"COMPARISON OF OCTENIDINE WOUND GEL DRESSING VERSUS POVIDONE-IODINE DRESSING IN HEALING OF CHRONIC DIABETIC FOOT ULCERS- A RANDOMISED CONTROLLED TRIAL FOR PERIOD OF ONE YEAR"

By

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LIST OF ABBREVIATIONS USED

DM	-	Diabetes Mellitus
DFU	-	Diabetic foot ulcer
IDF	-	International Diabetic Federation
PAD	-	Peripheral Arterial Disease
QOL	-	Quality of life
U.K	-	United Kingdom
ADA	-	American Diabetic Association
GDM	-	Gestational Diabetes Mellitus
RBS	-	Random blood sugar
HbA1c	-	Glycosylated Haemoglobin
OGTT	-	Oral Glucose Tolerance Test
PDGF	-	Platelet derived growth factor
FGF	-	Fibroblast growth factor
TGFβ1	-	Transforming growth factor beta 1
ECM	-	Extra cellular matrix
VEGF	-	Vascular endothelial growth factor
NADPH	-	Nicotinamide adenine dinucleotide phosphate
NAD	-	Nicotinamide adenine dinucleotide
NO	-	Nitric Oxide
IGF-1	-	Insulin like growth factor -1
MMP	-	Matrix metallo proteinase
ABPI	-	Ankle Brachial Pressure Index
g	-	Gram
TCC	-	Total Contact Cast

Spp	-	Species
S.Mutans	-	Streptococcus mutans
MIC	-	Minimal Inhibiory Concentration
FTU	-	Finger tip units
Sq.cm	-	Square centimetre
Wks	-	Weeks
S.D	-	Standard deviation
OHA	-	Oral Hypoglycemic Agents
CONS	-	Coagulase negative staphylococcus
K.pneumoniae	-	Klebsiella pneumonia
E.coli	-	Escherichia coli
PEDIS	-	Perfusion Extent Depth Infection and Sensation

ABSTRACT

Comparison of octenidine wound gel dressing versus povidone iodine dressing in healing of chronic diabetic foot ulcers- A randomised controlled trial for period of one year.

Introduction

DM is a widespread, non-communicable disease seen among world population.[1]Amongst the complication of DM, DFU is seen quite often. DF disorders consists of the ulcers over the foot related with infection, PAD and neuropathy. It is a noteworthy reason for lower extremity amputation. Infection of DFU is one among the common complications seen in DM patients. One of the major problem in health sector is antibiotic resistance. Increasing antibiotic resistance has restricted the use of systemic antibiotics. In this situation topical antiseptics with broad spectrum of activity and minimal or no resistance plays an important role in management of chronic infected ulcers.

Octendine, an antiseptic known since 20 years. It has been used first in 1990 by U.K health care professionals. Till now many in vitro and animal based studies have been done in evaluating the advantages of octendine, very few clinical studies done. Specific characters of no resistance and good tissue tolerability of octenidine and very few clinical studies made us to compare healing of diabetic foot ulcers, between octenidine and povidone iodine dressings.

Objectives

To compare octenidine wound gel dressing versus povidone iodine dressing in healing of chronic diabetic foot ulcers in terms of mean percentage reduction in ulcer area.

Methods

This hospital based randomised controlled study was done between Jan 2018 to Dec 2018.Total 80 cases of chronic diabetic foot ulcers between 35-75 years were selected and randomized(SNOSE technique) in to two groups, group A(study group) octendine dressing done and group B(control group) povidone iodine dressing done . Demographic data including duration of disease, hypertension, neuropathy and HbA1c levels were recorded. The wound healing was calculated as mean reduction in ulcer area and mean percentage reduction in ulcer area. The wound healing was than compared between two groups

Results

Of the 80 patients, 55(68.8%) were males and most of them(48 of 80 or 60%) aged more than 55 years. 50 of 80 or 62.5% belonged to low socio economic status. All of these parameters and ulcer parameters such as mode of onset, site of ulcer showed no significant difference in distribution among the groups. Presence of neuropathy, hypertension and HbA1c levels which are implicated as risk factors for DFU healing did not show statistically significant difference in distribution between groups. Ulcer healing was early in group A (octenidine dressing group) compared to group B (povidone iodine dressing group), mean percentage reduction in ulcer area

was 25.51 ± 9.26 sq.cm and 14.48 ± 6.54 sq.cm in group A and group B respectively (p-value <0.001). The percentage of patients with bacterial growth on wound culture (D14) was 15% and 32.5% in group A and group B respectively.

Conclusion

When octenidine wound gel was added to the treatment regimen of the patients with diabetic foot ulcers, it has shown good progress of ulcer healing in terms of ulcer area reduction compared to povidone iodine dressing.

Keywords Diabetes mellitus, diabetic foot ulcer, octenidine wound gel, wound healing, povidone iodine

TABLE OF CONTENTS

LIST OF TABLES

LIST OF GRAPHS

LIST OF FIGURES

LIST OF PHOTOGRAPHS

LIST OF FLOWCHARTS

INTRODUCTION

DM is a widespread, non-communicable disease seen among world population[1].Amongst the complication of DM, DFU is seen quite often due to neuropathy and vascular insufficiency states seen in these patients. DFU not only has high morbidity rates in DM, but also result in a loss of limb.[2]

As indicated by the IDF measurements it states that "every 7 seconds somebody is assessed to die from DM or its complications, with 50% of those deaths (4 million altogether for every year) happening younger than 60 years".[3]

The prevalence of DM in 2017 in the world was seen to be 8.8%, standardised for 20-79 years of age. This prevalenceby the year 2045 is expected to rise to 9.9% of the worlds population.[3]

The long standing condition of DM results in chronic hyperglycemic states that cause damage and dysfunction to multiple organs most commonly involving the kidneys, heart, eyes, nerves and blood vessels.[4]

Microvascular complications incorporate retinopathy, nephropathy and neuropathy, while macro vascular complications comprise of atherosclerotic changes which lead to cardiovascular compromise, PAD and stroke.[4,5]

DF disorders consists of the ulcers over the foot related with infection, PAD and neuropathy. It is a noteworthy reason for lower extremity amputation.Foot illness includes almost 6% of individuals with DM.[4,6,7]

Infection of DFU is one among the common complications seen in DM patients and is related with hospital admissions for the same and unsatisfactory

clinical outcomes.The unsatisfactory outcomes includes increased risk of lower limb amputation, decreased QOL, and a high mortality risk.[2] According to recent literatures, it is stated that "amongst the DFU patients, 0.03% to 1.5% of patients require an amputation". Hence prevention of infection and its management, if present, are important parts in management of DFU for salvaging the limb.[6,8]

Management of infected DFU includes debridement of the ulcer, the application of topical antimicrobial and antiseptic agents and systemic antibiotics selected based on pathogen sensitivity, if there is any systemic infection.[8]

One of the major problem in health sector is antibiotic resistance. Increasing antibiotic resistance has restricted the use of systemic antibiotics. In this situation topical antiseptics with broad spectrum of activity and minimal or no resistance plays an important role in management of chronic infected ulcers.[9,10]

Due to bad history from previous studies suggest that antiseptics are harmful for healing process, there are certain requirements for them to fulfil.

Broad spectrum activity,

Organic substances should not inhibit their function

No induction of bacterial resistance

Toxicologically safe for repeated usage

No impairment of wound healing

Low local/percutaneous absorption or no systemic side effects.[9]

Topical antiseptics help in wound healing by eliminating or killing the pathogens and protecting the wound from further infection. Most of the antiseptics available clinically belong to the guanidine group. Substances belonging to this group are polyhexadine, chlorhexidine and octenidine dihydrochloride.[11,12]

Another most commonly used antiseptic solution clinically is iodine based, povidone iodine. It has good antimicrobicidal properties and has been in usage for antisepsis since years. The disadvantages of povidone iodine are its cytotoxicity to human cells, risk of systemic absorption and delayed wound healing. [9]

In search for new antimicrobial agent which fulfil above requirements, we came across octenidine di hydrochloride. Octendine an antiseptic known since 20 years it has been used first in 1990 by U.K health care professionals. They used octenidine to improve wound care and manage nosocomial infections.[10]

Octendine has a unique chemical structure making it a power cationic substance to interact with anionic substances of organism cell and lead to its death.[10]

The recent studies have shown the advantages of Octenidine Dihydrochloride. It is stated to be a broad spectrum antimicrobial agent having no microbial resistance till date. It has viricidal and antimycotic properties[10]. Its bacteriological index,(index which is used to measure the antimicrobicidal efficacy and cyto toxicity) is high compared to other antiseptics indicating its efficacy in antimicrobicdal activity and good tissue tolerability.[13]

It has the property of persistent action at the wound site making the redressing frequency decreased. Percutaneous absorption of octendine has not been reported till now.

It has synergistic property when used along with systemic antibiotics.

Biofilms protect organisms from the antibiotic treatment which can be overcome by using topical octenidine application.[10]

Hydrogel based preparation of octendine wound gel has additional properties of hydrogel which play role in wound healing. Hydrogels are complex structures that keeps the dead tissue on wound surface rehydrated and helps in autolysis of such tissue. The moist environment from hydrogel based dressings help in healing of ulcer.[11,12]

Till now many in vitro and animal based studies have been done in evaluating the advantages of octendine, very few clinical studies done on healing of venous ulcers, diabetic foot ulcers and skin donor sites.

All these mentioned characters of octenidine and very few clinical studies made us to compare healing of diabetic foot ulcers, between octenidine and povidone iodine dressings.

AIM AND OBJECTIVE

To compare octenidine wound gel dressing versus povidone iodine dressing in healing of chronic diabetic foot ulcers in terms of mean percentage reduction in ulcer area.

REVIEW OF LITERATURE

Diabetes Mellitus:

Definition

According to ADA, DM is defined as "a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both".[1]

Epidemiology

DM is one among the world's greatest challenges in health care and a leading cause of morbidity all over the world.In the year 2016, it has been estimated that 1.6 million deaths were directly caused secondary to DM. Another 2.2 million deaths were as a result of high glucose levels in the blood in the year 2012.[14]

India is the epicenter of the world's DM epidemic. In India there are over thirty five million people with DM - a number that is foretold to increase to eighty million by 2030. Moreover, Asian Indians have an ethnic susceptibility to Type 2 DM and a familial aggregation of the disease.[15]

Classification [5]

DM is classified as below:

-Type-1DM(beta -cell destruction due to autoimmune disorder, usually leading to absolute insulin deficiency).

-Type-2DM(due to a progressive decrease of insulin secretion by beta-cells, insulin resistance)

-Gestational DM mellitus (GDM) (diagnosed during pregnancy with no prior history)

-Specific types of DM due to other causes, like diabetic syndromes, drug induced

Criteria for diagnosis of DM Mellitus :[5](Table 1)

CRITERIA FOR DM DIAGNOSIS	
Symptoms of DM and RBS	>200 mg/dl
Fasting plasma glucose levels	>/= 126 mg/dl
HbA1C	>6.5%
OGTT 2 hr plasma glucose level	≥ 200mg/dL

Complications:

Hyperglycemia with ketoacidosis or the non ketotic hyper osmolar syndrome are the acute, grave consequences of DM in individuals with uncontrolled DM.

Long-term complications of DM include potential loss of vision due to retinopathy; renal failure due to nephropathy; peripheral neuropathy with risk of foot ulcers, amputations, and Charcot joints; and autonomic neuropathy causing gastrointestinal, genitourinary, and cardiovascular symptoms and sexual dysfunction.

Patients with DM have an increased incidence of coronary artery disease, peripheral arterial disease, and cerebrovascular disease due to atherosclerotic changes. Hypertension and disorders of lipoprotein metabolism are typically found in people with DM.

Death due to keto acidosis has been eliminated significantly due to the introduction of insulin therapy, however a longer lifespan combined with unsatisfactory metabolic control has been associated with an increased prevalence of major complications.[4,5]

Lower extremity complications in Dibetes Mellitus:

DM involves multiple systems of the body with important lower extremity complications, because of underlying peripheral neuropathy and peripheral vascular disease.

About sixty to seventy percent of diabetic patients have some form of neuropathic pathology in their lower extremities, this form of neuropathic disease

leads to decreased or loss of sensations over the plantar surface of the feet. This loss of sensation along with repetitive injury and other triggering factors, lead to skin breakdown and ulcer formation. Patients are usually unaware of an injury until full-thickness ulcerations occur.[8,16]

DFU:

Definition

According to the World Health Organization and to the International Working Group on the Diabetic Foot , diabetic foot is defined as "the foot of diabetic patients with ulceration, infection and/or destruction of the deep tissues, associated with neurological abnormalities and various degrees of peripheral vascular disease in the lower limb".[17]

Epidemiology of DFU

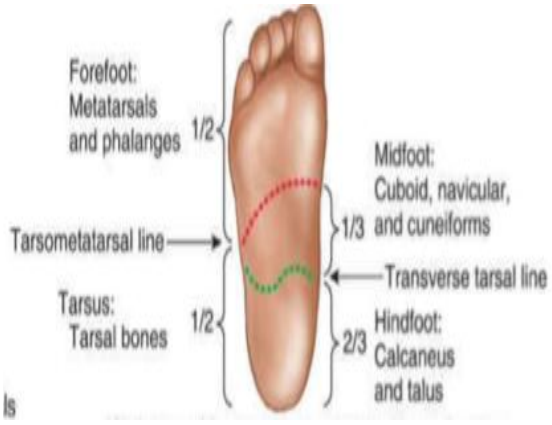
The life time risk of developing DFU during a person living with DM is fifteen percent but it could be up to twenty five percent.Annually around 3% of patients with DM develop DFU[8,18]. The leading reason for admission to hospital among patientswith DM is DFU. It's calculable to account for twenty five percent of all hospital admissions in patients with DM.[19]

Applied anatomy of foot

The better understanding of anatomy of foot is indictated for better care of the feet.The foot is the important part of body which supports the body while standing and helps in locomotion.[20,57]

The skeleton of foot is made up of 7 tarsal bones, 5 metatarsals and 14 phalanges. Foot is divided into three zones in terms of anatomy and function.

Talus and calcaneus forms Hindfoot.Navicular, cuboid and cuneiform forms Midfoot. Metatarsals and phalanges forms Forefoot.[57]



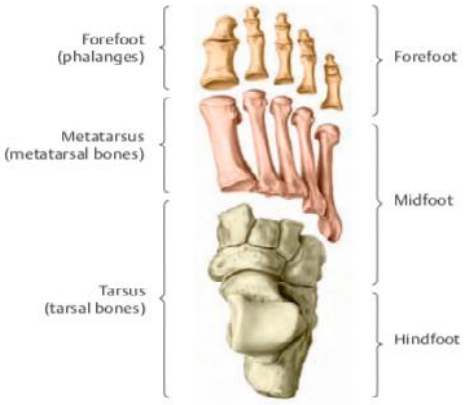


Fig 1A Surface anatomy of foot parts

Fig 1B Bones of foot

Skin and subcutaneous issue

Skin of foot show various modifications in relation to thickness and texture.The skin of plantar foot is much thicker and sensitive than skin on the dorsum of foot. The skin is more thick over the weight bearing areas of plantar foot which includes heel region proximally, ball of the foot distally and lateral margin. The skin over the plantar aspect is rich in sweat glands but no hair follicles. This rich population of sweat glands keeps skin moist and prevents ulceration.[20,57]

The subcutaneous tissue in the plantar foot is more of fibrous type compared to the dorsum. Fibrous bands divide the subcutaneous fat into small compartments which gives spring effect to arches of foot. Subcutaneous tissue over the dorsum of foot is loose, which explains the edema more prominent over the dorsum of foot.[20,57]

Deep fascia

Deep fascia forms plantar aponeurosis of foot, transverse ligaments between meta torso phalangeal joints and fibrous flexor sheaths.

The functions of deep fascia is protect foot from injury, support longitudinal arches of foot and hold or fix parts of foot together.[57]

Muscles of foot

Muscle family of foot includes 20 individuals, of 20 individual muscles 14 belong to plantar aspect, 4 are intermediate and 2 are on the dorsum.[57]

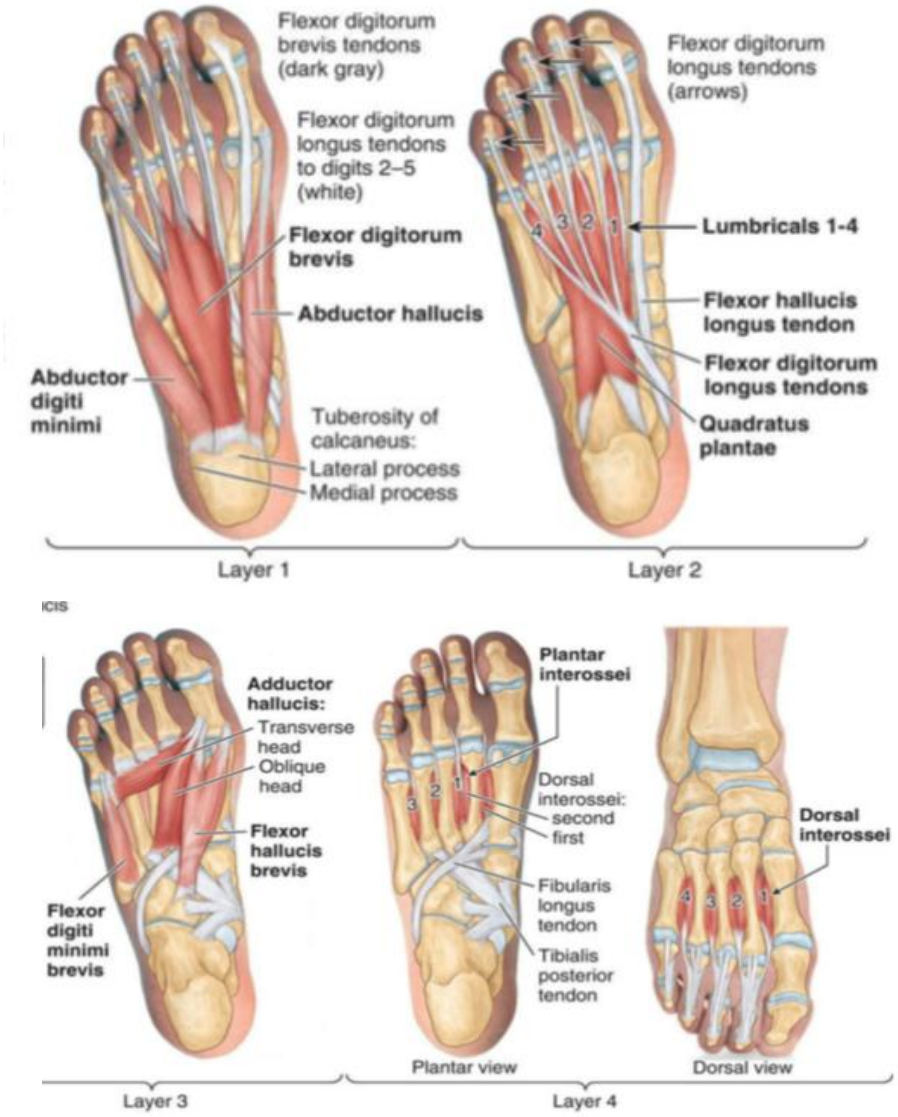


Fig 2 Muscle layers of foot

Nerves of foot

The cutaneous nerve supply of foot includes

Saphenous nerve

Superficial fibular nerve

Dorsal digital nerve it is extension of superficial and deep fibular nerve

Medial plantar nerve

Lateral plantar nerve

Lateral cutaneous nerve of foot which is termination of sural nerve

Medial calcaneal branch[57]

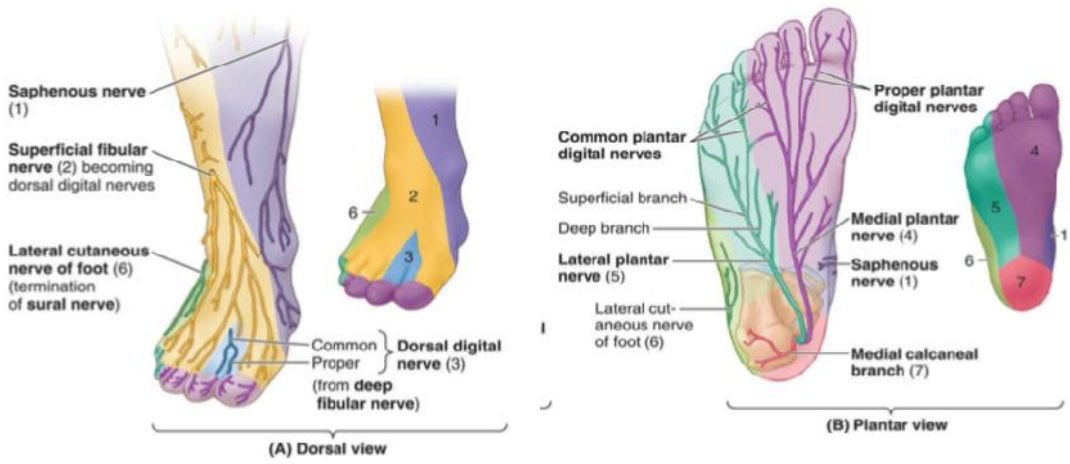


Fig 3 Cutaneous nerve supply dorsum and plantar aspects of foot

Ligaments of foot

Foot is made up of many ligaments. It is these ligaments that hold foot as single unit and prevents unnecessary mobility. When these ligaments lose their tensile strength it causes collapse of foot leading to unrestricted mobility and destabilisation of foot.[57]This loss of tensile strength is seen in diabetics which leads to destabilization.[58]

Arches of foot

The foot as discussed earlier needs to support body in standing position and help in locomotion. To meet these requirements it has developed a mechanism in the form elastic arches or springs.

Arches of foot are classified as

Longitudinal arch

A.medial

B.lateral

Transverse arch

A.anterior

B.posterior

Maintenance factors[57]

1. Unique shape of bones of foot

2. Intersegmental ligaments

3. Tie beams or bowstrings that connect two ends of arch

4. Slings that pull up arch

5. Suspension

Functions

Distribute body weight to specific weight bearing tough areas of foot

Its spring like action helps in locomotion

Protects the neuromuscular bundle by acting as shock absorbers.[20,57]

All these functions are lost if the arches collapse, causing increased trauma to soft tissue. Peripheral neuropathy in diabetics is one of the factor that causes the arches of foot to collapse.[58]

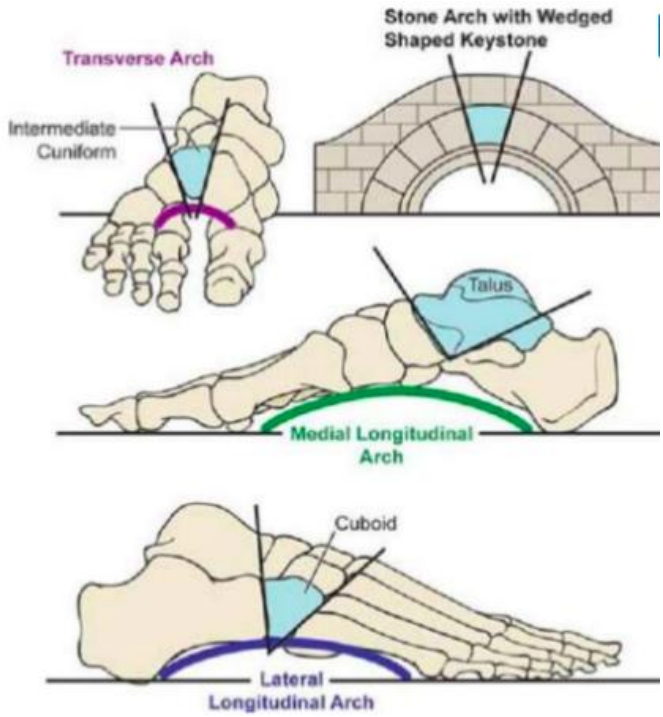


Fig 4 Arches of foot

Wound healing

Any injury or damage to the tissue triggers a co-ordinated process of coagulation to achieve haemostasis and proceed to further phases of inflammation, proliferation and remodelling. All these steps are linear and overlapping in the process of wound healing.[21,22]

Acute wounds go through these phases in a linear way and complete the process of wound healing earlier.[23]

The wound healing can be discussed under following four phases for a better understanding of the mechanism

1. Haemostasis

Immediate response by the body to an injury is to prevent loss of blood and achieve haemostasis. Vessels as large as 0.5 cms are completely constricted by this contraction.

