			HEALTHY	HEALTHY			SEROUS	SEROUS			STERILE	SS	15	19
10	SATISH	60	M	21250	YES	NO	9.7	10	21	20	18			HEALTHY	HEALTHY			SEROUS	SEROUS			STERILE	SS	14	19
11	RUDRAGO	60	M	22119	YES	NO	11	12	35	34	32	30	28	UNHEALTH	UNHEALTH	HEALTHY	HEALTHY	SEROPURU	SEROPURU	SEROUS	SEROUS	KLEBSIELLA	STSG	30	34
12	BABU	52	M	32891	YES	YES	8	6	28	26.5	25			HEALTHY	HEALTHY			SEROUS	SEROUS			S.AUREUS	STSG	16	20
13	SHRIKANT	65	M	57303	YES	NO	7.8	5	24	23	21			HEALTHY	HEALTHY			SEROUS	SEROUS			CITROBACTER	STSG	14	18
14	IRRANNA	65	M	39800	YES	YES	8.4	7	28	27	25			HEALTHY	HEALTHY			SEROUS	SEROUS			PSEUDOMONAS	STSG	17	20
15	BHIMANNA	44	M	41678	YES	NO	7.2	3	18	17	15			HEALTHY	HEALTHY			SEROUS	SEROUS			STERILE	SS	12	13
16	DANDAPPA	80	M	42576	YES	YES	9.1	25	26	25	23			HEALTHY	HEALTHY			SEROUS	SEROUS			E.COLI	STSG	15	19
17	PUTALABA	78	F	42555	YES	NO	8.5	15	35	33.5	31.5	30		UNHEALTH	HEALTHY	HEALTHY		SEROPURU	SEROUS	SEROUS		CITROBACTER	STSG	25	29
18	MADIWAL	70	M	39571	YES	NO	7.7	8	21	18	15			HEALTHY	HEALTHY			SEROUS	SEROUS			STERILE	SS	13	14
19	KALAWWA	51	F	4441	YES	NO	10.3	4	28	27	25	24		HEALTHY	HEALTHY	HEALTHY		SEROUS	SEROUS	SEROUS		STERILE	STSG	21	24
20	BASAPPA	68	M	2409	YES	NO	7.4	8	30	29	27	25		UNHEALTH	HEALTHY	HEALTHY		SEROPURU	SEROUS	SEROUS		KLEBSIELLA	STSG	22	25

21	ANASUYA	45	F	41808	YES	NO	7.2	3	28	27	25	23	HEALTHY	HEALTHY	HEALTHY		SEROUS	SEROUS	SEROUS		S.AUREUS	STSG	20	23
22	HANUMAN	69	M	41807	YES	YES	9.2	16	35	34	32	30	UNHEALTH	UNHEALTH	HEALTHY		SEROPURU	SEROPURU	SEROUS		S.AUREUS	STSG	22	26
23	PARAVATA	60	F	480	YES	NO	8.2	5	20	19	17		HEALTHY	HEALTHY			SEROUS	SEROUS	SEROUS		STERILE	SS	13	15
24	MD.HUSSA	65	M	640	YES	NO	9	7	18	17	16		HEALTHY	HEALTHY			SEROUS	SEROUS			STERILE	SS	12	15
25	NAGAPPA	70	M	2598	YES	NO	8.2	20	48	47	45	43	42	UNHEALTH	UNHEALTH	HEALTHY	SEROPURU	SEROPURU	SEROUS	SEROUS	KLEBSIELLA	STSG	30	33
26	RAMANNA	68	M	1787	YES	YES	8.6	9	28	27	25		HEALTHY	HEALTHY			SEROUS	SEROUS			S.AUREUS	STSG	19	23
27	KARINAGSI	68	M	1735	YES	NO	7.4	7	30	29	27.1	25	UNHEALTH	HEALTHY	HEALTHY		SEROPURU	SEROUS	SEROUS		PSEUDOMONAS	STSG	22	25
28	ISHWAR	58	M	3909	YES	NO	8.1	4	18	17	15		HEALTHY	HEALTHY			SEROUS				STERILE	STSG	14	17
