"COMPARISON OF HYALURONATE-IODINE AND ORNIDAZOLE COMPLEX WOUNDGEL DRESSING VERSUS POVIDONE-IODINE DRESSING IN HEALING OF CHRONIC DIABETIC FOOT ULCERS- A RANDOMISED CONTROLLED TRIAL FOR A PERIOD OF ONE YEAR"

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This is to certify that the dissertation entitled **"COMPARISON OF HYALURONATE-IODINE AND ORNIDAZOLE COMPLEX WOUND GEL DRESSING VERSUS POVIDONE-IODINE DRESSING IN HEALING OF CHRONIC DIABETIC FOOT ULCERS- A RANDOMISED CONTROLLED TRIAL FOR APERIOD OF ONE YEAR"** is a bonafide research work done by **REG NO. BH0118004.**

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ACCEPTANCE LETTER

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LIST OF ABBREVIATIONS USED

DM	-	Diabetes Mellitus
DFU	-	Diabetic foot ulcer
PVD	-	Peripheral Vascular Disease
U.K	-	United Kingdom
ADA	-	American Diabetic Association
GDM	-	Gestational Diabetes Mellitus
RBG	-	Random blood glucose
HbA1c	-	Glycosylated Haemoglobin
OGTT	-	Oral Glucose Tolerance Test
PDGF	-	Platelet derived growth factor
TNF-α	-	Tumor necrosis factor-alpha
IL	-	Interleukin
TLR	-	Toll like receptors
ECM	-	Extra cellular matrix
MMP	-	Matrix metallo proteinase
LMW-HA	-	Low molecular weight hyaluronic acid
HMW-HA	-	High molecular weight hyaluronic acid
ABPI	-	Ankle Brachial Pressure Index
g	-	Gram
FTU	-	Finger tip units
Sq.cm	-	Square centimetre
Wks	-	Weeks
S.D	-	Standard deviation
OHA	-	Oral Hypoglycemic Agents
P.aeruginosa	-	Pseudomonas aeruginosa

K.pneumoniae	-	Klebsiella pneumonia
E.coli	-	Escherichia coli
PEDIS	-	Perfusion Extent Depth Infection and Sensation

ABSTRACT

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

Back ground

Diabetes mellitus is a metabolic disorder characterized by increased glucose levels in the body, which can be caused by reduced secretion of insulin, decreased utilization of glucose or increased production of glucose.[1]Amongst the complications of diabetes mellitus, diabetic foot ulcer is one of the most frequently seen complication. Wound care has an important role in diabetic foot ulcer management, that involves aseptic cleansing of the ulcer and application of a dressing that can promote an optimum wound healing environment.[5]

Hyaluronan, one of the recent discoveries in the field of wound dressings has properties such as preserving tissue integrity, lubrication, and water absorption. Hyaluronic acid stimulates migration of mesenchymal and epithelial cells and differentiation, eventually improving deposition of collagen and angiogenesis for wound repair.[9]Because of these specific characters of hyaluronic acid, fortification of ornidazole and povidone iodine in the wound gel and very few clinical studies in the literature prompted us to compare healing of diabetic foot ulcers, between hyaluronate-iodine and ornidazole complex wound gel and povidone iodine dressings.

Objectives

To compare hyaluronate-iodine and ornidazole complex 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 2019 to Dec 2019. Total 80 cases of chronic diabetic foot ulcers between 25-75 years were selected and randomized(SNOSE technique) in to two groups, group 1(control group) povidone iodine dressing done and group B(test group) hyaluronate-iodine and ornidazole complex dressing. Demographic data including duration of disease, hypertension and neuropathy were recorded. The wound healing was calculated as mean reduction in ulcer area and mean percentage reduction in ulcer area. The wound healing was then compared between two groups

Results

Factors like age, gender, socioeconomic status group, site of ulcer, hypertension, neuropathy, fasting blood sugar have been regarded as possible reasons for diabetic foot ulcers. When analyzed, both the groups were comparable for all these parameters with no significant statistical difference detected(p value>0.05) thus, eliminating bias from our research.

But on assessment of the effect of the hyaluronate-iodine complex on diabetic wound healing when compared to the effect of just povidone-iodine, the mean percentage reduction in area of ulcer over 14 days in the control and test groups were noted 19.67% and 43.56%, respectively. This was a statistically significant difference in the mean percentage reduction in ulcer area in the test group when compared to the control group(p value = 0.0001).

Conclusion

When hyaluronate-iodine and ornidazole complex wound gel was added to the treatment regimen of the patients with diabetic foot ulcers, it has shown good results of wound healing in terms of ulcer area reduction compared to povidone iodine dressing.

Keywords: Diabetes mellitus, diabetic foot ulcer, hyaluronate-iodine and ornidazole complex wound gel, wound healing, povidone iodine

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INTRODUCTION

Diabetes mellitus is a metabolic disorder characterized by increased glucose levels in the body, which can be caused by reduced secretion of insulin, decreased utilization of glucose or increased production of glucose.[1] Because of its complex pathogenesis, it can lead to devastating complications if not treated optimally.

The worldwide prevalence of diabetes is 422 million as reported in 2016, with a global prevalence of 8.5% of total population. The disease is on a steady rise and the number is estimated to double by 2030.[2]

Various chronic complications are associated with Diabetes mellitus. The most prominent of them include retinopathy, nephropathy, cardiovascular diseases, neuropathy and limb complications. The other significant outcomes of diabetes is impaired wound healing and an increased rate of wound infection. This is because hyperglycemia and impaired glycemic control interfere with the normal process of wound healing leading to chronic ulcers, especially on the foot.[1]

Diabetic foot ulcer is now leading the causes of lower limb nontraumatic amputation.[2] The lifetime risk of a diabetic developing a foot ulcer is 15% out of which 14-24% are at risk of amputation.[3] This is reflective of the disastrous impact diabetes can have on its victim if it is not dealt with in an strict manner.

Multiple factors are involved in the pathogenesis of DFUs such as neuropathy, vasculopathy, infection, altered foot biomechanics and poor wound healing.[1]

The optimization of wound healing process in diabetic foot ulcers can be achieved by identifying such modifiable factors that affect wound healing. This stresses on the need for an effective management strategy to deal with the progression, outcomes and complications.

Successful tackling of this condition consists of three basic steps that are tissue debridement, offloading of the foot and local infection control.[4] This has to be supported by an optimum glycemic control in the patient in order to achieve desired results.

Wound care has an important role in diabetic foot ulcer management , that involves aseptic cleansing of the ulcer and application of a dressing that can promote an optimum wound healing environment.[5] One of the detrimental factors for diabetic foot ulcer healing is diabetic foot infection, which can be present in almost 50% of the cases.[6] Thus, there is a need for an effective treatment modality in the form a wound dressing which should not only possess antimicrobial activity but also be able to cause wound healing at a faster rate.

Nowadays, various wound dressings are commercially available such as hydrogels, hydrocolloids, alginates which are all targeted at different aspects of healing.[7] Even newer options such as topical phenytoin, honey and platelet derived growth factor have shown positive therapeutic effects when checked for diabetic wound healing capacity.

One such recent discoveries in the field of wound dressings is hyaluronan which belongs to the family of glycosaminoglycans, consists of two sugars, glucuronic acid and N-acetyl-glucosamine.[8] It has properties such as preserving tissue integrity, lubrication, and water absorption. Hyaluronic acid stimulates migration of mesenchymal and epithelial cells and differentiation, eventually improving deposition of collagen and angiogenesis for wound repair.[9]

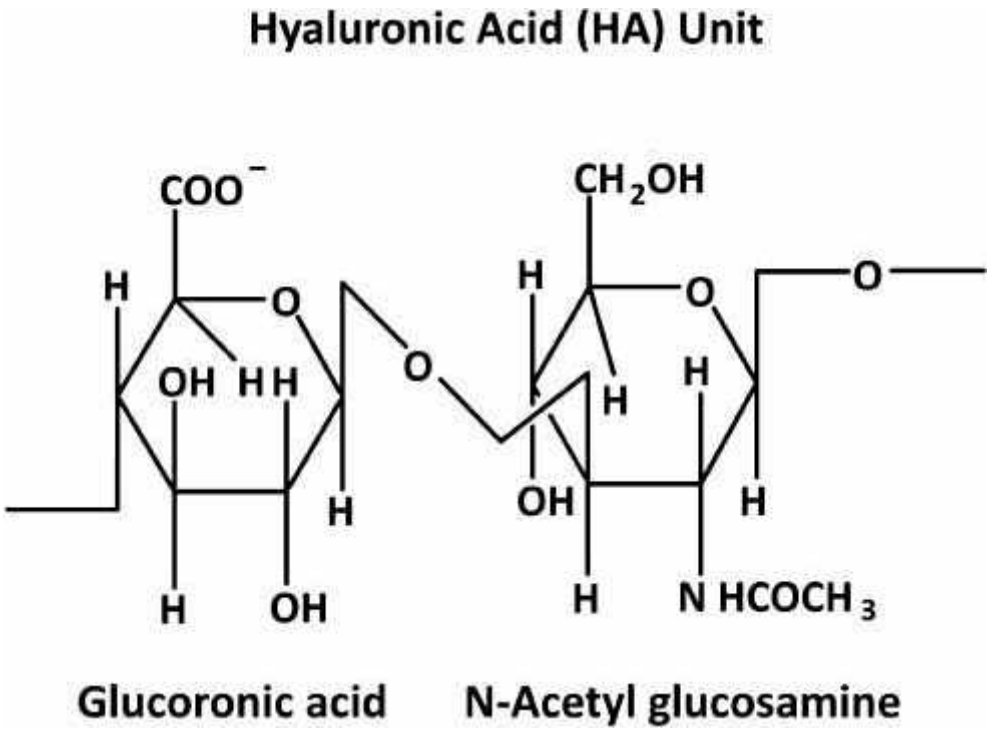


Figure 1 : Molecular structure of hyaluronic acid

Povidone iodine, commonly used iodophore, possess added benefits which include its broad antimicrobial spectrum, nondevelopment of bacterial resistance, efficacy against biofilms, good tolerability and aggressive anti-inflammatory ability.[10] However, it does harbour the adverse effect of cytotoxicity when used in high doses or when applied over granulating wounds. The other agent present in this ointment combination is ornidazole which is an antibiotic with antiprotozoal activity.

At a time when antibiotic wound dressings pose the hazard of antimicrobial resistance and various adverse effects affecting the long term use of topical modalities, this drug combination has the potential to be a promising topical formulation in management of diabetic foot ulcers.

The use of this hyaluronate-iodine complex in the management of diabetic foot ulcers has been recent with very few studies available in the literature

showcasing the effects of the formulation. The few clinical trials available have been excuted on ulcers with other etiological reasons such as vascular ulcers.

There is a need to evaluate the efficacy of this hyaluronate-iodine combination in diabetic wound healing as well as to identify its adverse effects if any. This study attempted to achieve the same by comparing the effect of the hyauronate-povidone complex on diabetic foot ulcer healing versus povidone-iodine dressing.

AIM AND OBJECTIVE

To compare hyaluronate-iodine and ornidazole complex gel dressing versus povidone iodine dressing in wound healing of chronic diabetic foot ulcers in terms of mean percentage reduction in ulcer area.

REVIEW OF LITERATURE

Diabetes mellitus:

Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action or both.[28]

Epidemiology

DM is one among the world's greatest challenges in health care and a leading cause of morbidity all over the world.[29]

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.[30]

Diabetes mellitus can be classified into the following types–

Type 1- near-total or complete deficiency of insulin.

Type 2 - more common and is characterized by variable degrees of resistance to insulin, impaired secretion of insulin, and glucose intolerance.

Gestational DM – glucose intolerance developed during pregnancy.

Other types – include impaired insulin secretion or action due to specific genetic defects and metabolic abnormalities that impair secretion of insulin.[1]

The risk factors for developing DM such as –history of diabetes running in the family, obesity, previously identified with impaired glucose tolerance, history of GDM, hypertension, hypertriglyceridemia and polycystic ovarian syndrome (PCOS).

Table 1: Criteria for diagnosis of DM (according to ADA)[1] –

Criteria	Value
Random blood glucose (RBG)	Symptoms of diabetes with RBG ≥ 200mg/dl
Fasting plasma Glucose	126 mg/dl
HbA1c	≥ 6.5%
2-hour Oral glucose tolerance test (OGTT)	Plasma glucose > 200 mg/dl

Complications of DM: The metabolic dysregulation associated with DM causes secondary pathophysiological changes in multiple organ systems that lead to various complications which are a major cause of morbidity and mortality associated with the disease.

The complications of DM include – retinopathy, macular edema,neuropathy – sensory, motor and autonomic,nephropathy ,coronary arterial disease, peripheral arterial disease, cerebrovascular disease,gastrointestinal (gastroparesis, diarrhoea), dermatological, diabetic foot and limb complications.[1]

Diabetic foot ulcer:

Definition

"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".[31]

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 DFUs.[52,33] The leading reason for admission to hospital among patients with DM is DFU. It's calculable to account for twenty five percent of all hospital admissions in patients with DM.[34]

Lower extremity complications including foot ulcers form a major cause of morbidity in diabetics. DM is one of the leading causes of non traumatic lower extremity amputation. Limb amputation greatly affects the quality of life of individuals and also places a burden on families and health care systems. The incidence of DFU in different populations is 1 to 4% and prevalence ranges from 5 – 10%. The risk of a developing diabetic foot ulceration in lifetime is around 15%. [35]

Applied anatomy of the foot:

The human foot symbolizes the evolution of humans to biped beings, helping in weight bearing and locomotion. It is an integrated and complex structure.

The foot can be divided into –

Forefoot – consists of phalanges (proximal, middle and distal) and metatarsal bones. It plays an pivotal role in the gait cycle when the foot leaves the ground during toe – off. In diabetic neuropathy, plantar pressure is increased due to toe and metatarsal deformities leading to ulcerations.

Midfoot – includes the 3 cuneiforms, navicular and cuboid. It articulates with the hindfoot through the Chopart's joint and the forefoot through the Lisfranc's joint

Hindfoot– consists of the talus and calcaneum. It supports the weight of the body while standing and walking.

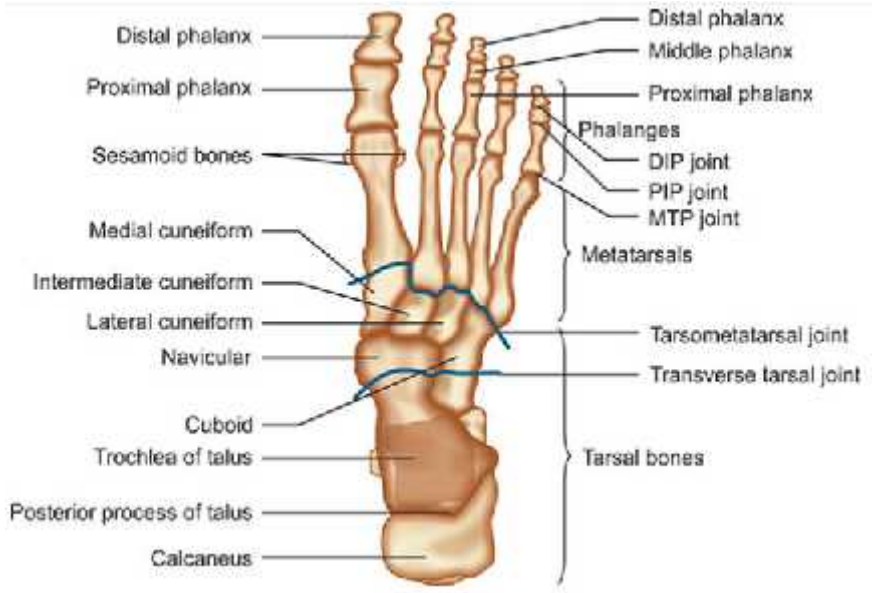


Figure 2 : Bones of the foot. [36]

The muscles of the foot include –

Extrinsic muscles – originate from the leg and insert into the foot. These are mainly involved in movement. It includes muscles of the anterior, lateral and posterior compartments of the leg.

Table 2: Extrinsic muscles of foot

Muscle group	**Muscles**	**Nerve supple**
Anterior compartment (dorsiflexors)	o Tibialis anterior o Extensor hallucis longus o Extensor digitorum longus	Deep peroneal nerve
Lateral compartment	o Peroneus longus o Peroneus brevis	Superficial peroneal nerve
Posterior compartment (plantar flexors)	o Gastrocnemius o Soleus o Tibialis posterior o Flexor digitorum longus o Flexor hallucis longus	Tibial nerve

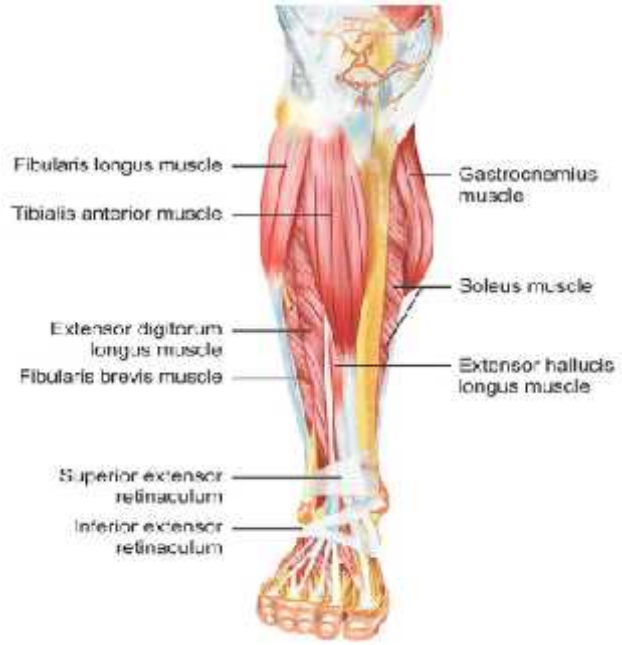


Figure 3 : Extrinsic muscles of foot.[36]

Intrinsic muscles – origin and insertion in the foot. These muscles and tendons contribute in supporting the arches of the foot. Neuropathy leads to dysfunction of these muscles which causes foot deformities. The muscles are dorsal and plantar. Plantar muscles consist of 4 layers.[36,37]

Table 3: Intrinsic muscles of foot

Muscle group	**Muscle**	**Nerve supply**
Dorsal muscles	Extensor digitorum brevis Extensor hallucis brevis	Deep peroneal nerve
Plantar muscles		
1st layer	Abductor hallucis Flexor digitorum brevis Abductor digiti minimi	Medial and lateral plantar nerve
2nd layer	Quadratus plantae Lumbricals	Medial and lateral plantar nerves
3rd layer	Flexor hallucis brevis Flexor digiti minimi brevis Adductor halluces	Medial and lateral plantar nerves
4th layer	Dorsal and plantar interossei	Lateral plantar nerve

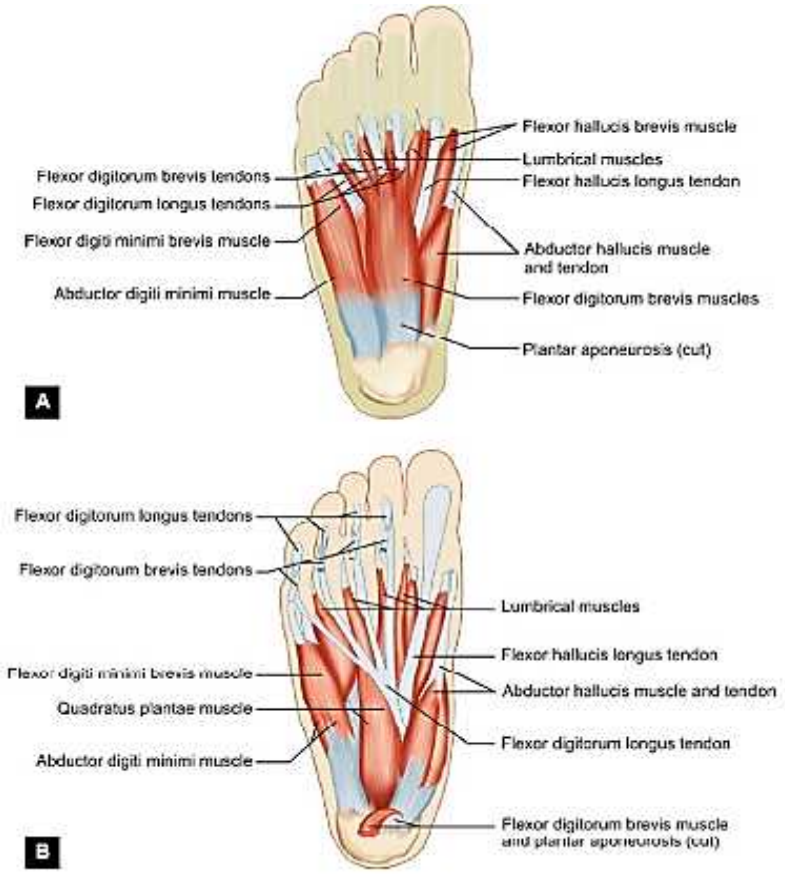


Figure 4 : Intrinsic muscles of foot.

Arches of the foot –

The bones of the foot do not lie in a horizontal plane, but are arched. Arches are formed by metatarsal and tarsal bones and are strengthened by ligaments and tendons of the foot. These arches have a protective role. They absorb and distribute the downward forces from the body while standing and walking.

There are 2 main arches –

Longitudinal arch: formed between the posterior end of calcaneum and metatarsal heads. It consists of medial and lateral part.

Transverse arch: is highest in the coronal plane. It cuts through the head of the talus and ends in the metatarsal.