Further haemostasis is achieved by the complex process of coagulation which involves formation of fibrin plug.This helps in protection of wound from the external environment besides haemostasis. Fibrin plug is a meshwork of fibrin, fibronectin, vitronectin and thrombospondin with embedded platelets.

Platelets, excluding the role in clot formation they also release multiple growth factors and cytokines which play important role in the healing cascade. These importantly include platelet derived growth factor (PDGF), fibroblast growth factor(FGF) and transforming growth factor(TGF) β1.[21–23]

2. Inflammation

As a result of wound the primary barrier of immunity i.e skin is lost, increasing the risk of infection. The important role of this phase is to prevent or control infection. The chronological order of inflammatory mediators in this phase is neutrophils, macrophages and lymphocytes.

Neutrophils, the first responders appear with in hours of injury and last till 48 hrs.The role of neutrophils is to eliminate bacteria, debris and release of various growth factors, chemo attractants and proteolytic enzymes.Neutrophils have no role in regulating the normal wound healing unless provided there is no infection or continuing trauma.

Macrophages are derived from the monocytes a leucocyte group of blood cells. Monocytes are usually circulating, they turn into tissue macrophages when they reside at the wound site.They reach their peak concentration in 48-72 hrs after injury.Macrophages have role in regulating the inflammatory process. They also have role in angiogenesis and forming granulation tissue.

Lymphocytes appear after 72 hrs of injury. Usually it is T-lymphocytes that have role in regulating the healing process. Lymphocytes regulate the wound healing by producing extracellular matrix scaffold and remodelling of collagen.[21–23]

3. Proliferation

This a complex phase of healing incorporating angiogenesis, formation of ECM, epithelialisation and wound retraction. All these occur simultaneously, but for understanding it is discussed under separated headings.

Angiogenesis

Neovascullariztion, formation of new blood vessels from the intact blood vessels and repair of damaged vessels is triggered by the TGF-β,FGF,PDGF released by the platelets and vascular endothelial growth factor(VEGF). Mixed metalloproteinase are a family of enzymes which promote angiogenesis through release of VEGF and remodellingof ECM.

Fibroplasia

Fibroblast proliferation is stimulated by FGF released by the platelets during fibrin plug formation. Fibroblast cells have important role ECM formation. It is fibroblast cells that release proteoglycans and glycosaminoglycans which are important components of ECM.

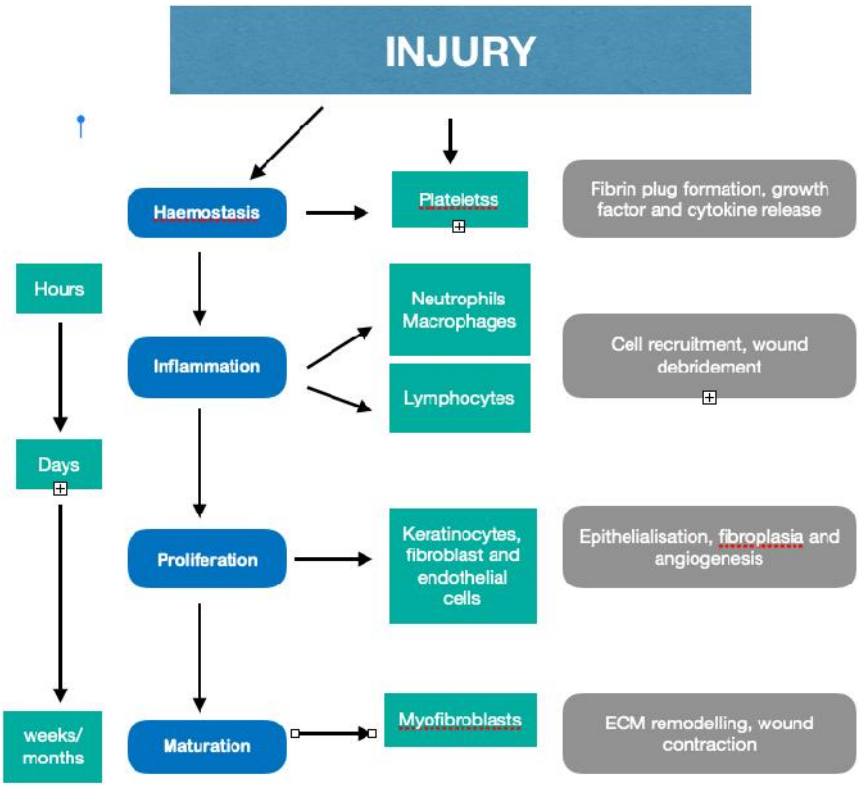
Epithelialization

Epithelialization starts with in hours of injury. If wound is partial thickness epithelialisation occurs soon, it is facilitated by the surrounding skin appendages like hair follicles. If the wound is full thickness epithelialisation takes longer duration, it needs keratinocyte cells from wound edges to migrate and cover the surface.[21–23]

4. Remodelling

Healing of wound ends with this phase. During this phase deposited collagen undergoes remodelling along with other proteins. They undergo remodelling to regain a structure similar to the normal unwounded healthy tissue. Type 1 collagen deposited initially is replaced by type 3 collagen. The basic need for remodellingisprovide strength for the newly formed tissue. At the end of healing wound tissue can regain eighty percent of original tensile strength.[21–23]

Flowchart 1 physiology of wound healing



Pathophysiology - Wound healing DFU:

A.Extrinsic factors

1.Neuropathy

The mechanism by which neuropathy leads to foot ulceration in diabetics is yet to be understood. Various theories proposed are discussed here.

Evidences from various studies suggest that " polyol " pathway is major pathological factor for neuropathy in diabetics. Co factors like NADPH and NAD are competitively utilised in this pathway resulting in decreased levels of reduced glutathione availability. Reduced glutathione is a potent anti oxidant. This leads to oxidative stress which causes impaired nerve cell function. The metabolites of this pathway also leads to osmotic nerve cell damage by causing oedema.

All types of neuropathy are involved in the DF ulceration.

Sensory neuropathy - Lack of pain sensation exposes the foot to repetitive unnoticed trauma and ulceration. Loss of temperature sensation also prevents withdrawl of foot when exposed to hot or cold objects.

Motor neuropathy - Impaire motor activity in foot muscles causes muscular atrophy, which leads to undue bony prominences and altered pressure distribution causing ulceration.

Autonomic neuropathy - It causes impairment of vascular response of small blood vessels which further leads to poor inflammatory response and delayed wound healing. [2,22,23]

2. Vascular

Understanding DM is a vascular disease helps in prevention and healing of foot ulcers. Pathogenesis can be explained under two categories macro vascular and micro vascular.

Macrovascular - Dysfunction of endothelial cells leads to the deficiency of important factor that is nitric oxide. Nitric oxide (NO) is important factor in inhibiting the vascular smooth muscle proliferation and promoting vasodilation. Because of inadequate availability of NO there is excessive smooth muscle proliferation causing atherosclerosis and vascular narrowing. This vascular narrowing causes resultant schema and ulceration.

Microvascular - Basement membrane thickening secondary to the deposition of metabolites due to non enzymatic reaction between sugars and proteins. Impaired neurogenic control and capillary thrombosis further worsen the ischemia and leads to foot ulceration.

Hypertension another co morbid condition in diabetics leads to ischemia and foot ulceration.[2,22,23]

3. Infections:

Infectons leading to foot ulceration is very rare but it plays a significant role in delayed wound healing and complicating the ulcer. Chronic wounds are usually colonised by bacteria. Bacteria in such wounds forms biofilms. It is not yet clear that at what point of this bio burden, healing process will be impaired. Increased infection causes damage of healing tissue and neutrophilicvasculitis.

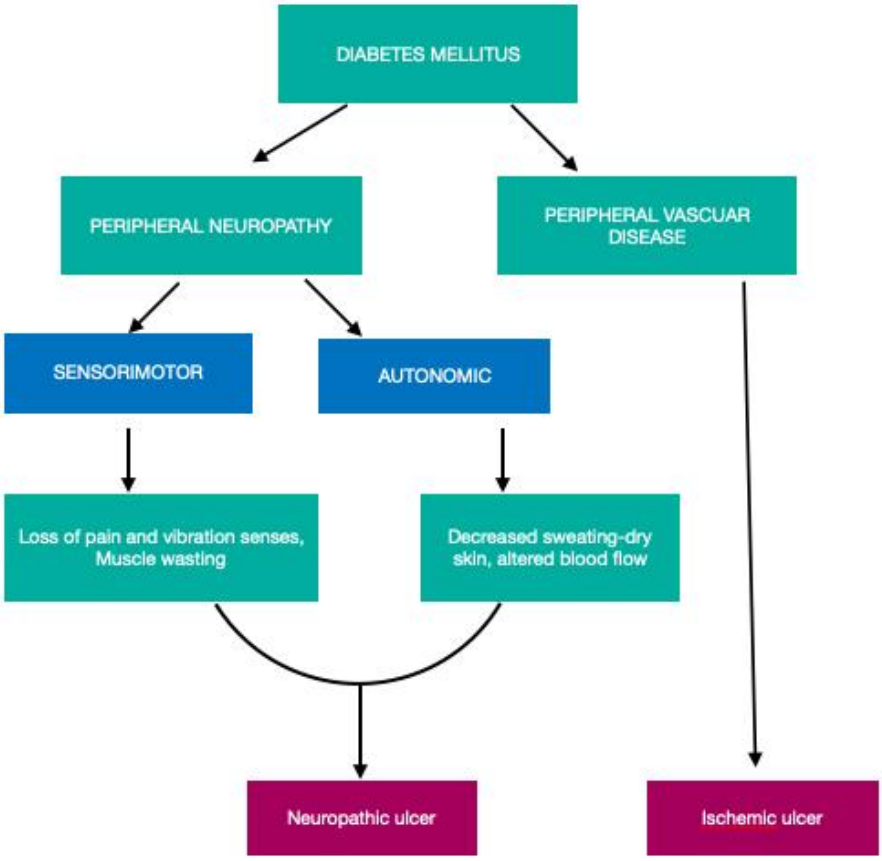
Majority of foot ulcers in diabetics are polymicrobial in nature.

Commonly isolated pathogens are gram positive cocci like staph aureus, staph epidermidis and streptococci species.

Among anaerobes peptostreptococcus Magnus and bacteroidesfragilis have been isolated.

Methicillin resistant staph aureus is associated with poor prognosis and difficult management with high treatment failure.[2,7,22]

Flowchart 2 Pathophysiology of diabetic foot ulcer



B.Intrinsic factors

Intrinsic factors includes altered bioavailability of growth factors and abnormal functioning of enzymes involved in proliferative phase of wound healing.

Growth factors like TGF and IGF-1 are altered in the patients of DFUs. Earlier studies suggest that there will be decreased bio availability of these factors resulting in the delayed wound healing.

Wound fluid in diabetics impairs the angiogenesis and blocks proliferation of cells. MMP's which are responsible for maintaining equilibrium between formation and degradation of extracellular matrix. Increased levels of MMP's results in unwanted degradation of wound healing favouring tissue proteins.

Defective migration of endothelial progenitor cells to the wound site occurs due to decreased NO.

All these factors results in delayed and impaired wound healing. [7,24]

Biomechanics of DFU:

Foot ulcers in DM are usually due to the pathophysiology changes like peripheral neuropathy, PAD, foot deformities and pressure changes. Pressure changes are one of the important factors in foot ulceration. This is explained by the increased chances of ulceration over the plantar surface compared to dorsal surface.[25]

Skin is considered to be the important mechanical link handling forces between intrinsic factors and external environment. In case of healthy individuals because of adequate sensation skin is protected from ulceration where as in DM individuals have decreased sensation which allows repetitive trauma to skin and break in the skin. Foot deformities are also responsible for excessive pressures.[25]

Thus pressures either excessive or repetitive are responsible for skin break down and ulceration in DM.

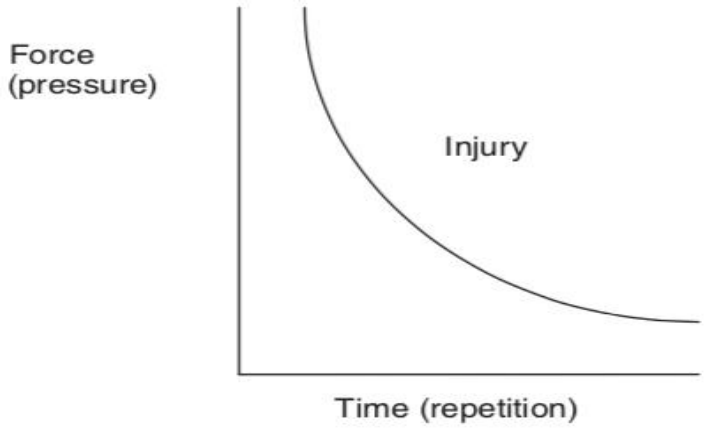
As proposed by earlier studies there are three pressure components that leads to ulceration [25,26]

1)Pressure for extended length of time- small pressures for extended duration leads to ischemia which further causes ulceration.

2)Pressure with increased magnitude- ulceration due to this mechanism can be explained by example like stepping on a thorn or nail.

3)Multiple pressures- ulceration by these component can be explained by the mechanical fatigue and loss of integrity of skin due to repetitive pressures.

Kosiak demonstrated the inverse time-pressure relationship in causing injury/ ulceration. This is represented in the figure below.[26]



Graph 1 inverse relationship of time and pressure

Classification of diabetic foot :

Diabetic foot classified based on pathophysiology into two types:

Neuropathy and vasculopathy are two main pathophysiological factors in DFU. It is classified as

1. The Neuropathic Foot: if the pathological factor underlying is predominantly neuropathy.
2. The NeuroischemicFoot: if the vasculopathy is the predominant pathology than neuropathy in causing ulceration.[8]

Separating between these elements is fundamental on the grounds that their manifestations are unique and they require distinctive remedial procedures.

The College of Texas Wound Characterization Framework is[27](Table 2)

Stages	Description
Stage A	No infection or ischemia
Stage B	Infection present
Stage C	Ischemia present
Stage D	Infection and ischemia present
Grading	
Grade 0	Epithelialized wound
Grade 1	Superficial wound
Grade 2	Wound penetrates to tendon or capsule
Grade 3	Wound penetrates to bone or joint

The characterization proposed by Wagner is [27] (Table 3)

Grade	Description of ulcer
0	intact skin in patients who are at risk
I	superficial ulcers with exposed subcutaneous tissue
II	exposed tendon and deep structures
III	ulcers extend to the deep tissue and have either associated soft tissue abscess or osteomyelitis
IV	ulcers include feet with partial gangrene
V	feet ulcers with more extensive gangrenous tissue

Assessment of feet

1.Physical assessment

Clinical assessment is always considered important in diagnosing any health condition. Thorough foot exemption in DM patients is of utmost importance in assessment of risk factors and diabetic foot ulceration.

Clinical assessment primarily includes history, patients with previous history of ulceration and toe amputation are at high risk of developing foot ulcers. History of intermittent claudication and rest pain suggest of PAD.

General examination to be done to rule out any signs of infection or sepsis. Clinical examination should be oriented towards ruling out any changes of neuropathy and vascular insufficiency. Thorough examination to be done and look for dryness of skin, fissures, callus, foot deformity, nail changes and interdigital skin cracks. Palpate all the arteries to know vascular compromise if any.[8,28]

2. Tests for neuropathy

It is important to look for peripheral neuropathy in DM as it is one of the important factor in foot ulceration.

Monofilament test is the cheap and most widely used for examination of foot at risk of neuropathy. The inability to sense or loss of sensation to10g pressure is the present guideline for defining loss of pain sensation. However the results of monofilament test are variable and it should be correlated with the results from other tests.[16,17,28]

The other tests for neuropathy evaluation in DM foot are bio-thesiometer and graduated tuning fork test. Both these tests are to assess vibration perception threshold.[8]

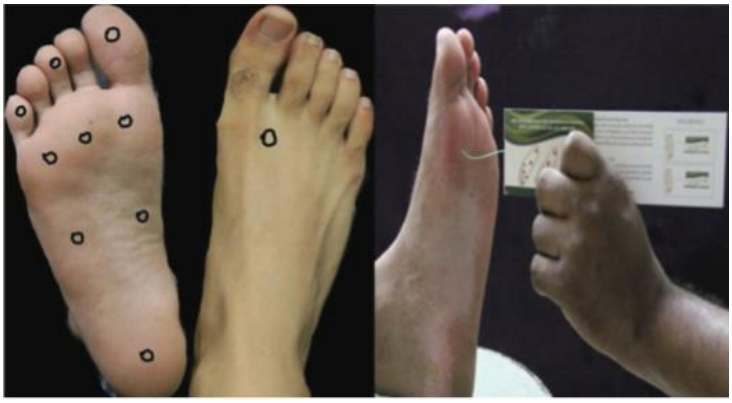


Fig 5 Monofilament test

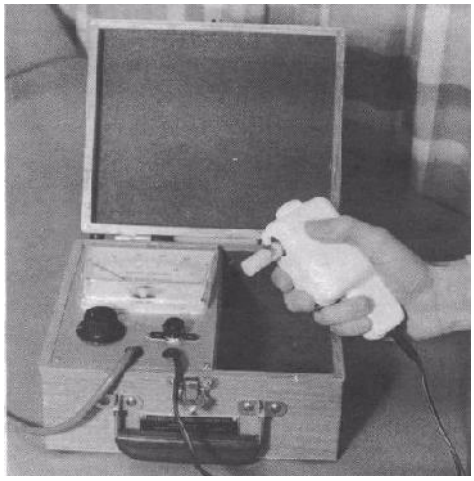


Fig 6 Bio-thesiometer

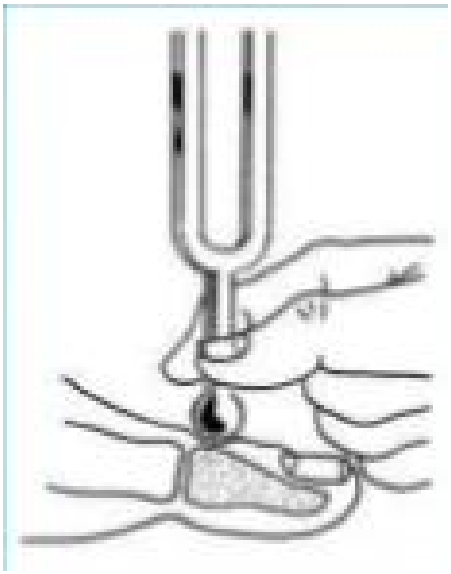


Fig 7 Tuning fork test

3. Tests for vascularity

A hand held Doppler is used to measure the ankle brachial pressure index (ABPI).It is the ratio of pressure at ankle to the pressure at arm, measured using Doppler. It is not standard as it has inter observer variability. Usually diabetics have thick calcified walls of arteries, which result in false ratios. The classification based on ABPI is tabulated below.[8,18](Table 4)

RATIO	INFERENCE
0.9-1.3	Normal
0.7-0.9	Mild obstruction
0.4-0.69	Moderate obstruction
<0.4	Severe obstruction
>1.3	Poorly compressible vessel

Management of Diabetic foot ulcer:

It includes investigations and treatment

Investigation

Apart from the assessment tests described above following investigations to be carried out

1. Complete blood picture to evaluate the total counts and rule out infection.

2 Renal function tests to rule out diabetic nephropathy.

3. Radiograph of foot to grade the wound and rule out osteomyelitis, foot drformities, and Charcot's joint.

4. Wound culture and sensitivity to know the bacterial colonisation and specific antibiotic therapy.

5. HbA1C to know status of sugar control, as wound healing depends on glycemic control.

6. Urine ketone bodies to rule out state of keto-acidosis.

Treatment

The previous studies and clinical experience indicate that DFU treatment requires

Good glycemic control,

Wound bed preparation and

Relieving pressure over the ulcer.[7,22]

1. Good glycemic control

Metabolic control of glycemia plays an important role in management of DFUs besides local wound care. This usually achieved by use of oral hypoglycaemic drugs and insulin therapy.

2.Wound bed preparation[7,16,18,22]

Wound bed preparation is optimisation of the condition of wound surface and edges of the wound. The techniques involved for this optimisation is debridement, infection control, minimisation of edema at the wound site, revascularisation if indicated and surgical correction of defect causing the wound.

Debridement

Debridement isremoval of debrisfrom the wound surface. The variousmethods and types to achievethis are discussedbelow.

Surgical debridement

Surgical debridement refers to the termsharp debridement. It includes clearing the wound site from the debris over the surface, fromcallus-hyperkoeratotic tissue at the woundedges and necroticmaterial if any. This isconsidered as most efficient

methodwound debridement. Aftersurgical debridement chronicwoundisturnedinto acute wound.

Autolytic debridement

Autolytic debridement includes the utilisation of dressings that can retain moisture and keep the wound surface moist. This method of debridement involves the phagocytic cells and body's protective enzymes to clear the devitalized tissue leaving the normal unwounded tissue intact.

Enzymatic debridement

Enzymatic debridement includes removal of the debris and necrotic tissue from the wound site without harm to the surrounding unwounded tissue. The enzymes usually used for this method is crab-inferred collagenase, collagen from krill, papain, a blend of streptokinase and streptodornase, and dextrans. However this method is not cost effective, needs expertise to apply and allergenic.

Mechanical debridement

Mechanical debridement include wet-dry guaze dressings, irrigation using high pressure and whirlpool hydrotherapy.

Initially guaze is made wet using normal saline and allowed to dry. Once guaze dries up and hardens it is removed from the wound surface along with the devitalised tissue. Disadvantages with this method is it is painful to the patient, unless the foot has neuropathy and along with devitalised tissue healthy tissue is also damaged delaying wound healing.

Biological debridement

Biological debridement includes using sterile slimy parasites to clear the debris from wound surface. These sterile maggots has like towards the bacteria and necrotic

tissue leaving behind the healthy tissue. However data on this method of debridement is limited.