29	BIRAPPA	50	M	3102	YES	NO	7.5	3	28	27	25	23	UNHEALTH	HEALTHY	HEALTHY		SEROPURU	SEROUS	SEROUS		CITROBACTER	STSG	20	23
30	KASHINATH	45	M	15137	YES	NO	7.8	1	15	14	14		HEALTHY	HEALTHY			SEROUS	SEROUS			S.AUREUS	STSG	16	19
31	DADIMA	76	F	15143	YES	NO	8.3	17	28	26	26		HEALTHY	HEALTHY			SEROUS	SEROUS			STERILE	STSG	18	22
32	BASVARAJ	43	M	4732	YES	NO	9.4	3	29.3	28	28.5	22	UNHEALTH	HEALTHY	HEALTHY		SEROPURU	SEROUS	SEROUS		S.AUREUS	STSG	22	26
33	BHIMRAY	38	M	12617	YES	NO	8.5	7M	20	20	18.5		HEALTHY	HEALTHY			SEROUS	SEROUS			KLEBSIELLA	SS	12	14
34	TIPANNA	56	M	15323	YES	NO	7.7	8	28	27	26		HEALTHY	HEALTHY			SEROUS	SEROUS			KLEBSIELLA	STSG	15	19
35	VITTAL	74	M	11	YES	YES	9.7	24	35	34	33	31	29	UNHEALTH	HEALTHY	HEALTHY	SEROPURU	SEROUS	SEROUS	SEROUS	CITROBACTER	STSG	28	32
36	BHIMANNA	45	M	41678	YES	NO	8.5	3	16	15			HEALTHY				SEROUS				STERILE	SS	6	7
37	JAGADISH	39	M	3630	YES	NO	7.7	1	15	15	14		HEALTHY	HEALTHY			SEROUS	SEROUS			E.COLI	STSG	14	17
38	MUTAPPA	50	M	2631	YES	NO	7.5	8	32	31	30		HEALTHY	HEALTHY			SEROUS	SEROUS			PSEUDOMONAS	STSG	14	19
39	KASHINATH	50	M	3577	YES	YES	8	4	8	7	6		HEALTHY	HEALTHY			SEROUS	SEROUS			E.COLI	SI	14	14
40	RAFIQ	56	M	3580	YES	NO	7.6	7	12	11	9		HEALTHY	HEALTHY			SEROUS	SEROUS			STERILE	SI	10	10

CONTROLS

Sl.N	NAME	A	G	IPNO	DIAB	HTN	HBA1	DURATION OF	FACE AREA OF ULCER IN					GRANULATION TISSUE				DISCHARGE				C/S	OUTCO	DUR	HOS
									DAY	7DAYS	14 DA	21 DA	28D	7 DAYS	14 DAYS	21 DAYS	28DAYS	7 DAYS	14 DAYS	21 DAYS	28 DAYS				
41	PRAKASH	50	M	6063	YES	NO	8.2	5	29	29	28	26	25	UNHEALTHY	UNHEALTHY	HEALTHY	HEALTHY	SEROPURULE	SEROPURULE	SEROUS	SEROUS	CITROBACTER	STSG	32	36
42	LALMASHAK	65	M	6066	YES	YES	9.5	15	34	33	32	31	31	UNHEALTHY	UNHEALTHY	HEALTHY	HEALTHY	SEROPURULE	SEROPURULE	SEROUS	SEROUS	KLEBSIELLA	STSG	30	35
43	MAHADEVI	38	F	6840	YES	NO	7.8	8MONTH	17	16	16.5	15		UNHEALTHY	UNHEALTHY	HEALTHY		SEROPURULE	SEROPURULE	SEROUS		S.AUREUS	STSG	24	28
44	GURURAJ	40	M	11388	YES	NO	8	1	27	26	25	24.5		UNHEALTHY	HEALTHY	HEALTHY		SEROPURULE	SEROUS	SEROUS		E.COLI	STSG	27	31
45	SANGANAGO	80	M	14692	YES	YES	11.2	27	34	34	33	32.5	31	UNHEALTHY	UNHEALTHY	HEALTHY	HEALTHY	SEROPURULE	SEROPURULE	SEROUS	SEROUS	S.AUREUS	STSG	31	36