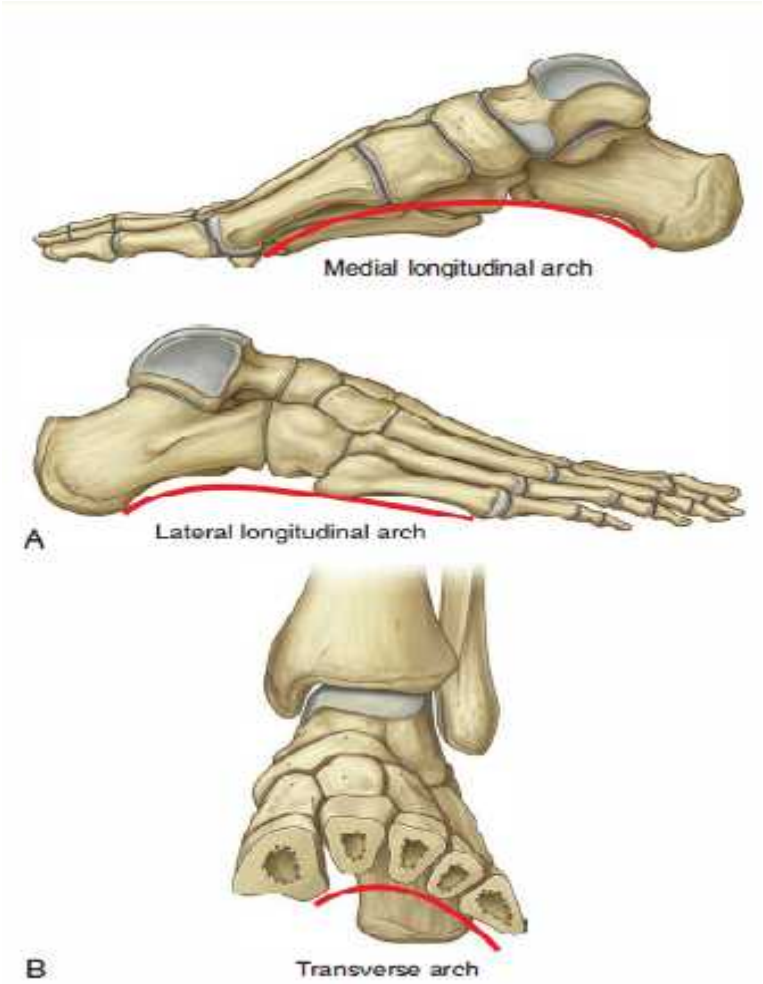


Figure 5 : Arches of foot[37]

Wound healing:

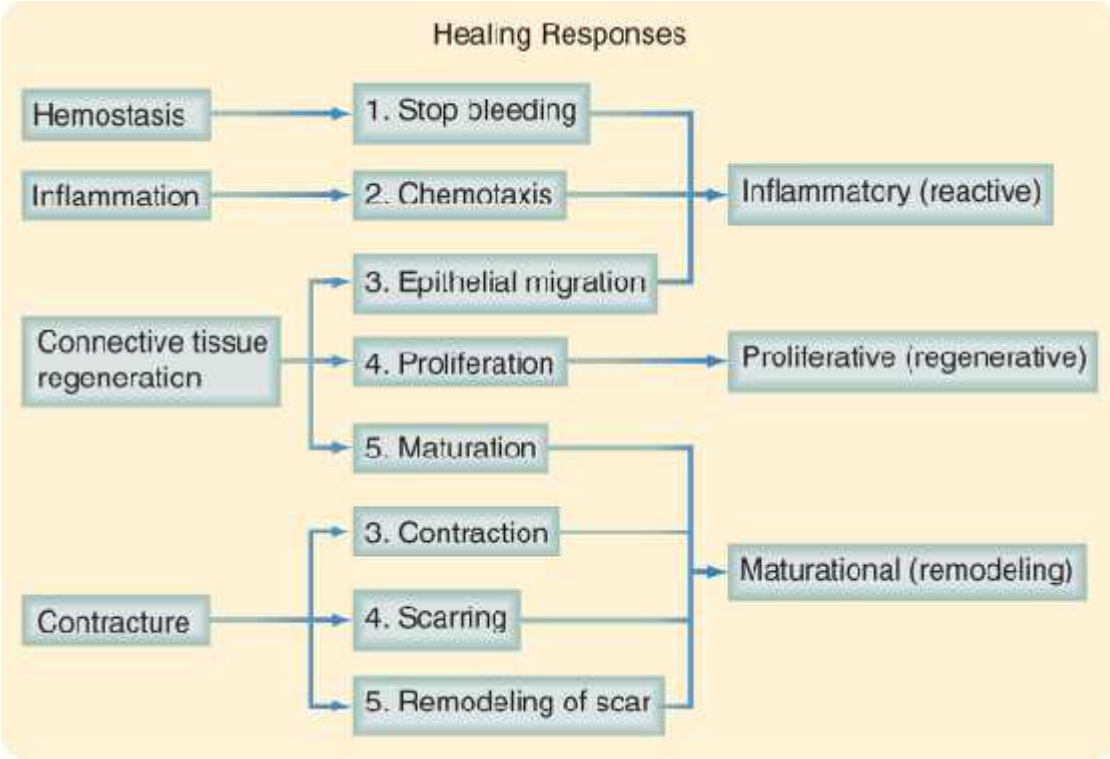
Wound healing is the dynamic process of injured tissues to replace devitalised tissue , restore their normal function and structural integrity.[38]

The wound healing process involves a sequence of cellular and biochemical events which all wounds need to undergo to successfully re-establish tissue integrity. This process can be divided broadly into the following phases:

Inflammatory phase

Proliferative phase

Maturation phase



Flowchart 1: Phases of wound healing

Inflammatory phase – consists of hemostasis and inflammation. Hemostasis initiates inflammation. Wounding causes subjection of subendothelial collagen to platelets which in-turn initiates aggregation of platelets, degranulation and coagulation cascade activation. Platelets also release a number of factors like fibronectin and serotonin, platelet derived growth factor (PDGF), which are chemotactic and increase the vascular membrane permeability. Due to this there is infiltration of the wound by cells. Polymorphonuclear cells are the first infiltrating cells within 24 – 48 hrs of injury. Their primary role is phagocytosis of bacteria and tissue debris. Macrophages infiltrate the wound next and play important role in healing. They peak in number by 48 to 96 hours and remain till healing is complete. They play a role in phagocytosis but the most important function is recruitment and activation of other cells necessary for proliferation, by releasing mediators such as cytokines and growth factors. T

lymphocytes are also included in infiltrating cells but their role is undetermined.[3,38]

Proliferative phase - is characterised by formulation of granulation tissue. It roughly lasts for 4 to 12 days and includes the following processes –

Angiogenesis – is the growth/formation of new blood vessels which is essential to support the wound environment. It is stimulated by cytokines which are produced by platelets and macrophages.

Fibroplasia – is the proliferation of fibroblasts. Fibroblasts are initially sparse then are chemoattracted to site of injury. They are activated by macrophages, platelet derived cytokines and growth factors. Their primary function is synthesis of collagen. Fibroblasts replace the fibrin matrix with collagen – rich matrix for developing granulation tissue. They also produce proteoglycans and glycosaminoglycans which form extra-cellular matrix.

Epithelialization – is the restoration of external skin barrier. It includes the following series of changes that occur in keratinocytes – detachment, migration, proliferation, differentiation and stratification. [3,38]

Maturational phase - is the final phase of wound healing and involves remodelling and re-organisation of collagen. This results in strengthening of the wound. Scar remodelling continues for almost 6 – 12 months post injury.

Contraction of the wound occurs due to movement of entire thickness of the surrounding skin centripetally, resulting in decrease in size of scar. It is carried out by specialised fibroblasts – myofibroblasts and their interaction with extracellular matrix.[3,38]

Factors affecting wound healing:

Factors that negatively affect or impede wound healing can either be local or systemic. If these factors are not corrected, it can result in wound complications and chronic non-healing wounds.

LOCAL -

Wound infection – leads to chronic inflammation and delay in healing process.

Foreign body in wound

Wound hypoperfusion or hypoxia

Ionizing radiation

Repeated trauma

SYSTEMIC -

Malnutrition and deficiency of vitamins (C, A, E) and minerals (zinc, iron).

Immunodeficiency

Metabolic disorders - Diabetes mellitus, obesity

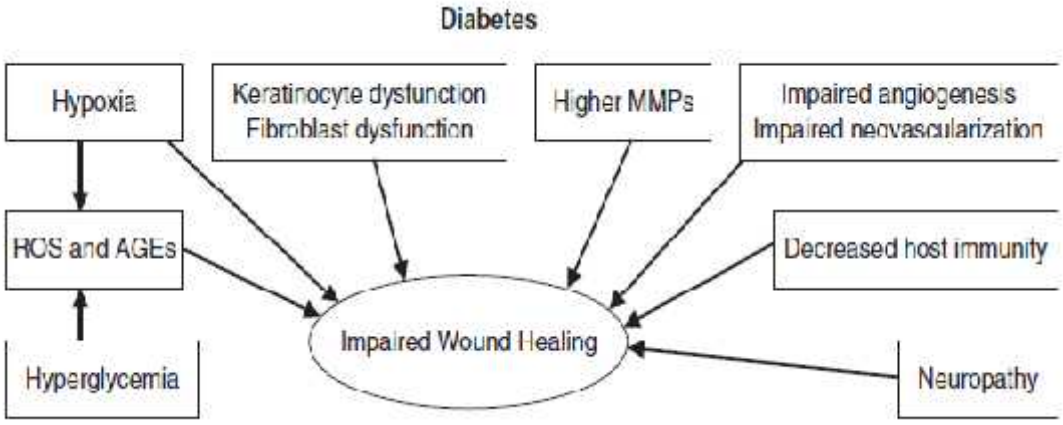
Drugs – steroids, cytotoxins.

Advanced age – altered immune response, delayed epithelialization, collagen synthesis and angiogenesis. [3,38,39]

Impaired wound healing in diabetics:

Due to increasing incidence and its epidemic nature, diabetes mellitus is now the most important systemic factor that is involved in delayed wound healing. It affects all stages of the wound healing process. Multiple factors and complex pathophysiological mechanisms are involved at the macroscopic and microscopic level in impaired wound healing in diabetics.

As discussed, DM is associated with neuropathy, atherosclerosis and infection. Neuropathy causes loss of protective sensation that inturn leads to repetitive trauma to tissues and atherosclerosis of large and small vessels contributes to tissue hypoxia and ischemia. Diabetic patients are more prone to infection due to weakened inflammatory response, hampered chemotaxis and impaired phagocytosis.[40,42]



Flowchart 2: Causes of impaired wound healing in diabetes

<u>Hyaluronic Acid in wound healing process[53]</u>-

After the skin injury occurs, the healing process begins immediately to re-establish the skin tissue architecture.To acheive this, platelets releases high molecular weight hyaluronic acid (HMW-HA), that facilitates the deposition of fibrinogen and initial clot formation. HA also promotes the deployment of neutrophils cells, involved in the phagocytosis and helps in release of tumor necrosis factor-alpha (TNF-α), IL-1β,IL-8.

The secretion of cytokines will contribute in fragmentation of HMW-HA into low molecular weight hyaluronic acid (LMW-HA) , which has a role in the recruitment of leucocytes and monocytes.

In the final stage of the inflammatory phase, migration of the lymphocytes and macrophages into the wound site occurs, where their toll-like receptors (TLR2 andTLR4) interact with LMW-HA, and help in the release of TNF-α and interleukins such as IL-6, IL-8 and IL-1β.

Additionally, LMW-HA together with fibronectin steer the fibroblasts invasion and proliferation, which is essential for collagen deposition in the wound, also helps in the differentiation of fibroblasts into myofibroblasts, that play a important role in the wound contraction.

HA fragments can encourage dermal fibroblast migration and proliferation, with the subsequent deposition of type III collagen, leading to the formation of a new extra cellular matrix.

In the re-epithelialization phase, CD44 receptors of keratinocytes cells interact with the LMW-HA present at the wound margins and help in regulation of the re-epithelialization process.

Pathophysiology of Diabetic foot ulcer:

The pathophysiological changes that occur in the foot of diabetics is now termed as ‘diabetic foot syndrome’ and foot ulcer forms a part of this. The following are implicated as risk factors for DFU and amputations – male sex, duration of diabetes > 10 years, abnormal foot structure, peripheral arterial occlusive disease, previous history of ulcer or amputation, smoking and uncontrolled diabetes.

Altered biomechanics of the foot in diabetes –

The human foot is a remarkable structure which has undergone evolutionary change enabling humans to walk upright with bipedal gait. The whole weight of the body is borne on the feet making it susceptible to stress and injury. Understanding of the biomechanics can help in prevention of such injury.

Gait cycle: is the sequence of movements occurring in the foot during walking or locomotion. It consists of 2 parts – stance phase and swing phase.

- Stance phase – is the weight bearing phase, when foot is in apposition with the ground. It is divided into 3 parts – contact of heel, midstance, propulsion.
- Swing phase – is when the foot is off the ground. It can be divided into – initial, mid and terminal swing.
- Due to neuropathy and hyperglycemia in diabetes, there is alteration in the normal anatomy of the foot. This results in abnormal foot biomechanics, predisposing the foot to injury and ulceration. The altered biomechanics include
- High plantar foot pressures – usually occurs at site of bony prominences. It is seen in deformed foot.
- Decreased plantar tissue thickness – loss of protective soft tissue (cushioning) in the plantar surface of the foot can occur due to atrophy of intrinsic muscles. It also leads to high foot pressures.
- Limited joint mobility – reduced range of movements in joints of the foot is thought to occur due to glycosylation causing stiffening of collagen in joints, tendons and ligaments.
- It also contributes to increased plantar pressure.[35,36]

The cause for foot ulceration and lower limb complications in diabetics is due to interaction between several factors which are –

- Neuropathy – sensory, motor and autonomic
- Peripheral vascular disease or ischemia
- Infection
- Poor or abnormal wound healing [1,32]

Neuropathy - distal lower limb neuropathy in diabetics affects all components of the nervous system – sensory, motor and autonomic and each of them contribute to development of ulceration.[41] Sensory neuropathy causes loss of sensations like pain, pressure, temperature and proprioception. These are protective to the foot and their loss makes the foot vulnerable to repeated trauma leading to ulcers.[43]Motor neuropathy causes atrophy and loss of power of intrinsic muscles of the foot thereby causing flexion deformities of the toes, loss of plantar arches and abnormal gait. Autonomic neuropathy leads to loss of sweat secretion (anhidrosis) which leads to dry, cracked skin which is susceptible to bacterial invasion. It also causes loss of sympathetic vascular tone which causes shunting of blood from arteries to veins, bypassing the capillaries and tissues. Neuropathy thus forms a major cause for ulceration in diabetes by altering foot biomechanics.[41,42]

Peripheral vascular disease and ischemia is the other major cause for foot ulceration. Atherosclerosis of lower limb vessels, usually distal, occurs more commonly in diabetics (2-3 times) than in normal population. PVD causes tissue ischemia which leads to tissue necrosis and ulceration. [41,42]

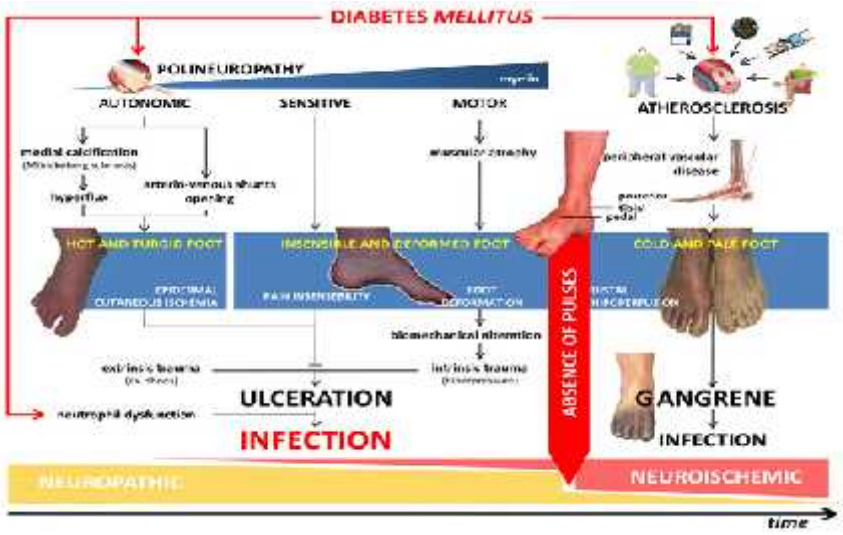
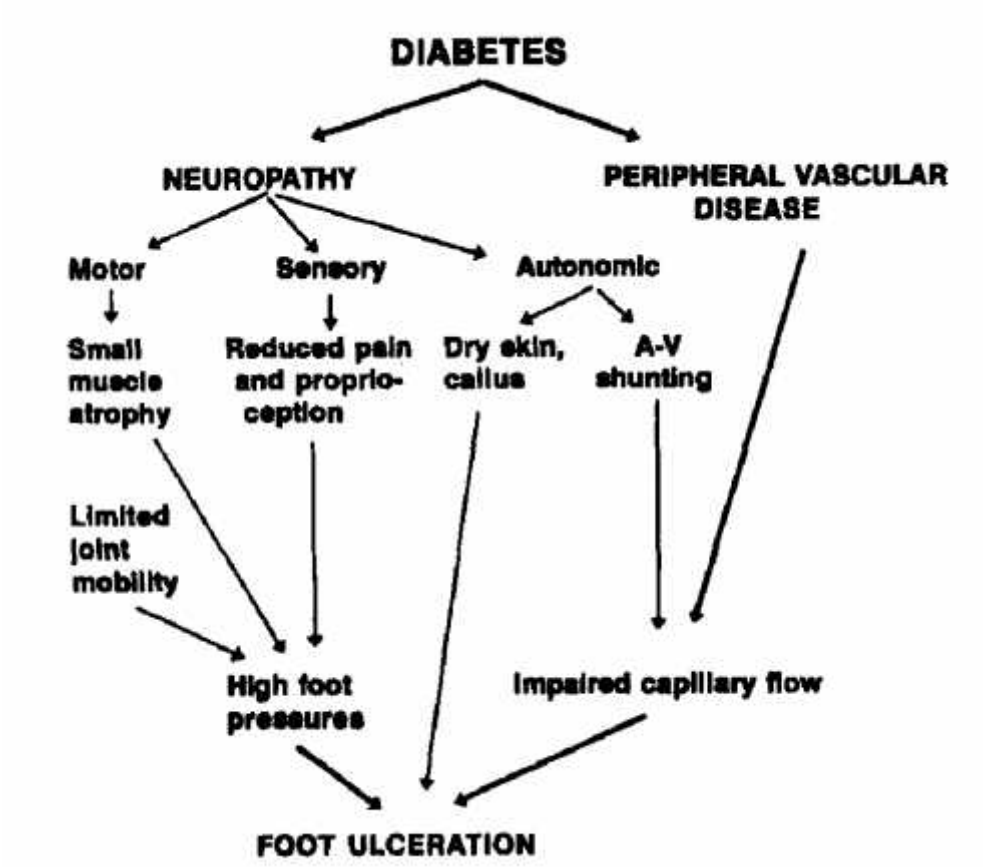


Figure 6 : Major causes of diabetic foot ulcers

Infection – is also implicated in pathogenesis of foot ulcers. Diabetics have increased susceptibility to infections due to impaired neutrophil function. Infected diabetic foot ulcers usually are polymicrobial containing both aerobic and anaerobic organisms. The most common organisms are staphylococci and streptococci. [43,44]



Flowchart 3: Pathogenesis of DFU.[43]

Classification of DFUs:

Classifying diabetic foot ulcers, aids to facilitate appropriate treatment, predict outcome and enable monitoring of healing process. There are many systems of classification that are in use.

The easiest method of classification is:

Neuropathic

Ischemic

Neuro-ischemic.

Meggit – Wagner system – most commonly used system, described by Meggit and Wagner. Foot ulcers graded based on depth of wound and extent of tissue necrosis.[32]

Table 4: Wagner's grading system

GRADE	LESION
0	no ulcer, susceptible foot deformity or cellulitis
1	Superficial ulcer
2	Deep ulcer involving tendon
3	Deep ulcer with abscess or osteomyelitis
4	Local gangrene of forefoot or heel
5	Gangrene of entire foot

Table 5 : University of Texas San Antonio (UTSA) system

Stage	Grade			
	0	1	2	3
A	Pre or post ulcerative lesions completely epithelized	Superficial wounds not involving tendon, capsule or bone	Wound penetrating to tendon or capsule	Wound penetrating to joint
B	Infected	Infected	infected	Infected
C	Ischemic	Ischemic	Ischemic	Ischemic
D	Infected and ischemic	Infected and ischemic	Infected and ischemic	Infected and ischemic

Table 6 : PEDIS system

Grade				
	1	2	3	4
Perfusion	Normal	Non- critical PAD	Critical limb ischemia	
Extent/size (cm^2)				
Depth tissue loss	Full thickness	Deep involving muscle	Bone and/ or joint	
Infection	None	Mild	Moderate/ severe	SIRS
Sensation	Intact	LOPS (loss of perceptive sensation)		

Assessment of DFUs:[35,41]

Assessment of diabetic foot is an integral part of examination in diabetics. It is done to detect at risk foot and also to assess presence of neurological or vascular deficits. Assessment is done by the following –

History – a comprehensive history may reveal symptoms and signs of neuropathy. History of duration of diabetes, duration of ulcer is noted. Many times, the patient is unaware of the foot ulcer as they are painless due to neuropathy.

Inspection – to look for skin changes like cracks and fissures, callosity, ulcer and deformities of the foot,dryness of skin,loss of hair, wasting of muscles.

Neurological assessment –

Semmes – Weinstein monofilament test – is used to test for presence or absence of protective sensation in the foot. It exerts a linear force of 10g. The important areas assessed are uncallused regions of plantar surface of metatarsal heads.

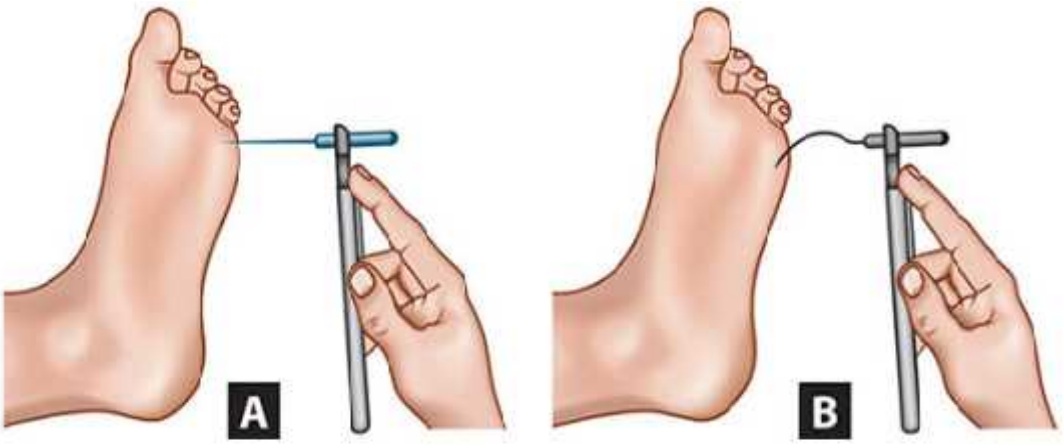


Figure 7: Monofilament test, placed perpendicular to plantar test area, force should be just enough to buckle the monofilament.

Vibration sensation or threshold is tested using a tuning fork.