Hydration and tissue oedema

Oedema at the site of wound increases risk of infection, and fluids from the wound inhibits proliferation of cells and neo vascularisation. So the wound site should be prepared with measures to control oedema and adequate hydration. This can be achieved by using dressings with good absorptive capacity and regular change of dressings. Use of negative pressure has shown good results with wound healing in earlier studies.

Ischaemia and hypoxia

Evaluation of diabetic foot should be done before planning for surgical debridement. Revascularisation should be planned if ischaemia is present. Evidence from previous studies show that hypoxia of tissues at wound site is associated with delayed wound healing. Recent studies suggest that hyperbaric oxygen therapy has shown better results with wound healing.

Infection control

Infection control is very important in diabetic foot, as they are at hight risk of limb amputaion. It should be treated aggressively because at times it may threaten life.Superficial foot infections are treated by using regular dressings and oral antibiotics. Moderate or deep infections needs admission to hospital and parenteral antibiotics. Antibiotic therapy should be based on the wound culture. Initially empirical therapy of antibiotics should be started till culture reports are available.

3.Off loading - relieving pressure[7,16]

Off loading in diabetic foot means relieving the ulcer site from pressure. It has been proven that pressure over the ulcer site delays wound healing and recurrence of healed ulcer. So proper measures should be taken to prevent pressure over the ulcer site. Usually people who use wheel chair or crutches have good rate of healing.

The gold standard method for offloading diabetic foot is total contact cast (TCC). However there are disadvantages with this technique like need of expertise for application of cast, inability to examine wounds daily and need for good patient compliance. Total contact casts are used in plantar ulcers in the forefoot and mid foot. Wound infection and osteomyelitis are absolute contraindications for the TTC application.

Other devices used for offloading are removable casts walkers and half shoes. These devices are made with room for dressing.

Fig8 various off loading devices and footwear

Wound care - dressings

History

Clay tablet, describes "three healing gestures - washing the wounds, making the plasters and bandaging the wound". Clay tablet is the medical manuscript of old age.[29]

Plasters which are equivalent to present day dressings were used to apply for wounds. These plasters used to contain mud or clay, plants, herbs and oil.

Another interesting known history of wound care was use of beer. An interesting for wound healing in Mesopotamian culture stated as "Pound together fur-turpentine, pine-turpentine, tamarisk, daisy, flour of inninnu strain; mix in milk and beer in a small copper pan; spread on skin; bind on him, and he shall recover."[30]

Egyptians were certainly the first people to use honey, grease and lint in the adhesive bandages for dressing. Honey was also used by Indians for wound dressings. Since than till now for thousands of years honey is the part of many dressings.[30]

A quote by Hippocrates about healing of wound is "For an obstinate ulcer, sweet wine and a lot of patience should be enough." [29]

In nineteenth century, Joseph Lister taught medical fraternity the need of keeping wounds clean and free of contamination through his publications on antisepsis.[29]

Dressings

The term dressing can be explained as material that helps in protecting the wound from the environment and assist in wound healing process. However over the period of evolution dressings have been upgraded with other properties like debridement ,regulation of wound moisture. [31,32]

The ideal characteristic features of dressing are as follows :[32]

Sterile, easy to use, cost effective,

To keep the wound surface moist,

Absorb excess exudates,

Non adherent/non toxic, non allergic,

To protect wound surface from the foreign particles,

Protect wound surface from micro organisms,

Allow gaseous exchange and control wound odour and

Provide thermal insulation and mechanical protection.

How ever there is no dressing that can meet all these characteristic features.

Dressings are broadly classified under following headings : [22,31,32]

Films

Semi permeable film dressings are thin sheets of material with an adhesive for contact with wound surface. These are used for superficial pressure ulcers, skin donor graft site and superficial burns.

Foams

Foam dressings have good degree of absorptive capacity. This absorptive feature helps in clearing the fluids over the wound surface which further helps in proliferation of cells and angiogenesis.

Hydrogels

Hydrogel dressings consists of hydrated polymers. These polymers have water as major percent of their weight. These dressings helps wound healing by autolytic debridement. Depending on the type of formulation each dressing differs in the ability to donate water ad absorb fluid from the wound surface.

Hydrocolloids

Hydrocolloids are moist rich dressings along with backing material and a layer of hydrophilic particles. In wounds with rich exudate, these dressings helps in absorbing the fluids and keeping the wound surface moist. In case of highly infected wounds these dressings have double edge role, hence its still under debate.

Alginates

Alginate dressings are available in different preparations based on proportions of calcium or sodium. They have both absorbing and haemostat properties which help in wound healing.

Topical antimicrobial therapy[9,33]

As discussed earlier DFU are at high risk of infection. Treatment of any infection almost always requires therapy with antimicrobial agents. Anti microbial therapy includes antibiotics and antiseptic agents. The presence of organisms hamper the healing process of wound. So some clinicians prescribe antimicrobial therapy especially in wounds with high chances of infection.

Microorganisms over the chronic wounds develop a protective wall called biofilm. Such kind of infections are difficult to treat. In such cases topical antimicrobial therapy helps as it could get into high concentrations at the site of wound.Other advantages of topical anti microbial therapy is minimal risk of toxicity compared with systemic therapy, can easily be applied by anyone and better patient compliance to treatment.Disadvantages with antimicrobials are systemic toxicity if used in large open wounds, some interfere with normal wound healing, risk of anaphylaxis and contact dermatitis, may require increased frequency of applications.[9,33]

Most clinically used antimicrobial gents belong to two main groups which will be discussed in detail.

Antibiotics

This groups include chemicals which are made naturally from micro organisms and plant products or artificially in the pharmacy labs. These group of antimicrobials act at specific target on microbes, have narrow spectrum of anti microbicidal property and more importantly microbes can develop resistance on prolonged usage.

Most of the topically used antibiotics like bacitracin and mupirocin have only gram positive coverage, however neomycin and silver sulphadiazine shown to have efficacy against gram negative organisms. Some of the systemic antibiotics are also used as topical applications.[9]

Antiseptics

This group includes chemicals which can be used over the intact skin for asepsis and over the surface of open wounds to kill and clear micro-organisms. These act on microbes at various different targets, have broad antimicrobial spectrum and residual anti infective activity. Disadvantage with antiseptics is that they are known to have toxicity to healthy host cells.

Chlorhexidine and povidone iodine are well known antiseptic agents. With time being new antiseptics have been developed, approved and promoted like octenidine and preparations that release silver ions.[9]

Povidone iodine

Iodine has role of antimicrobial agent in wound care. It has been used as an antiseptic agent since years.[34]

Povidone iodine is a complex of povidone, which is a synthetic polymer and iodine is the anti microbial. Povidone is the carrier for iodine in this preparation. Free

iodine is released into the solution till equilibrium occurs , the continuous release is due to the iodine consuming germicidal activity proceeds.[34]

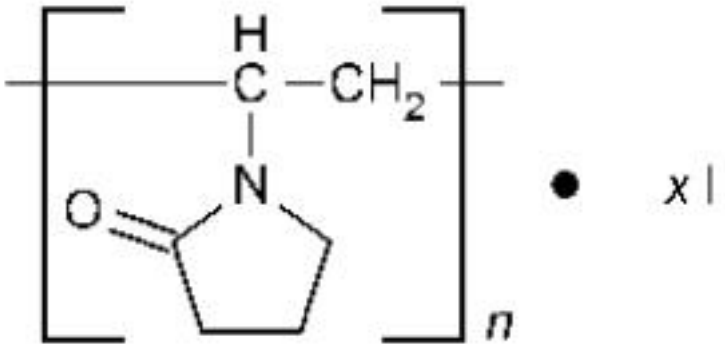


Fig 9 chemical structure of povidone iodine

The microbicidal activity of iodine is through oxidisation of nucleotides, fatty acids and amino acids in the cell wall of organisms. It desaturates and deactivates these organisms.[9]

Povidone iodine has broad spectrum of activity including bacteria, several viruses, fungi, spores, protozoa and amoebic cysts. No reports of acquired or cross resistance has been reported for povidone iodine. It has efficacy to heal wounds in the presence biofilms.[9,34]

Povidone iodine has been associated with less pain compared to cadexomer-iodine and silver dressings. In case of chronic wounds where the microbiology of wounds is anaerobic and gram negative, povidone iodine has a role. [9]

Disadvantage of iodine preparation is its systemic toxicity, when used on large wound surfaces it is absorbed systemically and causes toxicity of the same.[9]

Because of its toxicity and systemic absorption, it is contraindicated in thyroid disease, very low birth weight, known toxicity and in patients receiving radio iodine therapy.[9,34]

Comparison of routinely used antiseptics[9,33](Table 5)

Agents	Bacterial coverage	Advantages	Disadvantages	Comments
Chlorhexidine	Gram positive bacteria (e.g. staphylococcus aureus) and gram negative bacteria	Persistent activity upto 6 hrs after application	Hypersensitivity ranging from urticaria to anaphylaxis, injury to eye when it comes into contact	2% chlorhexidine used as surgical hand scrub, skin and wound cleanser.
Iodine compounds and tincture iodine	Microbicidal against bacteria, fungi, viruses, spores, protozoa and yeasts	Broad spectrum	High toxicity if ingested or significantly absorbed, should be used cautiously in patients with thyroid disorders.	Not used for asepsis now days
Povidone iodine	Broad spectrum includes Staph aureus and enterococci	Less irritating to skin and allergenic than iodine. Can be covered with dressing, resistance is very rare	Anti bacterial action requires at least 2 min of contact, May cause sting like pain and erythema, Efficacy reduced in presence of body fluids, Prolonged use many be associated with metabolic acidosis.	Superficial wounds, Pre operative skin cleansing.
Silver nitrate	Silver ions are bactericidal and have broad spectrum coverage including both gram positive and gram negative.	Low cost, easily applied.	Painful on application, Delays healing process, Higher concentrations may cause cauterisation and Inactivated by wound exudates and chlorine.	Previously widely used now replaced by other silver dressings.

Octenidine - Dihydrochloride

Octenidine a new alkanediylbis [pyridine] class of antiseptic based dressings are available for wound antisepsis since 20 years. It was first launched in U.K during 1990. It helped doctors and health care providers to manage hospital acquired infections and improve wound care.[10]

Chemical structure

It is a cationic group of anti septic similar to the chlorhexidine group. The chemical structure of octenidine has two long aliphatic hydrocarbon chains which separate the cationic active centres.[10,11]

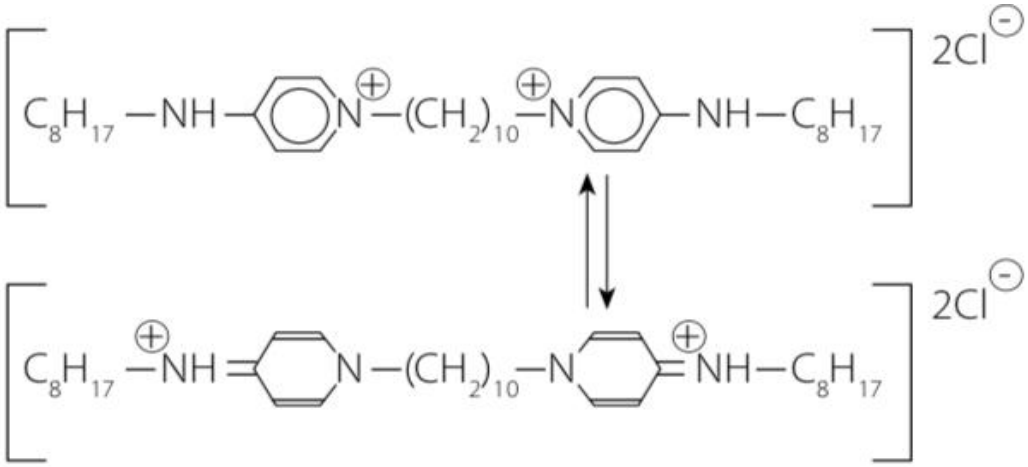


Fig 10 chemical structure of octenidine dihydrochloride

Physical and chemical properties

Octenidine is stable in wide range of pH ranging from 1.6 to 12.2, it can be stored at room temperature, it can be sterilised above the boiling point of water in aqueous solutions that is upto 130 degree centigrade. Antiseptic substance with such stability is required, because handling of substance is easy and substance not prone for hydrolysis.[10]

Mechanism of action

The cell membranes of bacteria are negatively charged because of polysaccharide and cardiolipin composition. The cationic component of octenidine readily attracts to these negatively charge particles in the bacterial cell wall. Along with interaction with polysachharides of cell wall it also influences cytoplasmic bacterial enzymatic systems, resulting in leakage of their cytoplasmic membrane and cell death. Because of this mechanism of antisepsis there is no risk of resistance with prolonged usage of octenidine.[10,11]

Because of this strong non specific association with cell wall and cell wall components octenidine has very broad spectrum of anti-microbial action. It is effective against gram positive, gram negative bacteria including resistant staph aureus species. It also has minimal viricidal and fungicidal properties. Because of its proven efficacy against broad range of micro organisms, octenidine became an alternative to other antiseptics like chlorhexidine or povidone iodine. [10,12]

Pharmacokinetics

Octenidine is usually not absorbed through skin and mucous membranes.

Animal studies were done in mice and rats. In mice after topic application of carbon labelled radioactive ocenidine, no radioactivity was detected in serum at any time. Similar results obtained in rats when octendine dosing was given orally, absorbed counts are <6%. Most of it was excreted in faeces.[10]

In vitro studies with artificially perfused, freshly prepared human placenta similar results were seen.

Systemic studies were not performed because of these results.[10]

Advantages of octenidine

Various studies suggest that octenidine has broad spectrum of antimicrobial activity against gram positive and gram negative organisms. It is also effective against Actinomycesspp and streptococcus mutans, plaque forming organisms.[10,11]

Ocenidine has more efficacy compared to chlorhexidine against S.mutans.

As per study by Bailey et al minimum inhibitory concentrations required for antibacterial effect by octenidine were 10 fold less compared to chlorhexidine.[11] Study by Harke et al has shown similar results comparing the MIC in both bacteria and yeast between octenidine and chlorhexidine.[11]

An in vitro study conducted earlier has shown that octenidine when compared with chlorhexidine has shown 3-10 times efficacy in terms of anti microbial activity.[35]

In vitro study conducted earlier, has shown results positive for octenidine when used along with antibiotics. Study has shown that octenidine when used along with antibiotics had synergistic action unlike the other antiseptics like chlorhexidine.[10]

Octenidine has no loss of antiseptic efficacy in presence of excessive exudate from wounds which interfere with healing process. In vitro study conducted comparing the efficacy of chlorhexidine and octenidine in presence of pus or 25% blood, octenidine did not loose its efficacy where aschlorhexidine efficacy was reduced 2.5 to 35 fold.[10,11]

With regarding to inactivation of biofilms, octenidine action against biofilms produced by commensals like s.epidermidis and pseudomonas aeruginosa was highly effective.[10]

Octenidine has action for prolonged duration and sustained anti microbial effect. This can be explained by the strong binding nature of octenidine with the

negatively charged particle of cell wall and poor absorption percutaneously. This persistent effect protect wounds from contamination even after 5 days decreasing the re dressing frequency.[36]

In vitro studies done earlier to evaluate cytotoxicity of octenidine, has shown results that it is cytotoxic to human cells. But these results didn't correlate with a randomised controlled clinical study conducted by Vanscheidt W et al on chronic venous ulcers. The study has shown good tissue compatibility and less adverse effects of octenidine when compared to ringer lactate when used for chronic venous ulcers.[37]

Miller G et al,conducted a study comparing antiseptic activity and cytotoxicity of various antiseptics against line of organisms and proposed a term "biocompatibility index" , substance like octenidine and polyhexadine has bio compatibility index >1 which means that they are more toxic to microbials than the host fibroblast,keratinocytes and epithelial cells. Povidone iodine had bio compatibility index less than 1.[13]

Octenidine forms complexes with human epithelial cells, murine fibroblasts and keratinocytes. These complexes reduce the cytotoxic efficacy without change of anti microbial properties.[10,11]

In vitro study conducted to compare antiseptic efficacy of triclosan, povidone iodine otenidine, polyhexanide and chlorhexidine ,their efficacy with microbistatic and microbicidal concentration has been ranked as ployhexanide = octenidine >chlorhexidine>triclosan> povidone - iodine. [38]

Octenidine wound gel presently used in our study, is the hydrogel based preparation of octenidine. Hydrogels have molecular structure which can rehydrate the dead tissue and cause autolytic debridement. This preparation reduces the frequency of dressing changes, it is changed once in 1-3 days depending on amount of

exudates. In addition gel is easy to apply and it will not run away. Even though it absorbs so much secretions it doesn't have significant increase in size.[12]

This gel based preparation is available, with 0.05% octenidine w/w. The dosage of application measured in finger tip units (FTU).[39]

New lipid formulation of octenidine is available now. Octenidine being a hydrophobic compound needs an organic solvent for effective administration. Phenoxyethanol is being used now. This new lipid formulation is known to cause minimal irritation of mucous membrane surfaces compared to phenoxyethanol. [40]

Most of the studies conducted on octenidine are in vitro or animal models, very few clinical studies are available. Clinical studies available are performed in chronic venous ulcers. Case studies on diabetic foot ulcer healing has shown good progress in healing in terms of wound contraction time. Further clinical studies are needed for better understanding of tissue compatibility, cost effectiveness and adverse effects if any.

MATERIALS AND METHODS

The source of data were the patients with diabetic foot ulcers admitted under department of general surgery at KLES Dr.Prabhakar Kore Charitable Hospital and Medical ResearchCentre, Nehru Nagar. Belagavi, in the year 2018 between January to December.

a)Study design:A randomised control trial

b)Study Period: (Year 2018 between January to December)

c)Study Population: Patients with diabetic foot ulcers, admitted in general surgical wards, measuring less than 6 * 6 sq.cms of Wagner grade 1 of 4wks duration.

Patients are enrolled after debridement of ulcer.

d) Selection criteria

1) Inclusion criteria

-Type 2 Diabetic patients aged 35 to 75 years.

-Patients having ulcers measuring less than 6*6sq.cms.

-Patients with grade 1 ulcers based on Wagner's classification.

-Duration > 4 weeks

2)Exclusion criteria

-Patients not willing to participate in the study

-Pulse lessness

-Immunocompromised

-Diabeticketoacidosis

-Diabetic gangrene

-Connective tissue disorder

-Skin malignancy

e) Sampling procedure-

The patients are divided into group A and group B basedon SNOSE (sequentially numbered, opaque, sealed envelope)technique.

f)Sample size

Total sample size of 80 cases. 40 in group A and the other 40in group B.

Sample size calculation

The minimum sample size(n=40) in each group is based onformula below after pilot study

$$n = \frac{S^2 (Z_\alpha + Z_\beta)^2}{d^2}$$

$$S = \frac{S1 + S2}{2}$$

S_1 = S.D of wound healing in group B = 0.354

S_2=S.D of wound healing in group A = 0.652

d = Mean difference = 0.4241

Z_α = 1.96 at 5% αerror

Z_β = 21.037 at 85% power

There by total sample size is 80.

g)Procedure

Ethical clearance was given by the Ethical research committee of JNMC, Belagavi.

Data collection instrument is used for data collection.

All the patients after debridement who satisfied the inclusion criteria are subjects of study. The patients are then enrolled into the study after taking written and informed consent.

Demographic data of the patients is noted in a predesignedproforma.

Detailed history of the patient is taken.

Empirical antibiotics ceftriaxone and metronidazole orcefotaxime and metronidazole are started and later specific antibiotic therapy is started after culture and sensitivity report is obtained.

All the patients are managed by OHA's and insulin therapy as advised by physician.

In both the groups normal saline wash is given and topical management and dressing is done daily once as follows.

Group A

In this group topical management and dressing is doneusing octenidine wound gel (Zotobac gel). The gel applied was calculated by finger tip units (FTU), amount to be applied was based on a study by C.C Long and A.Y Finlay "Finger tip unit - A new practical measure". [39] One FTU=0.5gm covers 2% of body surface area.

Group B

In this group topical management and dressing is done using povidone-iodine 10% w/v solution and normal saline.one soaked gauze of povidone-iodine is used for topical application.

Characteristics of the two groups with respect to age, gender are determined.

Outcome

Observation of healing of ulcer is done in terms ofreduction in wound area at the beginning (D0) and fifteenth day(D14).

The dimensions of the ulcer i.e length, width and area are measured by using a mobile software application- “imitomeasure”.

A digital photograph of the ulcer is taken using an android phone with the installed software with a marker beside the ulcer as specified by application. The software then calculated the measurements of the ulcer automatically.

Fig 11 ulcer area measurement using imitomeasure application

Calculation of wound area

The ulcer dimensions are measured on day 0(x) = initial wound area andday 14(y) = final wound area. The reduction in area and percentage reduction in area are calculated as follows:

Wound area on D0 = x

Wound area on D14 = y

Reduction in wound area = x-y

% Reduction in wound area = $\frac{x-y}{x} x100$

All the data collected from the patients was then tabulated in Microsoft excel spreadsheet. The data was statistically analysed.

STATISTICAL METHODS

The present study is conducted in KLE'S Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi and the findings are tabulated as below.

During the study year from January 2018 to December 2018, 80 patients with diabetic foot ulcers are randomized into study (Topical octenidine wound gel dressings) and control (povidone iodine dressings) groups. These groups were studied for the effect of povidone iodine dressings versus octenidine wound gel dressing on reduction in size of the ulcer.

A total of 80 patients satisfied the selection criteria, analysis was done by using independent't' test, and chi square test.

'P' value less than 0.05 considered significant statistically.

Statistical analysis was done using IBM SPSS version 22.0

RESULTS

The present study is conducted in KLE'S Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi, During the study period from January 2018 to December 2018,

A total of 80 patients with diabetic foot ulcers are randomized into study (Topical octenidine wound gel dressings) and control (povidone iodine dressings) groups. These groups were studied for the effect of povidone iodine dressings versus octenidine wound gel dressing on reduction in size of the ulcer.

Data obtained was entered into Microsoft excel spreadsheets. The data was analysed and the results obtained were tabulated as represented below.

'P' value less than 0.05 considered significant statistically.

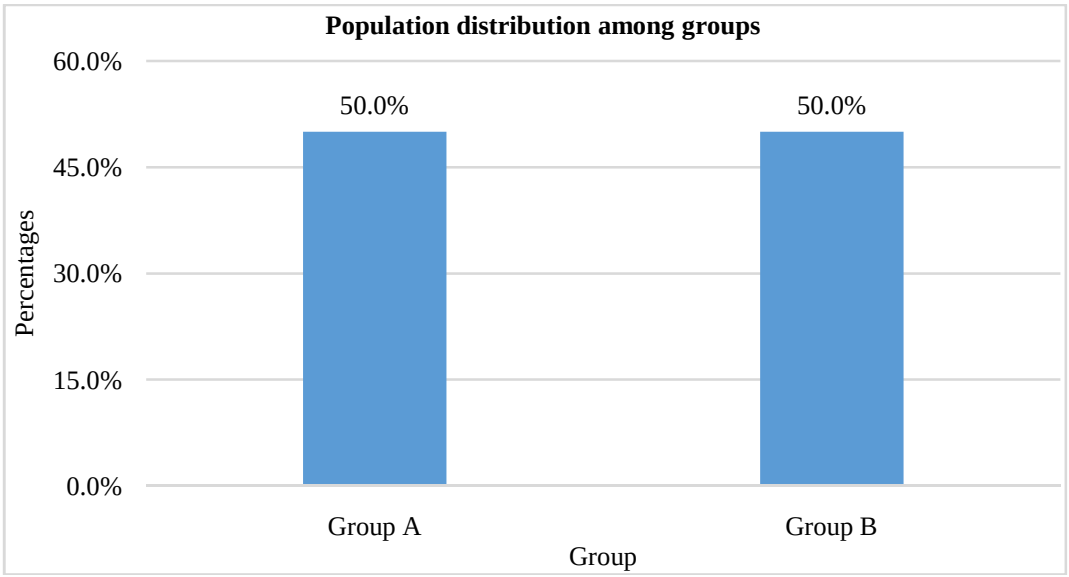
Results:

A total of 80 subjects were included in the final analysis.