46	BASAVARAJ	42	M	27180	YES	NO	8.5	6MONTH	29	28	27	26.5	26	UNHEALTHY	UNHEALTHY	HEALTHY	HEALTHY	SEROPURULE	SEROPURULE	SEROUS	SEROUS	KLEBSIELLA	STSG	33	37
47	SHANTAWAA	65	F	27400	YES	NO	8	10	14	14	13			HEALTHY	HEALTHY			SEROUS	SEROUS			STERILE	SS	17	18
48	BHIMANNA	60	M	33240	YES	NO	9.4	7	23	22	21	20		UNHEALTHY	HEALTHY	HEALTHY		SEROPURULE	SEROUS	SEROUS		KLEBSIELLA	STSG	22	26
49	SHANTABAI	60	F	42504	YES	NO	8.2	10	27	26	25	24		UNHEALTHY	HEALTHY	HEALTHY		SEROPURULE	SEROUS	SEROUS		CITROBACTER	STSG	21	24
50	SIDAPPA	57	M	41782	YES	YES	7.3	9	35	35	34	33	32	UNHEALTHY	UNHEALTHY	HEALTHY	HEALTHY	SEROPURULE	SEROPURULE	SEROUS	SEROUS	E.COLI	STSG	29	33
51	RITESH	37	M	1975	YES	NO	8.4	8MONTH	31	30	30	29		UNHEALTHY	HEALTHY	HEALTHY		SEROPURULE	SEROUS	SEROUS		S.AUREUS	STSG	25	28
52	IRRAYYA	65	M	1129	YES	YES	9.1	9	34	33	32	31.5		UNHEALTHY	HEALTHY	HEALTHY		SEROPURULE	SEROUS	SEROUS		S.AUREUS	STSG	28	32
53	SHRISHAIL	38	M	36554	YES	NO	8.5	1	29	28.5	27.5	26.4		UNHEALTHY	HEALTHY	HEALTHY		SEROPURULE	SEROUS	SEROUS		PSEUDOMONA	STSG	22	26
54	HEMA	45	F	6423	YES	NO	7.4	3	34	33	32.5	31.5	31	UNHEALTHY	UNHEALTHY	HEALTHY	HEALTHY	SEROPURULE	SEROPURULE	SEROUS	SEROUS	CITROBACTER	STSG	29	33
55	RAMESH	36	M	9661	YES	NO	8.4	6MONTH	23	22	21	20		UNHEALTHY	HEALTHY	HEALTHY		SEROPURULE	SEROUS	SEROUS		KLEBSIELLA	STSG	24	27
56	SHANWAR	39	M	11701	YES	NO	9.2	2	29	28	27.5	26.5		UNHEALTHY	UNHEALTHY	HEALTHY		SEROPURULE	SEROPURULE	SEROUS		CITROBACTER	STSG	26	29
57	SUMITRA	43	F	2885	YES	NO	8.7	2	32	32	31	30.5		UNHEALTHY	HEALTHY	HEALTHY		SEROPURULE	SEROUS	SEROUS		PSEUDOMONA	STSG	22	25
58	SHEKAPPA	54	M	43173	YES	YES	7.4	7	41	40.5	40	39	38	UNHEALTHY	UNHEALTHY	HEALTHY	HEALTHY	SEROPURULE	SEROPURULE	SEROUS	SEROUS	CITROBACTER	STSG	32	35
59	ISMAIL	45	M	37311	YES	NO	8.5	4	23	22	21.5			HEALTHY	HEALTHY			SEROUS	SEROUS			STERILE	STSG	12	15
60	MALLAPA	78	M	2217	YES	NO	8.4	15	12	12	11.5	10.5		UNHEALTHY	HEALTHY	HEALTHY		SEROUS	SEROUS	SEROUS		KLEBSIELLA	SI	21	21

61	ASHOK	40	M	4205	YES	NO	7.6	2	31	30.5	30	29	UNHEALTHY	HEALTHY	HEALTHY		SEROPURULE	SEROUS		S.AUREUS	STSG	21	25
62	PEERSAB	75	M	6574	YES	YES	10.4	25	34	33.5	32.5	31.5	UNHEALTHY	UNHEALTHY	HEALTHY		SEROPURULE	SEROUS	SEROUS	E.COLI	STSG	28	32