Ankle reflex

Prickling sensation

Temperature discrimination

Vascular assessment – to assess the peripheral circulation:

Palpation of distal arteries

Ankle brachial pressure index (ABPI)- is the ratio of systolic blood pressure at the ankle to the blood pressure in the upper arm. It is determined by Doppler ultrasonography and is used to indicate adequacy of peripheral arterial blood flow. Normal value is 0.9 to 1.2. Values less than 0.9 indicate significant ischemia.

Colour 23xidiza – to look for patency of blood flow in peripheral arteries.

Transcutaneous oxygen tension in toes - < 40 mm of hg suggests severe ischemia.

Radiological assessment – baseline radiograph of the foot is advised for all patients with DFUs to evaluate the foot anatomy for changes that indicate neuroarthropathy (Charcot's joint). It may also reveal presence of osteomyelitis.

Plantar pressure measurement – increased plantar pressure is associated with foot ulcers. Quantitative estimation of foot pressures during different activities helps in preparing appropriate footwear. It can be detected using – Harris mat and other digital methods like Podiascan and podometry.

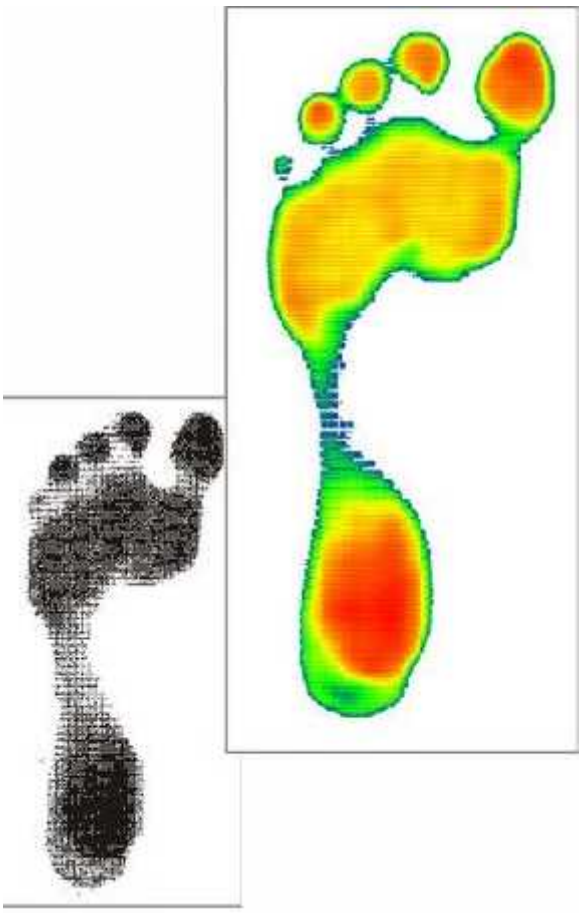


Figure 8 : Podiascan

Infection – presence of infection is confirmed by wound culture and leucocytosis in blood.

Glycemic control – Inadequate glycemia control is associated with higher risk of neuropathy, ischemia and ulceration of foot. The blood sugar control is monitored by FBG, random blood glucose and HbA1c.

Management of DFU:[46]

Multiple etiological factors play a role in DFU pathogenesis. Hence the treatment of diabetic foot ulcers is a multidisciplinary approach which involves both local and systemic approaches.

Wound control – can be achieved by the following:

Debridement – is the removal of devitalised tissue. It reduces bioburden of ulcer, converts chronic wounds to acute wounds and aids in formation of granulation tissue. It can be achieved by various methods.

- **Surgical debridement** is performed using a scalpel or scissors. It is also known as 'Sharp method'.

- **Chemical debridement** includes use of specific chemicals such as acetic acid, hydrogen peroxide, sodium hypochlorite and eusol to remove necrotic tissue. Enzymatic debridement makes use of various enzymes such as collagenase, papain and streptokinase which remove necrotic tissue without damaging normal tissues.

- **Autolytic debridement** involves the use of normal saline, hydrocolloid and hydrogel dressings that create a moist wound environment to clear the necrotic tissue by host defence mechanisms (neutrophils and macrophages).

- **Biological debridement** has been used recently. It is the application of biological agents which have the ability to clear the surface debris, bacteria and necrotic tissues, leaving the healthy tissues intact.

Dressing – ideal dressings should be sterile and non – adherent. Dressings can be done by conventional methods which is made of fabric material such as gauze and tulle grass which contains paraffin. Dressings containing silicon polymer are also used as they are less adherent and cause minimal trauma. Recently studies have shown that use of biological dressing that contains collagen and elastin such as Dermagraft are

superior to conventional dressing.

Pressure relief or mechanical control– aims to redistribute plantar pressures and protect the vulnerable parts of the foot. This is achieved by usage of various off-loading methods.

- Total contact casts (TCC) are well moulded padded casts that maintain contact with entire surface of foot. It completely offloads the foot, protects from infection and promotes ambulation. But these casts are not suitable for infected or ischemic ulcers.

- Alternative to TCC is removable plastic walkers. They are popular because of their ease of use and comfort.

Peripheral vascular disease – improved blood flow in foot ulcers lead to faster healing. This can be achieved by revascularization methods such as angioplasty or bypass. Antiplatelet drugs are used to delay progression of vascular disease. Their main role is to maintain the flow that is already present and prevent further thrombotic occlusion.

Infection control– culture from infected diabetic foot ulcers usually yield multiple bacteria which can be Gram positive, Gram negative aerobes and anaerobes. Therefore, combination of broad spectrum systemic antibiotics which target all these groups are administered to reduce the infection and promote healing.

Topical antimicrobial therapy[47,48]

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.[47,48]

Ornidazole

It is a member of imidazoles, a C-nitro compound, a secondary alcohol and an organochlorine compound. It is used in the management of protozoal infections and for the treatment of anaerobic infections. It has a role as an antiprotozoal drug, an anti infective agent, an antibacterial drug, an antitrichomonal drug and an epitope.[54]

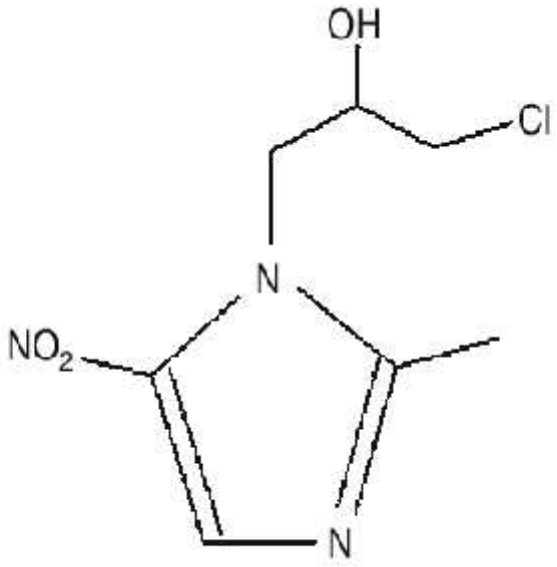


Figure 9 : Chemical structure of Ornidazole

Antiseptics

This group includes chemicals which can be used over the intact skin for asepsis and over the surface of external wounds for antimicrobial action.. Disadvantage with antiseptics is that they are known to have toxicity to healthy host cells.

Chlorhexidine and povidone iodine are well known antiseptic agents.[47]

Povidone iodine

Iodine has role of antimicrobial agent in wound care. It has been used as an antiseptic agent since years.[49]

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.[49]

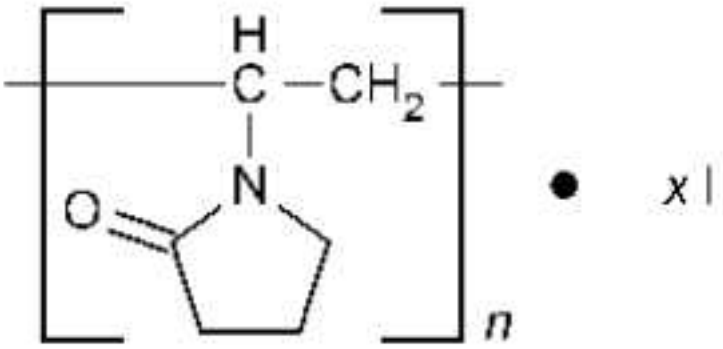


Figure 10: Chemical structure of povidone iodine

The microbicidal activity of iodine is through oxidization of nucleotides, fatty acids and amino acids in the cell wall of organisms. It desaturates and deactivates these organisms.[47]

Povidone iodine has wide range of antimicrobial activity. Reports of cross resistance or acquired resistance haven't been reported so far for povidone iodine. It has efficacy to heal wounds in the presence biofilms. [47,49]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.[47]

Disadvantage of iodine preparation is its systemic toxicity, when used on large wound surfaces it is absorbed systemically and causes toxicity of the same.[47]Because of its toxicity and systemic absorption, it is contraindicated in thyroid disease, in patients undergoing radio iodine therapy,low birth weight babies. [47,49]

Metabolic control – Most foot ulcers in diabetics is caused by inadequate control of blood glucose. Chronic hyperglycemia is associated with neuropathy which is a major cause of DFU.

Other therapies (newer and adjuvant therapies) **–**

Hyperbaric oxygen – is used as an adjunct therapy for DFUs. It involves the delivering of 100% oxygen at high pressures to the wound which promotes wound healing.

Growth factors – are produced by recombinant DNA technology. They include platelet derived growth factors (PDGF) and Becaplermin. Local application of these is found to promote wound healing as diabetic wounds are found to be deficit in growth factors.

Low intensity laser therapy – acts by photo bio-modualtion. It stimulates inactivated tissue components and promotes wound healing.

Vacuum assisted closure – involves the application of negative pressure to wounds to promote faster healing.

Prevention of DFUs: [41,45]

Prevention of ulceration and recurrence of ulcers in diabetics should be the goal of any diabetic foot therapy. A diabetic patient must be educated appropriately regarding the following strategies.

The preventive measures consist of the following–

Lifestyle modification – involves leading healthy lifestyle, regular physical activity to keep weight in check and prevent comorbidities.

Nail and skin care – include trimming of toe nails frequently and preventing cracks and fissures on plantar surface of the feet.

Annual comprehensive foot examination – yearly testing and examination of the feet by health experts to look for neuropathy, vasculopathy or foot deformities.

Appropriate foot wear – wearing footwear which is well fitting and provides adequate protection.

Blood pressure control

Glycemic control – maintaining blood sugar levels with appropriate medications.

Daily self-examination of feet is recommended for diabetic patients. The patients inspect their feet on a daily basis and look for any skin changes, cracks and calluses. This is especially recommended in patients with established neuropathy as they have loss of sensations.

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 Research Centre, Nehru Nagar, Belagavi, in the year 2019 between January to December.

1) **Study design:**A Randomised Control Trial

2) **Study Period:** 1 Year (2019 between January to December)

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

Patients were enrolled after debridement of ulcer.

d) **Selectioncriteria**

1) Inclusion criteria

-Type 2 Diabetic patients in the age group of 25 to 75 years.

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

-Pulselessness / PVD

-Immunocompromised

-Diabeticketoacidosis

-Diabetic gangrene

-Connective tissue disorders

-Skin malignancies

e) **Sampling procedure**-

The patients were divided into group 1 and group 2 based on SNOSE (sequentially numbered, opaque, sealed envelope) technique.

f)**Sample size**-

Total sample size of 80 cases. 40 in group 1 and the other 40 in group 2.

Sample size calculation -

The minimum sample size (n=40) in each group is based on formula 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% α error

Z_β = 21.037 at 85% power

There by total sample size is 80.

g)**Procedure**

Ethical clearance obtained from 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 predesigned proforma.

Detailed history of the patient is taken.

Empirical antibiotic amoxicillin and clavulanic acid combination started and later specific antibiotics started as per culture and sensitivity report.

Diabetes mellitus of all the patients manin the age group of as advised by physician.

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

Group 1

In this group topical management and dressing is done using povidone-iodine 10% w/v solution and normal saline.

Group 2

In this group topical management and dressing is done using wound gel (Bionect ointment).

The gel applied was calculated by finger tip units (FTU), amount to be applied was based on a study " Finger tip unit - A new practical measure".[51]

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

Outcome

Observation of healing of ulcer is done in terms of reduction 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".

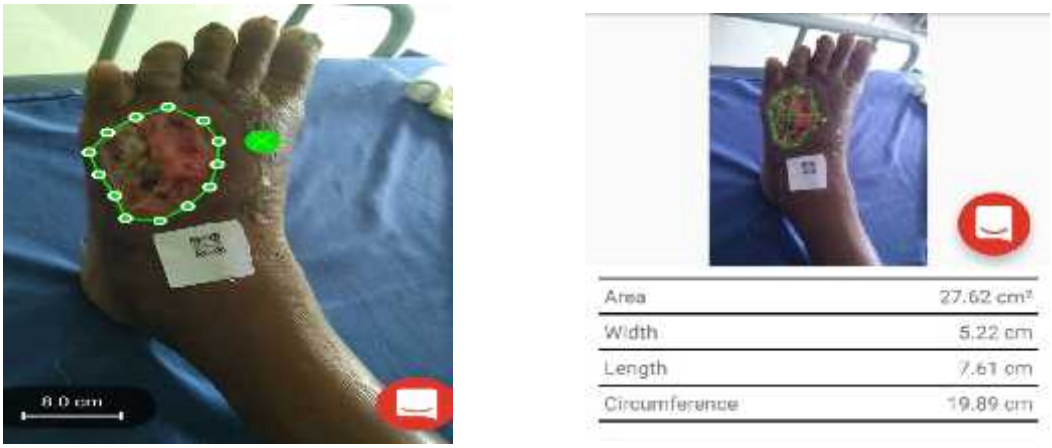


Figure11:Ulcer area measurement using imitomeasure application

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.

Calculation of wound area

The ulcer dimensions are measured on day 0(x) = initial wound area and day 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 KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi and the findings are tabulated as below.

During the study year from January 2019 to December 2019, 80 patients with diabetic foot ulcers are randomized into study (hyaluronate-iodine and ornidazole complex wound gel dressings) and control (povidone iodine dressings) groups. These groups were studied for the effect of hyaluronate-iodine and ornidazole complex wound gel dressing versus povidone iodine 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.

RESULTS

This clinical study has been conducted at KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi, during the period from January 2019 to December 2019,

This study included 80 patients in total with diabetic foot ulcers, randomized into test (Hyaluronate-iodine wound gel) and control (povidone iodine and normal saline) groups. These groups were assessed for the effect of povidone iodine dressings versus octenidine wound gel dressing on decrease in size of the ulcer.

The data obtained was tabulated in Microsoft excel spreadsheets. The results were analysed and the outcomes attained were organized as represented below.

'P' value < 0.05 has been considered to have statistical significance.

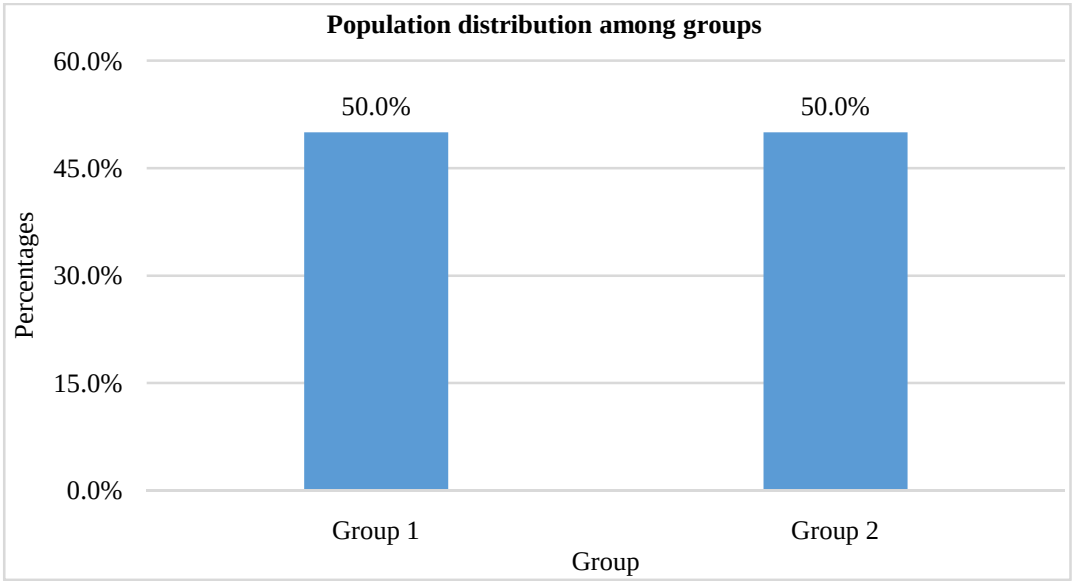
Results:

80 patients in total were studied in this research.

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

Group	Frequency	Percentages
Group 1	40	50.00%
Group 2	40	50.00%

Graph 1 : Bar chart of group in the study population (N=80)



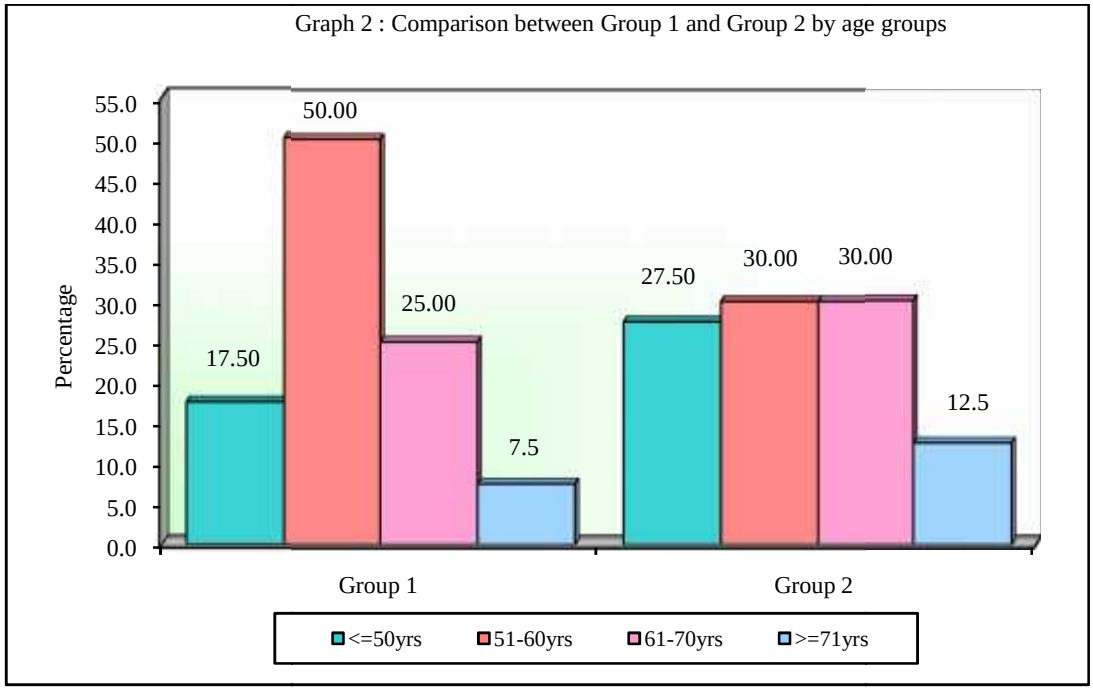
The study population included 40 patients (50%) in group 1 and remaining 40patients (50%) in group 2. (Table 7 & Graph 1)

Group 1 - CONTROL GROUP – Dressing with povidone iodine and saline done.

Group 2 – TEST GROUP – Dressing with Hyaluronate-iodine wound gel done.