Table 6: Descriptive analysis of group in the study population (N=80)

Group	Frequency	Percentages
Group A	40	50.00%
Group B	40	50.00%

Graph 2: Bar chart of group in the study population (N=80)



Among the study population 40(50%) participants were in group A and remaining 40(50%) participants were in group B. (Table 6& Graph 2)

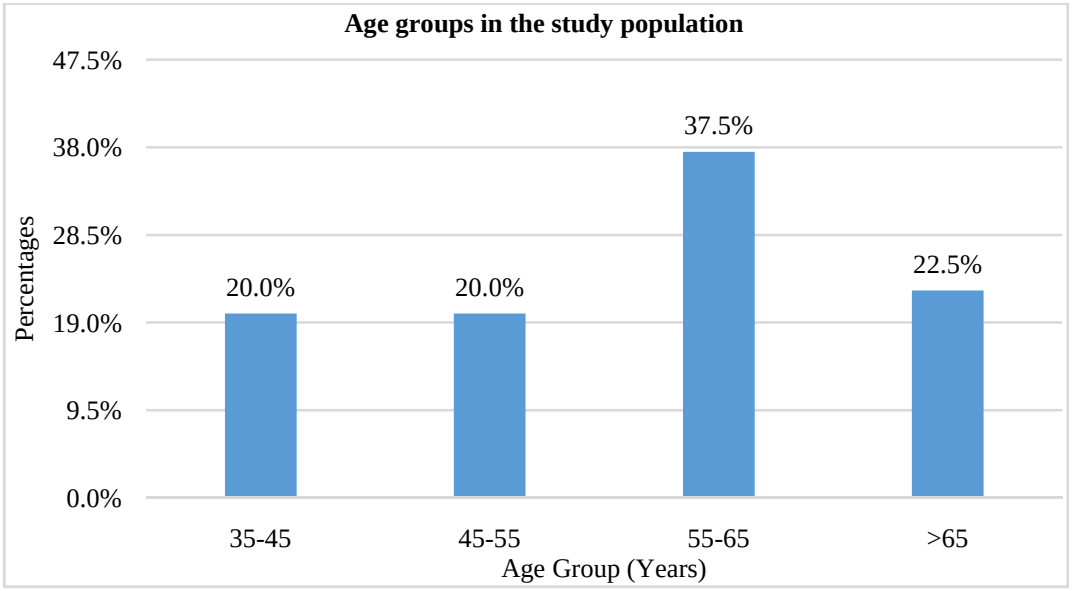
Group A - STUDY GROUP - population where octenidine wound gel dressing done.

Group B - CONTROL GROUP - population where povidone iodine dressing done.

Table 7: Descriptive analysis of age group in the study population (N=80)

Age Group (Years)	Frequency	Percentages
35-45	16	20.0%
45-55	16	20.0%
55-65	30	37.5%
>65	18	22.5%

Graph 3: Bar chart of age group (years) in the study population (N=80)

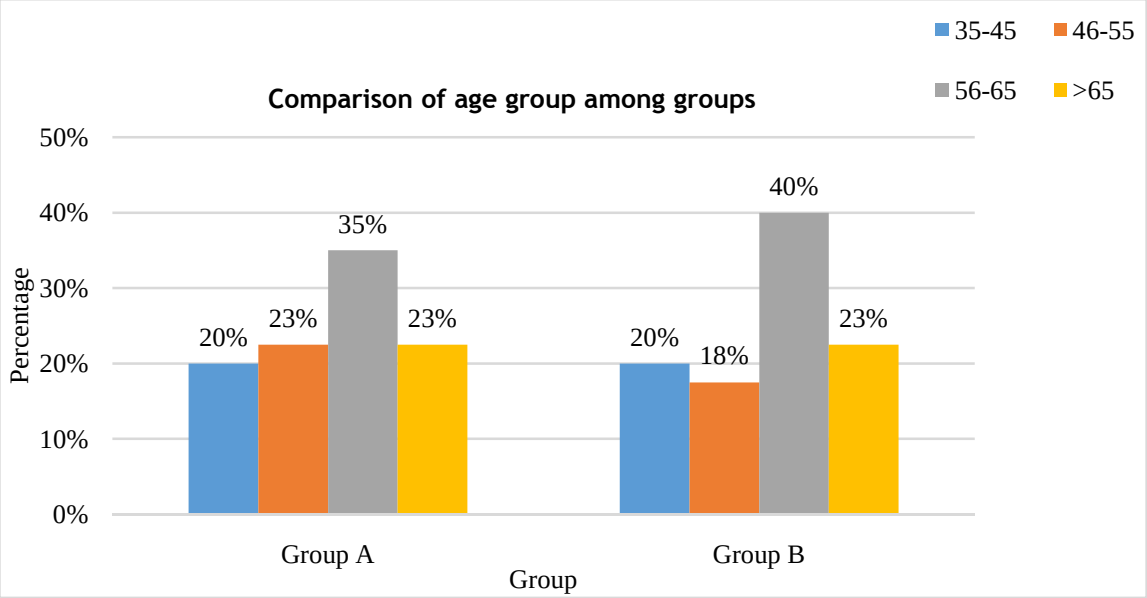


Among the study population 16(20%) were aged between 35 to 45 years, 16(20%) were aged between 45 to 55 years, 30(37.5%) were aged 55 to 65 years and remaining 18(22.5%) were aged more than 65 years. 60% of study population were above 55 years of age. These increased risk of foot ulceration in fifth and sixth decade was consistent with findings from the study conducted by Surriah et al.[41](Table7 & Graph3).

Table 8: Comparison of age group between two groups (N=80)

Age Group (Years)	Group		Chi square	P value
	Group A (N=40)	Group B (N=40)		
35-45	8 (20%)	8 (20%)	0.383	0.944
46-55	9 (22.5%)	7 (17.5%)		
56-65	14 (35%)	16 (40%)		
>65	9 (22.5%)	9 (22.5%)		

Graph 4: Cluster bar graph for comparison of age group between two groups (N=80)

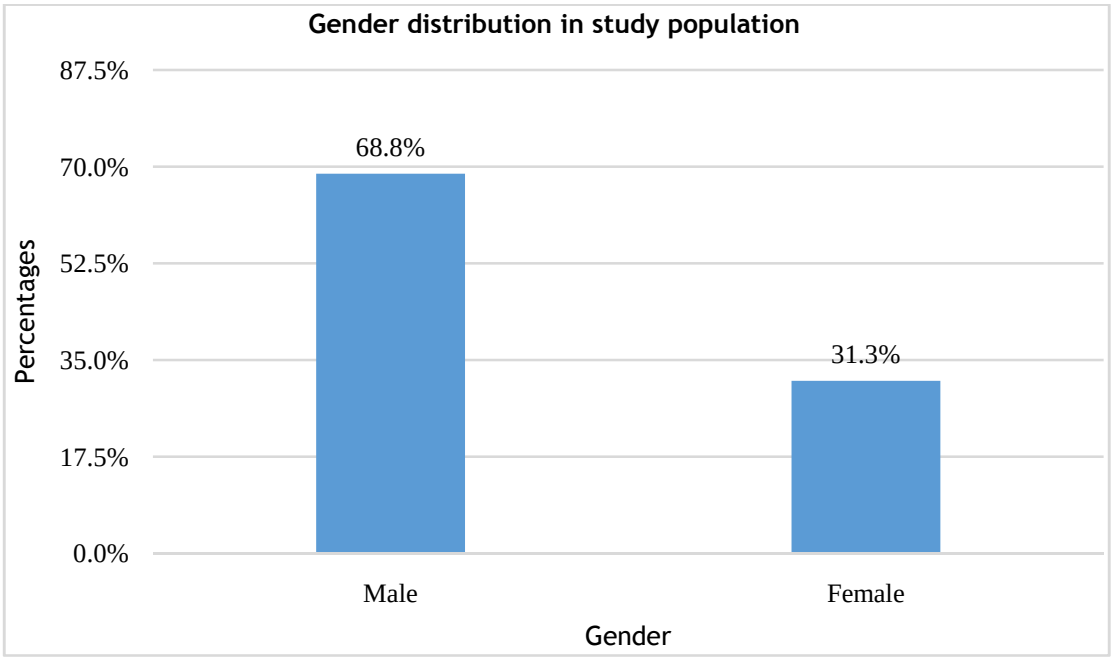


Among group A,8 (20%) were aged between 35 to 45 years, 9 (22.5%) were aged 46 to 55 years, 14 (35%) were aged 56 to 65 years, 9 (22.5%) were aged more than 65 years. Among group B, 8 (20%) were aged between 35 to 45 years, 7 (17.5%) were aged 46 to 55 years, 16 (40%) were aged 56 to 65 years, 9 (22.5%) were aged more than 65 years. There was no statistically significant differences among the groups as per age distribution was considered. (P value 0.944). (Table8 & Graph4)

Table 9: Descriptive analysis of gender in the study population (N=80)

Gender	Frequency	Percentages
Male	55	68.75%
Female	25	31.25%

Graph 5: Bar chart of gender in the study population (N=80)

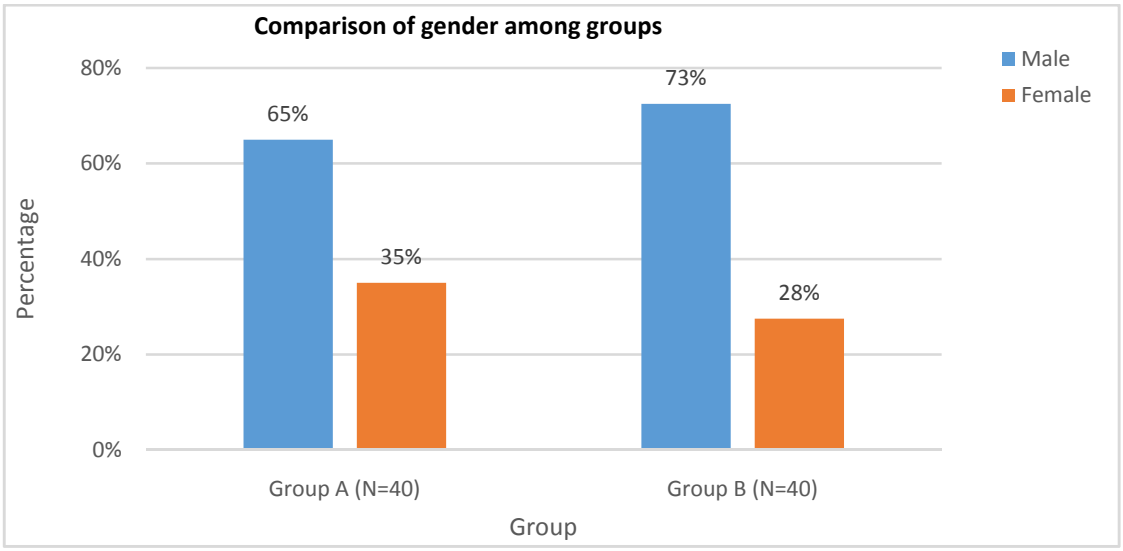


Among the study population 55(68.75%) participants were males and remaining 25(31.25%) participants were females. Male to female ratio in study population is 2.2:1.The male preponderance in this study was consistent with the study by P Zhang et al.[42](Table 9& graph5)

Table 10: Comparison of gender between two groups (N=80)

Gender	Group		Chi square	P-value
	Group A (N=40)	Group B (N=40)		
Male	26 (65%)	29 (72.5%)	.524	0.469
Female	14 (35%)	11 (27.5%)		

Graph6: Cluster bar graph for comparison of gender between two groups (N=80)

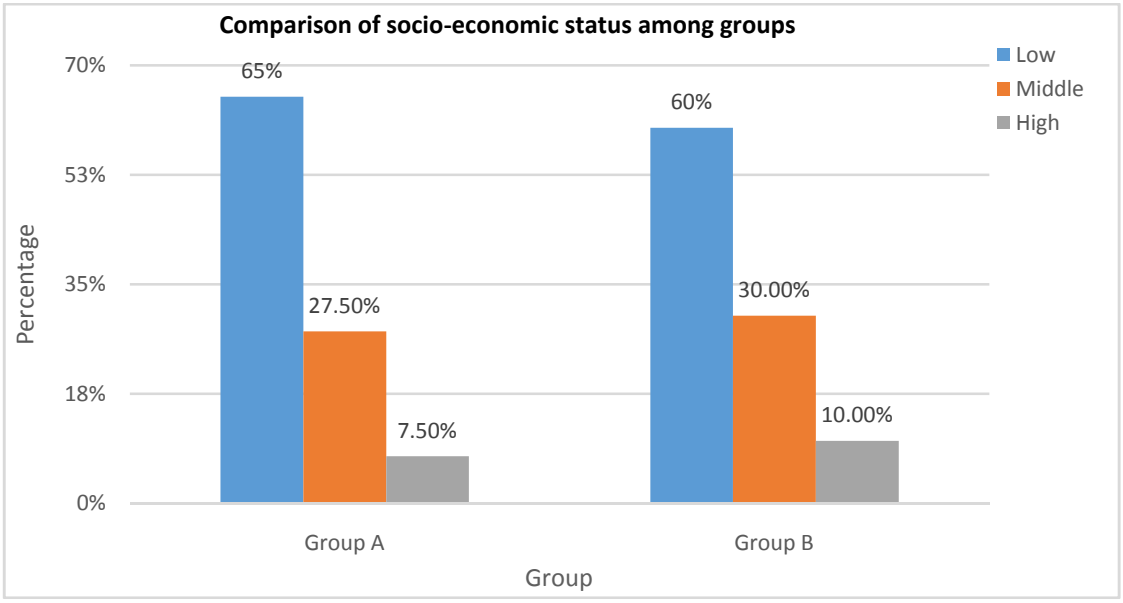


Among group A, 26 (65%) were males, 14 (35%) were females. Among group B, 29 (72.5%) were males, 11 (27.5%) were females. There was no statically significant difference among the groups as per gender distribution was considered. (P value 0.469). (Table 10& graph6)

Table 11: Comparison of socioeconomic status between two groups (N=80)

Socioeconomic status	Group		Chi square	P value
	Group A (N=40)	Group B (N=40)		
Low	26 (65%)	24 (60%)	0.266	0.875
Middle	11 (27.5%)	12 (30%)		
High	3 (7.5%)	4 (10%)		

Graph 7: Cluster bar graph for comparison of socio economic status between two groups (N=80)

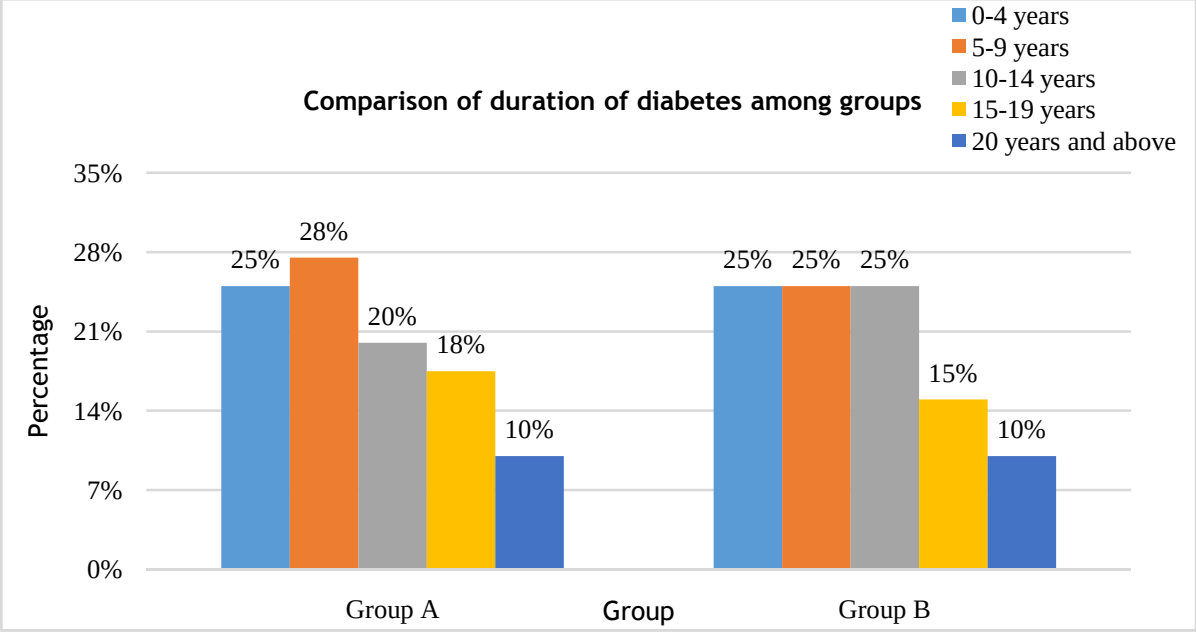


Among group A,26 (65%) were belonged to low socioeconomic status, 11 (27.5%) were belonged to middle class, 3 (7.5%) were belonged to high class. Among group B, 24 (60%) were belonged to low socioeconomic status, 12 (30%) were belonged to middle class, 4 (10%) were belonged to high class.There was no statically significant difference among the groups as per socio economic status distribution was considered. (P value 0.875). (Table 11& graph7). The classification was done based on Modified B.G Prasad classification for economic status.The findings were consistent with "community based study to assess the prevalence of diabetic foot syndrome and associated risk factors among people with diabetes mellitus" conducted by Vibha et al.[43]

Table 12: Comparison of duration of diabetes (in years) between two groups (N=80)

Duration Of Diabetes	Group		Chi square	P value
	Group A (N=40)	Group B (N=40)		
0-4 Years	10 (25%)	10 (25%)	0.347	0.987
5-9 Years	11 (27.5%)	10 (25%)		
10-14 Years	8 (20%)	10 (25%)		
15-19 Years	7 (17.5%)	6 (15%)		
20 Years And Above	4 (10%)	4 (10%)		

Graph 8: Cluster bar graph for comparison of duration of diabetes (in years) between two groups (N=80)

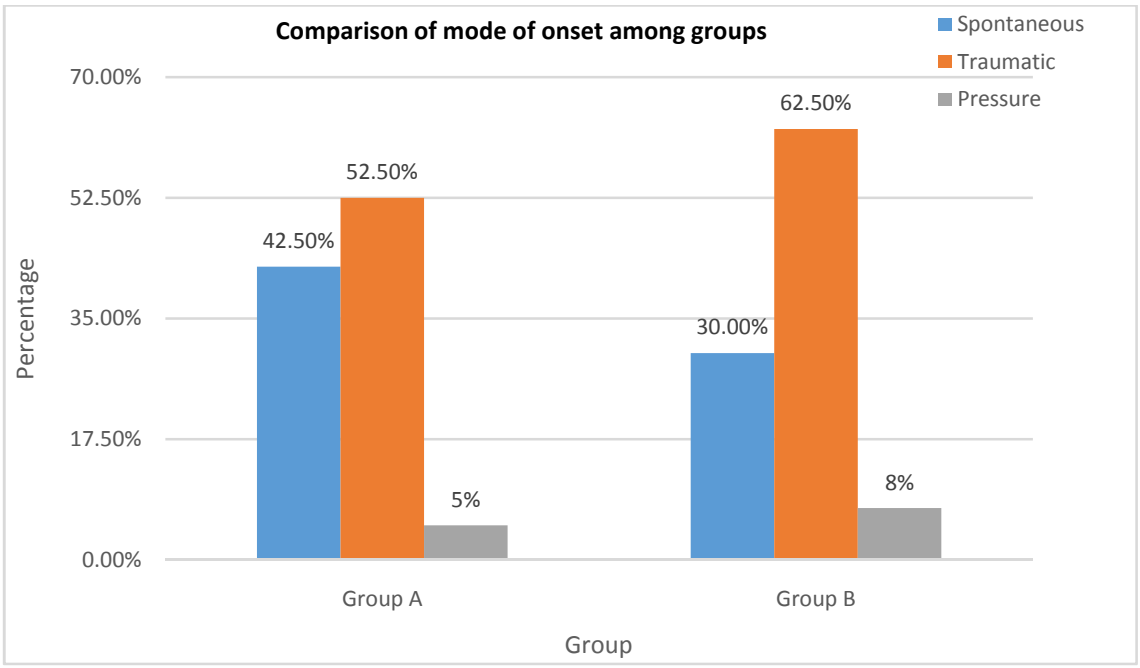


Among group A, 10 (25%) had diabetes duration 0 to 4 years, 11 (27.5%) had diabetes duration 5 to 9 years, 8 (20%) had duration 10 to 14 years, 7 (17.5%) had duration 15 to 19 years, 4 (10%) had duration 20 years and above. Among group B, 10 (25%) had diabetes duration 0 to 4 years, 10 (25%) had diabetes duration 5 to 9 years, 10 (25%) had duration 10 to 14 years, 6 (15%) had duration 15 to 19 years, 4 (10%) had duration 20 years and above.There was no statistically significant difference among two groups as per duration of diabetes was considered. (Table 12& graph8)

Table 13: Comparison of mode of onset between two groups (N=80)

Onset	Group		Chi square	P value
	Group A (N=40)	Group B (N=40)		
Spontaneous	17 (42.5%)	12 (30%)	1.410	0.494
Traumatic	21 (52.5%)	25 (62.5%)		
Pressure	2 (5%)	3 (7.5%)		

Graph 9: Cluster bar graph for comparison of mode of onset between two groups (N=80)