63	RHAKU	42	M	7723	YES	NO	8.2	2	23	22	21		UNHEALTHY	HEALTHY			SEROPURULE	SEROUS		S.AUREUS	SS	14	16
64	ABDUL GAFER	60	M	8579	YES	YES	9.4	10	17	16.5	16		UNHEALTHY	HEALTHY			SEROPURULE	SEROUS		CITROBACTER	SS	15	17
65	NOOR AHME	52	M	12767	YES	NO	7.2	4	17	16	15		UNHEALTHY	HEALTHY			SEROPURULE	SEROUS		PSEUDOMONA	SS	14	15
66	SHIVAPPA	57	M	1593	YES	NO	8.3	7	27	26.5	25.5	25	UNHEALTHY	HEALTHY	HEALTHY		SEROPURULE	SEROUS		S.AUREUS	STSG	21	25
67	RAJSHEKAR	45	M	5398	YES	NO	7.5	3	29	28.5	27.5	27	UNHEALTHY	HEALTHY	HEALTHY		SEROPURULE	SEROUS		KLEBSIELLA	STSG	22	25
68	MODINSAB	50	M	19199	YES	YES	8.6	7	14	13.5	12.5		HEALTHY	HEALTHY			SEROUS	SEROUS		STERILE	SS	14	16
69	SHRISHAIL	65	M	18437	YES	NO	8.1	12	17	16.5	16	15	UNHEALTHY	HEALTHY	HEALTHY		SEROPURULE	SEROUS		CITROBACTER	STSG	22	26
70	GIRIMALLAYA	65	M	26678	YES	YES	11.2	18	16	15.5	14		UNHEALTHY	HEALTHY	HEALTHY		SEROPURULE	SEROUS		S.AUREUS	SS	18	20
71	MAHADEV	48	M	30043	YES	NO	7.7	4	31	30.5	29.5	28.5	UNHEALTHY	UNHEALTHY	HEALTHY	HEALTHY	SEROPURULE	SEROUS	SEROUS	KLEBSIELLA	STSG	29	33
72	BASAVVVA	60	F	30948	YES	NO	8.5	6	28	27	26.5	25	UNHEALTHY	HEALTHY	HEALTHY		SEROPURULE	SEROUS		E.COLI	STSG	22	26
73	CHANDRAMM	60	M	6908	YES	NO	7.1	3	24	23	22		HEALTHY	HEALTHY			SEROUS	SEROUS		STERILE	STSG	14	17
74	SULOCHANA	54	F	13327	YES	NO	9.1	5	24	23	22	21.5	UNHEALTHY	HEALTHY	HEALTHY		SEROUS	SEROUS		S.AUREUS	STSG	25	29
75	MALLU	47	M	34136	YES	NO	10.2	7	30	29	28	27.5	UNHEALTHY	HEALTHY	HEALTHY	HEALTHY	SEROPURULE	SEROUS	SEROUS	KLEBSIELLA	STSG	30	33
76	SHIVAPPA	61	M	40481	YES	NO	8.2	5	28	27	26	25.5	UNHEALTHY	HEALTHY	HEALTHY		SEROPURULE	SEROUS		CITROBACTER	STSG	22	25
77	MANGALA	54	F	43385	YES	NO	7.3	9	20	19.5	19	18	UNHEALTHY	HEALTHY	HEALTHY		SEROPURULE	SEROUS		CITROBACTER	SS	21	24
78	MALLAMA	64	F	24611	YES	NO	8	8	24	24	23	22	UNHEALTHY	HEALTHY	HEALTHY		SEROPURULE	SEROUS		S.AUREUS	SS	23	26
79	YAMUNABAI	60	F	37552	YES	YES	8.5	10	28	27.5	26.5	25.5	UNHEALTHY	UNHEALTHY	HEALTHY	HEALTHY	SEROPURULE	SEROUS	SEROUS	PSEUDOMONA	STSG	28	31
80	REVANSIDDA	65	M	43885	YES	YES	7.8	17	28	27	26.5	25	UNHEALTHY	HEALTHY	HEALTHY	HEALTHY	SEROPURULE	SEROUS	SEROUS	E.COLI	STSG	30	33