Table 8: Comparison between Group 1 and Group 2 by age groups

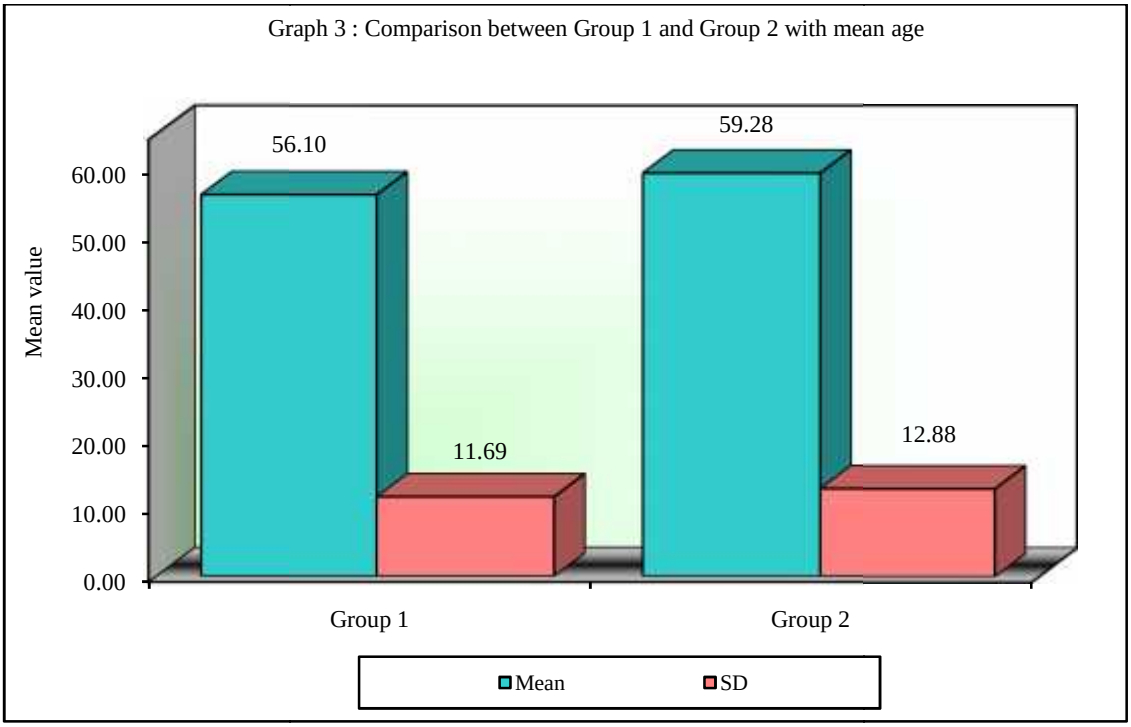
Age groups	Group 1	%	Group 2	%	Total	%
<=50yrs	7	17.50	11	27.50	18	22.50
51-60yrs	20	50.00	12	30.00	32	40.00
61-70yrs	10	25.00	12	30.00	22	27.50
>=71yrs	3	7.50	5	12.50	8	10.00
Total	40	100.00	40	100.00	80	100.00
Chi-square=3.5710 P = 0.3120						



The control group (group 1) included 7(17.50%) patients who were in the age group of <= 50 years, 20(50%) who were in the age group of 51-60 years, 10 (25%) who were in the age group of 61 to 70 years and 3 (7.5%) who were in the age group of more than 71 years. In the test group (group 2), 11 (27.5%) were in the age group of <=50 years, 12 (30%) were in the age group of 51 to 60 years, 12 (30%) were in the age group of 61 to 70 years, 5 (12.5%) were in the age group of more than 71 years. This was not statistically significant between the two groups according to the age distribution. (P value 0.3120). (Table 8 and Graph 2)

Table 9: Comparison between Group 1 and Group 2 with mean age by independent t test

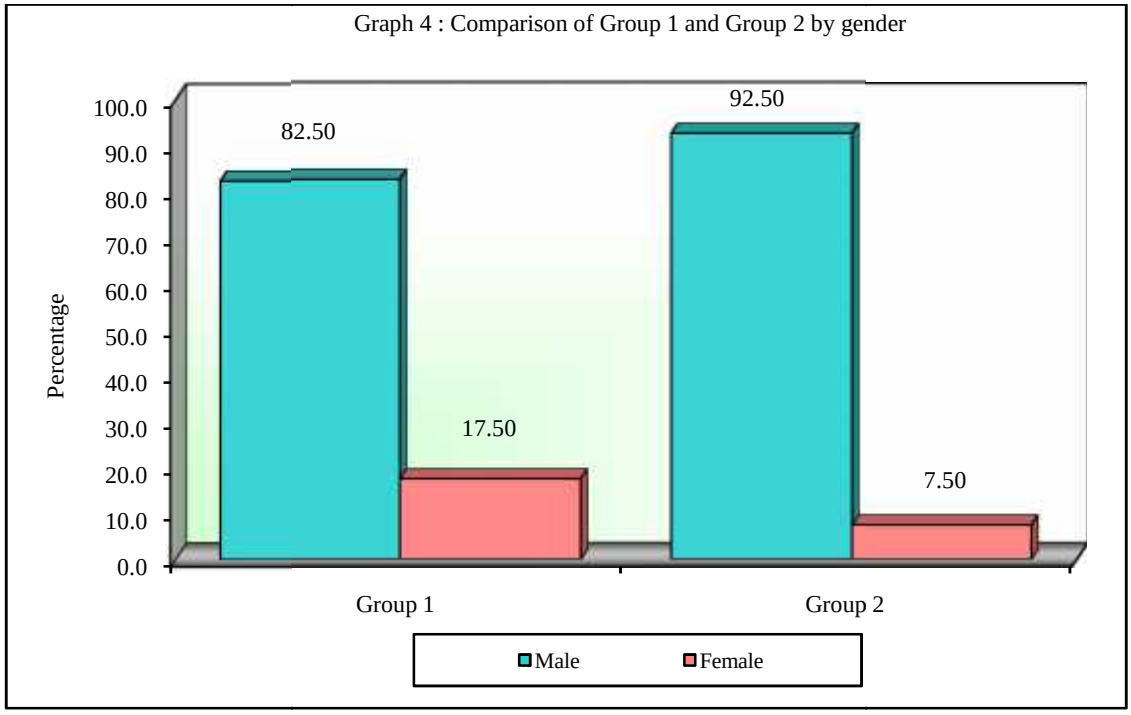
Groups	Mean	SD	SE	t-value	P-value
Group 1	56.10	11.69	1.85	-1.1546	0.2518
Group 2	59.28	12.88	2.04		



Based on the independent t test, the average age in both the control and test groups were 56.10 and 59.28 years, respectively. This was a comparable value with no statistical significance between the two groups (p value = 0.2518) (Table 9 and graph 3)

Table 10 : Comparison of Group 1 and Group 2 by gender

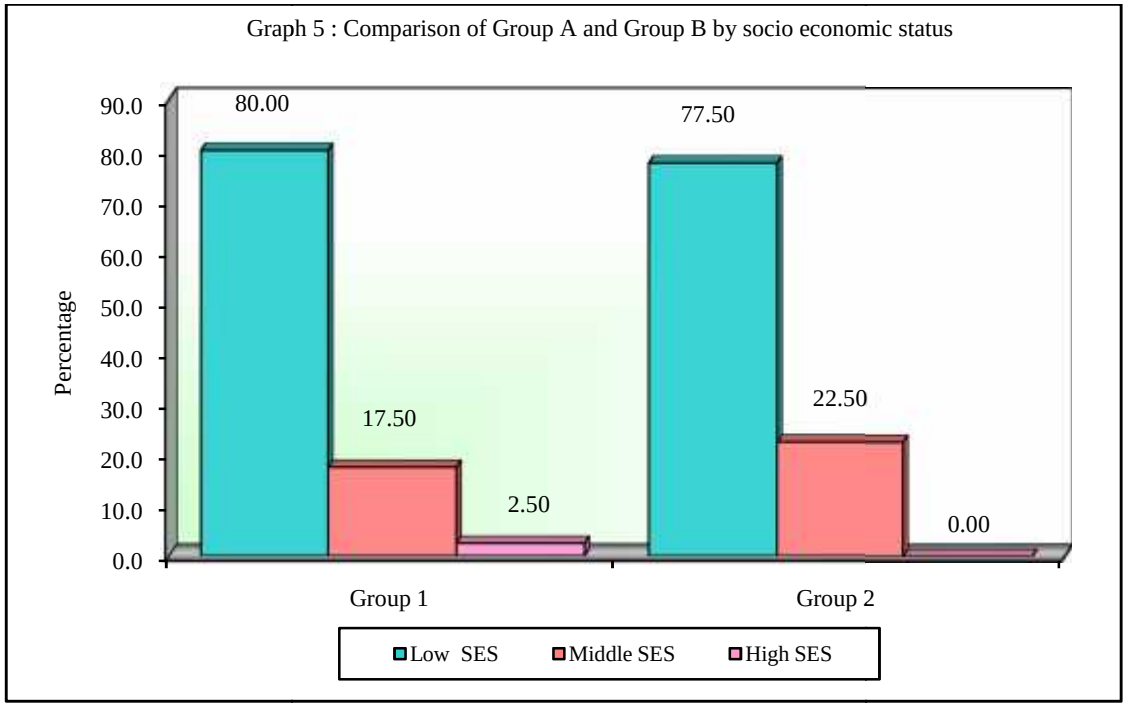
Gender	Group 1	%	Group 2	%	Total	%
Male	33	82.50	37	92.50	70	87.50
Female	7	17.50	3	7.50	10	12.50
Total	40	100.00	40	100.00	80	100.00
Chi-square = 1.8291 P = 0.1762						



The control group had 33(82.50%) male patients and 7(17.50%) female patients. The test group had 37(92.50%)males and 3(7.5%)females. There was no statically significant difference between the two groups on the basis of gender categorization. (P value 0.1762). (Table 10 and graph 4)

Table 11: Comparison of Group 1 and Group 2 by socio economic status

SES	Group 1	%	Group 2	%	Total	%
Low SES	32	80.00	31	77.50	63	78.75
Middle SES	7	17.50	9	22.50	16	20.00
High SES	1	2.50	0	0.00	1	1.25
Total	40	100.00	40	100.00	80	100.00
Chi-square = 1.2660 P = 0.5312						

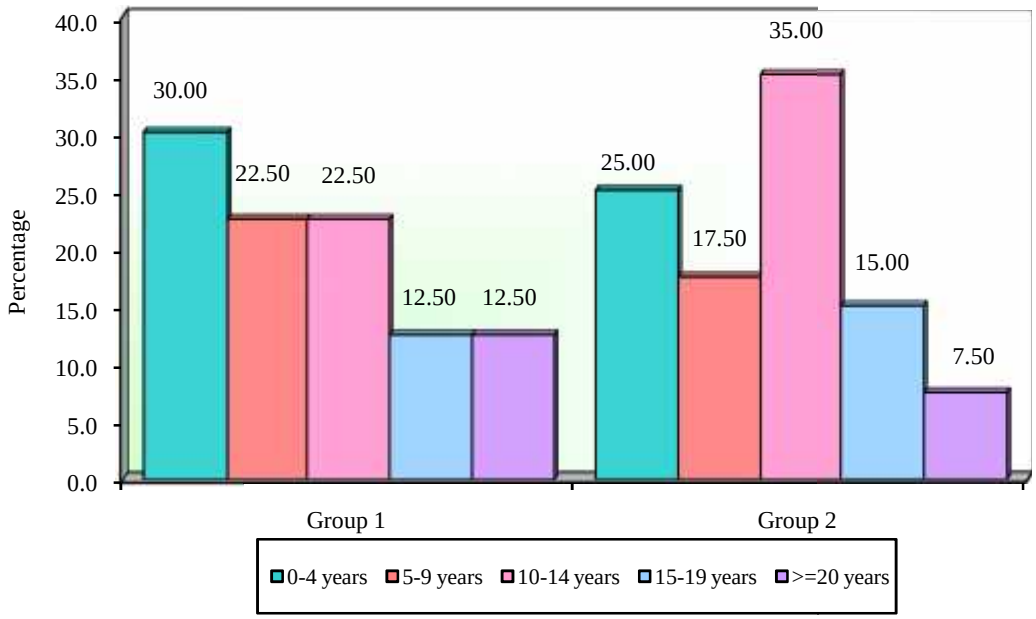


The control group had 32 (80%) were belonged to low socioeconomic status, 7 (17.50%) were belonged to middle class, 1 (2.5%) were belonged to high class. The test group included 31 (77.50%) were belonged to low socioeconomic status, 9 (22.5%) were belonged to middle class, and no patient belonging to high class. There was no statically significant difference in the results of the groups as per the socio economic status distribution. (P value 0.5312). (Table 11& graph 5). The classification was done based on Modified B.G Prasad classification for economic status.[50]

Table 12 : Comparison of Group 1 and Group 2 by duration of diabetes

Duration of diabetes	Group 1	%	Group 2	%	Total	%
0-4 years	12	30.00	10	25.00	22	27.50
5-9 years	9	22.50	7	17.50	16	20.00
10-14 years	9	22.50	14	35.00	23	28.75
15-19 years	5	12.50	6	15.00	11	13.75
>=20 years	5	12.50	3	7.50	8	10.00
Total	40	100.00	40	100.00	80	100.00
Chi-square = 2.1101 P = 0.7162						

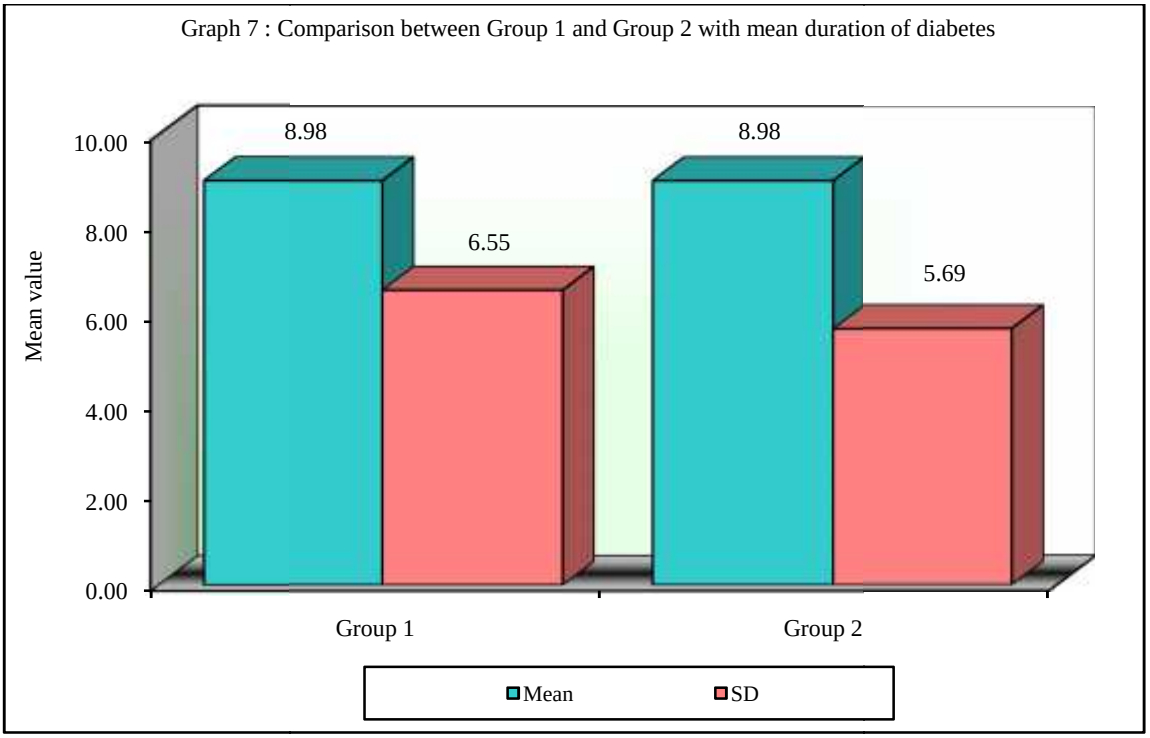
Graph 6 : Comparison of Group 1 and Group 2 by duration of diabetes



The control group included 12 (30%) patients with a duration of diabetes ranging from 0 to 4 years, 9 (22.50%) with duration of 5 to 9 years, 9(22.50%) with duration of 10 to 14 years, 5 (12.5%) with duration of 15 to 19 years and 5 (12.50%) with duration of 20 years and above. The test group included 10 (25%) patients with diabetes duration of 0 to 4 years, 7(17.50%) with duration of 5 to 9 years, 14 (35%) with duration of 10 to 14 years, 6 (15%) with duration of 15 to 19 years and 3 (7.5%) with duration of 20 years and above. This was not statistically significant between the two groups as per the duration of diabetes(p value= 0.7162). (Table 12 and graph 6)

Table 13: Comparison between Group 1 and Group 2 with mean duration of diabetes by independent t test

Groups	Mean	SD	SE	t-value	P-value
Group 1	8.98	6.55	1.04	0.0033	0.9974
Group 2	8.98	5.69	0.90		

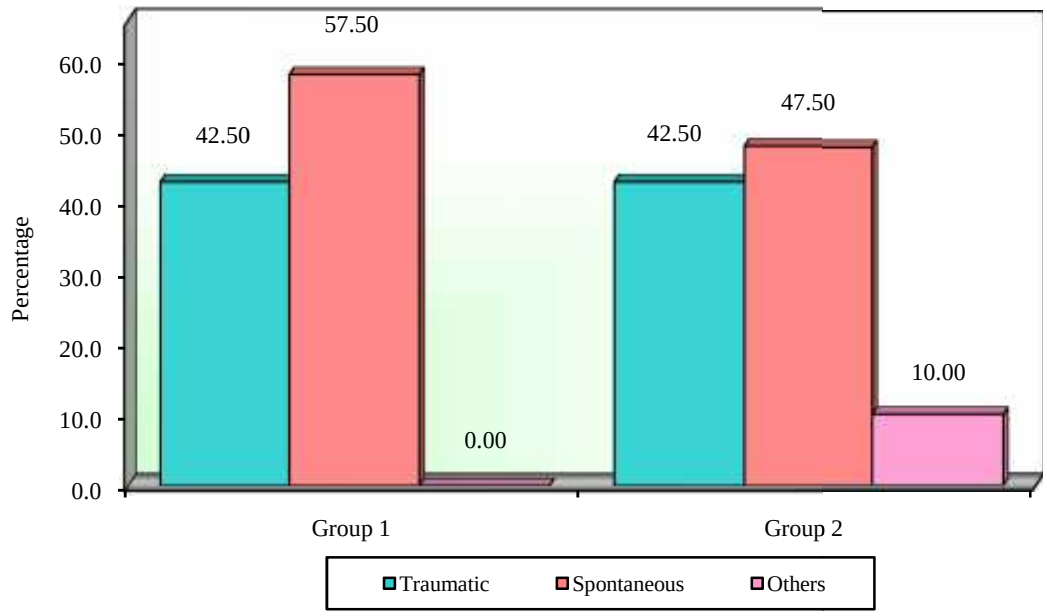


Based on the independent t test, the mean duration of diabetes in both the control and test groups were 8.98. This was no significant statistically difference between the two groups (p value = 0.9974)(Table 13 and graph 7).

Table 14 : Comparison of Group 1 and Group 2 by onset of disease

Onset	Group 1	%	Group 2	%	Total	%
Traumatic	17	42.50	17	42.50	34	42.50
Spontaneous	23	57.50	19	47.50	42	52.50
Others	0	0.00	4	10.00	4	5.00
Total	40	100.00	40	100.00	80	100.00
Chi-square = 4.3812 P = 0.1121						

Graph 8 : Comparison of Group 1 and Group 2 by onset of disease

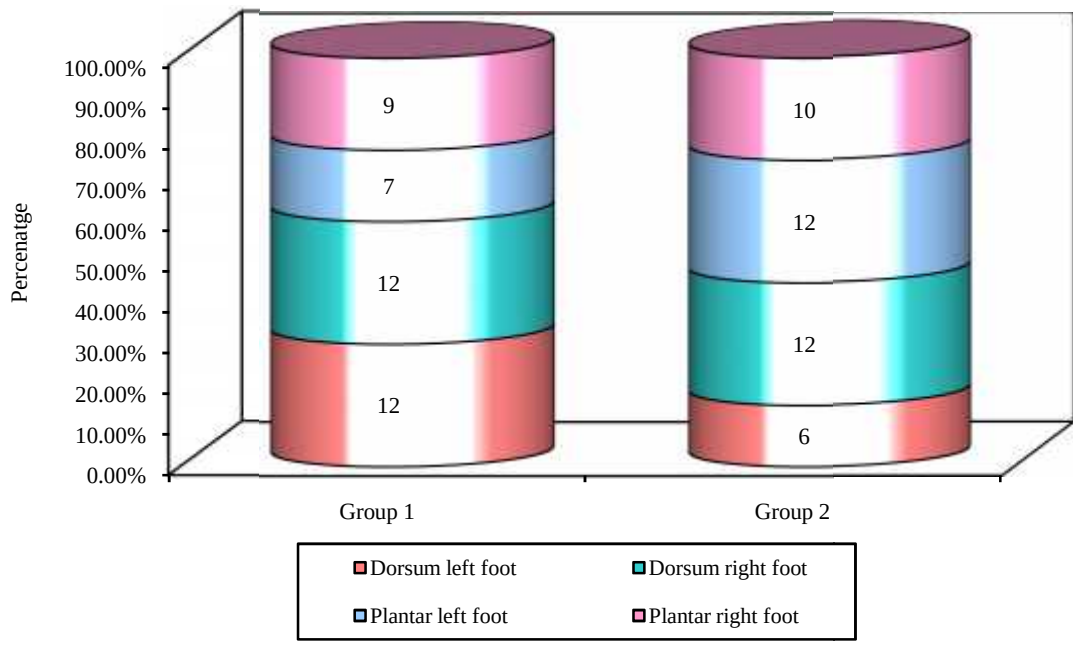


In control group(group 1)**,** 17 (42.5%) had traumatic onset, 23 (57.50%) had spontaneous onset. In test group(group 2), 17(30%) had traumatic onset, 19 (62.5%) had spontaneous onset, 4(10%) had other onset due to other reasons. This was not statistically significant between the two groups on the basis of mode of onset(P value=0.1121)(Table 14 and graph 8).

Table 15 : Comparison of Group 1 and Group 2 by sites

Sites	Group 1	%	Group 2	%	Total	%
Dorsum left foot	12	30.00	6	15.00	18	22.50
Dorsum right foot	12	30.00	12	30.00	24	30.00
Plantar left foot	7	17.50	12	30.00	19	23.75
Plantar right foot	9	22.50	10	25.00	19	23.75
Total	40	100.00	40	100.00	80	100.00
Chi-square = 3.3682 P = 0.3381						

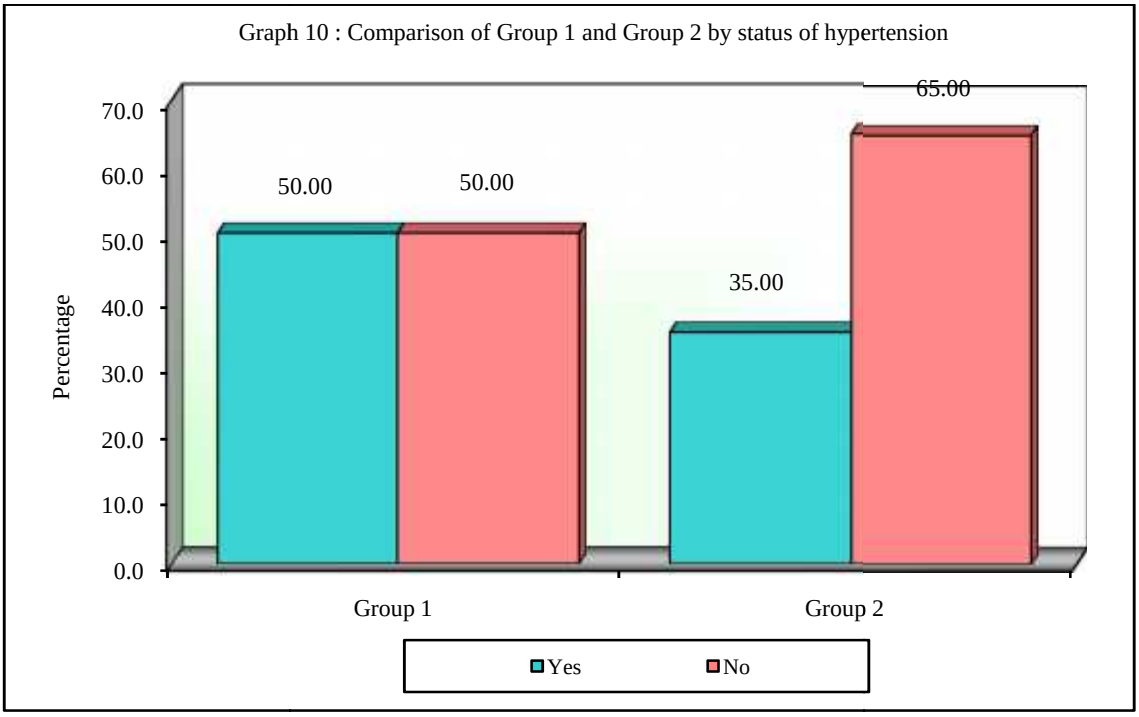
Graph 9 : Comparison of Group 1 and Group 2 by sites



In control group(group 1), 12 (30%) had ulcer on dorsum of left foot, 12 (30%) had ulcer on dorsum of right foot, 7 (17.5%) had on plantar surface of left foot, 9 (22.5%) had on plantar surface of right foot. In test group(group 2), 6(15%) had ulcer on dorsum of left foot, 12 (30%) had ulcer on dorsum of right foot, 12(30%) had ulcer on plantar surface of left foot, 10 (25%) had ulcer on plantar surface of right foot. This was not statistically significant between the groups as per site of ulcer(P value=0.3381)(Table 15 and graph 9).