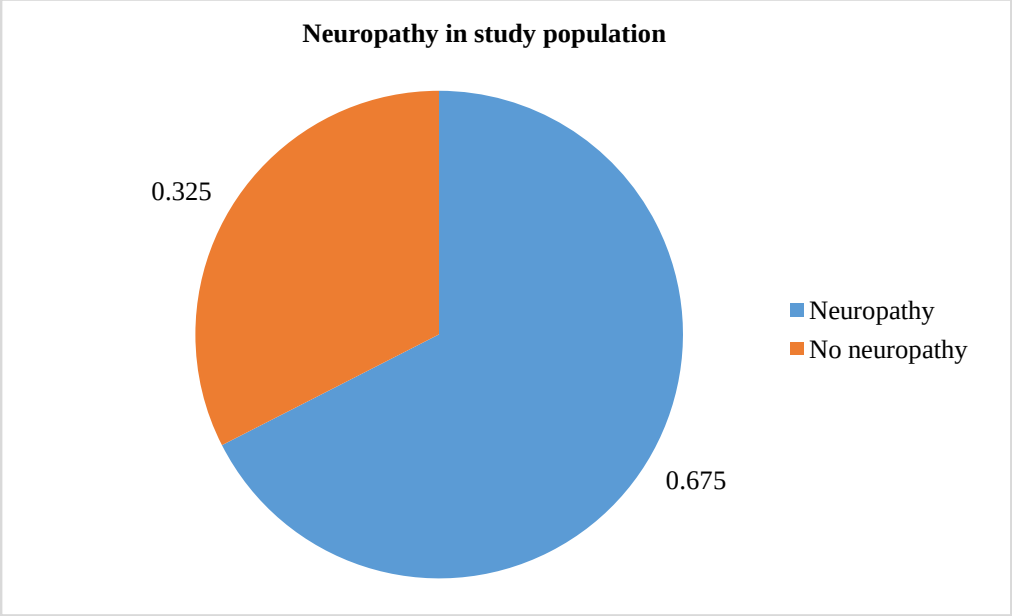


Among group A**,** 17 (42.5%) had spontaneous onset, 21 (52.5%) had traumatic onset, 2 (5%) had pressure onset. Among group B, 12 (30%) had spontaneous onset, 25 (62.5%) had traumatic onset, 3 (7.5%) had pressure onset. There was no statistically significant difference among two groups as per mode of onset was considered.(P value 0.494). (Table 13& graph9)

Table 14: Descriptive analysis of neuropathy in the study population (N=80)

Neuropathy	Frequency	Percentages
Yes	54	67.5%
No	26	32.5%

Graph 10: Pie chart of neuropathy in the study population (N=80)

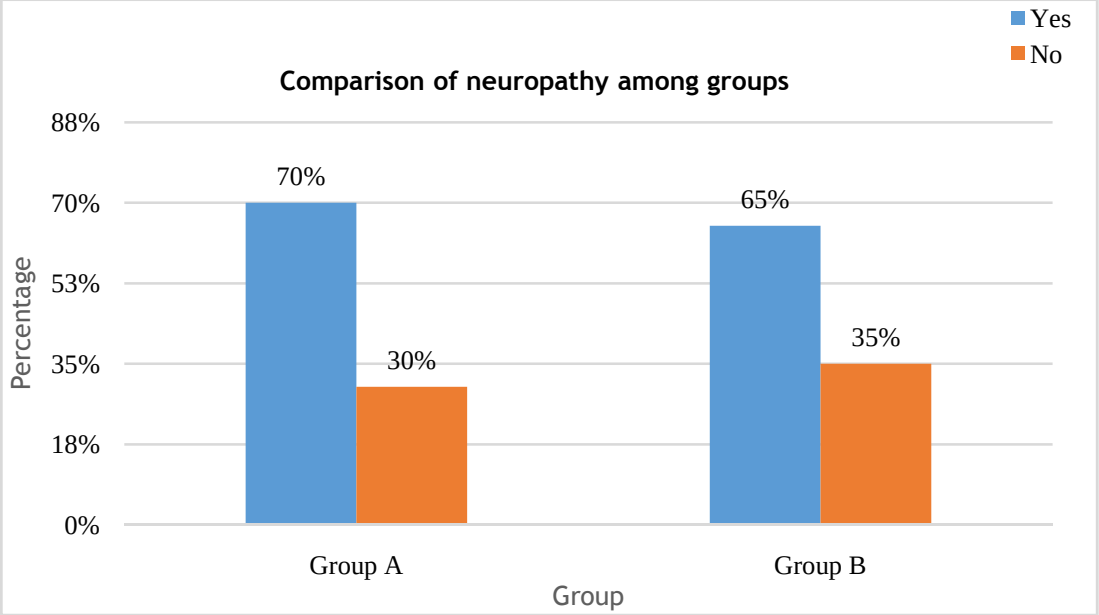


Among the study population 54(67.5%) participants had neuropathy. (Table 14& graph10)

Table 15: Comparison of neuropathy between two groups (N=80)

Neuropathy	Group		Chi square	P value
	Group A (N=40)	Group B (N=40)		
Yes	28 (70%)	26 (65%)	0.228	0.633
No	12 (30%)	14 (35%)		

Graph 11: Cluster bar graph for comparison of neuropathy between two groups (N=80)

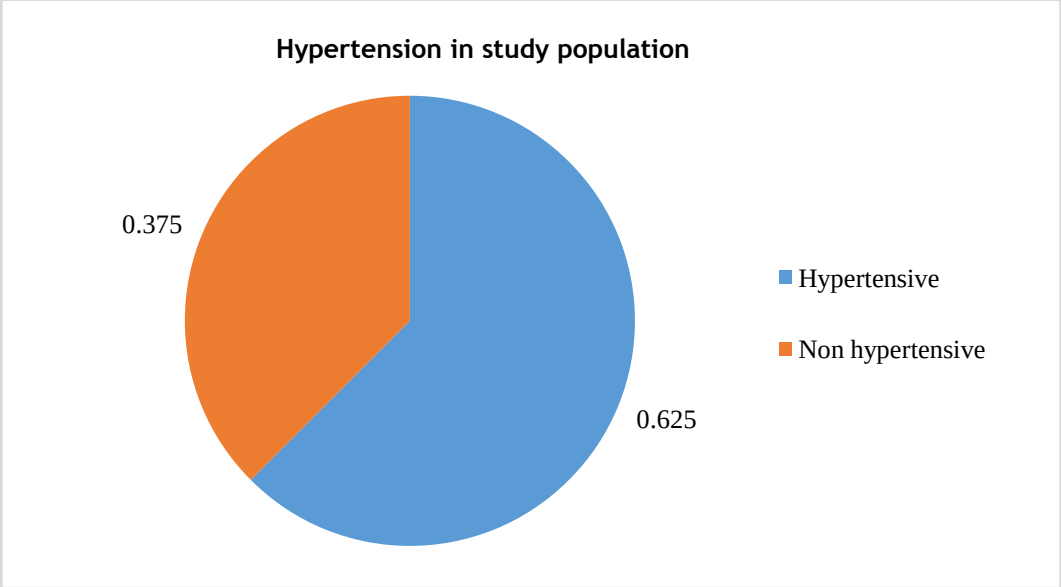


Among group A, 28 (70%) had neuropathy. Among group B, 26 (65%) had neuropathy. There was no statistically significant difference among the groups as per neuropathy distribution was considered. (P value 0.633). (Table15 & graph11)

Table 16: Descriptive analysis of hypertension in the study population (N=80)

Hypertension	Frequency	Percentages
Yes	50	62.50%
No	30	37.50%

Graph 12: Pie chart of hypertension in the study population (N=80)

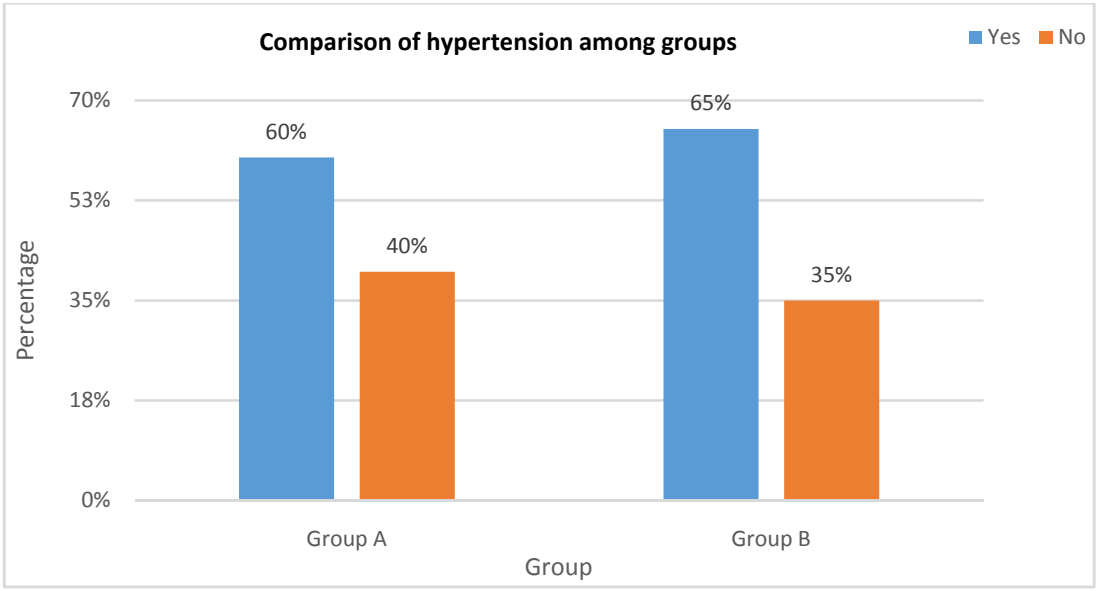


Among the study population 50(62.50%) participants had hypertension. (Table16&graph12)

Table 17: Comparison of hypertension between two groups (N=80)

Hypertension	Group		Chi square	P value
	Group A (N=40)	Group B (N=40)		
Yes	24 (60%)	26 (65%)	0.213	0.644
No	16 (40%)	14 (35%)		

Graph 13: Cluster bar graph for comparison of hypertension between two groups (N=80)

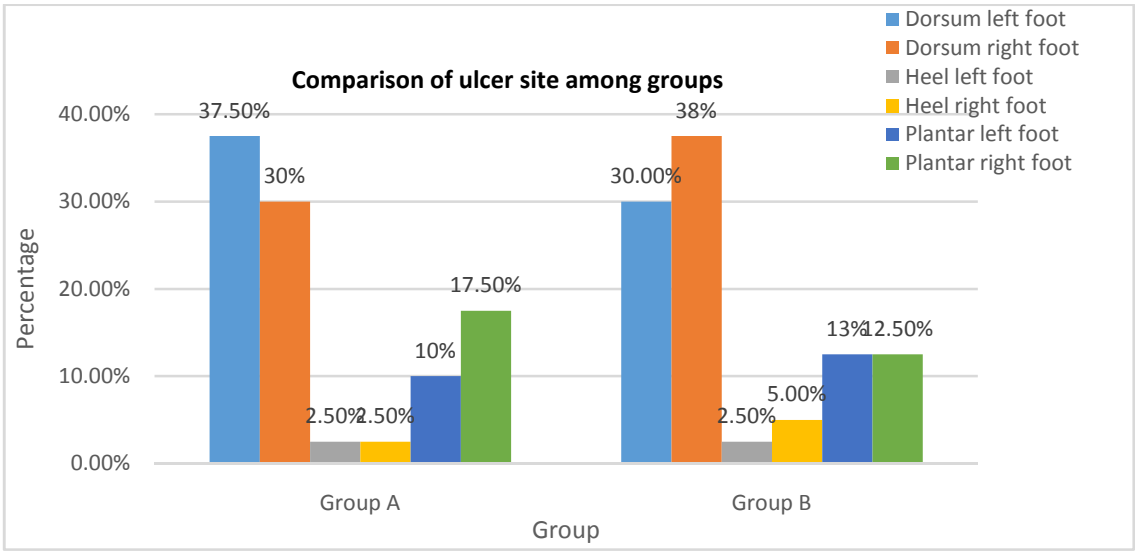


Among group A, 24 (60%) had hypertension. Among group B, 26 (65%) had hypertension.There was no statistically significant difference among the groups as per hypertension was considered.(P value 0.644). (Table 17& graph13)

Table 18: Comparison of site of ulcer between two groups (N=80)

Site	Group		Chi square	P value
	Group A (N=40)	Group B (N=40)		
Dorsum left foot	15 (37.5%)	12 (30%)	1.444	0.919
Dorsum right foot	12 (30%)	15 (37.5%)		
Heel left foot	1 (2.5%)	1 (2.5%)		
Heel right foot	1 (2.5%)	2 (5%)		
Plantar left foot	4 (10%)	5 (12.5%)		
Plantar right foot	7 (17.5%)	5 (12.5%)		

Graph 14: Cluster bar graph for comparison of ulcer site between two groups (N=80)

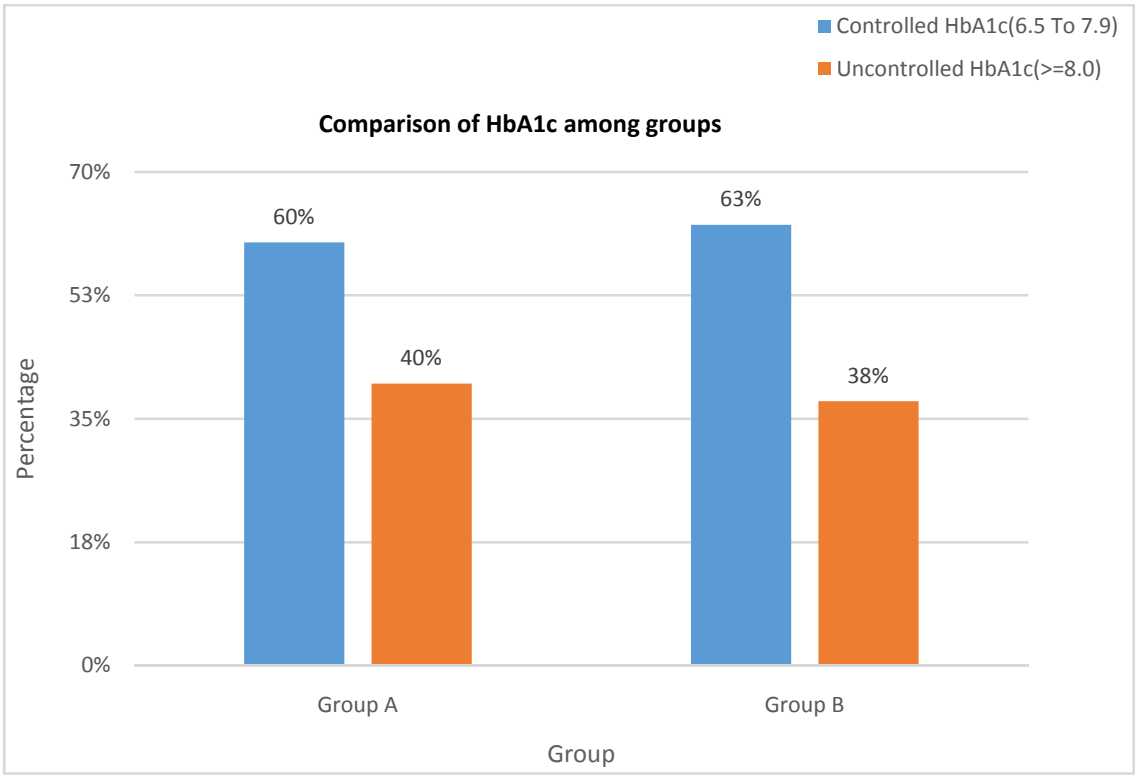


Among group A, 15 (37.5%) had site of ulcer at dorsum left foot, 12 (30%) had at dorsum right foot, 1 (2.5%) had at heel left foot, 1 (2.5%) had at heel right foot, 4 (10%) had at plantar left foot, 7 (17.5%) had at plantar right foot. Among group B, 12 (30%) had site of infection at dorsum left foot, 15 (37.5%) had at dorsum right foot, 1 (2.5%) had at heel left foot, 2 (5%) had at heel right foot, 5 (12.5%) had at plantar left foot, 5 (12.5%) had at plantar right foot.There was no statistically significant difference among the groups as per site of ulcer was considered. (P value 0.919). (Table 18& graph14)

Table 19: Comparison of HbA1c between two groups (N=80)

HbA1c	Group		Chi square	P value
	Group A (N=40)	Group B (N=40)		
Controlled(6.5 To 7.9)	24 (60%)	25 (62.5%)	0.053	0.818
Uncontrolled(>=8.0)	16 (40%)	15 (37.5%)		

Graph 15: Cluster bar graph for comparison of HbA1c between two groups (N=80)



Among group A, 24 (60%) had controlled HbA1c, 16 (40%) had uncontrolled HbA1c. Among group B, 25 (62.5%) had controlled HbA1c, 15 (37.5%) had uncontrolled HbA1c. There was no statistically significant difference among the groups as per HbA1c was considered. (P value 0.818). (Table 19& graph15)

Table 20: Comparison of mean ofparameters of ulcer area (sq.cm) between the study groups (N=80)

Parameter	Group (Mean± SD)		P value
	Group A (N=40)	Group B (N=40)	
Initial Area D0	26.37 ± 6.24	25.82 ± 7.73	0.730
Final Area D14	19.44 ± 4.5	22.25 ± 7.27	0.041
Reduction in ulcer area	6.92 ± 3.38	3.57 ± 1.54	<0.001
Percentage reduction in ulcer area	25.51 ± 9.26	14.48 ± 6.54	<0.001

The ulcer dimensions are measured on day 0(x) = initial wound area andday 14(y) = final wound area.

The reduction in area and percentage reduction in area are calculated as follows:

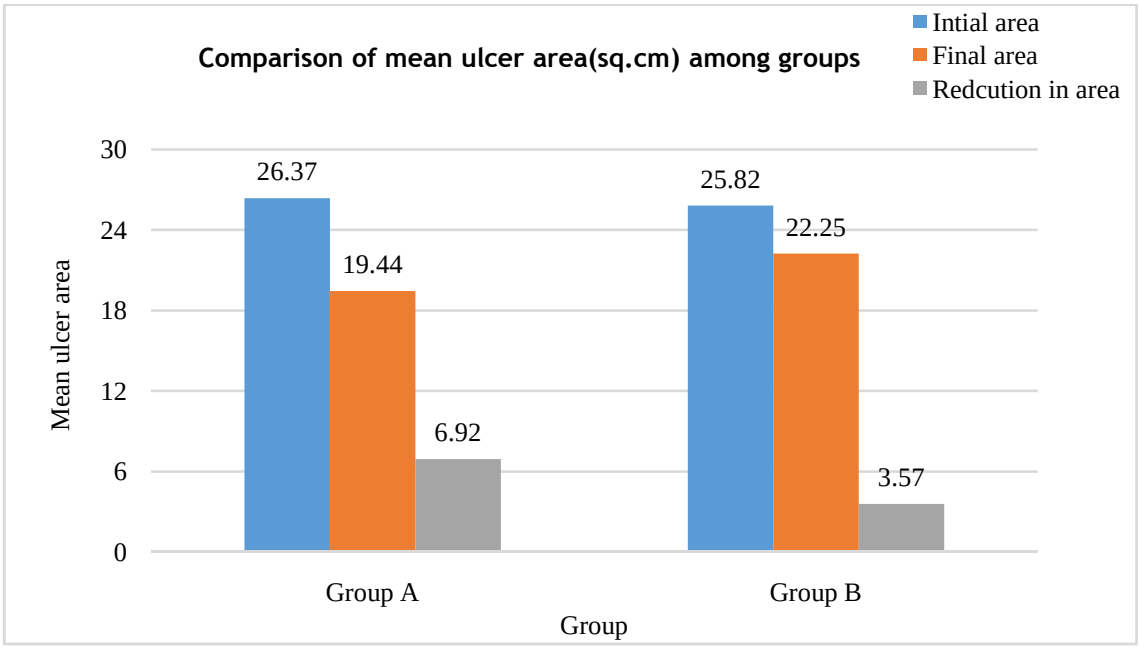
Wound area on D0 = x

Wound area on D14 = y

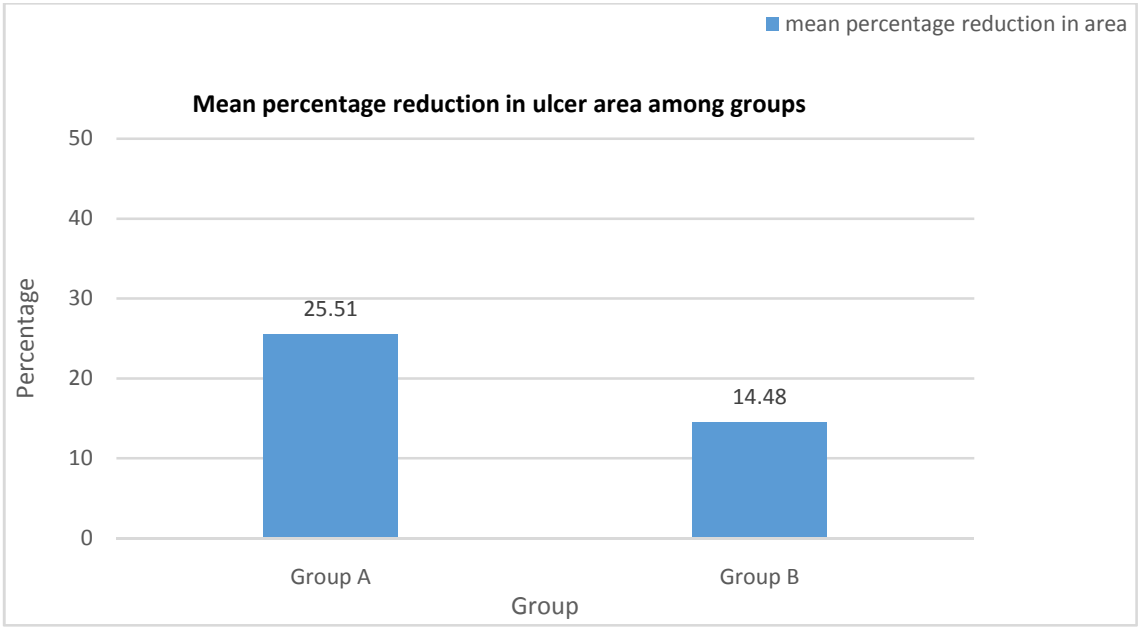
Reduction in wound area = x-y

% Reduction in wound area = $\frac{x-y}{x} x100$

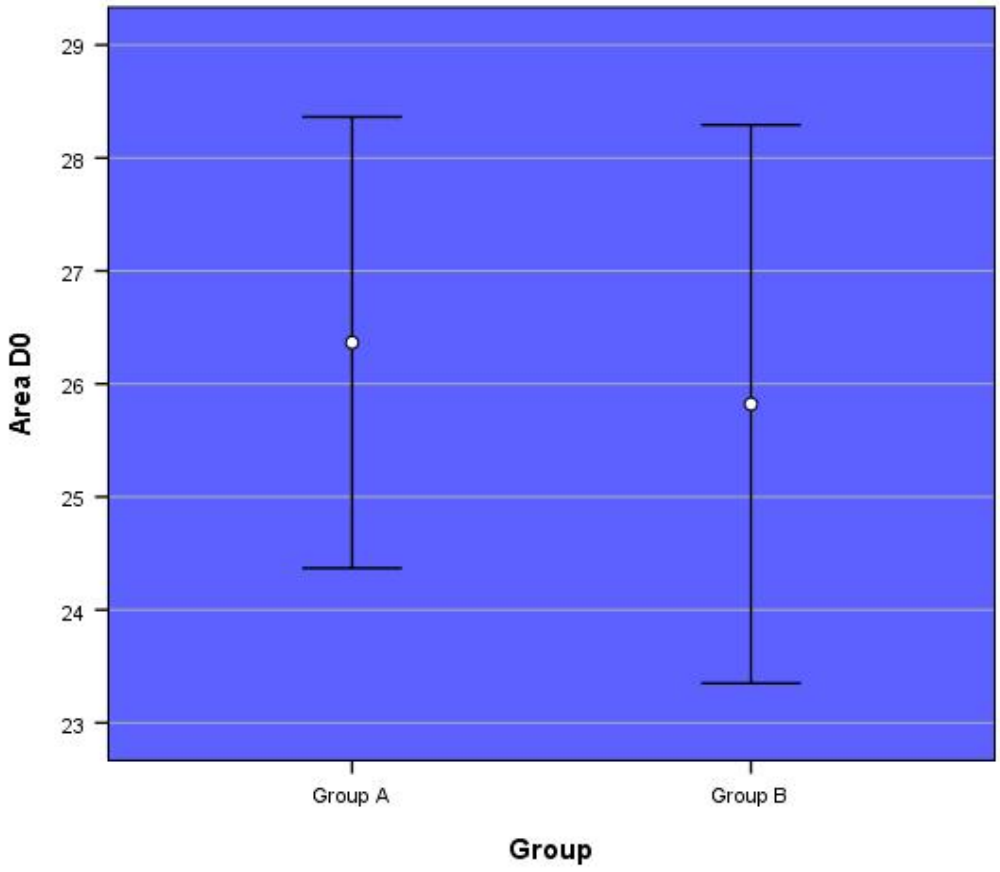
Graph16: Cluster bar graph for comparison of mean ulcer area (sq.cms) between two groups(N=80)



Graph 17: Bar chart of mean percentage reduction in ulcer area among groups (N=80)

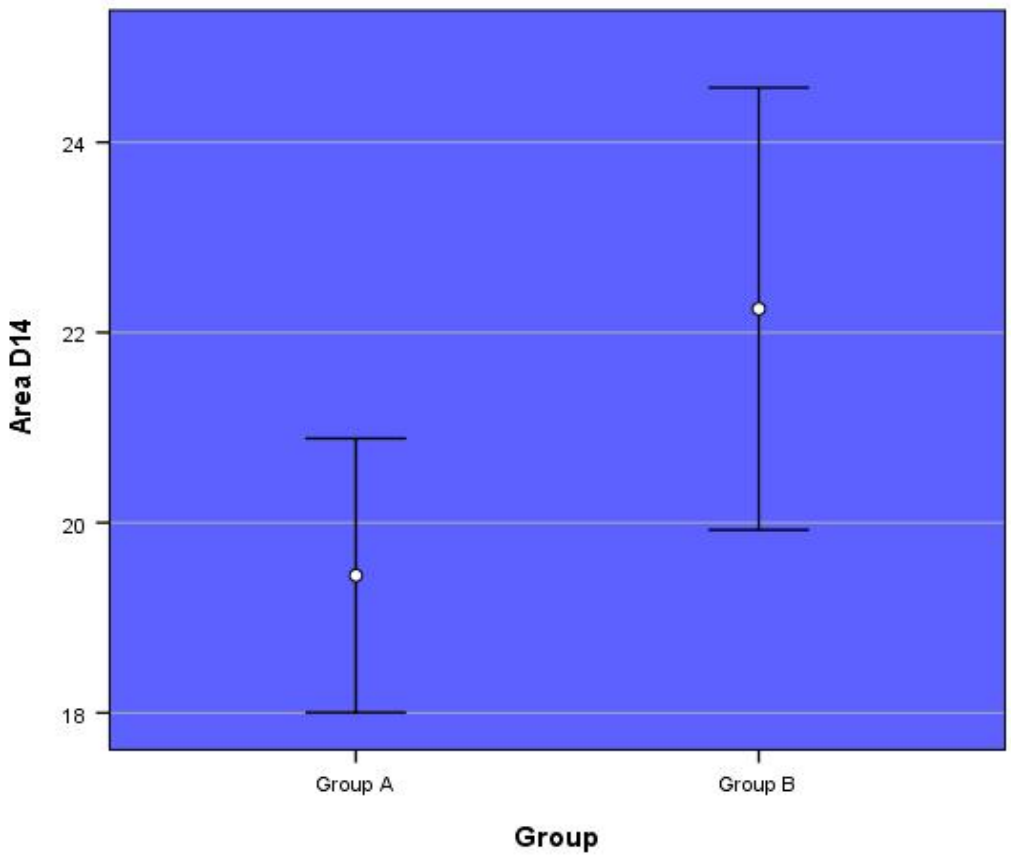


Graph 18: Error bar chart of comparison of mean initial ulcer area D0 between two groups (N=80)



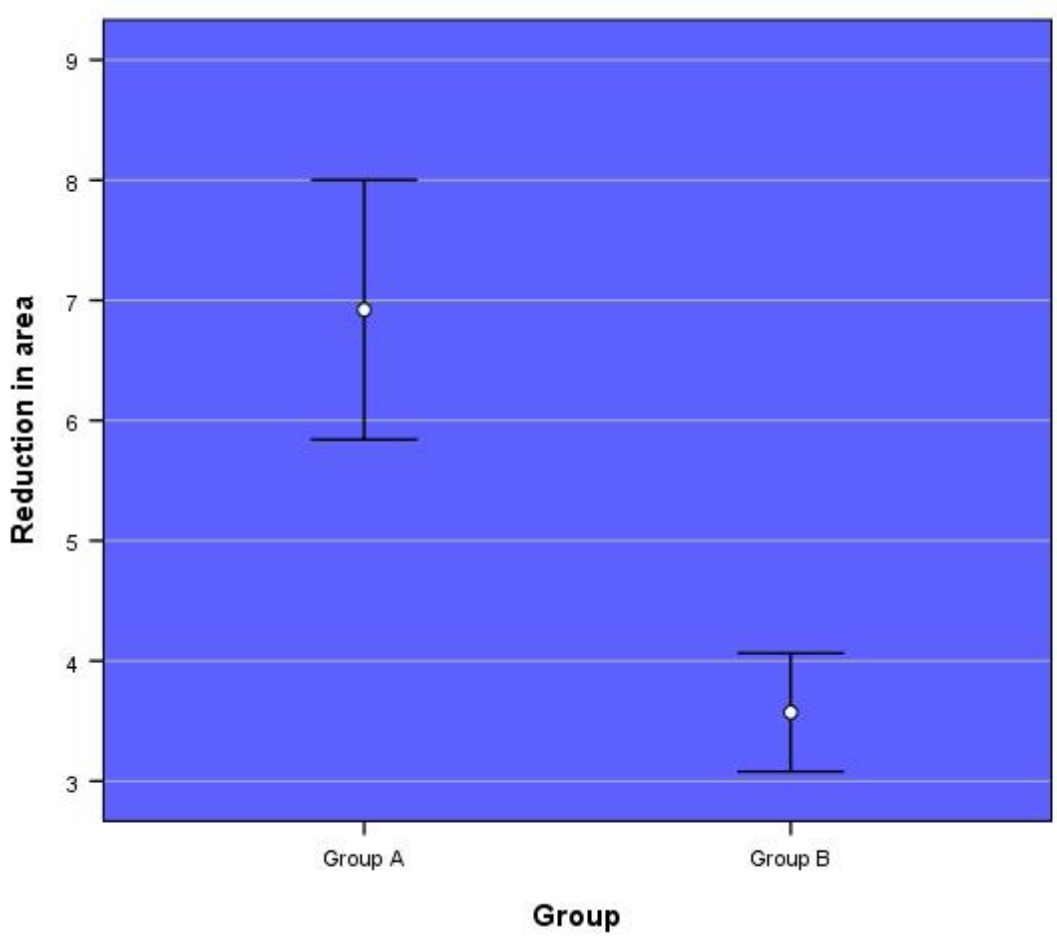
The mean initial ulcer area (D0) in group A was 26.37 ± 6.24(sq.cm), it was 25.82 ± 7.73(sq.cm) in group B.The difference in area D0 between two groups was statistically not significant. (P value 0.730). Mean initial ulcer area between two groups is similar.(Table20 & graph16,18)

Graph 19: Error bar chart of comparison of mean final ulcer area D14 between two groups (N=80)



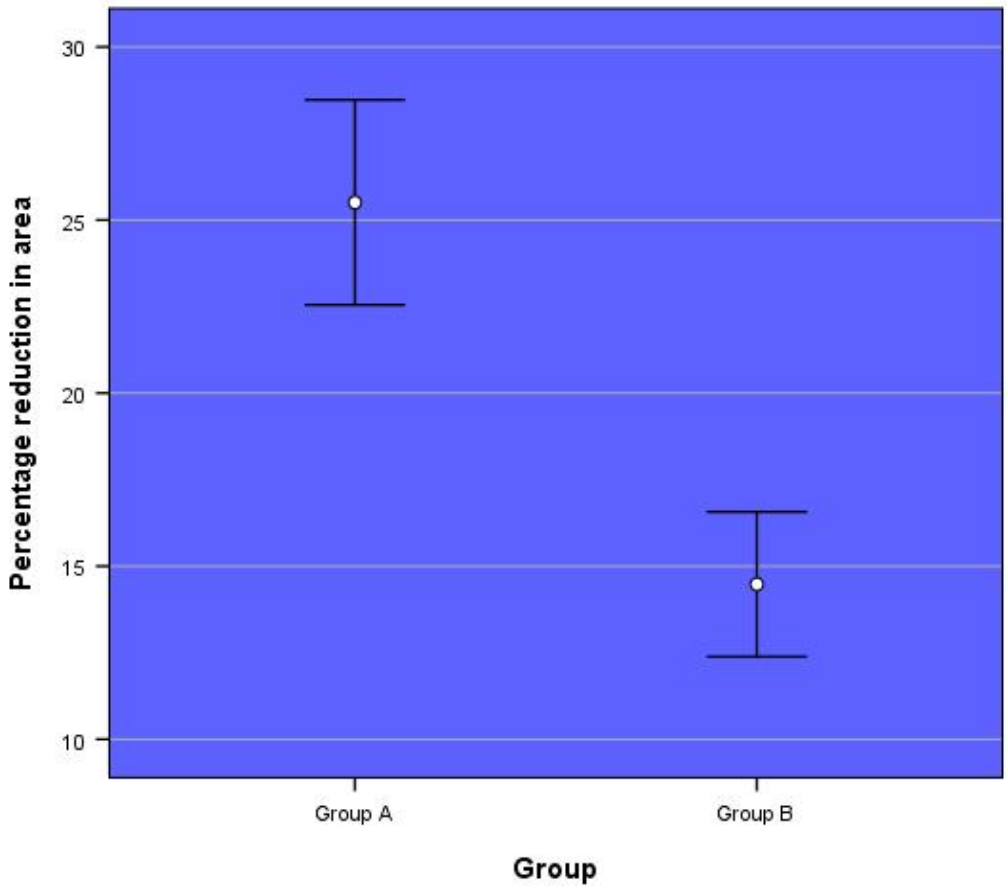
The mean final ulcer area (D14) in group A was 19.44 ± 4.5(sq.cm), it was 22.25 ± 7.27(sq.cm) in group B. The difference in area D14 between two groups was statistically significant. (P value 0.041). Mean final ulcer area between two groups was statistically significant.(Table20 & graph 16,19)

Graph 20: Error bar chart of comparison of mean reduction in ulcer area between two groups (N=80)



The mean reduction in ulcer area in group A was 6.92 ± 3.38(sq.cm), it was 3.57 ± 1.54(sq.cm) in group B. The difference in reduction of ulcer area between two groups was statistically significant. (Pvalue <0.001). Mean reduction in ulcer area was significant in Group A compared to Group B. (Table20 & graph16,20)

Graph 21: Error bar chart of comparison of mean percentage reduction in ulcer area between two groups (N=80)



The mean percentage reduction in area in group A was 25.51 ± 9.26(sq.cm), it was 14.48 ± 6.54(sq.cm) in group B. The difference in percentage reduction in area between two groups was statistically significant. (P value <0.001). Mean percentage reduction in ulcer area was significant in Group A compared to Group B.(Table20 & graph17,21). That is, ulcer healing was good in group where octenidine wound gel was used for dressing.(Table20&graph 16, 17,18,19,20,21)

Table21: Comparison of culture D0 between two groups (N=80)

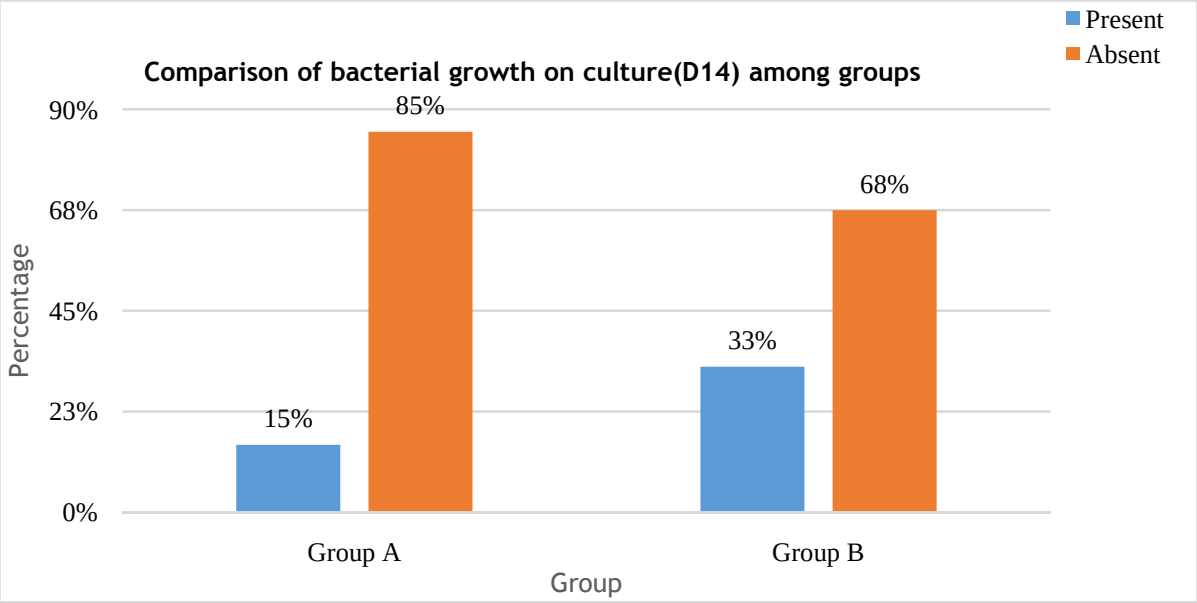
Culture D0 (Bacterial growth)	Group	
	Group A (N=40)	Group B (N=40)
Present	40(100%)	40(100%)
Absent	0(0%)	0(0%)

All the participants in the study had organism growth on culture (D0).

Table22: Comparison of culture D14 between two groups (N=80)

Culture D14 (Bacterial growth)	Group		Chi square	P value
	Group A (N=40)	Group B (N=40)		
Present	6 (15%)	13 (32.5%)	3.382	0.066
Absent	34 (85%)	27 (67.5%)		

Graph 22: Cluster bar graph for comparison of bacterial growth onculture(D14) between two groups (N=80)

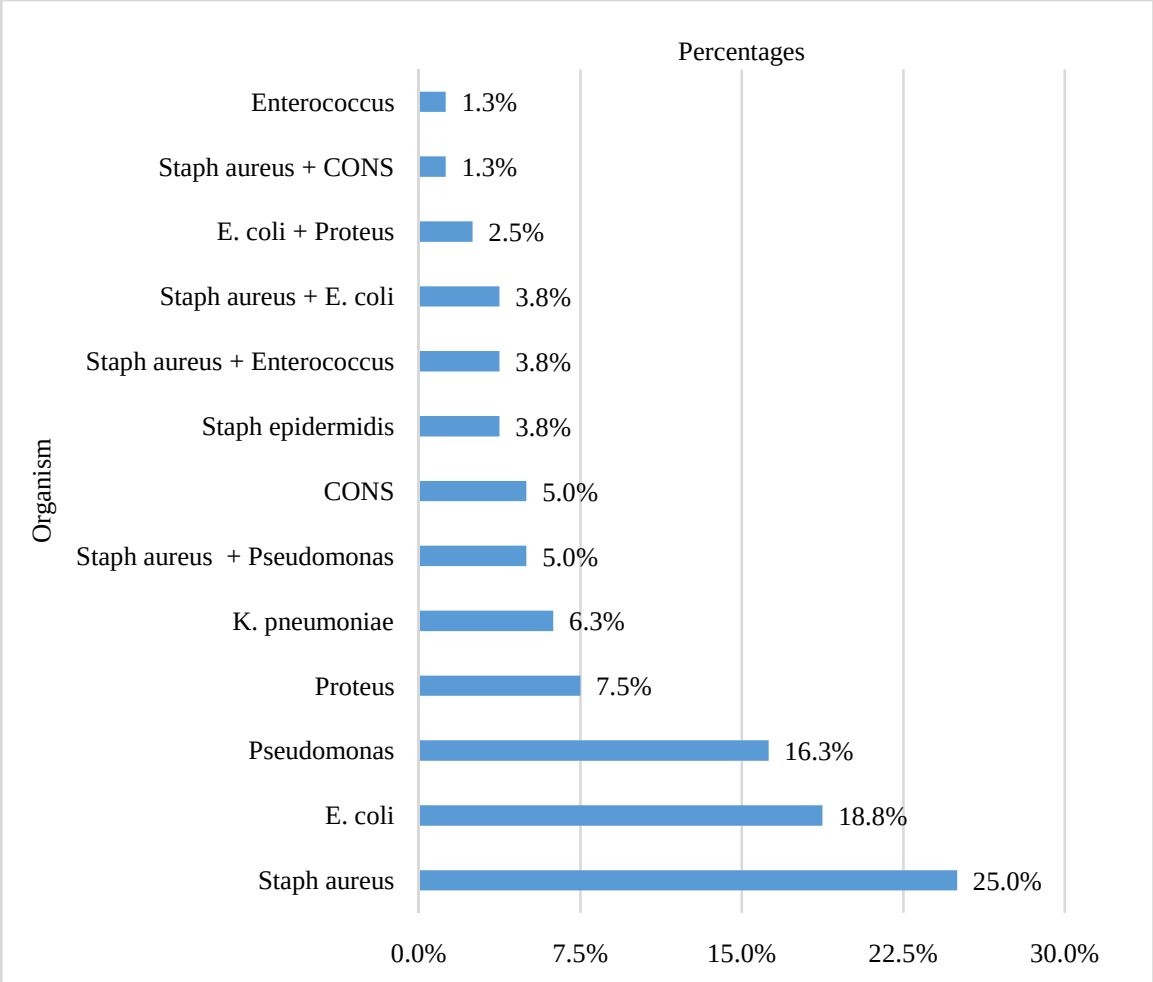


Among group A, 6 (15%) had culture at day 14. Among group B, 13 (32.5%) had culture. There was no statistical significance difference among two groups as per infection was considered.(P value 0.066). (Table 22& graph22)

Table23: Descriptive analysis of organism in the study population (N=80)

Organism	Frequency	Percentages
Staph aureus	20	25.0%
E. coli	15	18.8%
Pseudomonas	13	16.3%
Proteus	6	7.5%
K. pneumoniae	5	6.3%
Staph aureus + Pseudomonas	4	5.0%
CONS	4	5.0%
Staph epidermidis	3	3.8%
Staph aureus + Enterococcus	3	3.8%
Staph aureus + E. coli	3	3.8%
E. coli + Proteus	2	2.5%
Staph aureus + CONS	1	1.3%
Enterococcus	1	1.3%

Graph 23: Bar graph for organism in study population (N=80)



Majority of study population 20(25.0%) had Staph aureus in culture, 15(18.8%) had E. coli, 13(16.3%) had pseudomonas, 6(7.5%) had Proteus, 5(6.3%) had K. pneumoniae, 4(5.0%)had CONS, 3(3.8%) had Staph epidermidis, 1(1.3%) had Enterococcus and 13(16.2%) had polymicrobial nature. (Table23 & graph23)

Table24: Comparison of organism between two groups (N=80)

Organism	Group	
	Group A (N=40)	Group B (N=40)
Staph Aureus	10 (25%)	10 (25%)
E. Coli	9 (22.5%)	6 (15%)
Pseudomonas	7 (17.5%)	6 (15%)
K. Pneumoniae	2 (5%)	3 (7.5%)
Cons	2 (5%)	2 (5%)
Staph Aureus + Enterococcus	2 (5%)	1 (2.5%)
Enterococcus	0 (0%)	1 (2.5%)
Staph Aureus + Cons	0 (0%)	1 (2.5%)
Staph Epidermidis	2 (5%)	1 (2.5%)
Proteus	3 (7.5%)	3 (7.5%)
Staph Aureus + Pseudomonas	1 (2.5%)	3 (7.5%)
Staph Aureus + E. Coli	1 (2.5%)	2 (5%)
E. Coli + Proteus	1 (2.5%)	1 (2.5%)

**No statistical test was performed due to 0 subjects in the cells*

Majority of study population in group A, 10 (25%) had Staph aureus in culture, 9 (22.5%) had E. coli, 7 (17.5%) had pseudomonas and 2 (5%) had K. pneumoniae. Majority of study population in group B, 10 (25%) had Staph aureus in culture, 6 (15%) had E. coli, 6 (15%) had pseudomonas and 3 (7.5%) had K. pneumoniae. (Table19).

DISCUSSION

Diabetes is considered the new emerging epidemic of the world with an impact on almost every developing and developed country. It is estimated that half of the patients are ignorant about their disease and are at high risk of developing complications. Neuropathy, peripheral vascular disease are the complications of diabetes that predispose to foot ulceration in diabetics.[4,5,15]

Infection is commonly seen in diabetic foot ulcers. As per the study by Prompers L et al. around 58% of individuals presenting to the podiatry clinic have an infection at their initial presentation, and this percentage may go up to 82% of the diabetic foot ulcer patients admitted to hospital.[44] As per the study by Lavery LA et al. the patients with diabetic foot ulcers and infection are at 150 times more risk for lower extremity amputation when compared to the patients with diabetes and no foot ulcer.[45] So effective control of infection helps in the healing of ulcers thus reducing the number of lower extremity amputations in diabetic foot ulcers.

Besides adequate wound debridement and antibiotic therapy, dressing plays an important role in the healing of diabetic foot ulcers. Usage of topical antimicrobial or topical antiseptic agents is still considered as an option in infected ulcers.[9] However, their usage is debatable because of its cytotoxic nature.[33]

Octenidine, a new antiseptic with a unique chemical structure and wide antimicrobial activity is now available as an antiseptic for chronic infected ulcers. Recent studies on octenidine suggest that it is less cytotoxic, tissue compatible with good antimicrobial activity.[10,35]

However, most of the data on octenidine is preclinical. Clinical data of octenidine in ulcer healing is very limited. Whatever the clinical data available is mostly on chronic ulcers due to other etiology like venous insufficiency rather than diabetes.

This prompted us to undertake the study to find the effect of octenidine wound gel vs povidone iodine dressings in the healing of diabetic foot ulcers with emphasis on percentage reduction of ulcer area.

This randomised control study was done under the department of general surgery at KLES Dr. Prabhakar Kore Charitable Hospital and Medical Research Centre, Nehru nagar. Belagavi, between January 2018 to December 2018. A total number of 80 patients with diabetic foot ulcers satisfying the selection criteria and willing to participate in the study were included for study. These patients are divided into two groups of 40 each, to receive treatment with octenidine wound gel dressing (Group A) and povidone iodine dressing (Group B).