Table 16: Comparison of Group 1 and Group 2 by status of hypertension

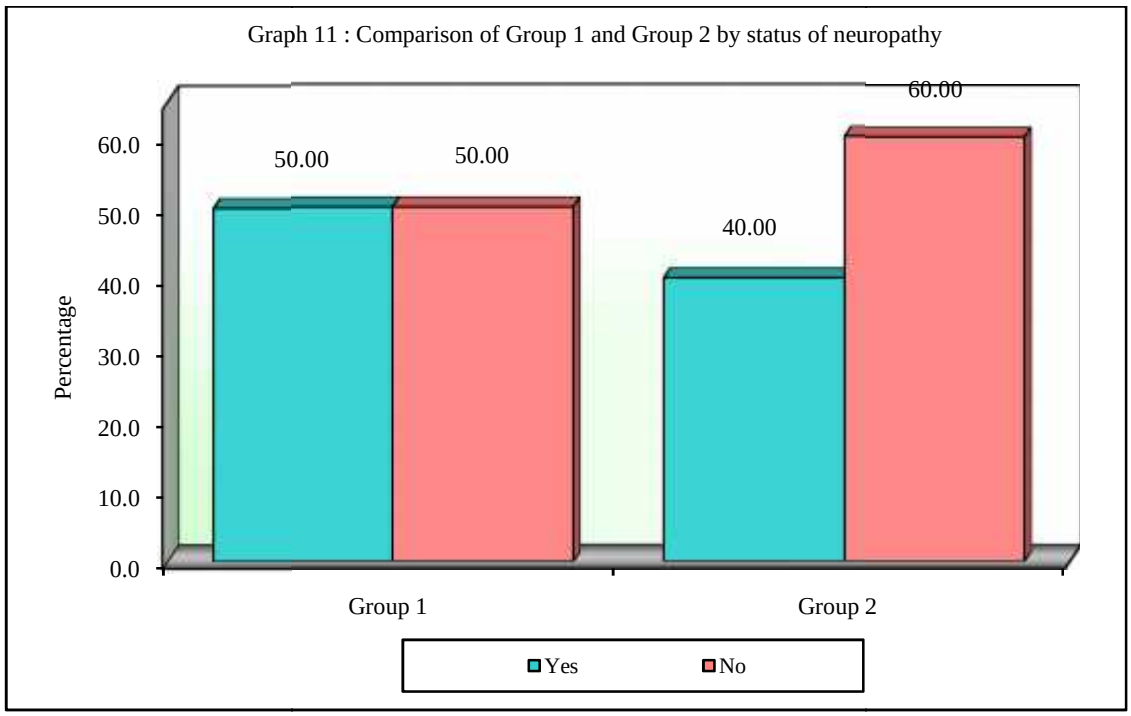
Status of hypertension	Group 1	%	Group 2	%	Total	%
Present	20	50.00	14	35.00	34	42.50
Absent	20	50.00	26	65.00	46	57.50
Total	40	100.00	40	100.00	80	100.00
Chi-square = 1.8414 P = 0.1755						



The control group(group 1) had 20(50%) patients with hypertension and the test group(group 2) had 14(35%) patients with hypertension. This was not statistically significant between the groups on the basis of hypertension(P value=0.1755)(Table 16 and graph 10).

Table 17: Comparison of Group 1 and Group 2 by status of neuropathy

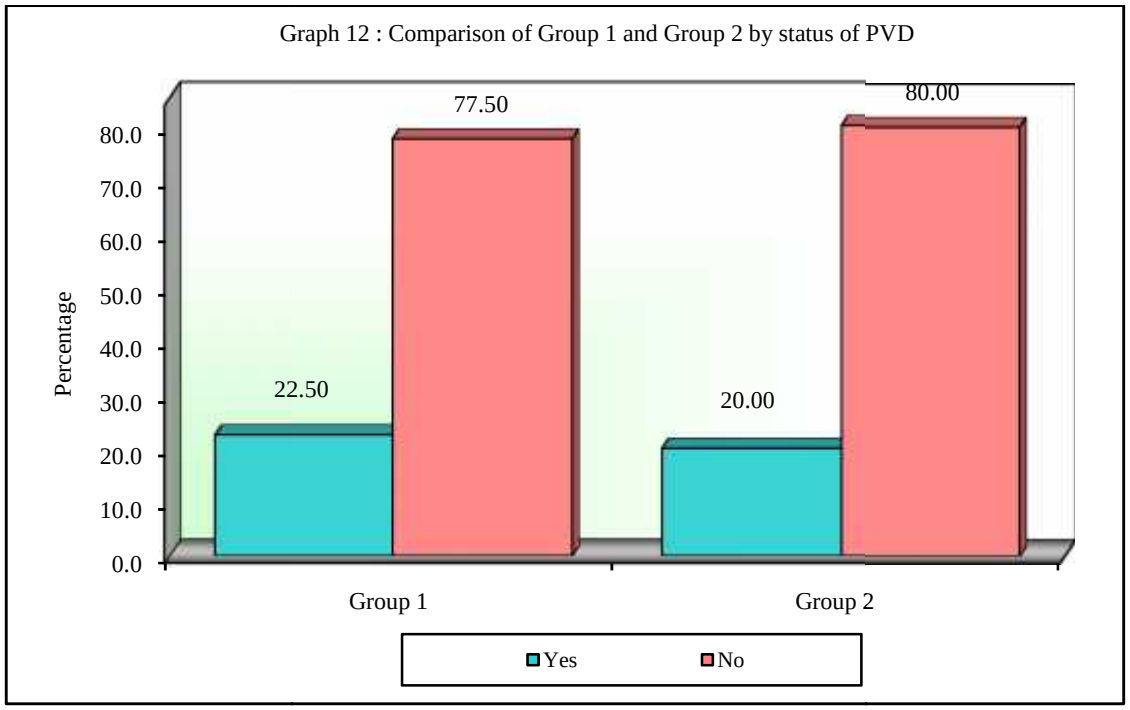
Status of neuropathy	Group 1	%	Group 2	%	Total	%
Yes	20	50.00	16	40.00	36	45.00
No	20	50.00	24	60.00	44	55.00
Total	40	100.00	40	100.00	80	100.00
Chi-square = 0.8083 P = 0.3692						



The control group(group 1) had 20(50%) patients with peripheral neuropathy and the test group(group 2) had 16(40%) patients with peripheral neuropathy. This was not statistically significant between the groups on the basis of peripheral neuropathy(P value=0.3692)(Table 17 and graph 11).

Table 18: Comparison of Group 1 and Group 2 by status of PVD

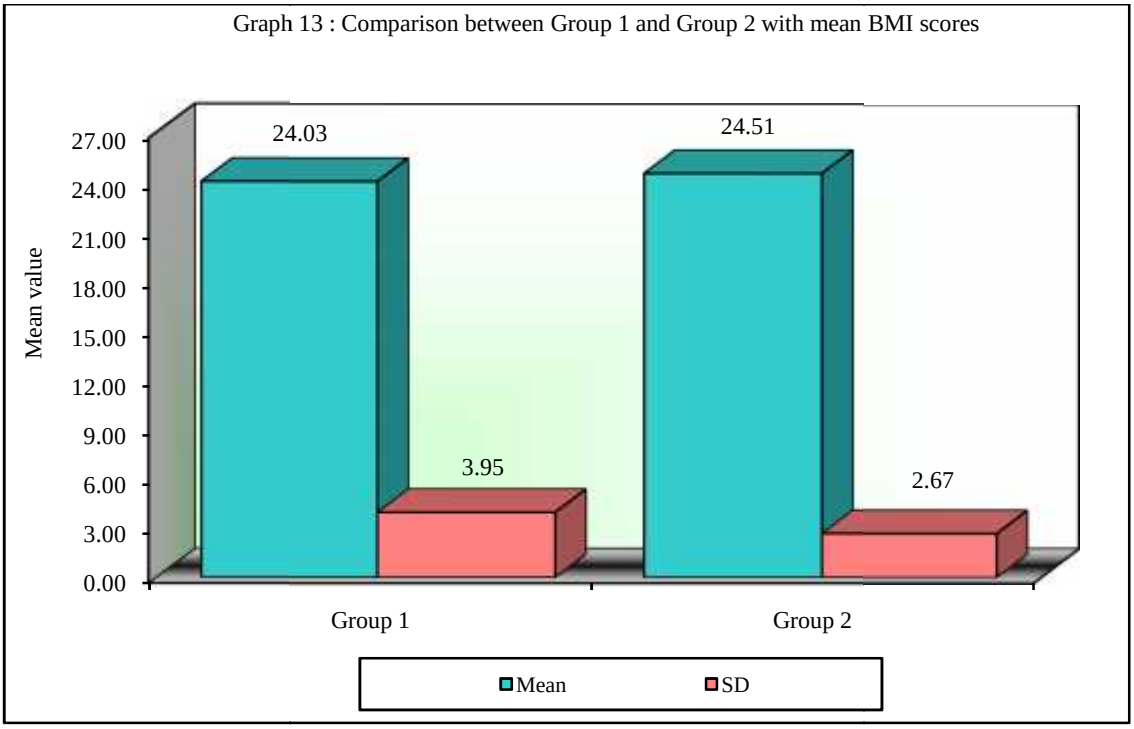
Status of PVD	Group 1	%	Group 2	%	Total	%
Yes	9	22.50	8	20.00	17	21.25
No	31	77.50	32	80.00	63	78.75
Total	40	100.00	40	100.00	80	100.00
Chi-square = 0.0752 P = 0.7851						



The control group(group 1) had 20(22.5%) patients with peripheral vascular disease and the test group(group 2) had 16(20%) patients with peripheral vascular disease. This was not statistically significant between the groups on the basis of peripheral vascular disease(P value= 0.7851)(Table 18 and graph 12).

Table 19 : Comparison between Group 1 and Group 2 with mean BMI(in kg/m^2) by independent t test

Groups	Mean	SD	SE	t-value	P-value
Group 1	24.03	3.95	0.62	-0.6395	0.5244
Group 2	24.51	2.67	0.42		



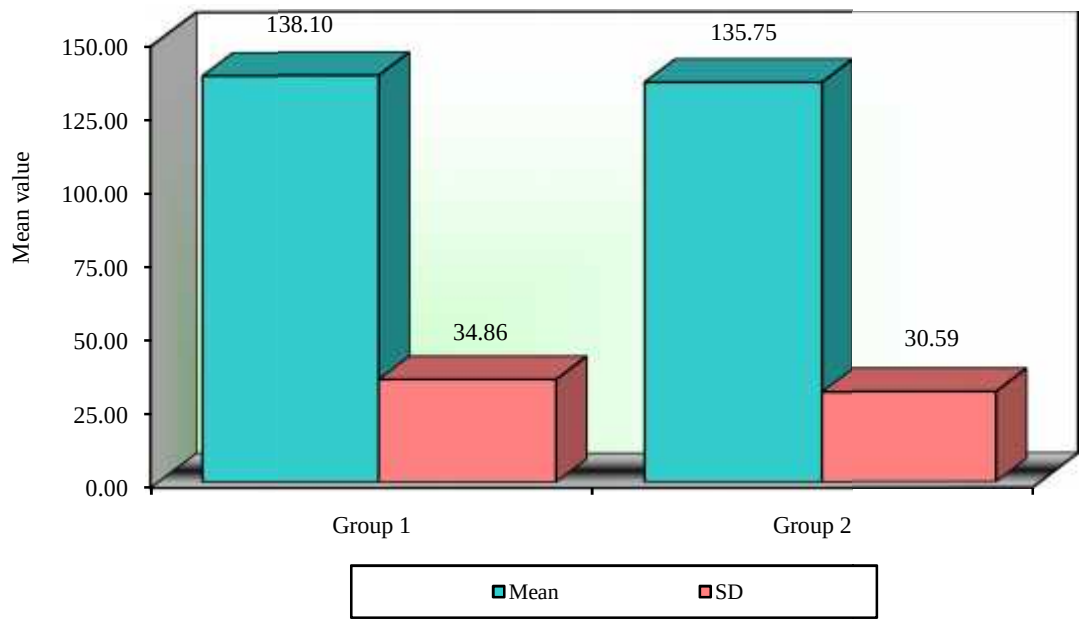
The mean body mass index in the control group(group 1) was 24.03 kg/m^2 and that in the test group(group) was 24.51 kg/m^2. This was not statistically significant between the groups as per the body mass index(P value=0.5244)(Table 19 and graph 13).

Table 20 : Comparison between Group 1 and Group 2 with mean FBS(in mg/dL) by independent t test

Groups	Mean	SD	SE	t-value	P-value
Group 1	138.10	34.86	5.51	0.3205	0.7495
Group 2	135.75	30.59	4.84		

‘

Graph 14 : Comparison between Group 1 and Group 2 with mean FBS scores

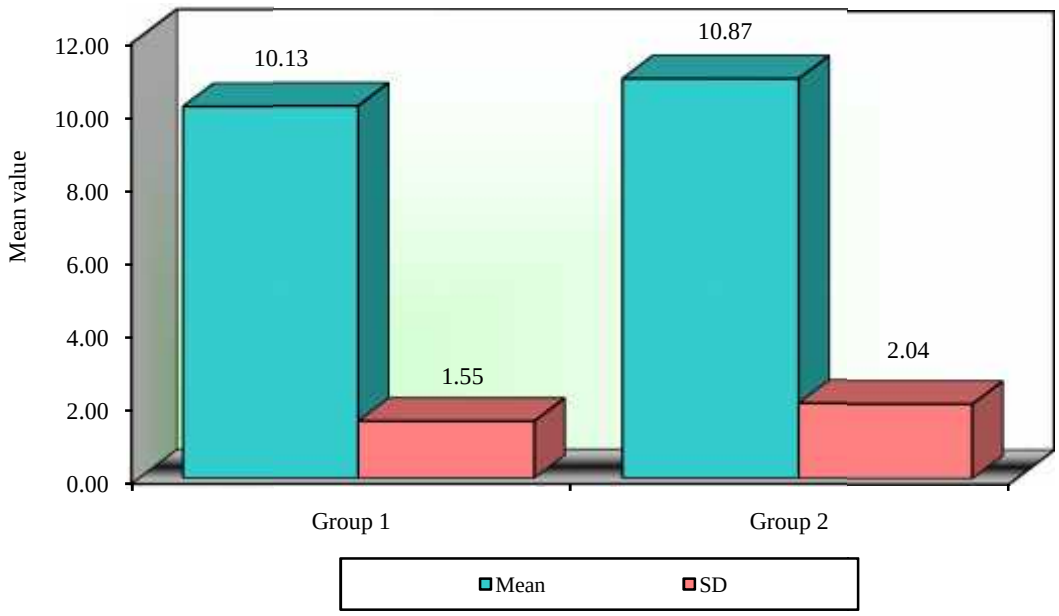


The mean fasting blood sugar in the control group(group 1) was 138.10 mg/dL and that in the test group(group) was 135.75mg/dL. This was not statistically significant between the groups as per the fasting blood sugar levels(P value=0.7495)(Table 20 and graph 14).

Table 21: Comparison between Group 1 and Group 2 with mean Hb(in g/dL) by independent t test

Groups	Mean	SD	SE	t-value	P-value
Group 1	10.13	1.55	0.25	-1.8335	0.0705
Group 2	10.87	2.04	0.32		

Graph 15 : Comparison between Group 1 and Group 2 with mean Hb levels

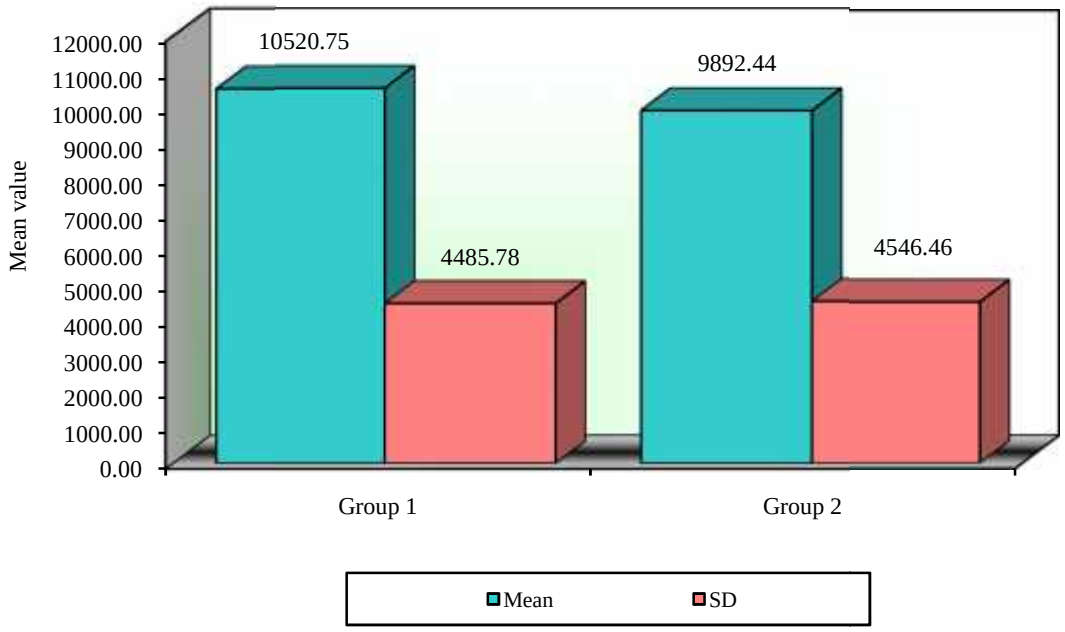


The mean haemoglobin in the control group(group 1) was 10.13g/dL and that in the test group(group) was 10.87g/dL. This was not statistically significant between the groups as per the haemoglobin levels(P value=0.0705)(Table 21 and graph 15).

Table 22 : Comparison between Group 1 and Group 2 with mean TLC(cells/ microL) levels by independent t test

Groups	Mean	SD	SE	t-value	P-value
Group 1	10520.75	4485.78	709.26	0.6222	0.5356
Group 2	9892.44	4546.46	718.86		

Graph 16 : Comparison between Group 1 and Group 2 with mean TLC levels

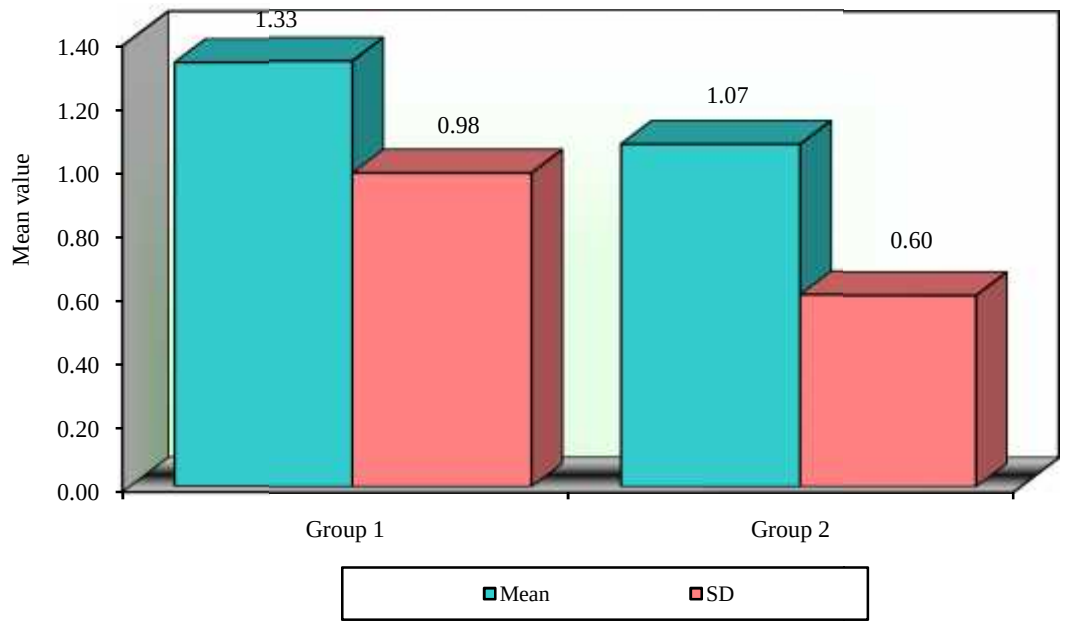


The mean total leukocyte count in the control group(group 1) was 10520.75 cells/microL and that in the test group (group) was 9892.44 cells/microL. This was not statistically significant between the groups as per the total leucocyte count levels(P value=0.5356)(Table 22 and graph 16).

Table 23: Comparison between Group 1 and Group 2 with mean creatinine(in mg/dL) levels by independent t test

Groups	Mean	SD	SE	t-value	P-value
Group 1	1.33	0.98	0.16	1.4389	0.1542
Group 2	1.07	0.60	0.10		

Graph 17 : Comparison between Group 1 and Group 2 with mean creatinine levels



The mean creatinine in the control group(group 1) was 1.33 mg/dL and that in the test group(group) was 1.07mg/dL. This was not statistically significant between the groups as per the creatinine levels(P value=0.1542)(Table 23 and graph 17).'