In our study, among the study population, 16(20%) were aged between 35 to 45 years, 16(20%) were aged between 45 to 55 years, 30(37.5%) were aged 55 to 65 years and remaining 18(22.5%) were aged more than 65 years. The maximum percentage of participants in the study population belonged to 55-65 years age group. These increased risk of foot ulceration in the fifth and sixth decade was consistent with findings from the study conducted by Surriah et al.[41]

Several studies done earlier to evaluate the risk factors for diabetic foot ulceration have shown that males are at increased risk compared to females. In our study, among the study population, 55(68.75%) participants were males and the

remaining 25(31.25%) participants were females. The Male to female ratio among the study population was 2.2:1. Among group A, 26 (65%) were males, 14 (35%) were females. Among group B, 29 (72.5%) were males, 11 (27.5%) were females. The male preponderance in this study was consistent with the study by P Zhang et al.[42] Though there was male preponderance the distribution of the male population between group A and group B was comparable.

In our study among group A, 26 (65%) have belonged to low socioeconomic status, 11 (27.5%) belonged to the middle class, 3 (7.5%) belonged to high class. Among group B, 24 (60%) belonged to low socioeconomic status, 12 (30%) belonged to the middle class, 4 (10%) belonged to high class. These suggest that participants belonging to low socioeconomic status are 50(62.5%), middle economic status is 23(28.75%) and high economic status is 7(8.75%). This increased prevalence of foot ulceration in low socioeconomic groups may be due to the economic constraints to afford treatment and poor awareness about health care. The findings were consistent with "community-based study to assess the prevalence of diabetic foot syndrome and associated risk factors among people with diabetes mellitus" conducted by Vibha et al.[43]

In a study conducted by Younis et al,[46] on the frequency of foot ulcers in type-2 DM, 61% of the study population had ulcers on the plantar surface, 31% had ulcers on the dorsal surface remaining 8% had an ulcer on both plantar and dorsum. The results in our study were among group A, 15 (37.5%) had site of ulcer at dorsum left foot, 12 (30%) had at dorsum right foot, 1 (2.5%) had at heel left foot, 1 (2.5%) had at heel right foot, 4 (10%) had at plantar left foot, 7 (17.5%) had at plantar right foot. Among group B, 12 (30%) had site of ulcer at dorsum left foot, 15 (37.5%) had at

dorsum right foot, 1 (2.5%) had at heel left foot, 2 (5%) had at heel right foot, 5 (12.5%) had at plantar left foot, 5 (12.5%) had at plantar right foot. These suggest that 54(67.5%) had ulceration over the dorsum, 26(32.5%) had ulceration over plantar surface and heel. Though the findings in our study were not in accordance with earlier studies, there was no statistically significant difference among the groups as per the site of the ulcer was considered. (P-value 0.919).

As per the study conducted by Younis et al[46], it was found that patients with peripheral neuropathy had 23 times the risk of developing diabetic foot ulcers compared to nonneuropathic patients. The findings in our study were in accordance with the study by Younis et al. In the present study, 54(67.5%) participants had neuropathy.

Among group A, 28 (70%) had neuropathy. Among group B, 26 (65%) had neuropathy. The difference in the proportion of neuropathy between the two groups was statistically not significant. (P-value 0.633) ruling out bias in the outcome. During the study period, all the patients were taken care of off-loading and rest to the foot with ulceration, thereby minimising its influence on ulcer healing.

In a study conducted by P Zhang et al[42], it was noted that 63.4% of patients with diabetic foot ulcers had hypertension suggesting hypertension as a risk factor for DFU. The findings in our study were in accordance with the study by P Zhang et al. In our study 50(62.50%) participants had hypertension.

Among group A, 24 (60%) had hypertension. Among group B, 26 (65%) had hypertension. The difference in the proportion of hypertension between the two groups was statistically not significant. (P-value 0.644) ruling out bias in the outcome.

The study population with hypertension was managed with antihypertensives and regular blood pressure monitoring done to ensure hypertension under control.

Another study by Hasan et al[47] found that patients with diabetic foot ulcers had higher HbA1c levels (86% of patients with DFU had high HbA1c). Hence HbA1c levels may be considered as a risk factor and predictor of wound healing in diabetic foot ulcers. In our study, among group A, 24 (60%) had controlled HbA1C, 16 (40%) had uncontrolled HbA1C. Among group B, 25 (62.5%) had controlled HbA1C, 15 (37.5%) had uncontrolled HbA1C. The difference in the proportion of HbA1C between the two groups was statistically not significant. (P-value 0.818). Patients were regularly monitored with blood sugar levels, OHA's and Insulin therapy was given as per needed after physician opinion, thereby minimising its influence on ulcer healing.

Based on studies done earlier, we considered that the age group, sex, socioeconomic status, site of ulcer, neuropathy, hypertension, and HbA1C as risk factors for diabetic foot ulceration. Considering the 'p' value for the above factors, the difference in the proportion of distribution between two groups was (P- value< 0.05) statistically insignificant, ruling out bias in the outcome.

As per studies conducted by Urbach m et al and Klein D et al, in the treatment of wounds post-traumatic amputation and splinter injuries which were colonised with MDRO antiseptic wound care with octendine have shown a decrease in the infection.[48]Another study by Conceicao et al, shown the efficacy of Octenidine in decreasing load of Staph aureus by >6log10 in 30 secs.[49]

In the present study, all participants at the time of enrolment (D0) were positive for wound culture(100%). On the final day of follow up (D14), Among group A, 6 (15%) had a culture positive. Among group B, 13 (32.5%) had a culture positive. The difference in the proportion of culture D 14 between the two groups was statistically not significant. (P-value 0.066).

Though there was no statistically significant change in wound culture status between two groups on the fifteenth day, participants in octenidine dressing group had fewer participants with persistent microbial growth at the ulcer site compared to povidone iodine dressing group. These findings were in accordance with the studies mentioned above.

When the organisms isolated from the ulcer site were listed we found that staphylococcus aureus(25%) was the most common pathogen isolated followed by E.coli (18.8%) and pseudomonas spp (16.3%). Even the study conducted by Saseedharan et al, most common pathogen isolated was staph aureus.[50] Some studies conducted in northern parts of India most common pathogen isolated was E.coli in some studies and Pseudomonas in others.[51] However, the microbial nature of diabetic ulcers may vary depending upon geographic distribution.

In the present study, the mean initial area (D0) in group A was 26.37 ± 6.24 sq.cm, it was 25.82 ± 7.73 sq.cm in group B, no significant difference in initial wound area between two groups. The mean final area (D14) in group A was 19.44 ± 4.5 sq.cm, it was 22.25 ± 7.27 sq.cm in group B, no significant difference in final wound area between two groups. The mean reduction in area in group A was 6.92 ± 3.38 sq.cm, it was 3.57 ± 1.54 sq.cm in group B. The difference in reduction in the area between the two groups was significant. (P-value <0.001). The mean percentage

reduction in area in group A was 25.51 ± 9.26 sq.cm, it was 14.48 ± 6.54 sq.cm in group B. The difference in percentage reduction in the area between the two groups was significant. (P-value <0.001). These findings suggest that dressing and topical application of octenidine wound gel favours ulcer healing compared to dressing and topical application of povidone iodine. These findings were consistent with the study by Hammerle G et al to find efficacy and cost-effectiveness of Octenidine.[52]

The earlier wound healing process in this study can be explained by the effective antimicrobial and autolytic property of Octenidne wound gel. The autolytic activity of this ocetenidine wound gel is due to the gel-based form of antiseptic. This gel rehydrates the nonviable tissue and plays a role in the process of natural autolysis.

To date, the studies on octendine were mostly in vitro, pre-clinical and animal studies, there are very few clinical studies available.

A study was conducted by Hammerle G and Strohal H to find efficacy and cost-effectiveness of octenidine in treating chronic venous ulcers, they included 49 wounds into three different arms of dressings as either modern wound dressings alone (n = 17), octenidine wound gel plus modern wound dressings (n = 17) or octenidine wound gel alone (n=15). The reduction in ulcer was significant in both arms where octenidine wound gel was used compared to wound dressings alone.[52]

Another was a study conducted by Eisenbeiβ W et al to find the efficacy of octenidine wound gel on bacterial colonisation and epithelialisation of skin graft donor sites in burn patients, they included total of 61 patients in the study. Randomisation was done into octenidine group (n=31) and Octenidine free wound gel

group (n=30). The group with octenidine based wound gel shown a significant reduction in bacterial colonisation of wounds and no delay in the epithelialisation.[53]

The above two studies were conducted in ulcers due to other etiology, Here are the studies conducted in diabetic foot ulcers.

An observational follow-up study was conducted by Korzon-Burakowska et al[54] on the healing of neuropathic diabetic foot ulcers with topical antiseptics. 35 patients with PEDIS grades 1-2 have been included in the study. Patients were treated with two antiseptics 10% resin salve or octenidine solution 31% of patients treated with Octenidine had complete epithelialisation of ulcer and the number of positive bacterial cultures from the ulcers was lower in the follow up period when compared to the initial day of study.

A case series was done by Sharpe A et al[55] using octenidine in the management of diabetic foot ulcers. It was summarised that topical application of octenidinewound gel shown good progress in diabetic foot ulcer healing and suggested the usage of octenidine wound gel whenever biofilm is suspected. Another study done by Sharon Huntcomparingoctenilin wound gel and betadine gel on the healing of diabetic foot ulcer found that octenidine wound gel has turned a static nonhealing ulcer into the one with the potential to heal.[56]

Overall the present study has shown that topical use of octenidine wound gel in dressing for selected patients with diabetic foot ulcers had favourable outcomes in terms of percentage reduction in ulcer area and bacterial colonisation. No adverse effects were noted in participants treated with octenidine wound gel during the study period. Participants tolerated octenidine dressing well.

LIMITATIONS OF STUDY

The study population in our study was 80 and conducted at a single center. However further large scale randomised control trials and multicenter studies are required to further establish the efficacy and properties of Octenidine wound gel.

CONCLUSION

Based on the results from this study we conclude that, when octenidine wound gel is added to the treatment regimen of the patients with diabetic foot ulcers, it has shown good progress of ulcer healing in terms of ulcer area reduction compared to povidone iodine dressing.

Though the reduction in bacterial colonization was not statistically significant, the patient group treated with octenidine wound gel dressing had a better reduction in the bioburden compared to the povidone iodine dressing group.

The early healing of diabetic foot ulcers in the group with topical octenidine wound gel dressing is due to the broad antimicrobial and autolytic property of the octenidine wound gel.

SUMMARY

Octenidine Dihydrochloride is a topical antiseptic available from 20 years in the European countries. In spite of its efficacy and tissue tolerability it is not widely used for wound antisepsis. This made us undertake the present study.

The objective of the present study was to compare the healing of diabetic foot ulcers between octenidine wound gel dressing and povidone iodine dressing in terms of percentage reduction in ulcer area.

The study was conducted on 80 selected in-patients admitted for diabetic foot ulcer treatment in KLE Dr.Prabhakarkore charitable hospital and MRC, Belagavi.

The participants randomised into two groups, the study group(Group A) and the control group(Group B). Group A dressing was done with topical octenidine wound gel and Group B dressing done with povidone iodine.

There was no statistical difference between participants of two groups in terms of age, sex, socioeconomic status, duration of diabetes, site of ulcer, hypertension, neuropathy, and HbA1C.

The mean percentage reduction in ulcer in Group A was 25.51 +/- 9.26 sq.cm whereas in Group B it was 14.48 +/- 6.54 sq.cm. This mean of percentage reduction in ulcer area was significantly higher in the group treated with octendine wound gel ($P < 0.01$).

Though the bacterial colonisation was not significantly reduced between the two groups, Group A (15%) had less bacterial colonisation compared to Group B (32.5%).

From the findings of this study, it may be concluded, healing in diabetic foot ulcers dressed with topical octenidine wound gel was early compared to povidone iodine dressing.

In countries like India where the prevalence of diabetes is raising better dressing options like octenidine wound gel are needed to reduce morbidity and antibiotic resistance.

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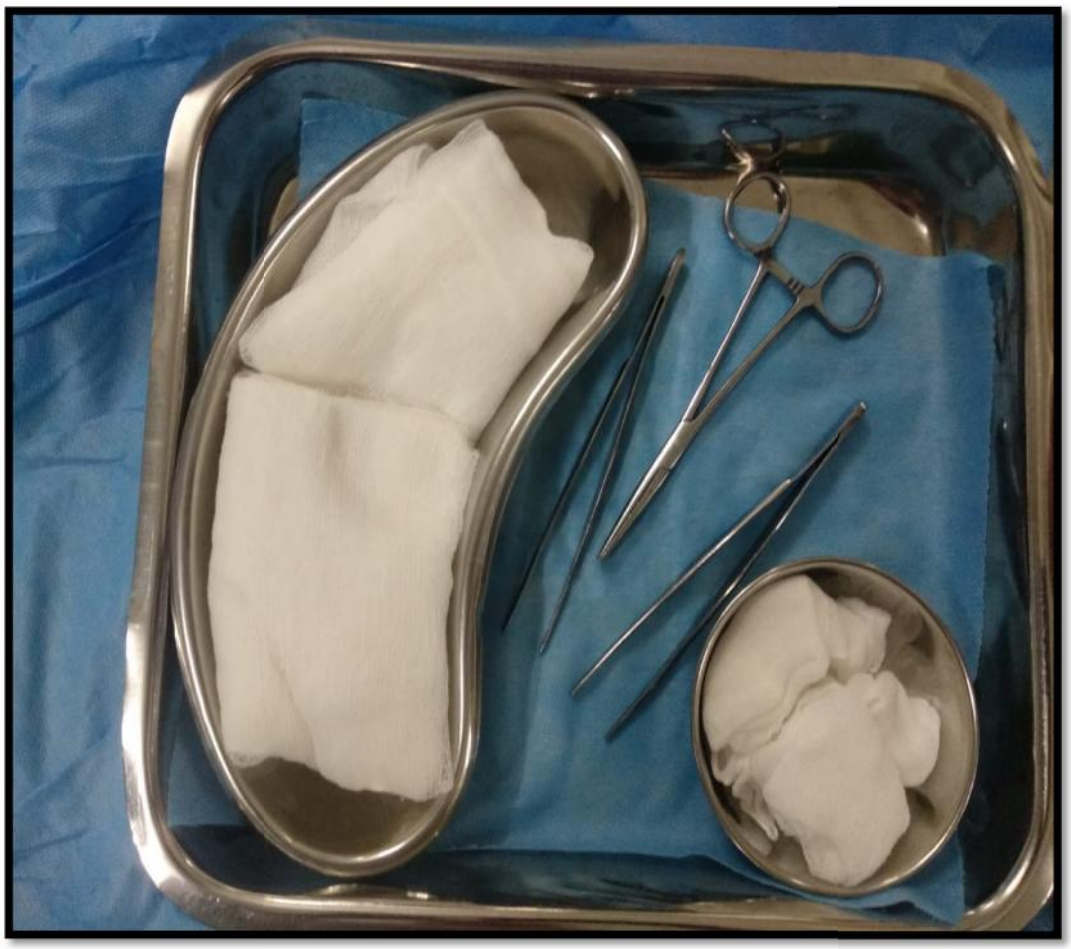
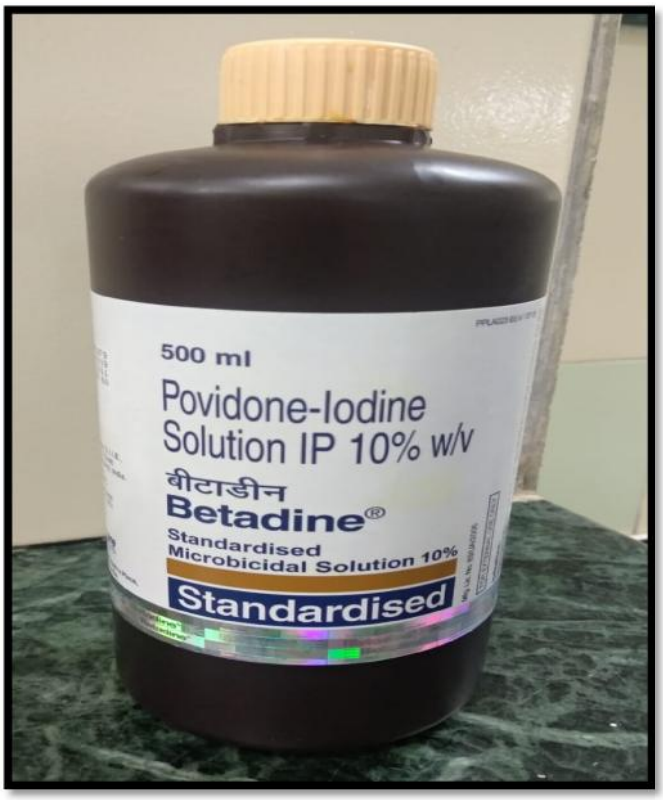
ANNEXURE I – PHOTOGRAPHS

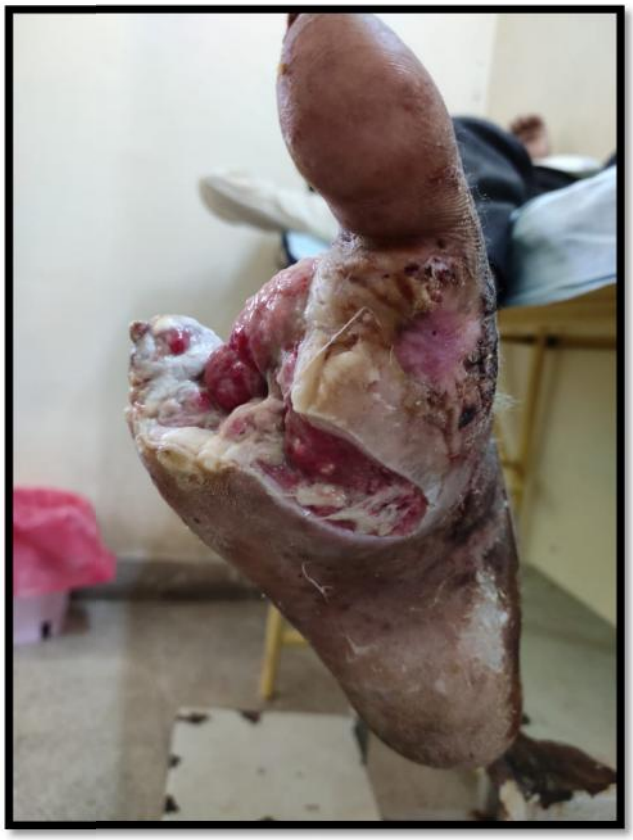


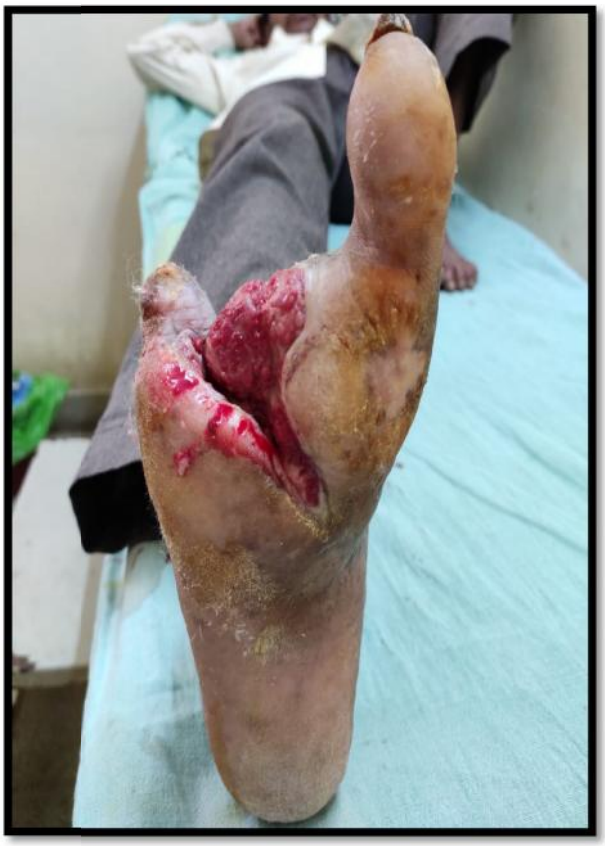
PHOTOGRAPH-1: DRESSING EQUIPMENT

PHOTOGRAPH -2: OCTENIDINE WOUND GEL.

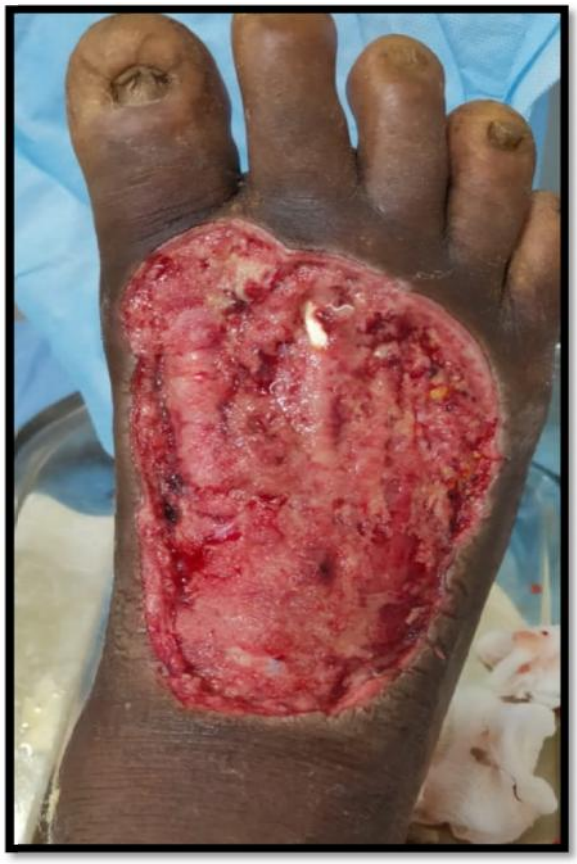


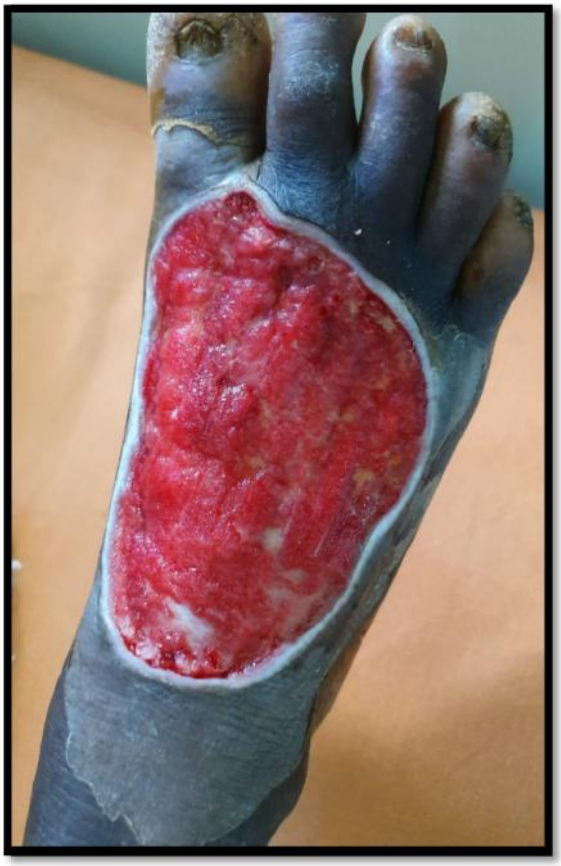
PHOTOGRAPH-3: POVIDONE-IODINE SOLUTION 10% W/V





PHOTOGRAPH -4. ULCER ON DAY 0 AND DAY 14 IN GROUP A.