ULCER AREA REDUCTION

The ulcer dimensions are measured on day 0(x) = initial wound area and area measured on day 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

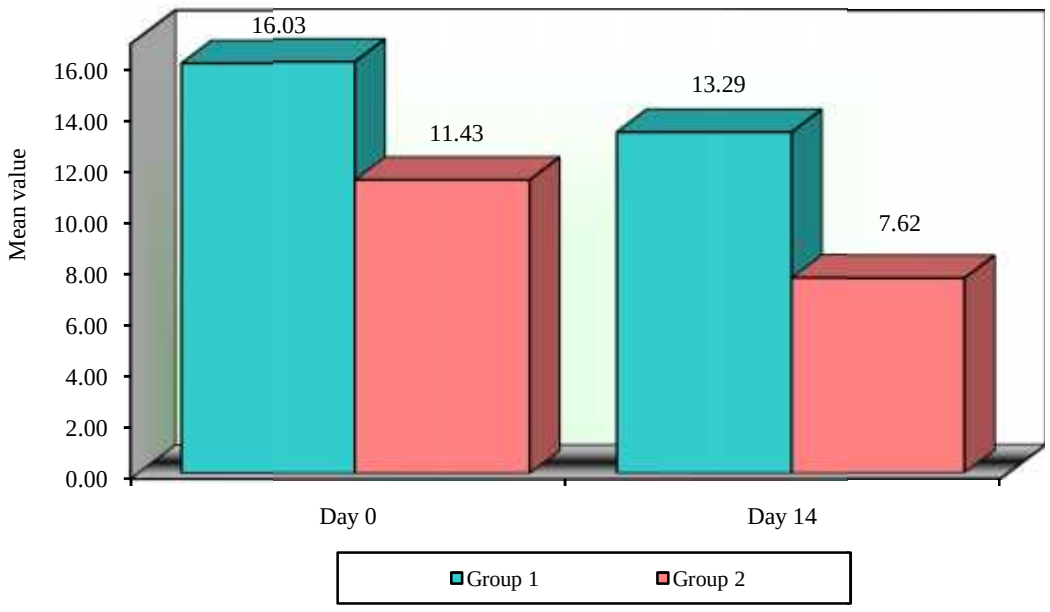
% Reduction in wound area = $\frac{x-y}{x}x100$

Table 24: Comparison between Group 1 and Group 2 with area of ulcer(cm^2) on day 0 and day 14 by independent t test

Time points	Groups	Mean	SD	SE	t-value	P-value
Day 0	Group 1	16.03	10.61	1.68	1.9398	0.0569
	Group 2	11.43	10.60	1.68		
Day 14	Group 1	13.29	9.28	1.47	2.8199	0.0061*
	Group 2	7.62	8.72	1.38		
Reduction	Group 1	2.73	1.61	0.25	-2.3284	0.0225*
	Group 2	3.81	2.45	0.39		

*p<0.05

Graph 18 : Comparison between Group 1 and Group 2 with area of ulcer on day 0 and day 14



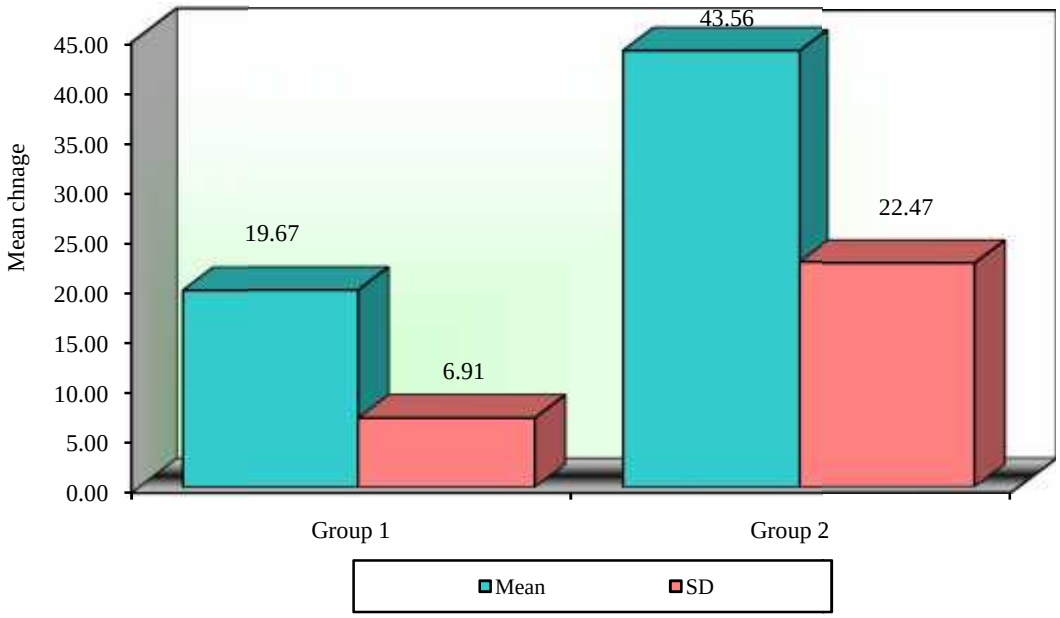
By independent t test, the mean area of the ulcer on day 0 in the control group is 16.03 cm^2 and in the test group is 11.43 cm^2. The mean area of the ulcer on day 14 in the control group is 13.29 cm^2 and in the test group is 7.62 cm^2 . There was no significant statistical difference between the mean area of the ulcer in both the groups observed on day 0(p value = 0.0569). However, there was significant statistical difference between the mean area of the ulcer in both the groups observed on day 14(p value = 0.0061).The mean ulcer area reduction was 2.73 cm^2 in the control group whereas it was 3.81 cm^2 in the test group. This was a statistically significant difference between the two groups(p value=0.0225) (Table 24 and graph 18).

Table 25 : Comparison between Group 1 and Group 2 with mean percent reduction in area of ulcer on day 0 and day 14 by independent t test

Groups	Mean	SD	SE	t-value	P-value
Group 1	19.67	6.91	1.09	-6.4302	0.0001*
Group 2	43.56	22.47	3.55		

*p<0.05

Graph 19 : Comparison between Group 1 and Group 2 with mean percent reduction in area of ulcer on day 0 and day 14



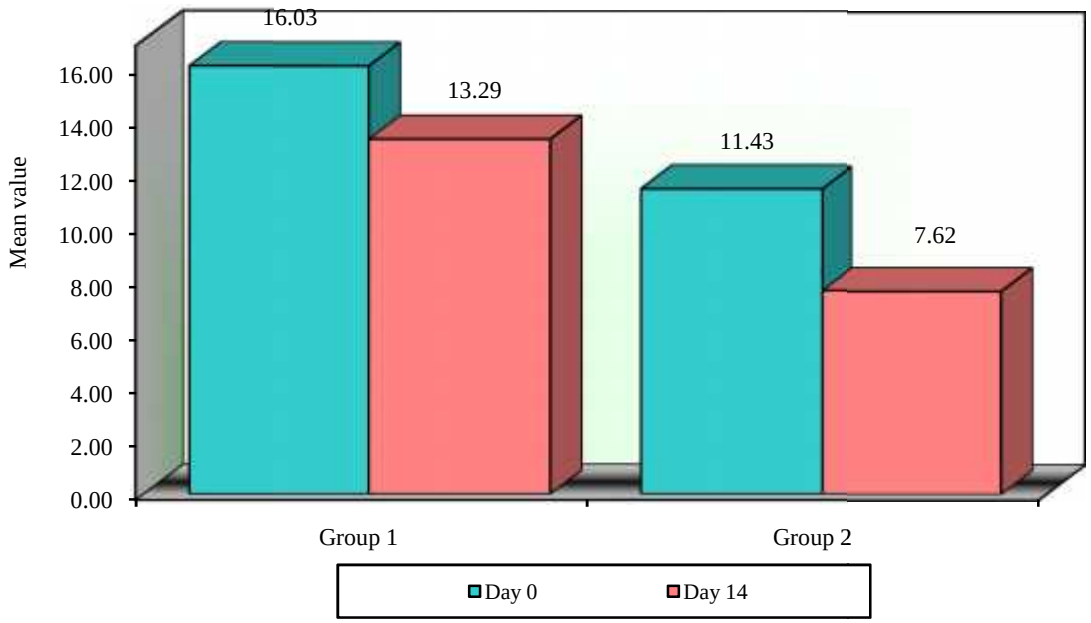
By independent t test, the mean percentage reduction in area of ulcer over 14 days in the control and test groups are 19.67% and 43.56%, respectively. This was statistically significant difference in the mean percentage reduction in ulcer area in the test group in comparison to the control group(p value = 0.0001)(Table 25 and graph 19).

Table 26: Comparison of mean area(cm^2)of ulcer on day 0 and day 14 in Group 1 and Group 2 by dependent t test

Groups	Time points	Mean	Std.Dv.	Mean Diff.	SD Diff.	t-value	P-value
Group 1	Day 0	16.03	10.61	2.73	1.61	10.7381	0.0001*
	Day 14	13.29	9.28				
Group 2	Day 0	11.43	10.60	3.81	2.45	9.8519	0.0001*
	Day 14	7.62	8.72				

*p<0.05

Graph 20: Comparison of mean area of ulcer on day 0 and day 14 in Group 1 and Group 2



By dependent t test, the mean area of the ulcer in the control group on day 0 is 16.3cm^2 and on the day 14 is 13.29 cm^2. There was significant statistical difference in the control group individually based on the decrease in the mean area of the ulcer over 14 days(p value = 0.0001)(Table 26 and graph 20) By dependent t test, the mean area of the ulcer in the test group on day 0 is 11.43cm^2 and on the day 14 is 7.62cm^2. There was significant statistical difference in the test group individually based on the decrease in the mean area of the ulcer over 14 days(p value = 0.0001) (Table 26 and graph 20).

Table 27 : Comparison of Group 1 and Group 2 by status of culture at day 0

Status of culture at day 0	Group 1	%	Group 2	%	Total	%
Citrobacter species	1	2.50	0	0.00	1	1.25
Coag.neg staph.	0	0.00	3	7.50	3	3.75
E. Faecalis	0	0.00	1	2.50	1	1.25
E.coli	6	15.00	4	10.00	10	12.50
Enterobacter species	1	2.50	0	0.00	1	1.25
K. Oxytoca	2	5.00	0	0.00	2	2.50
K.pneumoniae	3	7.50	6	15.00	9	11.25
MRSA	3	7.50	3	7.50	6	7.50
P.acuriginosa	1	2.50	0	0.00	1	1.25
P.aeruginosa	7	17.50	5	12.50	12	15.00
P.mirabilis	1	2.50	1	2.50	2	2.50
P.vulgaris	1	2.50	2	5.00	3	3.75
Providencia species	2	5.00	0	0.00	2	2.50
S.agalactiae	0	0.00	1	2.50	1	1.25
S.pneumoniae	0	0.00	1	2.50	1	1.25
Staph.aureus	2	5.00	0	0.00	2	2.50
Staph.epidermidis	0	0.00	1	2.50	1	1.25
Staph.species	1	2.50	0	0.00	1	1.25
TOTAL	31	77.50	28	70	59	75.25

The most common microorganisms observed in the control group on day 0 were Pseudomonas aeruginosa (17.5%), Escherichia coli(15%), Klebsiella pneumonia (7.5%) and Methicillin resistant Statphylococcus aureus(7.5%). The most common microorganisms observed in the test group on day 0 were the same as in control group but with different percentages that is Pseudomonas aeruginosa (15%), Escherichia coli(12.5%), Klebsiella pneumonia (11.25%) and Methicillin resistant Statphylococcus aureus(7.5%)(Table 27).

The control group had a total of 31 (77.50%) patients with positive wound culture on day 0 and 28(70%) patients with positive wound culture on day 14(Table 27)

Table 28: Comparison of Group 1 and Group 2 by status of culture at day 14

Status of culture at day 14	Group 1	%	Group 2	%	Total	%
Citrobacter species	1	2.50	0	0.00	1	1.25
E.coli	2	5.00	2	5.00	4	5.00
E.faecalis	0	0.00	1	2.50	1	1.25
Enterobacter species	1	2.50	0	0.00	1	1.25
K.oxytoca	1	2.50	2	5.00	3	3.75
K.pneumoniae	0	0.00	1	2.50	1	1.25
MRSA	1	2.50	1	2.50	2	2.50
P.aeruginosa	1	2.50	1	2.50	2	2.50
Proteus mirabilis	1	2.50	0	0.00	1	1.25
S.agalactiae	2	5.00	0	0.00	2	2.50
Staph.aureus	0	0.00	1	2.50	1	1.25
TOTAL	10	25	9	22.50	19	23.75
DIFFERENCE AFTER 14 DAYS	21	67.74	19	67.85		

The most common microorganisms observed in the control group on day 14 were Escherichia coli(5%) and Streptococcus agalactiae(5%). The most common microorganisms observed in the test group on day 14 were Escherichia coli (5%) and Klebsiella oxytoca(3.75%)(Table 28).

The test group had a total of 10(25%) patients with positive wound culture on day 0 and 9(22.5%) patients with positive wound culture on day 14(Table). This signified that the in the control group, there was a reduction in the extent of microbial colonization by 67.74% and that in the test group was 67.85 %(Table). Thus, the usage of hyaluronate-iodine complex dressing in the test group witnessed a marginally more reduction in the bioburden as compared to the control group where povidone-iodine dressing was used.

DISCUSSION

Diabetes mellitus is a multisystemic complex metabolic disorder that can lead to life threatening complications in patients worldwide in the long run. The Indian Heart Association expects India to harbour as many as 109 million diabetics by 2035.[11] This is reflective of the major problem statement this disease offers and necessitates an aggressive management protocol for the same.

Diabetic foot ulcers are one of the commonest complications of diabetes with an yearlyincidence of 9.1 to 26.1 million people worldwide.[12] This condition is a chronic manifestation in diabetics and is further aggravated by other factors such as peripheral neuropathy, peripheral arterial disease, immunosuppression and wound infection.

Impaired management of these diabetic foot ulcers has the capacity to cause physical, emotional and psychological disability of the patient. Lower limb amputation is a potential sequelae of diabetic foot ulceration and can progress to cause significant morbidity and

mortality.[13]

The optimum management of diabetic foot ulcers is thus crucial and demands identification of specific risk factors, careful planning and application of the clinical strategies to attain a holistic improvement in the diabetic wound healing. The main hallmarks of the treatment include local wound management in the form of dressings, control of infection, offloading of the foot and a strict glycemic control.

The control of the local wound environment has always posed as a challenge owing to the severe and non-healing nature of the diabetic foot ulcers.[8] There is a variety of wound dressings with promising results that have been developed over the decades. Some of them include hydrogels, hydrocolloids, honey, topical insulin,

silver, platelet derived growth factor, hyperbaric oxygen therapy, etc. However, the difficulties of antibacterial resistance, severe side-effects, high costs and inaccessibility have often been a hindrance in the universal acceptability of one perfect topical modality for dressings.

Hyaluronic acid is a natural polymer belonging to the glysosaminoglycan family that is usually present in the synovial fluid of joints, cartilage, tissue of eyes and skin. Studies have proved that this compound can positively affect all stages of normal wound healing.[9,14]Its most prominent actions include its ability to provide a moist environment, stimulate direct cell proliferation, fibroblast migration, angiogenesis, regulation of tissue hydrodynamics and stabilization of the newly developed extracellular matrix.[14]

Inspite of this formulation being a lucrative option for diabetic wound healing, there is not enough clinical research that can establish the same. The available studies have mostly been done on other types of ulcers such as vascular ulcers. This study was undertaken to provide an insight into this regard. We attempted to evaluate the efficacy of hyaluronate-ioidine complex on wound healing in diabetic foot ulcers in the form of mean ulcer area decrease over a period of 14 days when compared with a conventional topical modality like povidone-iodine. This hyaluronate-iodine complex is commercially available.

This study was conducted under the department of general surgery at KLES Dr. Prabhakar Kore Charitable Hospital and Medical Research Centre, Nehru nagar, Belagavi, between January 2019 to December 2019. The total study population included 80 patients in total who had diabetic foot ulcers. They satisfied the selection criteria and were ready to participate in this study. These patients in the study group were divided into two separate groups of 40 each, in which the control group(group 1)

underwent dressing with povidone iodine and test group (group 2) underwent dressing with hyaluronate-iodine complex.

This study had a population with the mean age in the control and test groups being 56.10 and 59.28 years, respectively. These findings were in congruence with the study conducted by Parisi et al, which had a mean age of participants to be 57.67 years.[15]This was reflective of the fact that age more than 50 years had a significant impact on the wound healing process in diabetics, predisposing them to diabetic foot ulcers.

The control group had 33(82.50%) male patients and 7(17.50%) female patients whereas the test group had 37(92.50%)males and 3(7.5%)females. This had similarity with the finding of Al-Rubeaan et al. The latter stated that although the frequency of various diabetic foot complications was similar for both the genders, the diabetic males(68.47%) were more affected by the condition of foot ulcers than the females(31.43%).[16]

According to the modified BG Prasad classification, this study had categorized the population of the control and test groups as per the patients' socio-economic status into low (85%), middle(13.33%) and high(1.67%) socio-economic status groups. The study population had a remarkable proportion of its people belonging to the low socioeconomic strata. The lack of socio-economic upliftment has a significant impact on the progression and prognosis of the diabetic foot ulcer as also reiniforced by a study done by Venermo et al. The latter concluded that low socio-economic position was associated with worse outcomes in the diabetic population with foot ulcers. The risk ratio of the first major amputation in the high socio-economic group was lower than that in the low socio-economic group by 2.16 times (p value<0.001).[17] Thus,

there was a need for socioeconomic development of those deprived of it in the society so as to achieve reduction in the frequency and severity of complications.

In control group(group 1), 12 (30%) had ulcer on dorsum of left foot, 12 (30%) had ulcer on dorsum of right foot, 7 (17.5%) had on plantar surface of left foot, 9 (22.5%) had on plantar surface of right foot. In test group(group 2), 6(15%) had ulcer on dorsum of left foot, 12 (30%) had ulcer on dorsum of right foot, 12(30%) had ulcer on plantar surface of left foot, 10 (25%) had ulcer on plantar surface of right foot.). These results concluded that the majority of the ulcer were on the dorsal(60%) surface of the foot in the control group whereas that in the test group was on the plantar(55%) surface of the foot. However, This was not statistically significant between the groups on the basis of the site of ulcer(P value=0.3381). Younis et al in his study in his research to identify the site of the foot more at risk for ulcer formation, discovered that 61.22% of the patients developed ulcer on the sole, 30.80% on the dorsum and 8.08% on both the sole and dorsum.[18]This emphasizes that the sole of the foot is more vulnerable to ulceration by virtue of weightbearing, presence of peripheral neuropathy and consequently, the possibility of repeated, neglected microtrauma.

In this study, the control group(group 1) had 20(50%) patients with hypertension and the test group(group 2) had 14(35%) patients with hypertension. Both the groups were comparable with no significant difference in statistics between the groups on the basis of hypertension(P value=0.1755).Study done by Khan et al to assess the possible risk components for foot ulcer formation in diabetics found that the majority of the diabetics also had hypertension. Hypertension in the diabetic population has higher risk of cardiovascular diseases and mortality. The presence of a raised blood pressure

could lead to the development of nephropathy, retinopathy and diabetic cardiomyopathy in diabetics.[19]

Yazdanapanah et al in his study identified peripheral neuropathy as a factor with significant risk for the development of ulceration over foot in diabetic patients. In their evaluation, 70% of the diabetics with foot ulcer were observed to have concomitant peripheral neuropathy which was statistically significant(p value-<0.001).[20] However, in our study, the control group(group 1) had 20(50%) patients with peripheral neuropathy and the test group(group 2) had only 16(40%) patients with peripheral neuropathy. In the recent times, this may be attributed to a good glycemic control by adequate anti-diabetic medication and subsequent prevention of damage to the peripheral nerves. This was not statistically significant between the groups on the basis of peripheral neuropathy(P value=0.3692).

The correlation between fasting blood sugar and diabetic foot ulcer was evaluated by Guraya et al. In his study, 57.1% patients had a fasting blood sugar level more than 220mg/dL with 51.9% of the patients with grade 4 and grade 5 diabetic foot ulcers as defined by the Meggitt-Wagner ulcer classification system. This was a clear reflection of the fact that uncontrolled diabetes mellitus could complicate diabetic foot ulcers in the form of osteomyelitis and gangrene.[21] However, in our study, majority of the patients did not have such high fasting blood sugar levels. The average fasting blood sugar in the control group(group 1) was 138.10 mg/dL and that in the test group(group) was 135.75mg/dL. This could be because of appropriate glycemic control with the help of oral hypoglycemic agents or insulin therapy. This was not statistically significant between the groups as per the fasting blood sugar levels(P value=0.7495).

Factors like age, gender, socioeconomic status group, site of ulcer, hypertension, neuropathy, fasting blood sugar have been regarded as possible reasons for diabetic foot ulcers. When analyzed, both the groups were comparable for all these parameters with no significant statistical difference detected(p value>0.05) thus, eliminating bias from our research.

Hyaluronic acid has depicted promising effects on healing when used topically on wounds by affecting multiple stages in the usual physiology of wound closure. In this study, the wound healing efficacy of hyaluronate-iodine complex as compared to povidone-iodine was evaluated based on the extent of decrease in the ulcer area over 14 days.

By dependent t test, the mean area of the ulcer in the control group on day 0 was 16.3cm^2 and on the day 14 was 13.29 cm^2. There was significant statistical difference in the control group individually based on the decrease in the mean area of the ulcer over 14 days(p value = 0.0001). Similarly, the mean area of the ulcer in the test group on day 0 was 11.43cm^2 and on the day 14 was 7.62cm^2. There was significant statistical difference in the test group individually based on the decrease in the mean area of the ulcer over 14 days(p value = 0.0001).

On assessment of the effect of the hyaluronate-iodine complex on diabetic wound healing when compared to the effect of just povidone-iodine, the mean percentage reduction in area of ulcer over 14 days in the control and test groups were noted 19.67% and 43.56%, respectively. This was a statistically significant difference in the mean percentage reduction in ulcer area in the test group when compared to the control group(p value = 0.0001).

There are several studies which are in conjunction with our study's findings. Tagliagambe et al, in his case report, studied the effect of 0.2% hyaluronic acid

sodium salt gel for the treatment of a chronic, recurrent, nonhealing distal leg ulcer. Complete closure of the wound was accomplished in 4 weeks of treatment thus highlighting the wound healing superiority of hyaluronic acid over other conventional modalities.[22]

Lee et al, conducted a randomized prospective , placebo-controlled single centre study over 12 weeks to evaluate the effectiveness of hyaluronic acid in diabetic ulcer treatment. The study group(84.6%) revealed a significant higher complete healing rate when compared to the control group(41.6%) with a p value=0.041.In addition, the study group witnessed a faster ulcer healing velocity(p value=0.022) and lesser mean duration for accomplishing 50% ulcer size decrease(0.004).[23]

In another study done by Ye-na Lee et al in Korea, the clinical potency and safety of hyaluronic acid with that of the conventional dressing was checked for the treatment of diabetic foot ulcers. By third week, the mean percentage reduction in ulcer area was 51.6% in the experimental group and 29.7% in the control group (p value=0.184). Similarly, the mean percentage of increase in healthy granulation tissue area was 51.7% in the experimental group and 14.6% in the control group(p value= 0.60).Thus, the results were favourable despite not being of statistical significance.[24]

All these warranted an accelerated wound healing in diabetic foot ulcers when compared with the old conventional dressings.