PHOTOGRAPH- 5: ULCER ON DAY 0 AND DAY 14 IN GROUP B.

ANNEXURE II

INFORMED CONSET

Purpose of the study

I have been informed by Dr. _____ , Post Graduate in M.S.General Surgery under the guidance of Dr. _____ , Professor Department of General Surgery, J.N. Medical College, KLE University, Belagavi is conducting a study to compare octenidine wound gel dressing versus povidone-iodine dressing in healing of chronic diabetic foot ulcers at KLE'S DR.PRABHAKAR CHARITABLE HOSPITAL AND MEDICAL RESEARCH CENTRE, BELAGAVI.

Diabetic foot ulcers are a serious complication of diabetes, leading to disability and early mortality. Diabetic foot ulcers are the most common cause of non traumatic amputation around the world and the most costly type of chronic wound. Infection in a diabetic foot is limb threatening and at times life threatening, and therefore must be treated aggressively. The selection of wound dressings is also an important component of diabetic wound care management. The purpose of this study is to find if octenidine wound gel dressing is better than povidone-iodine dressing in healing of chronic diabetic foot ulcers.

Study procedure

Once you have signed the informed consent, necessary personal information and detailed medical history will be taken by the investigator. After this based upon randomisation you will be treated with octenidine wound gel dressing or povidone-iodine dressing. You will be subjected to examination of the foot ulcer along with measurement of the ulcer dimensions, slough tissue area, bacterial colonisation by culture and sensitivity and follow up will be done till 15 days of your hospital stay.

Potential risks

Allergic reaction and skin irritation to the drug used in the study are the possible risk factors

Benefits

The benefit of study is use of octenidine wound gel based dressings may help healing of chronic diabetic foot ulcers faster and there by decreasing morbidity, hospital stay and need for amputation.

Financial incentive for participation

You will not receive any payment for taking part in this study.

Alternatives

Your participation in this study is entirely voluntary. You are free to refuse to participate or withdraw from the study at any time. You will still receive standard medical care from the hospital. The investigator holds the right to terminate the study at any time

Privacy

To protect my privacy, all the collected information will be given a number rather than using my name. Any information collected during the study will remain confidential. My medical files will be reviewed only at the hospital (or study doctor's office) to check the information and verify the result without breaking my confidentiality.

Authorization to publish results

The information about me will be analysed together with other study participants.Results of this study will be published and presented to scientific groups for scientific purposes, but I will never be individually identified in the presentation of the study results.

Institutional policy

In case I have any questions related to the study, in future or in case of study related injury or illness, I can contact Dr. _____ , Department of General Surgery, KLE University's J.N Medical College, Dr. _____, Professor Dept. Of General surgery, KLE University's J.N Medical College, Belagavi

Voluntary participation

My participation in the study is voluntary. In case I need any further information regarding my rights as study participant, I may contact Dr. Roopa M Bellad, Professor of Paediatrics, as Chairman of J. N. Medical College Institutional Ethics Committee on Human Subjects Research, Phone No.0831 2473777 ext-1527 at J. N. Medical College, Belagavi. My doctor will take care of me during this study. I am free to stop participation in this study at any time and for any reason.

CONSENT FORM

Study title: Comparison of octenidine wound gel dressing versus povidone-iodine dressing in healing of chronic diabetic foot ulcers – at KLEs Dr Prabhakar Kore Charitable Hospital, Belagavi. A Randomized controlled trial for period of one year.

Please initial box

i. I confirm that I have read and understood the information sheet for the above study and have had the opportunity to ask questions. ☐

ii. I understood that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

iii. I understood that sponsor of the clinical trial, others working on the sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understood that my identity will not be revealed in any information released to third parties or published. ☐

iv. I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purposes. ☐

v. I agree to take part in the above study. ☐

Subject's name:

Signature / left thumb impression of subject:

Date:

Name of person obtaining informed consent:

Signature of person obtaining informed consent:

(If a patient has limited ability to read and write, an impartial witness should be present during the entire informed consent discussion and patient's legally acceptable representative should sign on the patient's behalf.) In these instances the patient his/her thumb impression taken in place of signature.

Patient's legally acceptable representative's statement: **NA** ☐

I, as the patient's legally acceptable representative was present during the consenting procedure and understand the preceding information describing this study. All of the questions regarding the study and the patient's participation in it have been answered to my satisfaction. I state that all aspects of the study were clearly presented during the consent procedure. The patient is willing to participate in this study and I sign below on his/her behalf testifying to this effect.

Name of the patient:

Name of representative:

Relationship to the patient:

Signature of representative:

Date:

Impartial witness declaration:

By signing the consent form I attest that the information was accurately explained to and apparently understood by the patient and the representative (if applicable) and that the informed consent was freely given by the patient.

Name of impartial witness:

Signature: Date –

ANNEXURE III.ETHICAL CLEARANCE.

K.L.E.UNIVERSITY'S
JAWAHARLAL NEHRU MEDICAL COLLEGE,
NEHRU NAGAR, BELAGAVI-590010 (KARNATAKA-INDIA)
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Ref: MDC/DOME/ 13 **Date: 22/11/2017**

To.

PG student in Surgery,
J.N.Medical College,
BELAGAVI.

Sub: Institutional Ethical Clearance for the study.

With reference to the above, we wish to inform you that your proposed research project titled **"COMPARISON OF OCTENIDINE WOUND GEL DRESSING VERSUS POVIDONE – IODINE DRESSING IN HEALING OF CHRONIC DIABETIC FOOT ULCERS – A RANDOMISED CONTROLLED TRIAL FOR PERIOD OF ONE YEAR AT KLE'S DR. PRABHAKAR KORE CHARITABLE HOSPITAL AND MEDICAL RESEARCH CENTRE, BELAGAVI"**, is ethical and justifiable. The proposed research project has been cleared by the JNMC Institutional Ethics Committee on Human Subjects Research.

(Dr. Arathi Darshan)
Member Secretary
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

(Dr. Roopa M Bellad)
Chairman,
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

ANNEXURE - IV – PROFORMA

Group: ☐ I.D NO: ☐☐☐

1.Name of the patient :_____

2.Age : ☐

3.Gender : 1. Male 2. Female ☐

4.DOA : ☐☐ ☐☐ ☐☐☐☐

5.DOD : ☐☐ ☐☐ ☐☐☐☐

6.Date of interview : ☐☐ ☐☐ ☐☐☐☐

7.IP no : ☐☐☐☐☐☐

8.Address : 1.Belagavi 2.Outside Belagavi ☐

9.Phno : ☐☐☐☐☐☐☐☐☐☐

10.Occupation : 1-Unemployed
2-Unskilled
3-Semi-skilled ☐
4-Skilled
5-Professional

11.Education : 1-Illiterate
2-Primary (1^{st}-7^{th} std) ☐
3-High school (8^{th}-10^{th} std)
4-Intermediate
5-Degree and above

12.Socio-economic status :1-Low ☐
2-Middle
3-High

Screening -

13.H/O diabetes : 1-Yes 2-No ☐

14.If yes, type of diabetes :

Type 1	
Type 2	

15.H/O other illness : 1-Yes 2-No

16.If yes :1-Malignancy
2-Asthma/COPD
3-HIV/AIDS
4-Autoimmune disorders
5-Hemoglobinopathy

17.Urine for ketone bodies :
1- Positive 2-Negative

18.Applicant is willing to give consent :
1-Yes 2-N0

19.**Final result**
1-Inelgible
2-Elgible but refused
3-Elgible and participating

Data collection instrument :

1.Duration of ulcer -1.<4 weeks 2.>4 weeks

2.Location of ulcer- 1.Left foot
2.Right foot

3.Mode of onset- 1.Traumatic
2.Spontaneous
3.Pressure
4.Other

4.Associated symptoms- 1.Fever
2.Pain
3.Discharge

5.Duration of diabetes-

6.On medication for diabetes-1.Yes ☐
2.No

7.If Yes, type of medication-1.Oral hypoglycemic agents ☐
2.Insulin

8.Complication:

	Yes	No
Neuropathy		
Vasculopathy		

9.H/O hypertension-1.Yes ☐
2.No

10.Medical history:

	Yes	No
Peripheral neuropathy		
Nephropathy		
PVD		
CVD		

Examination:

1.

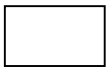
Height	Weight	BMI

2.

Pulse rate	Blood pressure	Temperature	Respiratory Rate

3. Peripheral pulsations of lower limb:

	Right lower limb	Left lower limb
1. Dorsalis pedis		
2. Anterior tibial		
3. Posterior tibial		
4. Popliteal		
5. Femoral		

4. Foot Deformity: 

1- Toe deformity 2 – Charcot's foot

5. Wound Observations:

	Day 0	Day 7	Day 14
1. Site of ulcer			
2. Shape 1 – oval 2 – circular 3 – irregular			
3. Margin 1- Regular 2- Irregular			
4. Edge 1- Indistinct, diffuse 2- Attached to base 3- Not attached, hanging 4- Rolled in 5- Hyperkeratotic/ callous like 6- Fibrotic/ scarred			
5. Floor 1- Red granulation tissue 2- Pale granulation tissue 3- Slough/necrotic tissue			
6. Base			

1- Fascia, tendons 2- Soft tissue 3- Bone			
7. Discharge 1- None 2- Serous 3- Purulent 4- Serosanguinous 5- Sero-purulent			
8. Surrounding skin 1- Edema 2- Eczema 3- Pigmented 4- Normal			

6.Wagner Grading:

1	
2	
3	
4	
5	

7.A.Ulcer dimensions:

	D_0	D_{14}
Length (c.m)		
Width (c.m)		
Area ($c.m^2$)		

7.B.Inference-

1.Wound area on D_0 =

2.Wound area on D_{14} =

3.Wound area reduction =

(Area on D_0-Area on D_{14})

Investigations

1.Complete blood count

2.Fasting blood sugar-2 consecutive readings

3.Serum creatinine

4.Blood urea

5.X-ray foot-anterio posterior and lateral view

6.Urine analysis-routine and microscopy

7.Wound tissue culture

8.HbA_1C

9.UKB

10.Colour Doppler if it is indicated

ANNEXURES V – KEY TO MASTER CHART

S.NO - Serial number

IP NO - Inpatient number

SEX - 1. Male 2. Female

SOCIOECONOMIC STATUS – 1. Low 2. Middle 3.High

DURATION OF DIABETES – 1.0-4 years 2.5-9 years 3.10-14 years 4.15-19 years 5.>/=20 years

ONSET – 1.Spontaneous 2. Traumatic 3. Pressure

NEUROPATHY - 1.Yes 2.No

HYPERTENSION – 1.Yes 2.No

HbA1c – 6.5-7.9 Controlled, >/=8.0 Uncontrolled

SITE – DRF Dorsum right foot, PRF Plantar right foot, DLF Dorsum left foot, PLF Plantar left foot, HRF Heel right foot, HLF Heel left foot

CULTURE: P Bacterial growth present AB Bacterial growth absent

GROUP A

S.NO	IP NO	AGE	SEX	SOCIOECONOMIC STATUS	DURATION OF DIABETES	ONSET	NEUROPATHY	HYPERTENSION	SITE	HBA1C	AREA D0	AREA D14	REDUCTION IN AREA	%REDUCTION IN AREA	CULTURE D0	CULTURE D14	ORGANISM
1	849992	56	1	1	3	1	2	1	DLF	7.1	23.50	18.96	4.54	19.31914894	P	AB	Staph aureus
2	851294	70	1	1	4	2	1	1	DRF	7.9	23.70	19.20	4.50	18.98734177	P	AB	Staph aureus
3	853932	54	2	2	2	2	2	2	DLF	6.9	32.40	20.50	11.90	36.72839506	P	AB	K.pneumonia
4	850692	63	1	1	5	1	1	1	DRF	9	14.30	12.86	1.44	10.06993007	P	P	Proteus
5	852863	52	1	1	2	2	2	1	PLF	8.4	15.40	12.00	3.40	22.07792208	P	AB	Pseudomonas
6	857196	64	1	2	3	3	1	2	PLF	7.1	25.40	15.60	9.80	38.58267717	P	AB	Staph aureus
7	857466	43	2	1	1	2	1	2	HRF	6.8	25.25	19.50	5.75	22.77227723	P	AB	Staph aureus+Enterococcus
8	858636	67	1	1	3	2	1	1	DRF	7.6	34.50	24.00	10.50	30.43478261	P	AB	Pseudomonas
9	850262	58	1	2	4	1	1	2	PLF	9.2	25.86	22.50	3.36	12.99303944	P	AB	E.coli
10	861234	53	1	1	1	2	2	2	DRF	6.7	35.63	21.00	14.63	41.06090373	P	AB	Staph aureus
11	861767	48	1	2	1	2	1	1	DLF	7.4	29.66	21.84	7.82	26.36547539	P	AB	E.coli
12	863271	70	2	3	3	1	1	2	PRF	6.8	27.34	16.56	10.78	39.42940746	P	AB	Pseudomonas
13	863345	60	1	1	1	1	2	1	DLF	7.6	31.10	22.00	9.10	29.26045016	P	AB	E.coli
14	864685	62	2	2	4	1	1	2	DLF	8.4	34.55	28.20	6.35	18.37916064	P	AB	Pseudomonas
15	864673	65	2	1	4	2	2	1	PRF	10.7	17.83	15.96	1.87	10.48794167	P	P	K.pneumonia
16	860001	40	1	3	2	2	1	1	DLF	7.7	27.20	20.30	6.90	25.36764706	P	AB	Staph aureus
17	870146	63	1	1	4	2	1	1	PRF	7.2	33.00	21.20	11.80	35.75757576	P	AB	E.coli
18	867262	72	1	2	3	1	1	1	DLF	7.5	25.40	17.26	8.14	32.04724409	P	AB	Staph aureus + E.coli
19	870033	68	1	1	5	1	1	1	DRF	10	21.96	19.80	2.16	9.836065574	P	P	E.coli
20	870936	75	2	1	3	3	1	2	HLF	9.3	24.60	20.30	4.30	17.4796748	P	AB	CONS
21	869816	65	1	2	2	2	1	2	DLF	7.6	14.30	10.10	4.20	29.37062937	P	AB	Proteus
22	870146	63	1	1	3	2	1	2	PRF	8.4	24.56	20.78	3.78	15.39087948	P	AB	Staph aureus
23	876888	52	1	1	2	1	2	2	DRF	7.7	15.50	11.66	3.84	24.77419355	P	AB	Staph aureus
24	873916	66	1	2	1	2	1	2	PRF	6.9	27.50	17.20	10.30	37.45454545	P	AB	E.coli
25	887355	65	2	1	3	1	1	1	DRF	6.8	36.00	25.70	10.30	28.61111111	P	AB	Staph epidermidis
26	879392	48	1	1	1	1	1	1	DLF	7.1	23.68	14.90	8.78	37.0777027	P	AB	Pseudomonas
27	889987	36	1	2	5	1	1	1	DLF	8.5	34.20	22.00	12.20	35.67251462	P	P	Proteus

28	910053	40	2	1	2	2	1	1	DLF	8.4	15.60	11.20	4.40	28.20512821	P	AB	Staph aureus
29	881985	42	1	1	1	2	2	2	PRF	7.2	32.80	22.00	10.80	32.92682927	P	AB	Pseudomonas
30	886346	60	1	1	2	1	1	1	DLF	8.2	25.48	16.24	9.24	36.26373626	P	AB	Pseudomonas
31	891843	60	2	2	2	2	2	1	DLF	9.9	25.60	22.40	3.2	12.5	P	P	E.coli + proteus
32	895868	50	2	1	1	2	1	2	DRF	6.7	26.8	19.6	7.2	26.86567164	P	AB	Staph aureus
33	895827	59	2	1	2	1	2	1	DLF	8	27.55	21	6.55	23.77495463	P	AB	E.coli
34	899637	51	1	1	4	1	1	1	PRF	10.4	32.44	29.8	2.64	8.13810111	P	P	Staph aureus+pseudomonas
35	883568	40	1	2	2	2	1	1	DRF	7.8	19.4	14.2	5.2	26.80412371	P	AB	Staph aureus+Enterococcus
36	897779	74	2	1	5	1	1	1	DLF	8.7	21.2	17.8	3.4	16.03773585	P	AB	E.coli
37	903373	43	2	1	1	2	2	2	DRF	7.7	33.5	23.3	10.2	30.44776119	P	AB	Staph aureus
38	918359	75	2	1	4	1	1	1	PLF	8.2	32.9	26.6	6.3	19.14893617	P	AB	Staph epidermidis
39	864491	41	1	1	1	2	2	1	DLF	7.7	27.7	21.2	6.5	23.46570397	P	AB	CONS
40	917175	55	1	3	2	2	1	2	DRF	7.6	29.34	20.56	8.78	29.93	P	AB	E.coli

GROUP B

S.NO	IPNO	AGE	SEX	SOCIOECONOMIC STATUS	DURATION OF DIABETES	ONSET	NEUROPATHY	HYPERTENSION	SITE	HBA1C	AREA D0	AREA D14	REDUCTION IN AREA	%REDUCTION IN AREA	CULTURE D0	CULTURE D14	ORGANISM
1	852047	60	1	1	3	1	1	1	PLF	7.9	35.46	31.82	3.64	10.26508742	P	AB	Staph aureus + E.coli
2	852227	73	1	1	4	1	1	1	PLF	8.2	31.34	28.35	2.99	9.540523293	P	P	Proteus
3	851722	72	2	2	2	2	2	1	DRF	8.4	26.81	23.66	3.15	11.74934726	P	AB	E.coli
4	854316	71	1	1	5	3	1	1	PRF	7.4	35.47	30.70	4.77	13.44798421	P	AB	K.pneumoniae
5	854405	60	1	2	3	1	2	1	PLF	6.8	11.65	9.80	1.85	15.87982833	P	AB	E.coli
6	857494	70	1	1	2	2	2	2	DRF	7.7	13.67	11.80	1.87	13.67959034	P	AB	Staph aureus
7	857288	62	2	1	4	2	1	2	DRF	8.9	35.23	31.67	3.56	10.10502413	P	AB	K.pneumoniae
8	857054	40	2	3	1	2	2	2	DLF	6.9	12.80	9.68	3.12	24.375	P	P	E.coli
9	859307	55	1	1	1	2	1	1	DLF	7.1	29.00	25.37	3.63	12.51724138	P	AB	Staph aureus
10	856627	64	2	2	2	1	1	1	PRF	7.8	26.78	23.45	3.33	12.43465273	P	AB	Staph aureus
11	862784	43	1	1	1	2	1	1	DLF	7	25.34	21.99	3.35	13.22020521	P	P	Pseudomonas
12	863922	69	1	2	5	3	1	1	HRF	9	32.18	28.94	3.24	10.06836544	P	P	Staph aureus + Pseudomonas
13	863311	64	1	2	3	2	1	2	DRF	7.2	16.78	14.16	2.62	15.61382598	P	AB	E.coli
14	863324	49	1	1	2	1	1	1	HLF	6.8	9.80	8.20	1.60	16.32653061	P	P	Staph aureus + CONS
15	865982	54	1	1	4	2	2	2	DRF	7.4	19.20	11.10	8.10	42.1875	P	AB	Staph epidermis
16	864491	41	2	2	3	1	1	1	DLF	8.8	23.56	21.34	2.22	9.422750424	P	AB	CONS
17	865651	64	2	1	2	2	2	1	DRF	6.7	14.72	12.56	2.16	14.67391304	P	P	E.coli + Proteus
18	870475	45	1	1	1	2	1	2	PRF	8.6	31.80	27.91	3.89	12.2327044	P	AB	Staph aureus + Pseudomonas
19	869934	55	2	1	3	1	1	1	PLF	10.2	25.60	22.86	2.74	10.703125	P	P	Staph aureus
20	879628	65	2	2	1	2	2	2	DLF	9	19.67	17.77	1.90	9.659379766	P	P	Pseudomonas
21	868418	60	1	1	1	2	1	1	DRF	7.6	33.18	29.42	3.76	11.33212779	P	AB	E.coli
22	870016	67	1	1	5	3	1	1	HRF	9.7	34.67	29.72	4.95	14.27747332	P	AB	Proteus
23	875546	60	1	2	4	2	1	2	PRF	7.9	22.34	18.79	3.55	15.89077887	P	AB	K.pneumoniae
24	878633	42	1	1	1	2	2	2	DLF	7.5	34.26	29.66	4.60	13.42673672	P	AB	Staph aureus

25	881994	74	1	1	5	2	1	1	DRF	8.3	25.00	20.78	4.22	16.88	P	P	CONS
26	882056	60	1	2	3	2	2	1	DRF	8.7	26.68	24.23	2.45	9.182908546	P	P	Staph aureus + Enterococcus
27	879392	43	1	1	1	2	1	2	DRF	7	30.65	27.67	2.98	9.722675367	P	AB	Pseudomonas
28	880769	72	1	1	4	2	1	1	DLF	8	6.36	5.38	0.98	15.40880503	P	AB	Staph aureus
29	880848	72	1	2	3	1	1	1	PRF	7.7	35.46	31.47	3.99	11.25211506	P	AB	Staph aureus
30	883463	65	1	1	2	2	2	1	DLF	6.8	27.70	23.30	4.40	15.88447653	P	P	Staph aureus + E.coli
31	887591	60	2	3	2	2	2	2	DRF	7.8	34.50	31.20	3.3	9.565217391	P	AB	Proteus
32	889101	65	1	2	3	1	1	1	PLF	10.5	28.1	24.6	3.5	12.45551601	P	AB	Staph aureus
33	893340	54	1	2	2	2	1	2	DRF	7.5	23.5	18.1	5.4	22.9787234	P	P	Pseudomonas
34	895783	45	2	3	2	1	1	1	DLF	7.9	24.7	22.8	1.9	7.692307692	P	P	Pseudomonas
35	919636	61	2	1	1	2	2	2	DRF	8.7	32.1	29.1	3	9.345794393	P	AB	E.coli
36	888737	45	1	1	3	1	1	1	DLF	7.4	25.6	20	5.6	21.875	P	AB	Staph aureus
37	890074	50	1	1	2	2	2	1	DRF	7.8	27.92	21.77	6.15	22.02722063	P	AB	Pseudomonas
38	897750	65	1	1	4	1	1	1	DLF	11	26.5	24.98	1.52	5.735849057	P	AB	Staph aureus
39	880870	60	1	3	1	2	1	2	DRF	6.7	26.32	19.12	7.2	27.3556231	P	AB	Enterococcus
40	910013	47	1	1	3	2	2	1	DLF	7.8	30.45	24.76	5.69	18.69	P	AB	Staph aureus + Pseudomonas