Hyaluronic acid has been reported to be involved in interfering with ligand-receptor interaction for bacterial adhesion, thus preventing bacterial colonization in local wound environments. This in turn plays a pivotal role in obstructing the production and proliferation of a biofilm over wounds, especially in diabetic ulcer. Hyaluronic acid, owing to its versatile properties of biocompatibility, non-immunogenecity, biodegradability and viscoelasticity has established itself to be a

perfect biomaterial to protect against various microbes. This compound has a bacteriostatic action against Staphylococcus aureus, Pseudomonas aeruginosa, beta hemolytic streptococci.[25]

However, there are limitations with respect to some bacteria producing hyaluronidase, an enzyme that can catalyze the degradation of hyaluronic acid.[26] In order to combat this, it has been proposed to load hyaluronic based hydrogels with antibiotics.[27] This option is feasible and can be clinically applied. The drug combination used in this study was an amalgamation of hyaluronic acid, iodine and an antibiotic in the form of ornidazole.

In this study, the most common microorganisms observed in the test group on day 0 were Pseudomonas aeruginosa(15%), Escherichia coli(12.5%), Klebsiella pneumonia(11.25%) and Methicillin resistant Statphylococcus aureus(7.5%). The most common microorganisms observed in the test group on day 14 were Escherichia coli(5%) and Klebsiella oxytoca(3.75%). After a course of 14 days of dressings, the control group depicted a reduction in microbial colonization by 67.74% whereas for the test group, it was 67.85%. This finding was in agreement with the available literature emphasizing the antibacterial property of hyaluronate-iodine complex. However, there are no sufficient clinical trials to assess the antibacterial nature of hyaluronic acid and demands further research in future.

Diabetic foot ulcer healing demands a multimodality approach for the optimum treatment of the local wound. The hyaluronate-iodine combination has multiple advantages that can aid an appropriate wound healing ass was proved in this study. During the course of the study, no serious side effects were noted in the test group, thus marking the drug to be safe for human application.

This study population here was only of 80 patients, 40 in test and 40 in control groups.The other limitation of this study was that it was carried out at a single center. There is a requirement in future for large scale clinical multicentre studies which can establish the effectiveness of the hyaluronate-iodine complex in the wound healing process of diabetic foot ulcers.

CONCLUSION

This study concluded that application of hyaluronate-iodine complex over diabetic foot ulcers warranted a notable decrease in the areas of the ulcer in comparison to dressing with povidone-iodine.

Additionally, this new topical modality has the higher potential of antimicrobial action in terms of reduction in the bioburden when compared with the control group. There were no side effects observed during the study duration, thus confirming its safety.

The promising results of this drug combination is because of its actions such as epithelialization, collagen deposition and angiogenesis.

There is a need for multiple, large human clinical trails in the future to assess the drug combination’s effects on diabetic foot ulcer healing. This would cement this formulation’s hold amongst the plethora of local wound dressings available and guarantee its usage in day to day clinical application.

SUMMARY

Hyaluronan is a glycosaminoglycan that possesses the benefits of natural wound healing by virtue of its actions on epithelial cell migration, collagen deposition, neovascularization, etc. Recently available commercial preparations of hyaluronate-iodine complex have led to their application on a variety of ulcers. However, there is a lack of sufficient research on the advantages and adverse effects of this formulation, especially on diabetic foot ulcers. This has been the rationale behind executing this study.

The aim of this study is to evaluate the wound healing capacity of hyaluronate-povidone complex when compared to povidone-iodine dressing on the basis of the mean percentage reduction in ulcer area in chronic diabetic foot ulcers.

Our study included 80 patients admitted to KLES Dr. Prabhakar Kore charitable hospital and MRC, Belagavi for the chronic diabetic foot ulcer management.

This study population was categorized into the Group 1 (control group) and the Group 2 (test group). The control group (Group 1) received povidone-iodine dressing whereas the test group(Group 2) received the intervention in the form of hyaluronate-iodine complex dressing.

This study reflected no statistically significant difference when compared between the two groups in terms of age, sex, socioeconomic status, duration of diabetes mellitus, site of the ulcer, onset of the ulcer, hypertension, neuropathy, peripheral arterial disease, fasting blood sugar and body mass index.

On assessment , the effect of the hyaluronate-iodine complex on diabetic wound healing when compared with just povidone-iodine, it was found that the mean percentage reduction in area of ulcer over 14 days in the control and test groups were

19.67% and 43.56%, respectively. This was statistically significant in the mean percentage reduction in ulcer area in the test group when compared to the control group.

The test group showed a decrease in the bioburden of the chronic diabetic foot ulcers which was comparable to that of the povidone-iodine dressing, thus proving the antibacterial capacity of the hyaluronate-iodine complex.

Our study thus concluded that the hyaluronate-povidone complex dressing had a superiority in healing of chronic diabetic foot ulcers over the conventional povidone-iodine dressing both on the basis of decrease in the ulcer area and bacterial bioburden.

For a country such as India with its ever rising prevalence of diabetes and patients with diabetic foot ulcers, there is a deficiency of an apt topical modality which can fulfil the criteria of no antimicrobial resistance and minimal side effects. The hyaluronate-povidone complex shows promising potential when it comes to these demands and thus, should be considered as a lucrative option for topical dressing.

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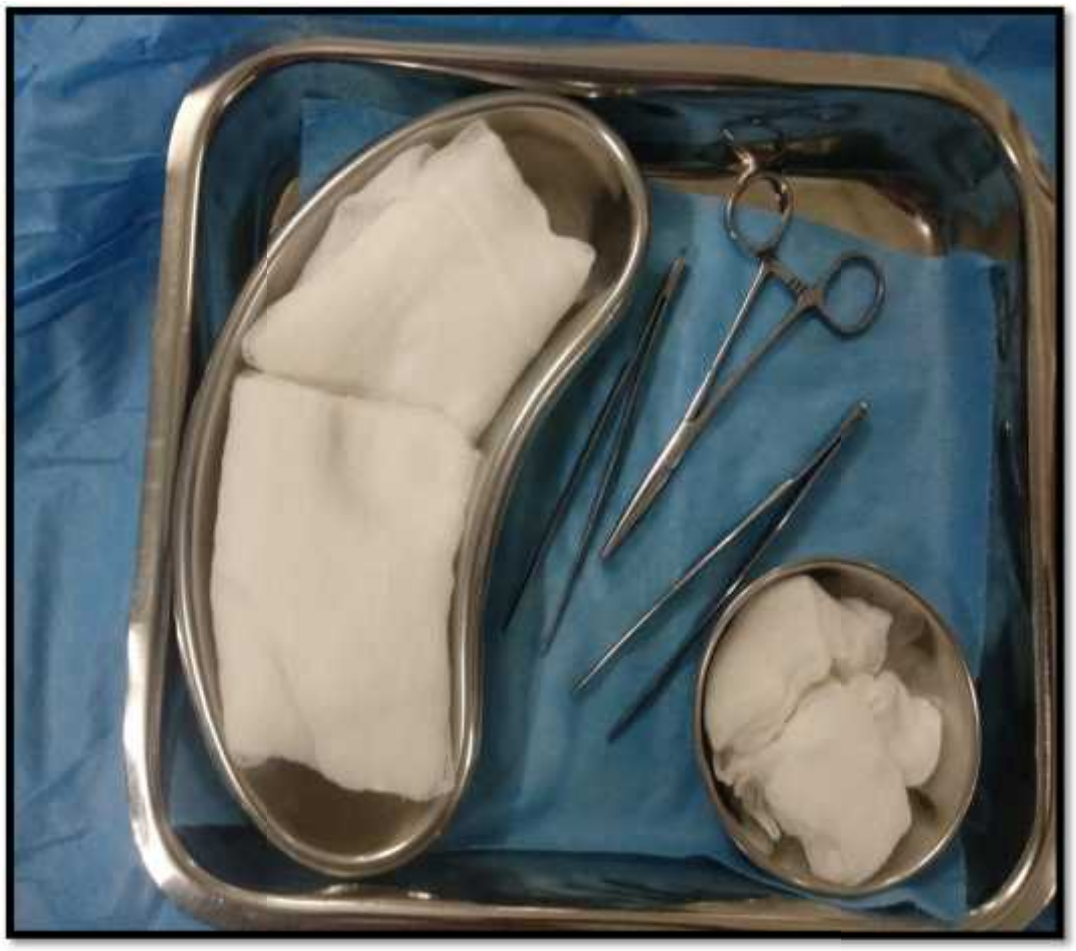
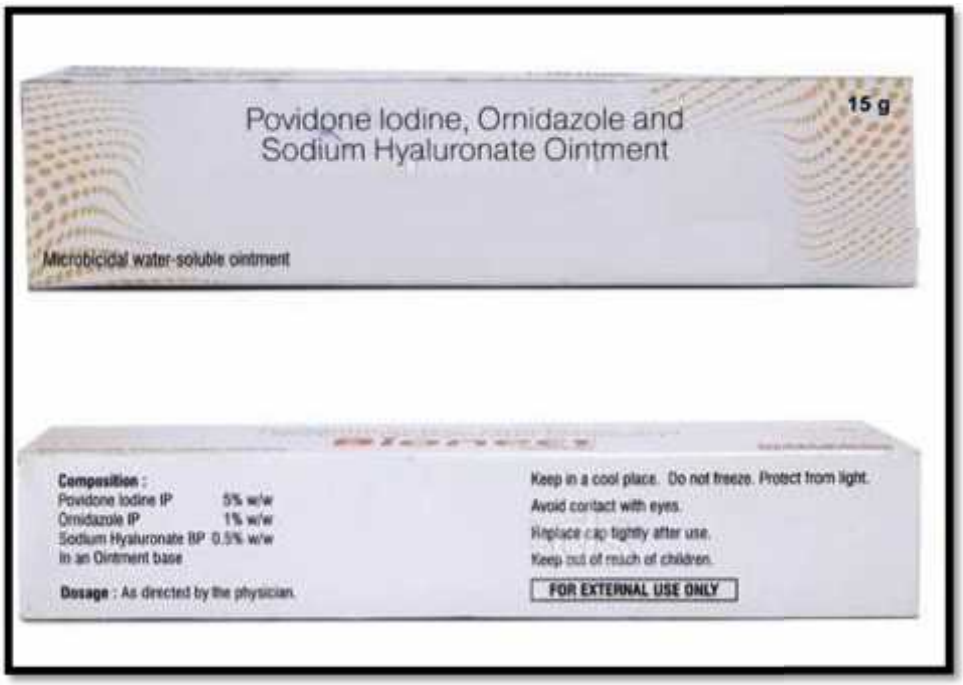
ANNEXURE I – PHOTOGRAPHS

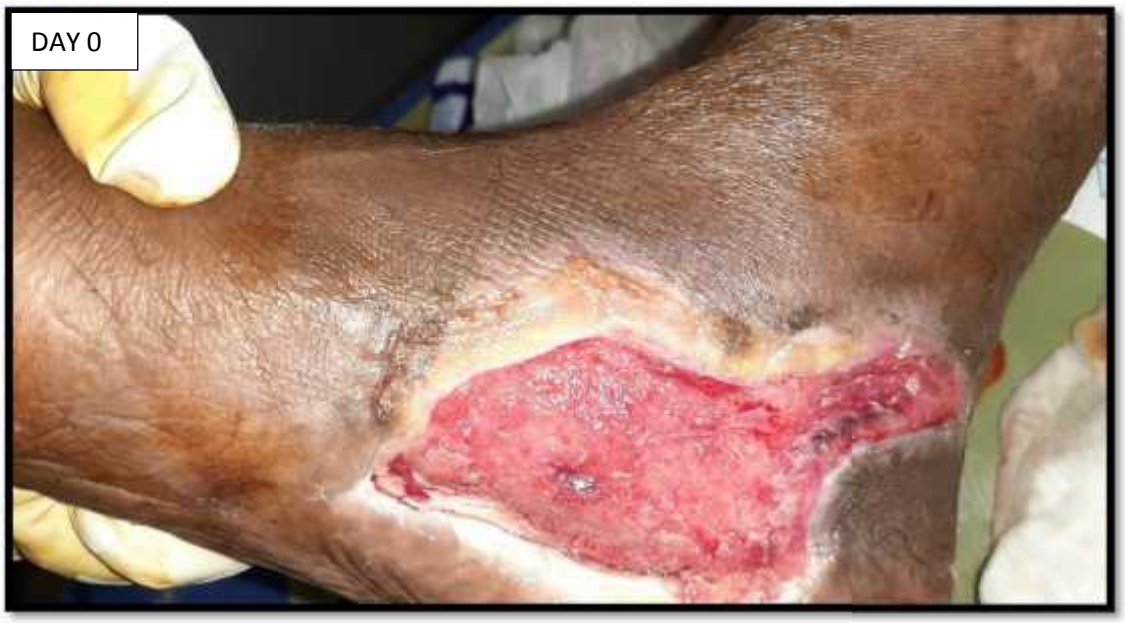


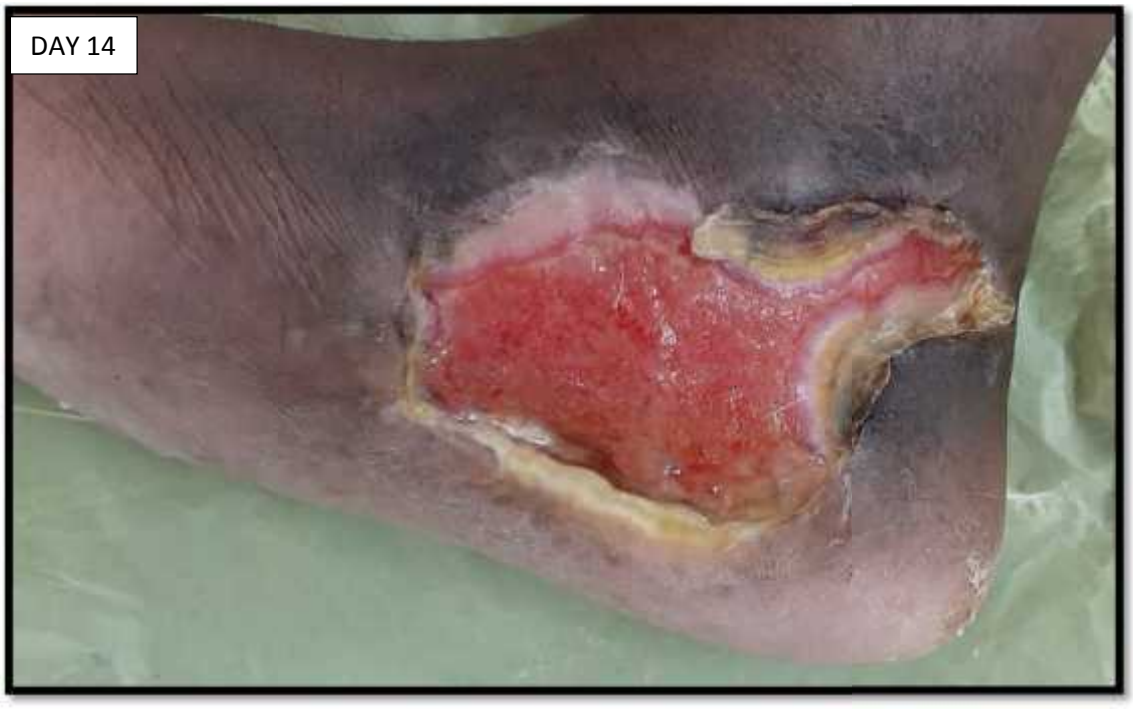
PHOTOGRAPH-1: DRESSING EQUIPMENT



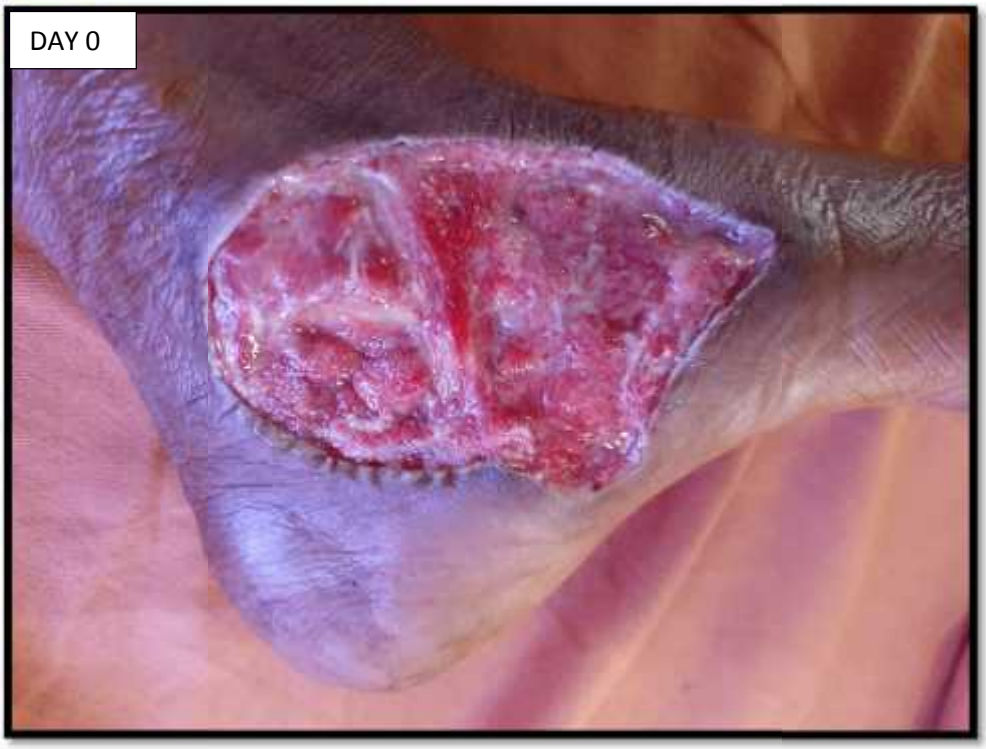
PHOTOGRAPH -2: HYALURONATE- IODINE AND ORNIDAZOLE COMPLEX GEL

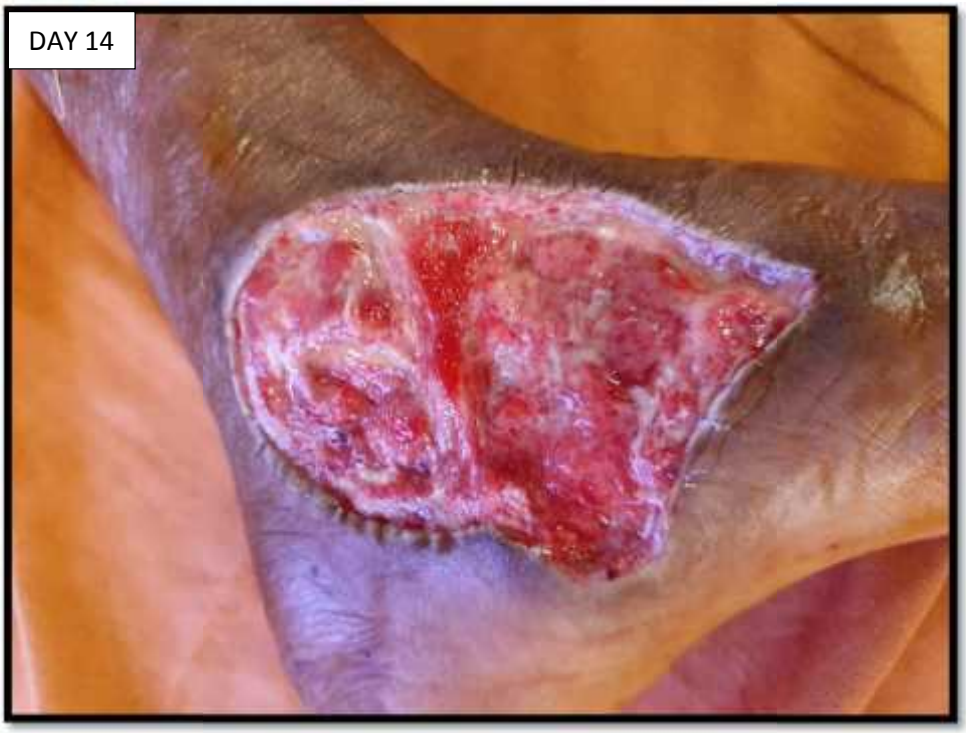
PHOTOGRAPH-3: POVIDONE-IODINE SOLUTION 10% W/V



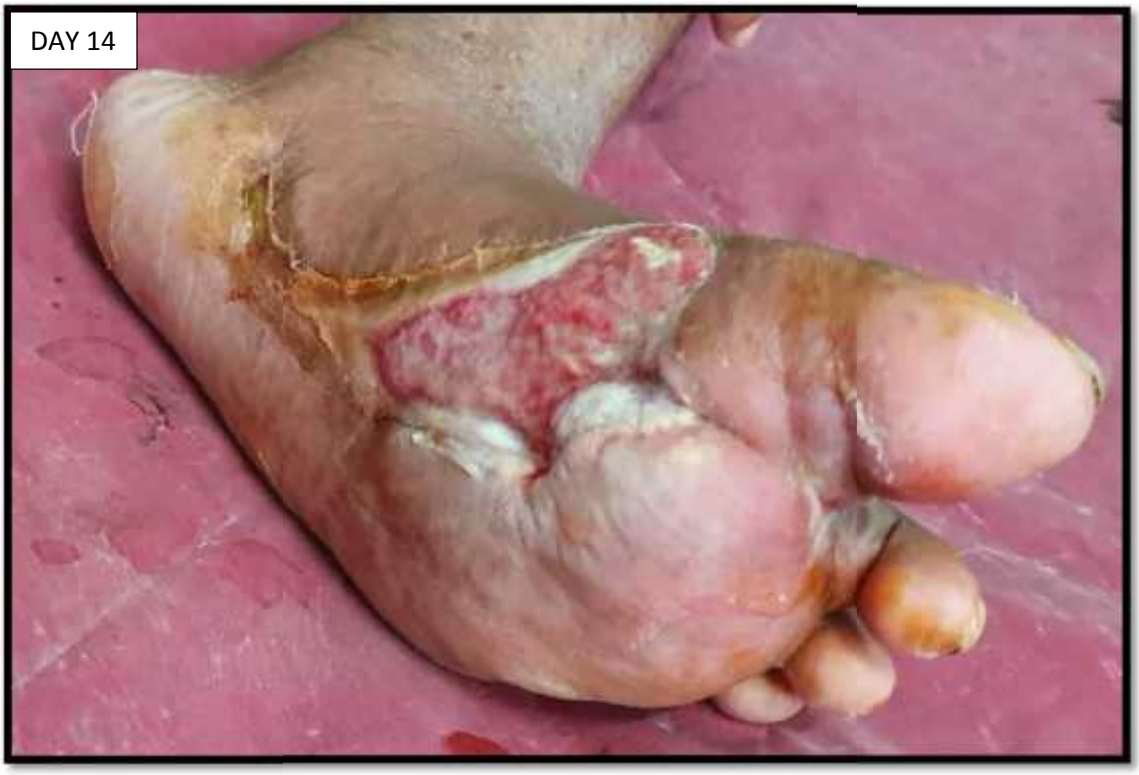


PHOTOGRAPH -4. ULCER ON DAY 0 AND DAY 14 IN GROUP 1





PHOTOGRAPH- 5: ULCER ON DAY 0 AND DAY 14 IN GROUP 1.



PHOTOGRAPH- 6: ULCER ON DAY 0 AND DAY 14 IN GROUP 2.

PHOTOGRAPH- 7: ULCER ON DAY 0 AND DAY 14 IN GROUP 2.

ANNEXURE II – CONSENT FORM

CONSENT FOR PARTICIPATION IN RESEARCH STUDY

INFORMED CONSENT

Purpose of the study

I have been informed by REG NO. BH0118004, Post Graduate in M.S.General Surgery under the guidance of Dr._____, Professor Department of General Surgery, J.N. Medical College, KAHER, Belagavi is conducting a study to compare HYALURONATE-IODINE AND ORNIDAZOLE COMPLEX wound gel dressing versus povidone-iodine dressing in healing of chronic diabetic foot ulcers at KLES DR.PRABHAKAR KORE 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 hyaluronate-iodine and ornidazole complex 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 hyaluronate-iodine and ornidazole complex

wound gel dressing or povidone-iodine dressing. You will be subjected to examination of the foot ulcer along with measurement of the ulcer dimensions, 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 hyaluronate-iodine ornidazole complex 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 you have any questions related to the study, in future or in case of study related injury or illness, you can contact REG NO. BH0118004, Department of General Surgery, KAHER J.N Medical College, Ph. No. _____or_____or Dr._____, Professor Dept. Of General surgery, KLE University's J.N Medical College, Belagavi,Ph.No._____.

Voluntary participation

Your participation in the study is voluntary. In case you need any further information regarding your rights as study participant, you 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. You are free to stop participation in this study at any time and for any reason.

Consent statement:

I, _____ voluntarily agree for participating in this study. By signing this consent form I am not giving up any of my legal rights, I may withdraw from the study anytime. I am signing the consent form after having read or been read form in my own vernacular language, including the risks and the benefits and having all my questions answered.

Participant Name : _____

Signature of the Left Thumb Print of Participant : _____

Investigators Name: _____ Signature: _____

Witness Name : _____ Signature: _____

Date: _____

सहमतिकथन:

मैं, _____
स्वेच्छासेइसअध्ययनमेंभागलेनेकेलिएसहमतहूं।इससहमतिफॉर्मेपरहस्ताक्षरकर केमैंअपनेकिसीभीकानूनीअधिकारकोनहींछोड़रहाहूं,
मैंकिसीभीसमयअध्ययनसेवापसआसकताहूं।मैंअपनेस्वयंकेस्थानीयभाषामेंपढ़ने यापढ़नेकेबादसहमतिफॉर्मेपरहस्ताक्षरकररहाहूं,
जिसमेंजोखिमऔरलाभशामिलहैंऔरमेरेसभीसवालोंकेजवाबदिएगएहैं।

भागलेनेवालेकानाम : _____
प्रतिभागीकेबाएंथंबप्रिंटकाहस्ताक्षर: _____

जांचकर्ताकानाम: _____ हस्ताक्ष : _____

साक्षीकानाम: _____ हस्ताक्षर: _____

तिथि: - _____

ಒಪ್ಪಿಗಹೇಳಿಕೆ:

ನಾನು, _____

ಈಅಧ್ಯಯನದಲ್ಲಿಪಾಲ್ಗೊಳ್ಳಲುಸ್ವಯಂಪ್ರೇರಣೆಯಿಂದಒಪ್ಪುತ್ತೇನೆ.ಈಸಮ್ಮತಿಯನಮೂನ
ಯಲ್ಲಿಸಹಿಹಾಕುವಮೂಲಕನನ್ನಯಾವುದೇಕಾನೂನುಹಕ್ಕುಗಳನ್ನುನಾನುಬಿಡುತ್ತಿಲ್ಲ,
ನಾನುಯಾವಸಮಯದಲ್ಲಾದರೂಅಧ್ಯಯನವನ್ನುಹಿಂತೆಗೆದುಕೊಳ್ಳಬಹುದು.ನನ್ನಸ್ವಂತದೇ
ಶೀಯಭಾಷೆಯಲ್ಲಿಓದಿದನಂತರಅಥವಾಫಾರ್ಮ್‌ಅನ್ನುಓದಿದನಂತರನಾನುಒಪ್ಪಿಗಫಾರ್ಮ್ಗೆಸ
ಹಿಹಾಕುತ್ತಿದ್ದೇನೆ,
ಅಪಾಯಗಳುಮತ್ತುಪ್ರಯೋಜನೆಗಳನ್ನುಒಳಗೊಂಡಂತಮತ್ತುನನ್ನಎಲ್ಲಪ್ರಶ್ನೆಗಳಿಗೆಉತ್ತರಿಸಿ
ದೆ.

ಭಾಗವಹಿಸುವವರು: _____

ಪಾಲ್ಗೊಳ್ಳುವವರಎಡತಮ್ಮುದ್ರಣದಸಹಿ: _____

ತನಿಖಾಧಿಕಾರಿಗಳುಹಸರು: _____ ಸಹಿ: _____

ಎಟ್ನೆಸ್ಹಸರು: _____ ಸಹಿ: _____

ದಿನಾಂಕ: _____

मंजूरीविधानः

मी, _____

याअभ्यासातसहभागीहोण्यासाठीस्वेच्छेनेसहमतआहे.यासंमतीफॉर्मवरस्वाक्षरीक
रुनमीमाझेकोणतेहीकायदेशीरअधिकारसोडूनदेतनाही,
मीकोणत्याहीवेळीअभ्यासमागेघेऊशकते.मीमाझ्यास्व :
च्यास्थानिकभाषेतीलवाचनकिंवावाचनकेल्यानंतरजोखमीआणिफायदेआणिमा
झ्यासर्वप्रश्नांचीउत्तरेघेतल्यानंतरसंमतीफॉर्मवरस्वाक्षरीकरीतआहे.

सहभागीनाव: _____
सहभागीच्याडाव्याथंबप्रिंटचीस्वाक्षरी: _____

तपासकर्त्याचेनाव: _____ स्वाक्षरी: _____

साक्षीदारांचीनावे: _____ स्वाक्षरी: _____

तारीख: _____

ANNEXURE III.

ETHICAL CLEARANCE.

K.L.E. ACADEMY OF HIGHER EDUCATION AND RESEARCH
(Deemed – to- be- University)
Accredited 'A' Grade by NAAC (2nd Cycle) Placed in Category 'A' by MHRD (GoI)
JAWAHARLAL NEHRU MEDICAL COLLEGE,
NEHRU NAGAR, BELAGAVI-590010 (KARNATAKA-INDIA)
Website: http//www.jnmc.edu
E-Mail : dome@jnmc.edu
Phone: (+ 91-(0)831 Office : 2472550
Principal: 2471701
Fax No. +91 (0)831 – 2470759

Ref: MDC/DOME/ 67 Date: 24/11/2018

To,

REG NO. BH0118004
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 HYALURONATE-IODINE AND ORNIDAZOLE COMPLEX 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 HOSPITAL AND MEDICAL RESEARCH CENTRE, BELAGAVI-590010"**, 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.Phone no : ☐☐☐☐☐☐☐☐☐☐

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-No

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		

11. Amputation 1. Yes

2. No

If yes, DATE

REASON

Examination:

Height	Weight	BMI

1.

Pulse rate	Blood pressure	Temperature	Respiratory Rate

2.

3. Foot Deformity:

1- Toe deformity 2 – Charcot's foot

4. 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			

5.Wagner Grading:

1	
2	
3	
4	
5	

6. Peripheral pulsations of lower limb:

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

7.Sensory system examination-i) Touch

ii)Pain

iii) Temperature

8.Regional lymph node examination-

ANALYSIS PLAN

1. Ulcer dimensions:

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

2. Wound culture and sensitivity on D_0 and D_{14}

a) Wound culture and sensitivity on D_0

1. No growth 2. Growth present ☐

If 2-

Organism present-

Sensitivity-

b) Wound culture and sensitivity on D_{14}

1. No growth 2. Growth present ☐

If 2-

Organism present-

Sensitivity-

3. 1)Wound area on D_0 =

2)Wound area on D_{14} =

3)Wound area reduction =

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

4) Percentage wound area reduction =

$\frac{(\text{Area on } D_0 - \text{Area on } D_{14})}{\text{Area on } D_0} \times 100$

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

CONTROL - 40 CASES (GROUP 1)

S.NO	IPNO.	AGE	SEX	SOCIOECONOMIC STATUS	DURATION OF DIABETES	ONSET	SITE	HYPERTENSION	NEUROPATHY	PVD	BMI	FBS	Hb	TLC	CREATININE	AREA D0	AREA D14	REDUCTION IN AREA	% IN REDUCTION OF AREA	CULTURE D0	CULTURE D14	
1	919284	65	F	1	20 YEARS	2	PLF	1	YES	NO	26.63	160	7	6410	1.3	30	27	3	10	MRSA	MRSA	
2	926410	61	M	1	10 YEARS	2	DRF	1	YES	NO	21.48	116	9.3	6950	0.8	20	18	2	10	P.AERUGINOSA	S.AGALACTIAE	
3	926875	51	M	1	10 YEARS	1	PLF	1	YES	YES	25.3	136	11	14030	1.2	25	20	5	20	CITROBACTER SPECIES	E.COLI	
4	927142	58	F	1	5 YEARS	1	PRF	2	NO	NO	24.44	124	10.3	8020	1.1	6	4.5	1.5	25	PROTEUS VULGARIS	_	
5	931195	52	M	1	7 YEARS	1	PRF	2	NO	NO	19.6	116	11.6	6900	2.1	6	4	2	33.33	STAPH.AUREUS	_	
6	931897	56	M	1	22 YEARS	1	PLF	2	NO	YES	23.87	150	14.4	8190	1.1	2	1.5	0.5	25	_	_	
7	936614	60	M	1	10 YEARS	1	DLF	1	YES	NO	27.68	89	9.8	6560	0.9	12	10	2	16.66	P.ACURIGINOSA	_	
8	937144	72	M	1	10 YEARS	1	DLF	1	YES	NO	28.125	132	10.2	5500	0.4	6	4	2	33.33	_	_	
9	939644	25	F	1	2 YEARS	2	DLF	2	NO	NO	23.78	215	9	9500	0.9	4	3	1	25	K.PNEUMONIAE	_	
10	939668	60	M	1	5 YEARS	2	PRF	2	NO	NO	29.13	125	9	5500	0.8	9	7.5	1.5	16.66	_	_	
11	941860	62	M	2	21 YEARS	1	DLF	1	YES	NO	22.03	181	9.1	16080	6.16	36	30	6	16.66	K.OXYTOCA	_	
12	945399	54	M	1	9 YEARS	2	DRF	2	NO	NO	22.49	157	10.7	14000	1.12	16	14	2	12.5	P.AERUGINOSA	_	
13	947548	52	F	1	25 YEARS	1	DLF	1	YES	NO	29.7	126	10.4	15500	0.42	9	7.5	1.5	16.66	P.AERUGINOSA	_	
14	949731	52	F	1	15 YEARS	2	DRF	1	YES	NO	20.2	121	9.6	10780	0.2	9	7.5	1.5	16.66	_	_	
15	951895	54	M	1	15 YEARS	2	DLF	1	YES	NO	20.76	120	10.4	8360	0.99	6	4	2	33.33	_	_	
16	952188	59	M	1	5 YEARS	1	DLF	2	NO	NO	24.38	210	11.5	9310	1.73	4	3	1	25	_	_	
17	953028	24	M	1	8 YEARS	1	DLF	1	YES	NO	23.87	132	11.6	9020	1.41	4	3	1	25	E.COLI	_	
18	953334	55	M	1	10 YEARS	2	DRF	2	NO	NO	27.34	200	8.3	30450	0.7	30	27	3	10	MRSA	ECOLI	
19	953690	62	M	2	2 YEARS	2	PRF	2	NO	NO	24.76	98	9.8	10600	0.9	12	9	3	25	P.AERUGINOSA	_	
20	954920	70	M	1	3 YEARS	2	PLF	1	NO	NO	19.53	128	11.7	14300	1.6	12	10.5	1.5	12.5	K. OXYTOCA	_	
21	956295	52	M	1	19 MONTHS	1	PRF	2	NO	NO	23.87	96	10.4	5640	1	9	7.5	1.5	16.66	_	_	
22	956630	50	M	1	10 YEARS	2	DRF	1	YES	NO	25.51	143	11.3	8400	0.9	20	16	4	20	E.COLI	_	
23	956682	40	M	1	9 MONTHS	2	DLF	2	NO	NO	22.49	136	12.4	7600	1	4	3	1	25	STAPH.AUREUS	CITROBACTER SPECIES	
24	957187	52	M	3	4 YEARS	2	DLF	1	NO	NO	23.04	160	11.8	9900	1.57	30	27	3	10	P.AERUGINOSA	_	
25	958202	79	M	2	10 YEARS	2	PLF	2	YES	YES	22.03	98	10.8	8700	2.68	7	6	1	14.28	_	_	
26	959304	53	M	2	20 YEARS	1	PRF	1	YES	YES	27.3	180	9.2	21200	4.1	12	10	2	16.6	PROVIDENCIA SPECIES	_	
27	959661	40	M	1	9 MONTHS	1	PLF	2	NO	NO	21.48	108	7.9	5460	1	6	4	2	33.33	E.COLI	K.OXYTOCA	
28	960633	65	M	1	10 YEARS	2	PRF	1	YES	NO	22.77	111	8.5	5760	0.7	36	30	6	16.66	E.COLI	P.AERUGINOSA	
29	961589	65	M	1	4 MONTHS	2	DRF	2	NO	NO	23.03	130	8.9	13690	1	30	27	3	10	P.AERUGINOSA	_	
30	962436	47	M	1	2 YEARS	1	PRF	1	NO	NO	26.6	142	10.2	4900	0.83	20	18	2	10	K.PNEUMONIAE	_	
31	967778	53	M	1	8 YEARS	2	DRF	1	NO	NO	18.51	112	12	6700	1.2	25	20.25	4.75	19	P.AERUGINOSA	S.AGALACTIAE	
32	969059	57	M	1	8 YEARS	1	DLF	2	YES	YES	18.51	140	8.6	7530	0.8	20	15	5	16.66	ENTEROBACTER SPECIES		

33	968156	65	F	1	15 YEARS	2	DRF	1	YES	NO	21.09	160	8.7	9800	1.22	36	30	6	16.66	PROVIDENCIA SPECIES	_	
34	976952	67	M	2	2 YEARS	1	PLF	1	NO	NO	31.63	124	11.3	8900	0.76	16	12	4	25	E.COLI	_	
35	982044	65	M	1	10 YEARS	2	DLF	2	YES	YES	24.22	96	10.2	7360	0.76	20	16	4	20	STAPH.SPECIES	NTEROBACTER SPECIES	
36	984981	54	M	1	4 YEARS	2	PRF	2	NO	NO	28.13	126	9.4	8200	1.2	16	12	4	25	K.PNEUMONIAE	_	
37	986535	60	M	2	6 YEARS	1	DRF	2	YES	YES	26.12	145	10	17500	1.3	30	25	5	16.66	PROTEUS MIRABILIS	PROTEUS MIRABILIS	
38	990373	56	M	1	15 YEARS	2	DRF	2	YES	YES	23.03	178	7.2	16490	1.44	20	15	5	25	MRSA	_	
39	990412	81	M	2	15 YEARS	2	DRF	2	YES	YES	23.43	109	6.5	8800	1.66	12	10	2	16.6	E.COLI	_	
40	996614	39	F	1	4 YEARS	2	DRF	1	NO	NO	28.57	142	10.6	11300	0.81	4	3	1	25	_	_	

TEST- 40 CASES (GROUP 2)

S.NO	IP.NO.	AGE	SEX		DURATION OF DIABETES	ONSET	SITE	HYPERTENSION	NEUROPATHY	PVD	BMI	FBS	Hb	TLC	CREATININE	AREA D0	AREA D14	REDUCTION IN AREA	% IN REDUCTION OF AREA	CULTURE D0	CULTURE D14
1	919616	50	M	2	10 YEARS	2	DRF	2	NO	NO	26.34	118	10.5	6300	0.4	36	33	3	8.33	COAG.NEG STAPH.	E.COLI
2	926381	65	M	1	10 YEARS	1	PLF	1	YES	NO	22.03	132	10.2	14900	1.71	6	4	2	33.33	_	_
3	926760	45	M	1	5 YEARS	1	DRF	2	NO	NO	20.2	98	12.2	15500	0.9	2	1	1	50	_	_
4	927381	58	M	1	3 MONTHS	2	DRF	2	NO	NO	23.43	115	11.2	13800	3.54	36	30	6	16.66	K.PNEUMONIAE	K.OXYTOCA
5	927383	89	M	1	5 YEARS	2	PLF	2	NO	NO	25.3	240	10.2	13200	0.63	6	4	2	33.33	_	_
6	928806	58	M	1	10 YEARS	2	DRF	2	NO	NO	20.6	110	13.7	8520	1.2	24	20	4	16.66	_	_
7	931501	60	M	1	4 YEARS	2	PRF	2	NO	NO	24.97	132	13	11300	0.62	6	4	2	33.33	E.COLI	_
8	932823	50	F	2	20 YEARS	2	DRF	1	YES	NO	22.85	130	10.5	10700	0.2	6	4	2	33.3	E.COLI	_
9	938892	83	M	1	5 YEARS	2	DRF	2	NO	NO	24.43	196	8.9	8900	0.4	4	3	1	25	K.PNEUMONIAE	_
10	940042	66	M	1	4 YEARS	2	PRF	2	NO	NO	26.17	224	11.2	7.4	1.61	6	4	2	33.33	_	_
11	947159	50	M	1	10 YEARS	2	DLF	1	YES	NO	24.44	160	9.5	13200	1.53	16	14	2	12.5	K.PNEUMONIAE	_
12	947714	75	M	1	15 YEARS	1	PLF	2	YES	YES	25.39	173	12.5	11500	1.2	36	24	12	33.33	STAPH.EPIDERMIDIS	_
13	949523	58	M	1	4 YEARS	2	DRF	2	NO	NO	23.75	137	7.1	15430	0.9	24	18	6	25	MRSA	MRSA
14	952545	65	M	2	10 YEARS	3	PLF	2	NO	NO	25.39	165	10.4	7100	2.19	2	1	1	50	P.AERUGINOSA	K.OXYTOCA
15	954709	58	M	1	10 YEARS	2	PRF	2	NO	NO	27.34	126	9	6390	0.81	4	3	1	25	P.AERUGINOSA	_
16	955111	60	M	1	20 YEARS	2	PRF	1	YES	YES	21.77	103	11	15470	1.4	30	24	6	20	E. FAECALIS	_
17	955960	60	M	1	5 YEARS	1	PLF	2	NO	NO	22.03	110	7.7	8690	1	4	2	2	50	_	_
18	956995	68	M	1	7 YEARS	1	PLF	1	NO	NO	27.76	146	14.8	15600	1.5	6	4	2	33.33	_	_
19	957201	57	M	1	5 YEARS	1	DLF	1	NO	NO	22.46	113	11.6	10960	0.9	6	4	2	33.33	K.PNEUMONIAE	_
20	957368	38	M	1	10 YEARS	1	DLF	2	NO	NO	20.76	160	13.3	6250	1	1	0.5	0.5	50	COAG.NEG STAPH.	_
21	958210	65	M	2	10 YEARS	2	DRF	1	NO	NO	25.71	118	11.4	10900	1.19	6	4	2	33.33	S.AGALACTIAE	P.AERUGINOSA
22	960115	34	M	1	3 MONTHS	1	DRF	2	NO	NO	29.38	110	9.3	20.16	1.2	4	2	2	50	MRSA	E.FAECALIS
23	960351	63	M	1	13 YEARS	2	PRF	1	YES	NO	22.49	120	13.4	5700	0.67	4	3	1	25	P.VULGARIS	STAPH.AUREUS
24	961331	58	M	1	9 YEARS	2	DLF	2	NO	NO	22.77	120	10.7	7560	0.9	4	3.4	0.6	15	P.AERUGINOSA	K.PNEUMONIAE
25	963691	67	M	1	15 YEARS	1	PLF	2	YES	NO	24.97	222	10.6	9270	1.2	20	15	5	20	_	_
26	964852	42	M	1	4 YEARS	2	PRF	2	NO	NO	22.77	139	10.1	10680	1.2	6	4	2	33.33	_	_
27	966511	44	F	2	12 YEARS	3	PLF	1	YES	NO	21.48	90	12.6	13100	0.83	0.5	0.25	0.25	50	COAG.NEG STAPH.	_
28	966530	45	M	1	10 YEARS	1	PLF	1	YES	NO	21.48	112	8.4	15600	1.29	36	30	6	16.66	P.AERUGINOSA	_
29	969511	56	M	1	10 YEARS	1	PRF	2	YES	YES	26.12	130	11.2	14660	1	12	9	3	25	MRSA	_
30	972960	38	M	2	10 YEARS	1	PLF	2	YES	YES	26.07	160	7.8	10800	1	1	0.5	0.5	50	S.PNEUMONIAE	E.COLI
31	974409	90	F	2	1 YEAR	1	DRF	2	NO	NO	19.53	110	10.6	11300	1	2	1	1	50	_	_
32	974694	62	M	1	15 YEARS	1	DLF	1	YES	YES	23.43	140	12.3	11700	1.14	3	2	1	33.33	P.AERUGINOSA	_
33	979086	55	M	2	15 YEARS	1	PRF	1	YES	YES	40.81	140	9.4	5400	1	2	1	1	50	E.COLI	_
34	979109	51	M	2	4 MONTHS	3	PLF	2	NO	NO	25.95	132	13.8	8600	1	4	2	2	50	K.PNEUMONIAE	_
35	983158	78	M	1	10 YEARS	4	PRF	2	NO	YES	20.95	124	9.7	12300	1.24	6	4	2	33.33	P.MIRABILIS	_
36	989233	48	M	1	20 YEARS	2	PLF	1	YES	NO	26.12	140	12.7	4700	0.8	12	9	3	25	_	_
37	990799	65	M	1	2 YEARS	1	DRF	2	NO	NO	20.59	126	15.5	10670	1.3	16	12	4	25	K.PNEUMONIAE	_
38	990994	66	M	1	18 YEARS	1	DRF	2	YES	YES	27.55	90	8.2	13180	0.9	20	16	4	20	E.COLI	